

THE ASSOCIATION BETWEEN SEVERE MENTAL  
ILLNESS AND CARDIOVASCULAR DISEASE:  
SYSTEMATIC REVIEW AND RETROSPECTIVE  
COHORT STUDIES USING ROUTINELY COLLECTED  
ELECTRONIC PRIMARY CARE DATA

by

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A thesis submitted to the University of Birmingham for the degree of  
DOCTOR OF PHILOSOPHY

Institute of Applied Health Research  
College of Medical and Dental Sciences  
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April 2024

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## ABSTRACT

Compared with the general population, people with severe mental illness (SMI), such as schizophrenia and bipolar disorder (BD) have shorter life expectancy, dying up to 20 years earlier. Death rates are two to three times higher than those without SMI and the mortality gap has not reduced in recent decades. Much of the premature mortality is due to preventable causes, with cardiovascular disease (CVD) being the most common cause of death in those with SMI.

This thesis aims to summarise the evidence on the relationship between SMI and CVD, describe changes over time, explore the factors associated with highest CVD risk and quantify their relative importance.

### Methods

Three different methodologies were used to assess the association between BD, schizophrenia, and CVD. A large-scale systematic review of SMI and CVD-related mortality and incidence; matched and unmatched cohort studies, which explored the effects of SMI on all-cause mortality, post-CVD case-fatality and CVD incidence; and a mediation analysis, which explored the effect of four mediators (smoking, diabetes mellitus (DM), obesity and blood pressure) on the causal pathway between SMI and CVD.

### Results

The systematic review found that CVD-related mortality was elevated for those with SMI compared with the general population. Meta-analyses showed that pooled standardised mortality ratios were 1.96, 95% confidence interval (CI): 1.61-2.39 and 1.65, 95% CI: 1.53-

1.77 for schizophrenia and BD, respectively. Deaths from individual CVD diagnoses of coronary heart disease (CHD), cerebrovascular accident (CVA) and heart failure (HF) were also high for people with SMI compared with the general population. There was a consistent association between SMI and increased incidence of CVA, CVD events and HF, and between BD and CHD. However, most pooled estimates showed no evidence of difference in CHD incidence between those with schizophrenia and the general population. Excess risk of CVD-related mortality appeared higher in the 1990s and 2000s compared with earlier decades and relative risk of CVD incidence appeared highest during 2000-2004. Risk of bias was high for most included studies, with only 12 incidence studies judged to be at low risk of bias.

The cohort studies found the risk of all-cause mortality was two to three times higher for people with SMI compared with the general population. Relative risk of death after CVD diagnosis for those with SMI was also around two-fold higher than the general population. Hazard ratios (HRs) adjusted for confounders were 1.67, 95% CI 1.42-1.96 and 1.97, 95% CI: 1.75-2.21 for BD and schizophrenia, respectively. Excess risks of CVD incidence, however, were more modest: HR=1.21, 95% CI: 1.15-1.29 and HR=1.12, 95% CI: 1.07-1.17 for BD and schizophrenia, respectively. There was no consistent evidence of changes in mortality over time, although some increases in relative risk of CVD incidence found during the period 2005-2014 in the matched study disappeared after 2015. In the unmatched study, there was no evidence of temporal changes when adjusted for all measured confounders.

Mediation analysis found that smoking was an important mediator of the association between SMI and CVD incidence, mediating 34.5% and 53.5% of the excess risk for BD and



schizophrenia, respectively. DM also had a substantial effect. However, obesity and hypertension had no significant mediating effect, after accounting for smoking and DM.

## Conclusions

This research highlights health disparities for people with SMI compared with the general population and the evidence that they are not improving over time suggests that current interventions are not effective. Development of smoking cessation and physical health monitoring interventions and investigation of differential access to treatments are important recommendations to improve the cardiovascular health of people with SMI.

## DEDICATION

To Katie and Joe for their interest and support during my whole PhD journey, and to my grandson Robin: now I'm free for plenty of Nanny and Robin adventures!

## ACKNOWLEDGEMENTS

I would like to thank the following people and organisations who have supported me during my PhD.

Firstly, I am extremely grateful to my supervisors, Professor Tom Marshall, Dr Helen Parretti, Dr Linda Nichols and Dr Ronan Ryan, without whose guidance, advice, feedback and support this PhD and thesis would not have been possible.

My thanks to Dr Wayne Harrison for inspiring me to do the PhD and for his suggestion to focus on severe mental illness.

I am grateful to those who helped with the systematic review, particularly Dr Danai Bem for help with the literature search strategy and Endnote, Dr Malcolm Price for statistical advice on the meta-analysis and Dr Emma Pearce for unstinting help with data extraction. Also, to everyone who acted as second reviewers or helped with piloting: Dr Emma Pearce, Dr Mark Riley, Dr Natalie Tyldesley-Marshall, Dr Tuba Saygın Avşar, Dr Gemma Matthewman, Dr Alexandra Lee, Dr Khaled Ahmed, Dr Maria Lisa Odland, Dr Arwa Abdel-Aal, Dr Danai Bem, Dr Helen Parretti and Professor Tom Marshall. Thanks also to Dr Marco Solmi and Professor Christophe Correll for their collaboration with the systematic review.

I am very appreciative of the technical support given by Dr Linda Nichols in extracting the data for the cohort studies, the statistical advice given by Andrea Roalfe, and advice on Read codes from Dr Rowena Jones.

Finally, my thanks to the National Institute for Health and Care Research for providing funding to enable me to do the PhD, and to IQVIA for supplying the THIN data used in the cohort studies in this thesis.

## STATEMENT OF CONTRIBUTIONS

The following paper has been previously published and included in this thesis in sections of Chapters 1, 2 and 3, reproduced here under [CC BY 4.0 licence](#):

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The introduction in Chapter 1 is the work of AML, with support from TM and HMP and contributions from MS.

For the systematic review presented in Chapters 2 and 3, AML developed and wrote the protocol, with assistance and feedback from TM, RR, HMP and Danai Bem (DB); designed, piloted and adapted the screening and extraction forms, with input from CUC and MS, and assistance from DB, MR, HMP and Arwa Abdel-Aal; conducted the searches, with guidance from DB; screened all titles and abstracts and full texts, with EP, MR, NTM, TSA, GM, AL, KA, MLO, HMP and TM acting as second reviewers. TM and HP also acted as third reviewers in the case of discrepancies. AML, supported by EP, extracted data and conducted risk of bias assessment. AML carried out the analysis, with feedback from MJP, and wrote the published article, with contributions and feedback from TM, HMP, MJP, CUC and MS. Additions to Chapters 2 and 3 were written by AML.

The cohort studies in Chapter 4 were conceived by TM and RR. AML developed the protocol, with support from TM, RR, HMP and Linda Nichols (LN). AML and LN identified Read and

drug codes, with assistance from TM, RR, HMP and Rowena Jones (RJ). LN abstracted the data and gave guidance on the analysis together with TM and HMP. AML performed the analysis, with advice on survival analysis from Andrea Roalfe. AML wrote the chapter with feedback from TM and HMP.

The idea for the mediation analysis in Chapter 5 was conceived by TM. AML developed the analysis plan with contributions from TM and HMP and carried out the analysis. The chapter was written by AML, with support from TM and HMP.

The discussion in Chapter 6 was written by AML with guidance and feedback provided by TM and HMP.

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## LIST OF ABBREVIATIONS

|        |                                                                                |
|--------|--------------------------------------------------------------------------------|
| A&E    | Accident and emergency                                                         |
| AHD    | Additional health data                                                         |
| AIC    | Akaike's Information Criterion                                                 |
| AMR    | Acceptable mortality reporting                                                 |
| BD     | Bipolar disorder                                                               |
| BMI    | Body mass index                                                                |
| BNF    | British National Formulary                                                     |
| BP     | Blood pressure                                                                 |
| CDE    | Controlled direct effect                                                       |
| CHD    | Coronary heart disease                                                         |
| CI     | Confidence interval                                                            |
| CPRD   | Clinical Practice Research Datalink                                            |
| CVA    | Cerebrovascular accident                                                       |
| CVD    | Cardiovascular disease                                                         |
| DAGs   | Directed acyclic graphs                                                        |
| DALYs  | Disability adjusted life years                                                 |
| DExtER | Data Extraction for Epidemiological Research                                   |
| DM     | Diabetes mellitus                                                              |
| DSM-5  | Diagnostic and Statistical Manual of Mental Disorders, 5 <sup>th</sup> Edition |
| FGA    | First generation antipsychotic medication                                      |
| FP1    | First-degree fractional polynomial                                             |

|                    |                                                                     |
|--------------------|---------------------------------------------------------------------|
| FP2                | Second-degree fractional polynomial                                 |
| GBD 2019           | Global Burden of Diseases study, 2019                               |
| GP                 | General practitioner                                                |
| HDL                | High density lipoprotein cholesterol                                |
| HES                | Hospital Episode Statistics                                         |
| HF                 | Heart failure                                                       |
| HIV                | Human immunodeficiency virus                                        |
| HR                 | Hazard ratio                                                        |
| ICD-10             | International Classification of Diseases, 10 <sup>th</sup> Revision |
| ICD-11             | International Classification of Diseases, 11 <sup>th</sup> Revision |
| IMRD               | IQVIA Medical Research Data                                         |
| INT <sub>med</sub> | Mediated interaction                                                |
| INT <sub>ref</sub> | Reference interaction                                               |
| IQR                | Interquartile range                                                 |
| IRR                | Incidence rate ratio                                                |
| Kg/m <sup>2</sup>  | Kilograms per metre squared                                         |
| LDL                | Low density lipoprotein cholesterol                                 |
| LR                 | Likelihood ratio                                                    |
| MI                 | Myocardial infarction                                               |
| mmHg               | Millimetres of mercury                                              |
| MRR                | Mortality rate ratio                                                |
| NHS                | National Health Service                                             |



|          |                                                                   |
|----------|-------------------------------------------------------------------|
| NICE     | National Institute of Health and Care Excellence                  |
| NOS      | Newcastle-Ottawa scale                                            |
| OR       | Odds ratio                                                        |
| PAD      | Peripheral arterial disease                                       |
| PCA      | Prescription cost analysis                                        |
| PCOS     | Polycystic ovary syndrome                                         |
| PIE      | Pure indirect effect                                              |
| PRISMA   | Preferred Reporting Items for Systematic Review and Meta-Analysis |
| PROSPERO | International Prospective Register of Systematic Reviews          |
| PTSD     | Post-traumatic stress disorder                                    |
| PYAR     | Person years at risk                                              |
| QOF      | Quality Outcomes Framework                                        |
| RR       | Risk ratio                                                        |
| RRatio   | Rate ratio                                                        |
| SD       | Standard deviation                                                |
| SES      | Socioeconomic status                                              |
| SGA      | Second generation antipsychotic medication                        |
| SIR      | Standardised incidence ratio                                      |
| SMI      | Severe mental illness                                             |
| SMR      | Standardised mortality ratio                                      |
| THIN     | The Health Improvement Network                                    |
| THIN1605 | THIN database dated 05/2016                                       |

|          |                             |
|----------|-----------------------------|
| THIN1901 | THIN database dated 01/2019 |
| TIA      | Transient ischaemic attack  |
| UK       | United Kingdom              |
| US       | United States               |

# CHAPTER 1 INTRODUCTION

## 1.1 Introduction to chapter

This chapter introduces severe mental illness (SMI) which, in this thesis, is defined as bipolar disorder (BD) and schizophrenia. It discusses the incidence and prevalence of the conditions, and treatments and health outcomes for individuals diagnosed with SMI. The final sections of this chapter detail the aims and objectives of the thesis and summarise the other chapters of the thesis.

## 1.2 Definition of severe mental illness

There is no standard set of diagnoses that define SMI. Typically, definition of SMI is based on three dimensions: diagnosis, duration, and disability. (1) The UK government defines those with SMI as

“people with psychological problems that are often so debilitating that their ability to engage in functional and occupational activities is severely impaired.” (2)

In the United States (US), the National Institute of Mental Health defines serious mental illness as

“a mental, behavioral, or emotional disorder resulting in serious functional impairment, which substantially interferes with or limits one or more major life activities.” (3)

Commonly, diagnoses included in SMI are limited to schizophrenia, BD, and major depression. (4) Some definitions also include personality disorders, post-traumatic stress disorder (PTSD) or anorexia nervosa. (1, 4)

In the UK the National Institute for Health and Care Excellence (NICE) defines SMI as

“a clinical diagnosis of schizophrenia, schizotypal and delusional disorders, or bipolar affective disorder, or severe depressive episodes with or without psychotic episodes.” (5)

NICE issues guidelines for treatment and management of broad categories of mental health conditions which include severe mental health conditions, personality and conduct disorders, eating disorders and common mental health conditions (including depression, generalised anxiety disorder, obsessive-compulsive disorder, and PTSD). (6)

In this thesis, SMI refers to schizophrenic disorders (schizophrenia, schizoaffective disorder, non-organic psychoses) and BD, except in the cohort studies described in Chapter 4 where depression with psychosis was also included, given there is a psychosis component within this diagnosis. Other major depression was not included due to the difficulty in discriminating between depression severity in the datasets used. Depressive disorder is a common mental health condition that can be categorised as mild, moderate, or severe but is generally less disabling than conditions such as psychotic disorder. (7, 8)

### 1.3 Description of severe mental illness

Severe mental illnesses, such as bipolar affective disorder and schizophrenia are disorders of thoughts, perceptions, emotions, behaviour, or mood that can have a profound effect on individuals, families, and society. (9-13) Psychotic disorders, such as schizophrenia, typically involve positive symptoms such as delusions, hallucinations, and disorganised thinking, as well as negative symptoms such as lack of motivation, social withdrawal, and cognitive impairment. (9, 14, 15) BD is characterised by shifts in mood which can range from high (mania) to low (depression). (16, 17) There is a spectrum of presentations which can be mild, moderate, or severe, depending on the number and severity of symptoms. (18) Episodes of

psychosis can also be experienced during periods of mania or depression in BD. SMI is often associated with other psychiatric comorbidities (depression, anxiety, post-traumatic stress disorder, substance misuse, personality disorders) which add to the disease burden. (19, 20) Both schizophrenia and BD are most commonly diagnosed in late adolescence or early adulthood. (15, 17)

SMI is currently diagnosed by either the Diagnostic and Statistical Manual of Mental Disorders, 5<sup>th</sup> Edition (DSM-5) or the International Classification of Diseases, 11<sup>th</sup> Revision (ICD-11). (18, 21) ICD-10, the previous revision of ICD-11 was in use until 2022, covering most of the period of work on this thesis. (22) In ICD-10, schizophrenia is part of a block of codes covering schizophrenia, schizotypal and delusional disorders (F20-F29); BD is part of the block containing mood (or affective) disorders (F30-F39). (22)

Table 1.1 shows ICD-10 and DSM-5 definitions for schizophrenia and BD. ICD-10 emphasises first rank symptoms for schizophrenia (*i.e.* symptoms that are highly suggestive of schizophrenia if present). (23) First rank symptoms have been shown to have low sensitivity and specificity for diagnosis of schizophrenia and ICD-11 places less emphasis on first rank symptoms. (23, 24) DSM-5 categorises BD into BD-I and BD-II, the difference being that a diagnosis of BD-I requires at least one episode of mania, whereas BD-II requires episodes of both hypomania and major depression. (18)

**Table 1.1: Diagnostic criteria for schizophrenia and bipolar disorder**

|                         | ICD-10                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | DSM-5                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
|-------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Schizophrenia</b>    | <ul style="list-style-type: none"> <li>• Distortions of thinking and perception, inappropriate or blunted affect (mood).</li> <li>• First-rank symptoms (highly suggestive of schizophrenia): thought echo; thought insertion or withdrawal; thought broadcasting; delusional perception and delusions of control; influence or passivity; hallucinatory voices commenting or discussing the patient in the third person; thought disorders and negative symptoms.</li> <li>• Symptoms last at least a month.</li> <li>• Course is continuous or episodic.</li> <li>• Can be episodes with remission.</li> </ul> | <p>A: Two or more of the following, lasting a month (or less if treated). At least one being 1,2 or 3.</p> <ol style="list-style-type: none"> <li>1. Delusions</li> <li>2. Hallucinations</li> <li>3. Disorganized speech</li> <li>4. Grossly disorganized or catatonic behaviour</li> <li>5. Negative symptoms</li> </ol> <p>B: Lower level of functioning (work, interpersonal or self-care) compared to pre-onset</p> <p>C: Symptoms last at least 6 months including one month with symptoms in criteria A.</p>                                                                                                                                                                                                                                                                                                                                                                                                 |
| <b>Bipolar disorder</b> | <ul style="list-style-type: none"> <li>• Two or more episodes with significantly disturbed mood and activity levels.</li> <li>• On some occasions mood and activity is elevated (hypomania or mania), on others mood and activity is lowered (depression).</li> <li>• Can consist of repeated episodes of mania or hypomania only, with no depression.</li> </ul>                                                                                                                                                                                                                                                | <p>Bipolar I – at least one lifetime episode of mania with following criteria:</p> <p>A: abnormally and persistently elevated (or irritable) mood and activity lasting at least a week</p> <p>B: 3 or more of the following (4 if mood is irritable)</p> <ol style="list-style-type: none"> <li>1. Inflated self-esteem</li> <li>2. Decreased need for sleep</li> <li>3. More talkative than usual</li> <li>4. Flight of ideas</li> <li>5. Distractibility</li> <li>6. Increase in goal-directed activity or psychomotor agitation</li> <li>7. Excessive involvement in risky behaviour</li> </ol> <p>C: Impaired functioning (social or work) or symptoms of psychosis</p> <p>D: Episode not due to medication or another medical condition</p> <p>Bipolar II disorder</p> <p>At least one hypomania episode plus at least one major depressive episode lasting at least 2 weeks, with the following criteria:</p> |

| ICD-10                                                                                                                                                                                 | DSM-5                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                                                                                                                                                                        | <p>Hypomania episode: criteria similar to mania episode except elevated mood and activity lasting at least 4 days, uncharacteristic change in functioning, but not severe enough to cause marked impairment.</p> <p>Major depressive episode:</p> <p>A: 5 or more of following most or every day</p> <ol style="list-style-type: none"> <li>1. Depressed mood</li> <li>2. Lack of interest in activities</li> <li>3. Weight loss or loss of appetite</li> <li>4. Insomnia</li> <li>5. Psychomotor agitation or retardation</li> <li>6. Fatigue</li> <li>7. Feelings of worthlessness</li> <li>8. Inability to concentrate</li> <li>9. Recurrent thoughts of death</li> </ol> <p>B: Symptoms cause significant distress or impairment in functioning</p> <p>C: Not attributable to substance or medical condition</p> |
| Sources: International Classification of Diseases, 10 <sup>th</sup> Revision (ICD-10),(22) Diagnostic and Statistical Manual of Mental Disorders, 5 <sup>th</sup> Edition (DSM-5) (18) |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |

## 1.4 Incidence and prevalence of severe mental illness

In 2019 the Global Burden of Diseases study (GBD 2019) estimated that worldwide there were 24 million people living with schizophrenia and a further 40 million diagnosed with BD. (25, 26) Recent (2015) systematic reviews have estimated the median lifetime prevalence of schizophrenia at 0.48% (interquartile range (IQR): 0.34%-0.85%, 30 studies) and the pooled mean lifetime prevalence of BD-I and BD-II at 1.06% (95% confidence interval (CI): 0.81-1.31, 20 studies) and 1.57% (95% CI: 1.15-1.99, 9 studies). (27, 28) In the UK, recent figures for the lifetime prevalence of schizophrenia and BD in primary care records have been reported to be 0.44% and 0.38%, respectively. (29) The figure for BD is lower than that obtained from a screening questionnaire in a 2014 national survey which reported a prevalence of 2.0%. (8) Another national survey in the same year reported prevalences, based on self-report, of 0.5% and 0.6% for schizophrenia (including other psychosis) and BD, respectively. (30) Prevalence of BD is higher for women than men, whereas it is reversed for schizophrenia, but in younger age groups only. (25, 29) For both conditions, the prevalence increases by socioeconomic deprivation, and by age, up to ages 51-60 years, after which it decreases. (29) Regarding ethnicity, schizophrenia is more prevalent in Black patients than other ethnic groups, whereas BD is most common amongst White patients. (29) Prevalence rates of both schizophrenia and BD are highest amongst World Bank high income countries compared with other countries. (31)

Global prevalence of schizophrenia increased from 266 per 100,000 person-years in 1990 to 305 per 100,000 person-years in 2019, an average annual increase of 0.5%. (31) Prevalence



of BD also increased globally, from 464 per 100,000 in 1990 to 511 per 100,000 in 2019, an annual increase of 0.3%. (31)

A recent systematic review that included mostly high-income countries reported pooled incidence rates of 18.6 per 100,000 (95% CI: 15.1-22.9, 26 studies) for schizophrenia and 6.1 per 100,000 (95% CI: 4.7-8.1, 15 studies) for BD. (32) These results are consistent with those from GBD 2019 for schizophrenia, but are much lower than GBD 2019 incidence rates for BD. GBD 2019 reported the global age-standardised incidence of schizophrenia as 16.3 new cases per 100,000 in 2019 but 43.3 per 100,000 for BD. (25, 31) Global incidence rates for both BD and schizophrenia have remained steady over the past three decades. (31)

## 1.5 Treatments for severe mental illness

Medications play an important part in the management of SMI, but there are other elements to management also recommended, for example by NICE (see Table 1.2). (12, 20)

Schizophrenia and BD can be treated effectively with psychotropic medications. (19, 20, 33, 34) These include antipsychotic medications, used to treat psychoses in both schizophrenia and BD, mood stabilisers such as lithium and anticonvulsants, used to treat episodes of mania in BD, and antidepressants, widely used to treat depression in BD, although there is limited evidence for the latter's effectiveness. (33, 34) However, recurrence of SMI is common due to discontinued adherence to medication, which for many patients have unacceptable side effects, including weight gain, type 2 diabetes mellitus (DM), cardiovascular disease (CVD), hormonal disturbances, involuntary movements, and other adverse side effects. (12, 19, 35)

**Table 1.2 National Institute for Health and Care Excellence (NICE) recommendations on the management of people with schizophrenia and bipolar disorder in primary care**

| Schizophrenia                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | Bipolar disorder                                                                                                                                                                                                                                                                                                                                                                |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <ul style="list-style-type: none"> <li>• Healthy eating, physical activity, and smoking cessation advice</li> <li>• Support for carers</li> <li>• Early referral to specialist mental health service or Early Intervention in Psychosis service for a first episode</li> <li>• Cognitive behavioural therapy in association with antipsychotic medication</li> <li>• Assessment for post-traumatic stress disorder and other mental health conditions</li> <li>• Monitoring of physical health, particularly cardiovascular health</li> <li>• A written care plan</li> </ul> | <ul style="list-style-type: none"> <li>• Psychological interventions for depression</li> <li>• Referral to secondary care for mania or severe depression</li> <li>• Mood stabilising or antipsychotic medication for mania</li> <li>• Monitoring of physical health, particularly cardiovascular health</li> <li>• Support for carers</li> <li>• A written care plan</li> </ul> |

Sources: National Institute for Health and Care Excellence. Psychosis and schizophrenia in adults: treatment and management. February 2014 [accessed May 13, 2017]. Available from: <https://www.nice.org.uk/guidance/cg178>. National Institute for Health and Care Excellence. Bipolar disorder: assessment and management. September 2014 [accessed May 15, 2017]. Available from: <https://www.nice.org.uk/guidance/cg185>.

## 1.6 Outcomes

People with SMI are known to be at increased risk of poor physical health outcomes.

Mortality rates are two to three times higher for those with psychotic conditions than the general population, (36-40) and people with SMI have reduced life expectancy, dying up to 20 years earlier than the general population. (41-45) Moreover, some studies have suggested that the mortality gap between those with SMI and the general population appears to be increasing over the last 40-50 years. (36, 46-50)

Recent systematic reviews have reported relative risks of all-cause mortality twice as high as the general population for BD and three times as high for schizophrenia. (39, 40) These reviews included 39 studies (38 cohort, one case-control) and 57 cohort studies for BD and schizophrenia, respectively. (39, 40)

It has been suggested that around 60% of the premature deaths for people with SMI may be avoidable and has been estimated that more than two thirds of the excess deaths in people with all mental disorders are due to natural causes. (37, 51) Many of the early deaths have been found to be caused by preventable illnesses such as CVD. (52-55) Indeed, CVD is the most common cause of death amongst people with SMI. (55)

CVDs are disorders that affect the heart and blood vessels. Coronary heart disease (CHD) affects the vessels supplying the heart, cerebrovascular disease affects vessels supplying the brain, and peripheral arterial disease affects vessels supplying the arms and legs. (56)

Commonly in CVD, fatty deposits, known as atherosclerosis, build up on the walls of blood vessels supplying the heart or brain and cause blockages. (56) Worldwide, in 2019, 32% of deaths in the general population were due to CVD and 85% of these were due to acute CVD events of heart attack and stroke. (56)

CVD-related mortality is particularly high in SMI relative to the general population. A recent systematic review and meta-analysis of 28 cohort studies found a risk ratio for CVD-related mortality in schizophrenia of 2.10 (95% CI: 1.80-2.45). (40) The risk of mortality due to CVD in BD has been reported to be lower than for schizophrenia but is still concerning. A recent large systematic review, including 678,353 participants with BD, reported risk ratios for CVD-related mortality in BD of 1.76 (95% CI: 1.53-2.01, 27 studies) for coronary-related mortality and 1.57 (95% CI: 1.34-1.84, 13 studies) for cerebrovascular mortality. (39) There is also

evidence of raised CVD incidence amongst people with SMI relative to the general population. A recent systematic review found hazard ratios (HRs) for CVD incidence of 1.95 (95% CI: 1.41-2.70, 14 studies) for schizophrenia and 1.57 for BD (95% CI: 1.28-1.93, 10 studies). (54) These figures may underestimate the scale of the excess risk for those with SMI, since even though mortality from CVD in individuals with SMI is high, and there is evidence of higher CVD incidence, the disease may remain undiagnosed in this population group. A recent study found that people with schizophrenia were 66% more likely not to be diagnosed with CVD prior to a CVD-related death than individuals without SMI. (57) Women with BD were 38% more likely than the general population without SMI to remain undiagnosed. (57)

Risk factors for CVD include tobacco use, physical inactivity and poor diet which can lead to problems with blood pressure, cholesterol, blood glucose and overweight or obesity. (56) CVD risk factors tend to be clustered in individuals with SMI. (55, 58) Obesity particularly, is associated with increased behavioural risk factors in SMI, but also treatment factors (psychotropic medications leading to weight gain) and disease factors (negative symptoms, disorganisation, depression). (55) Prevalence of type 2 diabetes mellitus is two to three times higher amongst those with SMI than the general population. (55) Poorer access to healthcare for people with SMI is also a factor. (59-63)

## 1.7 Variation in severe mental illness and cardiovascular disease

There is significant disability associated with severe mental disorders. In 2019, schizophrenia and BD worldwide accounted for 1.36% and 0.75% of Disability Adjusted Life Years (DALYs) for 15–49-year-olds, respectively. (31) Amongst World Bank High Income countries, the

percentages were higher, at 1.88% and 1.30% for schizophrenia and BD, respectively. (31)

There are also differences in the prevalence and course of schizophrenia in high-income compared with low-income countries. In developed, or higher income, countries the median prevalence of schizophrenia was found to be higher, at 3.3 per 1,000 compared with 2.6 per 1,000 in less developed countries. (64) However, remission rates from schizophrenia were lower in developed compared with less developed countries. In a World Health Organization study of 10 countries 36.8% vs 62.7% of patients experienced remission in developed vs less developed countries. (65)

Modest, but steady reductions in CVD incidence have been reported over the last three decades in the general populations of high-income countries. (66) Incidence of CHD and CVD decreased by 13% and 7%, respectively, between 1990 and 2019 in high-income countries. (31) Cardiovascular mortality in high-income countries, however, declined more rapidly, by about 20% between 1990 and 2010, but concerningly, from 2010 to 2019 the rate started to rise again in some locations, including the UK and parts of the US. (31, 67) Reasons for the decrease in CVD incidence in the general population may include reductions in CVD risk factors, particularly smoking and blood pressure, and improved treatments for CVD, which reduced mortality. (68, 69) However, the increase in recent years appears to be driven by increasing rates of CHD mortality which may be due to a levelling-off of long-term improvements in prevention and health care or health inequalities between different population groups. (67, 70)

## 1.8 Trend in cardiovascular mortality and incidence in severe mental illness

It is unclear whether CVD mortality and incidence have shown corresponding reductions for people with SMI. A recent large cohort study in Taiwan reported only a small reduction in CVD-related mortality between 2005 and 2010 compared with the general population for schizophrenia (standardised mortality ratio (SMR) reduced from 3.16 to 3.02), but a larger reduction for BD (SMR 2.08 to 1.87). (71) However, a cohort study in the UK found a widening gap in CVD-related mortality between 2005-09 and 2010-14 between SMI and the general population (HR 0.69 to 1.92 for BD; HR 1.13 to 1.57 for schizophrenia). (72) In contrast, a large Danish cohort study over a longer and earlier time period (1994-2006) found increasing mortality from heart disease for schizophrenia compared to the general population, but no increase for BD. (73) Other cohort studies in Sweden and the UK have found increasing CVD-related mortality in schizophrenia relative to the general population over the periods 1976 to 1995 and 1981 to 2006, respectively. (74, 75)

## 1.9 Policy context

The societal costs of SMI are high: the estimated service costs of National Health Service (NHS) care, social care, and informal care in 2007 amounted to £2.2 billion for schizophrenia and £1.6 billion for bipolar and related disorders, with lost earnings accounting for a further £5.4 billion (projected to increase to 8.4 billion by 2026). (76) More recent figures estimated the total NHS costs for SMI as 2.8 billion in 2019 terms. (77) In 2013/14 the median healthcare cost per SMI patient was estimated at £4,989 per year (£5,777 in 2019 terms), compared with an average of £1,631 for a member of the general population of a similar

age. (77) Only 52% of the cost for SMI patients related specifically to mental health, rather than physical health. (77)

Thus, it appears that costs of poor physical health for people with SMI are high, both to individuals and society. Policy now reflects the need to improve physical health for those with SMI. The UK Government strategy paper “No health without mental health”, published in 2011, stated as one of its objectives that “more people with mental health problems will have good physical health”. (78) This theme was continued in the report published in 2013 by the Royal College of Psychiatrists “Whole person care: From Rhetoric to Reality. Achieving parity between mental and physical health”, which also introduced the concept of “Parity of esteem” for people with mental health problems. (79)

## 1.10 Thesis aims and objectives

The current literature suggests that people with SMI have poorer health outcomes than the general population and CVD appears to play a significant part in this.

Therefore, the aims of this thesis are:

- To provide a comprehensive summary of the evidence on the association between SMI and both CVD mortality and incidence
- To explore the factors associated with the highest risk of poor outcomes in a real-world dataset
- To quantify the relative importance of different causal factors on the relationship between SMI and CVD

The objectives are:

- To conduct a comprehensive systematic review and meta-analysis of the association between SMI and CVD-related mortality and incidence, exploring the effects of different SMIs, different CVDs and changes over time
- To conduct a cohort study using routinely collected electronic health records to identify the major risk factors affecting mortality, CVD-related mortality, and CVD incidence
- To explore the use of mediation analysis to estimate the size of potential causal factors on the association between SMI and CVD incidence

### 1.11 Thesis summary

Chapter 1 of the thesis has presented an introduction to SMI and described how people with SMI experience poor health outcomes, particularly from preventable causes, with a focus on CVD. Chapter 2 presents the first part of a systematic review of the association between SMI and CVD-related mortality and CVD incidence, focussing on CVD-related mortality. Results from 59 studies were included in random effects meta-analyses, pooled estimates of relative risk were calculated for different SMI diagnoses and CVD outcomes, and heterogeneity due to world region, setting and decade were explored. Chapter 3 presents the second part of the systematic review, focussing on CVD incidence, in which 28 studies contributed to meta-analyses. Chapter 4 describes two retrospective cohort studies that explore the associations between schizophrenia and BD, and all-cause mortality and CVD incidence using a large primary care dataset of electronic health records. The first cohort study is a matched study including incident SMI diagnoses and a matched comparison group without SMI. The second



is an unmatched open cohort containing both prevalent and incident patients with SMI and the general population without SMI. Chapter 5 presents a mediation analysis using the unmatched cohort study data from Chapter 4 to assess the effects of four potential mediators of the association between SMI and CVD incidence. The mediators considered are diabetes mellitus, smoking, raised blood pressure and obesity. Chapter 6 contains a discussion of the findings of the thesis, considers implications on policy for the management of SMI and makes recommendations for areas that would benefit from further study.

## CHAPTER 2 SYSTEMATIC REVIEW OF THE RISK OF CARDIOVASCULAR MORTALITY AND INCIDENCE IN PEOPLE WITH SEVERE MENTAL ILLNESS COMPARED WITH THE GENERAL POPULATION

### 2.1 Introduction

This chapter describes a systematic review of the risk of cardiovascular mortality and morbidity for people with SMI compared with the general population.

Methods used to review studies reporting either cardiovascular mortality, or incidence of CVD are described in this chapter, together with results from the first part of the review, which covers studies reporting mortality outcomes. The results of the review of incidence studies are reported in Chapter 3.

Sections of this chapter and Chapter 3 have been previously published in the following paper, reproduced here under [CC BY 4.0 licence](#):

*Lambert AM, Parretti HM, Pearce E, Price MJ, Riley M, Ryan R, Tyldesley-Marshall N, Avşar TS, Matthewman G, Lee A, Ahmed K, Odland ML, Correll CU, Solmi M, Marshall T. Temporal trends in associations between severe mental illness and risk of cardiovascular disease: A systematic review and meta-analysis. PLOS Medicine. 2022;19(4):e1003960. (80)*

#### 2.1.1 Severe mental illness and cardiovascular disease

Previous reviews of the association between SMI and CVD have mainly focused on either a single SMI diagnosis (schizophrenia, BD) or a single cardiovascular outcome (myocardial infarction (MI), stroke). (36, 47, 54, 81-86) Some have evaluated cardiovascular morbidity (81-83); others have only included cardiovascular mortality. (36, 47, 84) Results have been inconsistent, with differences in the scale and direction of effects and significant

heterogeneity between included studies. Some reviews also had methodological limitations, particularly the exclusion of unpublished studies (54, 81-84) and lack of reporting of the quality of included studies, (47, 83, 84) but also the exclusion of non-English language studies (84) and limiting searches to only one database. (84) There are also several recent large studies not included in previous reviews. (87) Importantly, none of the previous reviews specifically investigated time trend of CVD-related mortality risk in those with schizophrenia and BD. According to meta-analyses, life expectancy for people with schizophrenia does not seem to have changed substantially over time, averaging at 64.7 years for schizophrenia and 66.9 years for BD. (42, 43) In contrast, life expectancy for the general population increased globally from 70.4 years to 73.5 years during the decade 2009 to 2019. (31) Some studies have reported an increasing gap in all-cause mortality between those with SMI and the general population. (36, 46-50) It remains unclear whether the gap between those with SMI and the general population has also remained unchanged for CVD-related mortality. A large, recently published cohort study reported a 10% reduction in SMR for BD (2.08 to 1.87) between 2005 to 2010, but did not describe substantial changes in CVD-related excess mortality in schizophrenia compared with the general population (SMR 3.16 to 3.02). (71) However, another cohort study found a widening gap in CVD-related mortality between SMI and the general population. (72) Yet, to the best of my knowledge, there is currently no comprehensive systematic review and meta-analysis of the trend over time of excess CVD-related incidence and mortality in schizophrenia and BD.

The next section summarises the current evidence separately for schizophrenia and BD, CHD, stroke and CVD, and mortality and incidence.

### 2.1.1.1 Schizophrenia

#### 2.1.1.1.1 Mortality

For people with schizophrenia, current evidence indicates a raised risk of mortality from CVD and CHD. A recent meta-analysis based on nine studies found a high risk of CVD-related mortality for people with schizophrenia (adjusted hazard ratio (HR): 2.45, 95% CI: 1.64-3.56), (54) while a 2007 systematic review also suggested an excess of CHD deaths (median SMR from seven studies 1.79, IQR: 1.40-2.49). (36) These findings are consistent with earlier systematic reviews. (85, 86) Recent studies not included in the above reviews include a large Finnish population register study, which also showed high rates of excess mortality for CHD. (87)

However, evidence of increased stroke mortality is less consistent. A 2014 systematic review of schizophrenia and stroke found an increased risk of stroke mortality for people with schizophrenia (relative risk 1.65, 95% CI: 1.31-2.08; 3 studies), (82) in contrast to two earlier reviews which reported reduced risks of stroke mortality for those with schizophrenia compared to the general population (median SMR=0.69, IQR: 0.61-1.30; SMR=0.81, 95% CI:0.73-0.87, respectively). (36, 85)

#### 2.1.1.1.2 Incidence

In a comprehensive 2017 systematic review, Correll and colleagues found an increased incidence of CVD (HR: 1.95, 95% CI: 1.41-2.70; 14 studies), stroke (HR: 1.57, 95% CI: 1.09-2.25; 5 studies), congestive heart failure (unadjusted RR: 1.80, 95% CI: 1.15-2.79; 3 studies) and CHD (HR: 1.59, 95% CI: 1.08-2.35; 5 studies) for people with schizophrenia. (54) Earlier reviews also found increased risks of CVD (relative risk: 1.53, 95% CI: 1.27-1.86; 4 studies),

(83) stroke (relative risk: 1.50, 95% CI: 1.25-1.80; 6 studies) (82) and heart failure, (relative risk: 1.81, 95% CI: 1.42-2.29; 5 studies) (83) but no increased risk of CHD (relative risk: 1.20, 95% CI: 0.93-1.53; 9 studies). (83) This latter review did not consider quality of included articles or search for unpublished studies, so may have had some methodological limitations.

#### 2.1.1.2 Bipolar affective disorder

##### 2.1.1.2.1 Mortality

As for schizophrenia, current evidence indicates an excess risk of CVD mortality in people with BD. Recent systematic reviews have found increased risks of CVD-related death in people with BD (HR: 1.65, 95% CI: 1.10-2.47; 3 studies), (SMR: 1.73 (95% CI: 1.54-1.94; 14 studies). (47, 54) An earlier review showed excess cardiovascular mortality in some studies using a wide definition of bipolar spectrum disorders. (84) However, this review was limited to published, English-language studies, from a single database. (84)

No systematic reviews were found reporting the association between BD and either CHD or stroke mortality. However, a recent Swedish population register study of over 6 million people supports the evidence of excess mortality from CHD amongst people with BD (males HR: 1.79, 95% CI: 1.46- 2.20; females HR: 2.04, 95% CI: 1.66-2.52). (53)

Evidence of an association between BD and cerebrovascular mortality is more limited: a recent Swedish cohort study found an excess of stroke deaths, once adjusted for other covariates, for women, but not for men (males HR: 1.43, 95% CI: 0.90- 2.27; females HR: 2.51, 95% CI: 1.89-3.34). (53)

#### 2.1.1.2.2 Incidence

One systematic review and meta-analysis reported total CVD events and this showed an increased risk of CVD incidence (HR: 1.57, 95% CI: 1.28-1.93; 10 studies) for people with BD. (54)

There is also evidence of increased risk of stroke incidence from two systematic reviews (HR: 1.60, 95% CI: 0.99-2.57; 4 studies), relative risk: 1.74, 95% CI: 1.29-2.35; 3 studies). (54),(81)

However, the same two reviews found no evidence of an association between CHD and BD (HR: 1.16, 95% CI: 0.76-1.78; 4 studies), (relative risk: 1.09, 95% CI: 0.96-1.24; 4 studies). (54),(81)

Evidence on incidence of heart failure for people with BD was only found in one systematic review, which reported an increased incidence (HR: 2.27, 95% CI: 1.49-3.45; one study). (54)

### 2.1.2 Rationale, Aim and Objectives of this review

#### 2.1.2.1 Evidence before this systematic review

Review evidence shows that CVD-related mortality and incidence are increased for people with both schizophrenia and BD. Reviews also show that CHD mortality is also increased for people with schizophrenia. Reviews show increased risk of stroke incidence in people with schizophrenia and BD.

However, there is inconsistent evidence regarding stroke mortality for people with schizophrenia and no review evidence on either CHD or stroke mortality for people with BD.

It is not known whether the risk of CHD incidence is increased amongst people with SMI.

It is not known whether the risk of CVD-related mortality or incidence or the risk of mortality from CHD has changed over time for people with SMI.

#### 2.1.2.2 Aims and objectives

Whilst the fact of excess mortality from CVD for people with SMI appears established from most review evidence, the relationship with CVD incidence is less clear. An up-to-date, comprehensive, systematic review of the association between SMI and CVD incidence and mortality was therefore indicated.

The aim of this systematic review and meta-analysis was to investigate changes over time of CVD-related mortality and incidence, in addition to providing updated pooled estimates of increased CVD mortality and incidence in those with schizophrenia and BD compared with the general population. It used robust methodology to search and evaluate the evidence, updating previous reviews and including all SMI diagnoses and a range of cardiovascular outcomes.

#### 2.1.2.3 Research questions

The two main review questions were:

- What is the risk of cardiovascular mortality and morbidity for adults with SMI in developed countries compared with the general population?
- Have these risks changed over time?

The protocol for this review has been registered with PROSPERO (CRD42017058068) and the review is reported according to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines. (88) Appendix I lists deviations that were made from the protocol.

## 2.2 Methods

### 2.2.1 Inclusion and exclusion criteria

Inclusion criteria are summarised in Table 2.1.

**Table 2.1: Inclusion and exclusion criteria**

| PECOS        | Include                                                                                                                                                                                                                                                                                                                                                           | Exclude                                                                                                                                                                                                                                                                |
|--------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Population   | Adults aged 16-65 years (if a study includes people over 65, include if the majority are aged 16-65)                                                                                                                                                                                                                                                              | Studies with the majority aged under 16 years or over 65 years                                                                                                                                                                                                         |
| Exposure     | SMI:<br>Schizophrenia<br>Bipolar disorder<br>Other psychotic condition<br>Mixed SMI                                                                                                                                                                                                                                                                               | Dis-associative, multiple personality disorders<br>Depression in the absence of psychosis or bipolar<br>Dementia<br>Learning disabilities<br>OCD<br>Puerperal psychoses                                                                                                |
| Comparator   | General population or people without SMI                                                                                                                                                                                                                                                                                                                          | Other chronic condition as comparator <i>e.g.</i> diabetes mellitus                                                                                                                                                                                                    |
| Outcome      | CVD mortality or morbidity<br>CHD event or diagnosis<br>Acute coronary syndrome, myocardial infarction, coronary thrombosis, angina<br>Coronary revascularisation<br>Cerebrovascular accident<br>Stroke/TIA<br>Heart failure                                                                                                                                      | CVD outcomes prior to SMI diagnosis<br>CVD risk factors, <i>i.e.</i> cardio-metabolic disease (diabetes mellitus, hypertension, hyperlipidaemia)<br>Cardiovascular risk ( <i>e.g.</i> Framingham 10-year risk score)<br>Cardiac complications of medication or surgery |
| Study design | Cohort studies<br>Case-control studies                                                                                                                                                                                                                                                                                                                            | Uncontrolled studies<br>Cross-sectional studies<br>Case series<br>Single case reports<br>Narrative reviews<br>Systematic reviews                                                                                                                                       |
| Setting      | Developed countries <sup>1</sup> :<br>Australia, Austria, Belgium, Canada, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hong Kong, Iceland, Ireland, Israel, Italy, Japan, Latvia, Lithuania, Luxembourg, Macao, Malta, Netherlands, New Zealand, Norway, Portugal, Puerto Rico, San Marino, Singapore, Slovak Republic, Slovenia, | Any other countries including emerging and developing Europe ( <i>e.g.</i> Croatia, Poland, Romania)                                                                                                                                                                   |



| PECOS     | Include                                                  | Exclude                      |
|-----------|----------------------------------------------------------|------------------------------|
|           | South Korea, Spain, Sweden, Switzerland, Taiwan, UK, USA |                              |
| Follow-up | One year or more                                         | Follow-up less than one year |

<sup>1</sup> International Monetary Fund advanced economy countries, SMI – severe mental illness, CVD – cardiovascular disease, OCD – obsessive compulsive disorder, CHD – coronary heart disease, TIA – transient ischaemic attack, RCTs – randomised controlled trials

### 2.2.1.1 Population

Studies with participants aged 16-65 years were eligible for inclusion. Some studies included in previous reviews included participants aged 15+ years to accommodate a peak in SMI incidence in adolescence, (81) therefore studies with individuals under 16 years were included if at least 90% of participants were aged 16 years or over. Onset of psychotic disorder is uncommon at older ages, (89) whereas dementia is increasingly prevalent. Acute and transient psychosis diagnosed later than age 60 years are also associated with dementia. (90) In the UK, estimates of probable psychosis (excluding psychosis due to dementia) in people aged 65-74 years indicate a prevalence of 0.1%, (89) compared to a total dementia prevalence of 6.5% for ages over 65 years, with rates increasing steeply beyond 75 years. (91) SMI diagnosed at ages over 65 years is thus likely to be related to dementia, rather than psychosis. Therefore, studies that included participants over 65 years were only included if at least 90% were aged under 65 years, or if it was apparent that diagnosis of SMI had been made at an earlier age.

Only studies conducted in developed countries were included. There are variations between developed and developing countries in the diagnosis, prevalence, treatment, and prognosis of SMI. (64, 65) In order to make the findings more relevant to the UK population, only studies set in developed countries were considered for inclusion in this review (defined as

International Monetary Fund “Advanced Economies” (92): Western Europe, Canada, United States, Australia, New Zealand, Taiwan, South Korea, Japan).

#### 2.2.1.2 Exposure

Studies were included that recruited participants aged 16-65 years with a diagnosis of serious mental illness, including schizophrenia, other psychoses and BD. SMI in the studies was defined by the Diagnostic and Statistical Manual of Mental Disorders (DSM), such as DSM-5, (18) International Classification of Diseases (ICD), such as ICD-10, (22) other clinical coding systems, (READ codes (93) OXMIS (94)), operational systems (OPCRIT, (95) medical claims data, SMI disability social security claims) or clinical diagnosis recorded in patient notes. Dissociative, multiple personality disorders, depression (in the absence of psychosis or BD), dementia, learning disabilities and obsessive-compulsive disorder were excluded.

#### 2.2.1.3 Comparator

Eligible studies compared people with SMI to controls without SMI or to the general population. Participants could be in an inpatient, outpatient, or community setting.

#### 2.2.1.4 Outcome

Primary outcomes were cardiovascular mortality or incidence, and their time trend, including CHD, cerebrovascular accident (CVA) or heart failure. Studies reporting only cardiovascular risk factors were excluded. Studies reporting mortality for all circulatory disease (*e.g.* ICD-10 Chapter I00-I99) were eligible as in the UK around two thirds of mortality events for all circulatory disease relate to CHD and stroke. (96) However, studies reporting incidence of CVD defined by all circulatory disease were not eligible. Incidence of

all circulatory disease diagnosis is more likely to relate to CVD risk factors such as hypertension, than diagnosis of CHD or CVA. For example, hospital admissions for CHD and stroke in England account for only 40% of ICD-10, I00-I99 admissions. (97) Studies were eligible for inclusion only if they reported outcomes of cardiovascular mortality or incidence subsequent to SMI diagnosis. If this was unclear, studies which reported a prevalence of CVD greater than 10% prior to diagnosis of SMI were excluded. Studies were eligible if the mean follow-up period was at least one year.

#### **2.2.1.5 Study design**

Eligible studies compared people with SMI to controls without SMI or the general population *i.e.* cohort or case-control studies, but not cross-sectional, case series, case reports or uncontrolled studies. Case-control studies compared the odds of SMI compared to no SMI in people diagnosed with CVD compared to matched controls.

#### **2.2.2 Search strategy**

A literature search for articles reporting primary studies was conducted from inception to 30 November 2021 using the following bibliographic databases: MEDLINE, MEDLINE in-progress and other non-indexed citations, EMBASE, PsycINFO via Ovid and CINAHL via EBSCO. The British Library's ZETOC and Web of Science Conference Proceedings Citation Index were searched for conference abstracts to the same date. The Cochrane Library CENTRAL database was searched to 1 December 2021 for relevant trials. In addition, citation searching of relevant reviews and included studies and searching of grey literature, including OpenGrey, was conducted. Initial searches were performed in September 2017 and updated

in March 2019 and November 2021. The updated searches were restricted to years of publication 2017-19 and 2019-21, respectively.

The search strategy used text words and index terms for the condition (SMI) and the outcome (CVD), with no restriction on date or language of publication. Search strategies used for each database are in Appendix II . Additional research using the search term “cause of death” revealed a small number of additional papers which were added to those found by the other searches. English translations were sought in the case of foreign language abstracts and articles.

### **2.2.3 Screening**

References were managed using EndNote X9 (Clarivate Analytics). Two independent reviewers screened titles and abstracts and full-text selection against the inclusion criteria. Disagreements were resolved by discussion and if necessary, by reference to a third independent reviewer.

### **2.2.4 Data extraction**

HRs, relative risks, rate ratios, odds ratios (ORs), risk ratios (RRs), SMRs or standardised incidence ratios (SIRs) measuring the association between SMI and cardiovascular mortality or incidence, or sufficient information to calculate them, were extracted from relevant articles. Risk measures adjusted for factors related to cardiovascular risk (*e.g.* socioeconomic factors, comorbidities, smoking, alcohol use) were extracted where available, otherwise measures adjusted for age and sex only were extracted. Risk measures were extracted from graphs if not reported in the text. Confidence intervals for RRs were extracted if reported, otherwise were calculated from available information.

Data extraction of included studies was carried out by a first reviewer using a standardised, piloted extraction form (Appendix III ) and checked by a second reviewer. The extraction form was adapted from a form provided by the authors of a 2017 systematic review (54) (personal communication). Disagreements were resolved by discussion and by reference to a third reviewer if unresolved. Study authors were contacted if the required information was unclear or not included.

Data were collected on (but not limited to): publication details, study characteristics (setting, study design, time frame), population characteristics (age, sex), comparator, details of SMI exposure and CVD outcomes, estimates of effects, length of follow-up, included covariates. Cardiovascular outcomes are more likely at older ages. Premature cardiovascular mortality and morbidity were of primary interest, so for studies that reported outcomes at multiple age groups, results for age groups under 65 years were extracted if available. If there were results for more than one group under 65 years, the oldest age group was selected.

Sensitivity analysis was used to check whether the age group selected made a difference to the results.

Sample sizes of exposed and unexposed were extracted where reported or calculated or estimated from the information available (see Appendix IV for example calculations).

Number of events were also extracted. In the case of SMRs the number of events for the control group was equivalent to the expected number of deaths, which were calculated if not reported directly. SMRs for males and females were combined to give a figure for persons if that was unreported. Confidence intervals were calculated using the method described by Kirkwood and Sterne (98), p270.

For studies that reported results over multiple discrete follow-up time periods, (73, 87, 99, 100) estimates for the whole period were selected if available, otherwise the earliest time period was selected to avoid a “healthy survivor” effect, whereby only those who survive the first time period can enter subsequent periods. In studies reporting SMRs with multiple periods of follow-up, (101) actual and expected deaths were summed and the ratio calculated to provide an overall SMR.

### **2.2.5 Risk of bias assessment**

Risk of bias was assessed using an adapted version of the Newcastle-Ottawa Scale (NOS). (102) Cohort studies were rated against ten criteria in three categories: selection, comparability, and outcome. The NOS instrument was adapted to include extra criteria on accuracy of outcome measurement and identification of confounders from the Critical Appraisal Skills Programme (CASP) checklist for cohort studies. (103) It was tailored further to apply to case-control study designs. Case-control studies were rated against eleven criteria in categories assessing selection, comparability, and exposure. The risk of bias forms for cohort and case-control studies are shown in Appendix V . Risk of bias was assessed independently by two researchers according to how well each study met the set of criteria specific to each study design. Discrepancies were discussed and consensus reached with the aid of a third reviewer when required.

### **2.2.6 Data synthesis**

Narrative synthesis of evidence was conducted for all included studies with study characteristics presented in tables. Where appropriate, meta-analysis was conducted using DerSimonian and Laird random-effects models due to expected population, clinical, and

methodological heterogeneity between studies. (104) Heterogeneity was measured using  $I^2$  and chi-squared statistics and 95% prediction intervals. (105) Effects from different SMIs, CVD outcomes and type of relative risk measurement (Table 2.2) were presented in separate forest plots and meta-analyses. Rate ratios were combined with HRs because they have the same interpretation.

**Table 2.2: Pre-specified subgroups used for forest plots and meta-analyses**

| Subgroups                 | Values                                                                                                                        |
|---------------------------|-------------------------------------------------------------------------------------------------------------------------------|
| Severe mental illness     | Schizophrenia and related conditions<br>Bipolar disorder<br>Mixed SMI                                                         |
| CVD mortality outcome     | Cerebrovascular accident/stroke<br>Coronary heart disease<br>All circulatory disease/combined CHD and stroke<br>Heart failure |
| Relative risk effect type | Rate ratio<br>Hazard ratio<br>Risk ratio<br>Odds ratio<br>Standardised mortality/incidence ratio                              |

SMI – severe mental illness, CVD – cardiovascular disease, CHD – coronary heart disease

Studies that may have included the same patients in overlapping periods of recruitment were not included in the same meta-analyses to avoid double counting outcomes. Rules were devised to determine which studies should be included if the period of overlap was greater than 10% of the total follow-up time (Appendix VI ). Those with fewer exposed cases, or shorter follow-up durations were excluded to minimise the risk of double counting events.

Results for both sexes were included in the meta-analysis where reported or calculable, otherwise separate results for males and females were used. For each meta-analysis with more than 10 studies, potential publication bias or small study effects were assessed visually using funnel plots and formally tested using Egger’s test. (106) If evidence of significant bias

was found a random effects trim-and-fill procedure was applied to estimate the effect of potential unpublished studies. (107)

To assess temporal trends, studies were allocated to decades according to the median year of follow-up. Further analysis increased the granularity by allocating to five-year periods according to the median year of follow-up.

All analyses were performed in Stata MP version 14.2 (StataCorp).

### 2.2.7 Subgroup analyses

Analysis of pre-specified subgroups was conducted (Table 2.3).

**Table 2.3: Potential sources of heterogeneity assessed by meta-regression**

| Study level source of heterogeneity | Values                                                                                                                                                                                                                                                                                                                                                                                 |
|-------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Change over time                    | Decade contributing highest number of years of outcomes (in the case of ties the median year was selected) <ul style="list-style-type: none"> <li>• 1950s-1970s</li> <li>• 1980s</li> <li>• 1990s</li> <li>• 2000s</li> <li>• 2010s</li> </ul>                                                                                                                                         |
| Setting                             | <ul style="list-style-type: none"> <li>• Community</li> <li>• Community and inpatient</li> <li>• Inpatient</li> </ul>                                                                                                                                                                                                                                                                  |
| World region                        | <ul style="list-style-type: none"> <li>• North America (USA and Canada)</li> <li>• UK</li> <li>• Scandinavia (Norway, Sweden, Denmark, Finland)</li> <li>• Other Western Europe &amp; Israel (Netherlands, Spain, France, Italy, Switzerland, Israel, Germany, and Austria)</li> <li>• Oceania (Australia and New Zealand)</li> <li>• Far East (Taiwan, Japan, South Korea)</li> </ul> |

If there were at least 10 study results, random-effects meta-regression was performed to explore potential sources of heterogeneity that were measured at study group level. (108, 109) Temporal trends, (decade of study conduct), setting (community; community and inpatient; inpatient) and world region (North America: USA and Canada); UK; Scandinavia: Denmark, Finland and Sweden; Other Western Europe & Israel; Oceania: Australia and New Zealand; Far East) were included as covariates in univariate meta-regressions for each



subgroup combination of SMI diagnosis (schizophrenia and related conditions; BD), and each mortality outcome (all circulatory disease; CHD; CVA). Heterogeneity was assessed for each meta-regression by comparing the  $I^2$  from the random effects meta-analysis and the residual  $I^2$  after fitting covariates. The amount of between-study variation accounted for by covariates was measured by calculating adjusted  $R^2$ . P-values for model fit were used to assess the association between covariates and SMI and outcomes. (110, 111) Subgroup analyses of cohort studies were conducted by sex and by age group at baseline and assessed by forest plots. Studies that reported results for ages  $\leq 60$  years were plotted separately from results for older groups or all ages.

#### **2.2.8 Sensitivity analyses**

Sensitivity analysis was performed to assess the effect of making different decisions on inclusion of studies in the meta-analyses, where studies were subject to overlapping periods of recruitment and thus may have included the same patients, as described above. The effect of inclusion of results for different age groups, medications or follow-up periods were also assessed in sensitivity analyses. As there was only one case-control study, this was combined with cohort studies.

### **2.3 Results**

A total of 16,223 records were identified through database searching and other sources. After removal of duplicates, 11,748 titles and abstracts were screened and 11,371 were excluded. Of 377 full-text articles assessed against eligibility criteria, 108 were included in the narrative review and 269 were excluded. A further 25 studies with overlapping periods of recruitment for exposed populations were excluded from quantitative analysis and a

further six articles did not have sufficient information to be included in any quantitative synthesis. The remaining 77 papers were included in quantitative analysis of either CVD mortality or incidence. Of these, 59 reported CV mortality data and 28 reported CVD incidence (Figure 2.1). Mortality studies included in the narrative review are listed in Appendix VII , incidence studies in Appendix VIII and studies excluded from the narrative review are listed, with reasons, in Appendix IX . The review of the studies reporting CVD incidence is reported in Chapter 3.

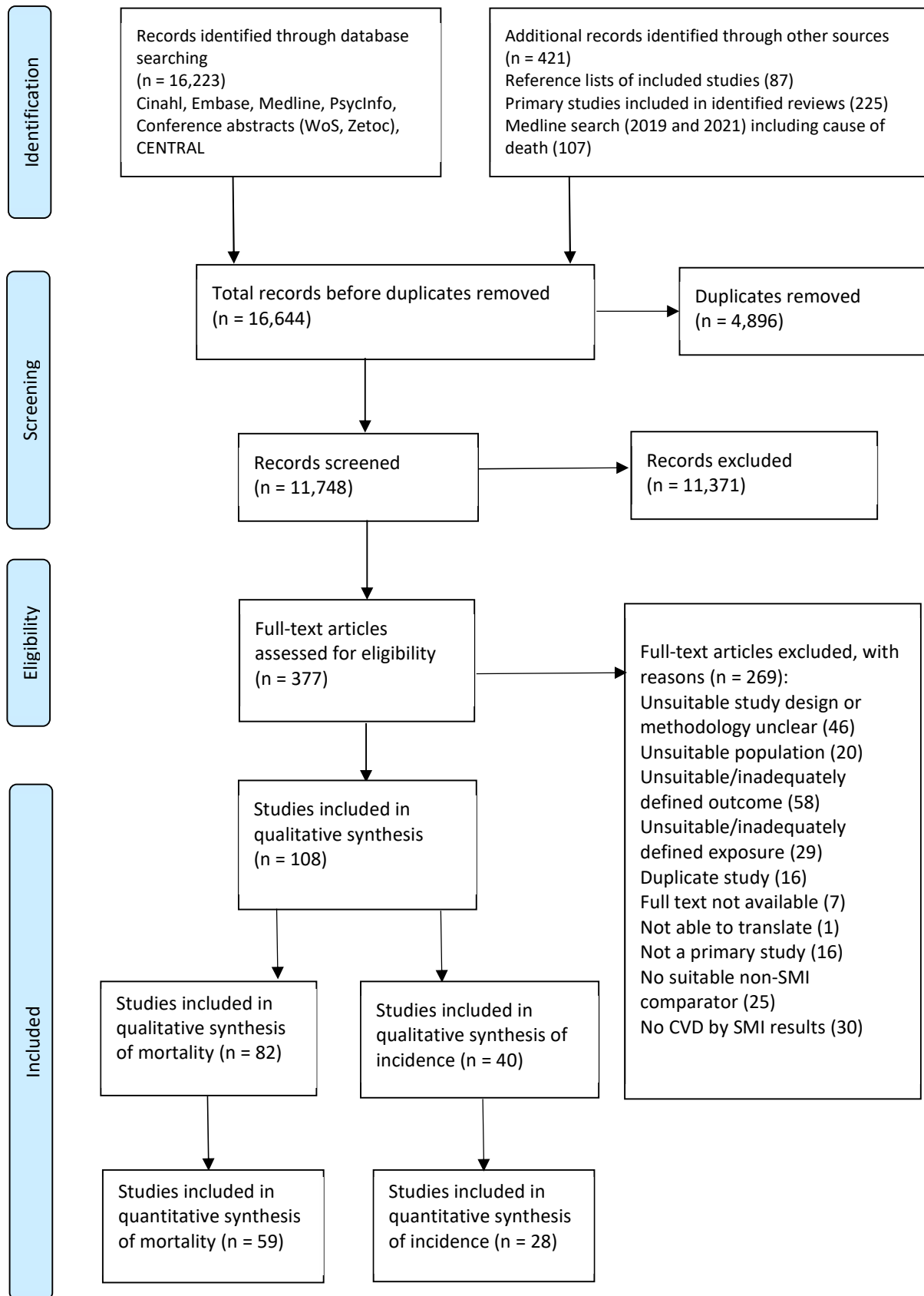


**Figure 2.1: PRISMA flow diagram**

### **2.3.1 Characteristics of included mortality studies**

All 82 studies included in the review reporting mortality outcomes were cohort studies (Appendix VII ). Table 2.4 presents the characteristics of the included studies. Of these, 66 included patients with schizophrenia or related conditions, 30 included patients with BD and six articles reported results for mixed SMI. For CVD mortality outcomes, 43 reported CHD, 31 reported CVA, one reported heart failure and 54 reported all circulatory disease mortality. SMRs were the most common measure of relative risk (48 papers). The others reported rate ratios or HRs apart from a single study that reported ORs. Combined results for both sexes were obtained from most articles (67 papers). Fifteen articles contributed outcomes from the 1970s or earlier; 18 from the 1980s, 20 from the 1990s, 29 from the 2000s and seven since 2010. Papers may have contributed results to more than one decade. 38 of the 82 mortality studies were from Scandinavia, 13 from North America, 12 from Western Europe and Israel (excluding UK and Scandinavia), 11 from the UK, five from the Far East and three from Oceania. 41 studies were inpatient-only; 17 were community-only and 24 were conducted in both inpatient and community settings. Five studies that did not include confidence intervals or standard errors were not included in the meta-analysis.

### **2.3.2 Risk of bias of included studies**

Most studies were rated to have high risk of bias mainly due to lack of adjustment for confounders, lack of clarity about presence of CVD at baseline, and controls being drawn from a different population to the SMI cohort (Appendix X ). Many studies assessed as being of higher risk of bias used general population mortality rates as the comparison. Half the studies included persons with SMI in the community, the other half included only inpatients.

Ascertainment of SMI was good, most studies used medical records. However, there was potential for bias due to a lack of clarity regarding ascertainment of all cardiovascular outcomes. Adequacy of reporting and duration of follow-up were rated as good for around half of the studies.

### **2.3.3 Meta-analysis**

Altogether 59 studies contributed HRs, rate ratios, ORs or SMRs of cardiovascular mortality in people with SMI for meta-analysis. Some studies contributed more than one result, *e.g.* different SMIs, multiple outcomes or separate male and female results. The number of included participants was not reported for some studies. However, the total amongst those that did report this information was 1,841,356 cases and 29,321,409 controls. The risk of CVD mortality for people with SMI was higher than controls, for each type of SMI, each CVD outcome and for each type of effect, except pooled HRs/rate ratios for all circulatory disease mortality in BD and SMRs for CVA in mixed SMI. Pooled effect sizes appeared larger for schizophrenia than BD. Pooled SMRs for SMI/CVD combinations with more than one study ranged from 1.55 (95% CI: 1.33-1.81,  $p<0.001$ ) for CVA in people with BD to 2.40 (95% CI: 2.25-2.55,  $p<0.001$ ) for CVA in schizophrenia (Table 2.5).

**Table 2.4: Characteristics of included mortality studies**

| Study, year       | SMI diagnosis | Country                           | Setting                 | Period of SMI exposure | Period of outcomes | Age at start of study (years) | Number of cases | Number of controls | Covariates adjusted for                                   | Mean follow-up (years) | Outcomes (mortality) | Sex     | Type of results |
|-------------------|---------------|-----------------------------------|-------------------------|------------------------|--------------------|-------------------------------|-----------------|--------------------|-----------------------------------------------------------|------------------------|----------------------|---------|-----------------|
| Ahrens, 1995      | BD            | Denmark, Germany, Canada, Austria | Inpatient               | 1967-1989              | 1967-1989          | Mean 41                       | 440             | Gen pop            | Age, sex, country, year of death                          | 7.2                    | CVD                  | P, M, F | SMR             |
| Ajetunmobi, 2013  | SCZ, BD       | UK                                | Inpatient               | 1986-2009              | 1986-2010          | 15+, median 42.6              | 44546           | Gen pop            | Age, sex, year of death, deprivation                      | Up to 25               | CVD                  | P       | SMR             |
| Allebeck, 1986    | SCZ           | Sweden                            | Inpatient               | 1971                   | 1971-1981          | Mean 45 (est)                 | 1190            | Gen pop            | Age, sex                                                  | 11                     | CVA, CHD             | P       | SMR             |
| Anderson, 1991    | SCZ           | UK                                | Inpatient               | 1975-1984              | 1975-1988          | NR                            | 532             | Gen pop            | Age, sex, year of death                                   | up to 14               | CVA, CHD             | P, M, F | SMR             |
| Angst, 2002       | BD            | Switzerland                       | Inpatient               | 1959-1963              | 1959-1997          | NR                            | 158             | Gen pop            | Age, sex, year                                            | 34-38                  | CVA, CHD, CVD        | P       | SMR             |
| Bjorkenstam, 2012 | SCZ           | Sweden                            | Community and inpatient | 2004-2005              | 2006-2007          | 20-79, mean 47.9              | 23158           | 6101893            | Age, sex                                                  | Up to 2                | CHD                  | M, F    | RRatio          |
| Brink, 2018       | SCZ           | Denmark                           | Inpatient               | 1970-1979              | 1980-2012          | 18-40                         | 4544            | 22597              | Age, sex, year, Charlson score, education, marital status | Up to 41               | CVD                  | P       | RRatio          |
| Brodersen, 2000   | BD            | Denmark                           | Inpatient               | 1981-1983              | 1981-1997          | 15-70, mean 40                | 133             | Gen pop            | Age, sex, year of death                                   | 16                     | CVD                  | P, M, F | SMR             |
| Brook, 1984       | SCZ           | Netherlands                       | Inpatient               | 31 Dec 1979            | 1980-1981          | 20+                           | 5226            | Gen pop            | Age, sex                                                  | 2                      | CVA, CHD             | P, M, F | SMR             |
| Brown, 2010       | SCZ           | UK                                | Community               | 1981                   | 1981-2006          | 16-65, mean 40.7              | 370             | Gen pop            | Age, sex, year                                            | Up to 25               | CVA, CHD, CVD        | P, M, F | SMR             |
| Buda, 1988        | SCZ           | USA                               | Inpatient               | 1934-1945              | 1934-1974          | NR                            | 332             | Gen pop            | Age, sex                                                  | Up to 40               | CVD                  | P       | SMR             |
| Callaghan, 2014   | SCZ, BD       | USA                               | Inpatient               | 1990-2005              | 1990-2005          | 35+ at mid-point of follow-up | 248820          | Gen pop            | Age, sex, race                                            | SCZ 7.4, BD 7.6        | CVA, CHD, CVD        | P, M, F | SMR             |

| Study, year      | SMI diagnosis | Country     | Setting                 | Period of SMI exposure | Period of outcomes | Age at start of study (years)   | Number of cases | Number of controls | Covariates adjusted for                                        | Mean follow-up (years)      | Outcomes (mortality) | Sex     | Type of results |
|------------------|---------------|-------------|-------------------------|------------------------|--------------------|---------------------------------|-----------------|--------------------|----------------------------------------------------------------|-----------------------------|----------------------|---------|-----------------|
| Casadebaig, 1999 | SCZ           | France      | Community and inpatient | 1993                   | 1993-1996          | 18-64                           | 3470            | Gen pop            | Age, sex                                                       | Up to 3                     | CVA, CHD             | P       | SMR             |
| Castagnini, 2013 | SCZ, BD       | Denmark     | Community and inpatient | 1995-2008              | 1995-2008          | 15-64, mean SCZ: 32.6, BD: 41.8 | 7776            | Gen pop            | Age, sex                                                       | Up to 14                    | CVA, CHD             | P       | SMR             |
| Chan, 2021       | BD            | Hong Kong   | Community and inpatient | 2002-2018              | 2008-2018          | 15+                             | 12556           | Gen pop            | Age, sex, and calendar year                                    | 8.5                         | CVA, CHD, CVD        | P, M, F | SMR             |
| Crump, 2013a     | SCZ           | Sweden      | Community and inpatient | 2001-2002              | 2003-2007          | 25+                             | 8277            | 6097834            | Age, sex, marital status, education, employment status, income | 5                           | CVA, CHD, CVD        | M, F    | HR              |
| Crump, 2013b     | BD            | Sweden      | Community and inpatient | 2001-2002              | 2003-2008          | 20+                             | 6618            | 6587036            | Age, sex, marital status, education, employment status, income | 6                           | CVA, CHD, CVD        | M, F    | HR              |
| Cunningham, 2014 | SCZ, BD       | New Zealand | Community and inpatient | 2002-2010              | 2002-2010          | 18-64, mean SCZ: 37.6, BD: 39.9 | 32139           | Gen pop            | Age, sex                                                       | Up to 9                     | CVD                  | P, M, F | SMR             |
| Curkendall, 2004 | SCZ           | Canada      | Community               | 1994-1995              | 1996-March 1999    | 18+, mean 49.6                  | 2405            | 9175               | Age, sex, >1 of HT, hyperlipidaemia, DM, CVD, COPD             | NR                          | CVD                  | P       | RRatio          |
| Dalgard, 1966    | SMI           | Norway      | Inpatient               | 1951-1955              | 1951-1961          | NR                              | 1126            | 1126               | Age, sex, marital status, occupation                           | 6.5                         | CVA, CHD             | P       | RRatio          |
| Das-Munshi, 2017 | SMI           | UK          | Community               | 2007-2014              | 2007-2014          | 15+                             | 18201           | Gen pop            | Age, sex, length of follow-up                                  | 6.36 (median) IQR 3.26-9.92 | CVD                  | P       | SMR             |
| Daumit, 2010     | SCZ, BD       | USA         | Community               | July 1992-June 1993    | 1994-2001          | 21-62, mean 41.6                | 3361 (est)      | Gen pop            | Age, sex, race                                                 | Up to 8.5                   | CHD                  | P       | RRatio          |
| Dutta, 2012      | SMI           | UK          | Community               | 1965-2004              | 1965-Mar 2007      | 16+                             | 2723            | Gen pop            | Age, sex, year                                                 | 11.5                        | CVD                  | P, M, F | SMR             |

| Study, year      | SMI diagnosis | Country     | Setting                 | Period of SMI exposure | Period of outcomes | Age at start of study (years)                   | Number of cases                                                               | Number of controls | Covariates adjusted for                                       | Mean follow-up (years)    | Outcomes (mortality) | Sex     | Type of results |     |
|------------------|---------------|-------------|-------------------------|------------------------|--------------------|-------------------------------------------------|-------------------------------------------------------------------------------|--------------------|---------------------------------------------------------------|---------------------------|----------------------|---------|-----------------|-----|
| Fors, 2007       | SCZ           | Sweden      | Community               | 1981-1990              | 1991-2000          | 18+                                             | 255                                                                           | 1275               | Age, sex, living area                                         | Up to 10                  | CVD                  | P, M, F | RRatio          |     |
| Giel, 1978       | SCZ           | Netherlands | Inpatient               | 31 Dec-1969            | 1970-1971          | 20+                                             | 4172                                                                          | Gen pop            | Age, sex                                                      | Up to 2                   | CVA, CHD             | P, M, F | SMR             |     |
| Girardi, 2021    | SCZ           | Italy       | Community and inpatient | 2008                   | 2008-2018          | 18-84, median 48                                | 12996                                                                         | Gen pop            | Age, sex, and calendar year                                   | 9.6                       | CVA, CHD, CVD        | P, M, F | SMR             |     |
| Grigoletti, 2009 | SCZ           | Italy       | Community               | 1982-2001              | 1982-2001          | 14+                                             | 556                                                                           | Gen pop            | Age, sex, year                                                | Up to 20                  | CVD                  | P       | SMR             |     |
| Hansen, 2001     | SMI           | Norway      | Inpatient               | Aug 1980-1992          | Aug 1980-1992      | NR                                              | NR                                                                            | NR                 | Age, sex                                                      | Up to 12.5                | CVD                  | M, F    | SMR             |     |
| Hayes, 2017      | SCZ, BD       | UK          | Community               | 2000-2014              | 2000-2014          | 16+, median SCZ: 42.5, BD: 42.8                 | 39838                                                                         | 219387             | Age, sex, time, deprivation, ethnicity, primary care contacts | median: SCZ 2.47, BD 2.32 | CVD                  | P       | HR              |     |
| Heiberg, 2018    | SCZ           | Norway      | Community and inpatient | 2009-2015              | 2009-2015          | 20-79, mean 45.6                                | 20537                                                                         | Gen pop            | Age, sex                                                      | Up to 6                   | CVD                  | P, M, F | SMR             |     |
| Heila, 2005      | SCZ           | Finland     | Inpatient               | 1980-1996              | 1980-1996          | All ages                                        | 58761                                                                         | Gen pop            | Age, sex, year                                                | Over 10                   | CHD                  | M, F    | RRatio          |     |
| Hiroeh, 2008     | SCZ           | Denmark     | Inpatient               | 1973-1993              | 1973-1993          | 15+                                             | 13000 (est)                                                                   | 4100000            | Age, sex                                                      | Up to 21                  | CVD                  | P, M, F | SMR             |     |
| Hoang, 2011      | SCZ, BD       | UK          | Inpatient               | 1999-2006              | 2000-2007          | Median: SCZ: 36 (M), 44 (F), BD: 44 (M), 48 (F) | 283227 patients discharged over study period (may be included more than once) |                    | Gen pop                                                       | Age, sex                  | 1                    | CVD     | P               | SMR |
| Høyve, 2011      | SCZ           | Norway      | Inpatient               | 1980-1992              | 1980-2006          | Mean 35.2                                       | 1111                                                                          | Gen pop            | Age, sex, year                                                | 14.5                      | CVD                  | P, M, F | SMR             |     |
| John, 2018       | SMI           | UK          | Community and inpatient | 2004-2013              | 2004-2013          | <45, 45-64                                      | 22359                                                                         | NR                 | Age, sex, calendar year                                       | 5.1                       | CVA, CHD, CVD        | P       | SMR             |     |



| Study, year      | SMI diagnosis | Country                  | Setting                 | Period of SMI exposure | Period of outcomes | Age at start of study (years) | Number of cases | Number of controls | Covariates adjusted for                                                                                                                | Mean follow-up (years) | Outcomes (mortality) | Sex     | Type of results |
|------------------|---------------|--------------------------|-------------------------|------------------------|--------------------|-------------------------------|-----------------|--------------------|----------------------------------------------------------------------------------------------------------------------------------------|------------------------|----------------------|---------|-----------------|
| Kelly, 2010      | SCZ           | USA                      | Community and inpatient | 1994-May 2000          | 1994-2004          | 20-69, mean 39                | 1686            | Gen pop            | Age, sex, race                                                                                                                         | 6 to 10                | CHD                  | P, M, F | SMR             |
| Kilbourne, 2009  | SCZ, BD       | USA                      | Community               | 1998 - 1999            | 2000-2006          | Mean SCZ: 56, BD: 55.5        | 38020           | 16072              | Age, sex, race, education, marital status, social support, financial hardship, living alone, service-connected disability, non-VA care | Up to 8                | CHD                  | P       | HR              |
| Kiviniemi, 2010  | SCZ           | Finland                  | Inpatient               | 1995-2001              | 2000s              | Mean 33.5                     | 7591            | Gen pop            | Age, sex, district, year                                                                                                               | 5                      | CVD                  | P, M, F | SMR             |
| Kredentser, 2014 | SCZ           | Canada                   | Community and inpatient | 1987-1998              | 1999-2008          | 10+, Mean 48.7                | 9038            | 969090             | Age, sex                                                                                                                               | Up to 10               | CVD                  | P       | RRatio          |
| Lahti, 2012      | SCZ           | Finland                  | Inpatient               | 1969-2004              | 1969-2004          | 25-70, median 35.3            | 204             | 12735              | Birth year, sex, socioeconomic status in childhood                                                                                     | Up to 35               | CVA, CHD             | P, M, F | HR              |
| Laursen, 2007    | SCZ, BD       | Denmark                  | Inpatient               | 1973-2000              | 1973-2000          | 15+                           | 29308           | 5191544            | Age, sex                                                                                                                               | Up to 27               | CHD                  | M, F    | RRatio          |
| Laursen, 2010    | SCZ, BD       | Denmark                  | Inpatient               | 1994-2006              | 1994-2006          | 15+                           | NR              | NR                 | Age, sex                                                                                                                               | Up to 13               | CHD                  | P, M, F | RRatio          |
| Laursen, 2013    | SCZ, BD       | Denmark, Finland, Sweden | Inpatient               | 1987-1999              | 2000-2006          | 15+                           | 105463          | Gen pop            | Age, sex                                                                                                                               | Up to 20               | CVA, CHD, CVD        | P, M, F | SMR             |
| Laursen, 2014    | SCZ, BD       | Denmark                  | Community and inpatient | 1995-2006              | 1998-2008          | 10+                           | 4500 (est)      | 1061532            | Age, sex, time, Charlson index                                                                                                         | Up to 14               | CHD                  | P       | RRatio          |
| Laursen, 2019    | SCZ           | Denmark                  | Community and inpatient | 1995-2015              | 1995-2015          | 10+                           | NR              | NR                 | Age, sex, calendar time                                                                                                                | Up to 21               | CVD                  | M, F    | RRatio          |
| Lawrence, 2003   | SCZ           | Australia                | Community and inpatient | 1980-1998              | 1980-1998          | NR                            | NR              | NR                 | Age, sex, year                                                                                                                         | Up to 18               | CHD                  | M, F    | RRatio          |

| Study, year         | SMI diagnosis | Country                  | Setting                 | Period of SMI exposure | Period of outcomes   | Age at start of study (years) | Number of cases    | Number of controls | Covariates adjusted for                             | Mean follow-up (years)                       | Outcomes (mortality) | Sex     | Type of results |
|---------------------|---------------|--------------------------|-------------------------|------------------------|----------------------|-------------------------------|--------------------|--------------------|-----------------------------------------------------|----------------------------------------------|----------------------|---------|-----------------|
| Lawrence, 2013      | SCZ           | Australia                | Community and inpatient | 1985-2005              | 1985-2005            | NR                            | NR                 | NR                 | Age, sex, year                                      | Up to 20                                     | CVA, CHD             | P       | SMR             |
| Lemogne, 2013       | SMI           | France                   | Community               | 1978-2010              | 1990-2010            | 35-50, mean 44                | 124                | 16261              | Age, sex, occupational grade, alcohol, smoking, BMI | 19.8                                         | CVD                  | P       | HR              |
| Lesage, 2015        | SCZ           | Canada                   | Community               | Apr 1999 to Mar 2012   | Apr 1999 to Mar 2012 | NR                            | 33660 (annual est) | 7525000            | Age, sex                                            | Up to 12                                     | CVD                  | M, F    | RRatio          |
| Lumme, 2016         | SCZ, BD       | Finland                  | Inpatient               | 1990-2010              | 1996-2010            | 25-64                         | NR                 | NR                 | Age, sex, year                                      | Up to 20                                     | CHD                  | M, F    | RRatio          |
| Manderbacka, 2012   | SCZ           | Finland                  | Inpatient               | 1998-2009              | 1998-2009            | 40+                           | 67659              | Gen pop            | Age, sex, year                                      | Up to 12                                     | CHD                  | P       | RRatio          |
| Morden, 2012        | SCZ           | USA                      | Community and inpatient | Oct 1999 to Sep 2007   | Oct 1999 to Sep 2007 | Mean 53.4                     | 65362              | 65362              | Age, sex, location                                  | Up to 8                                      | CHD, CVD             | P       | RRatio          |
| Mortensen, 1990     | SCZ           | Denmark                  | Inpatient               | 26-Sep-1957            | 1957-1986            | NR                            | 6178               | Gen pop            | Age, sex, calendar period                           | Up to 29                                     | CVA, CHD             | P, M, F | SMR             |
| Mortensen, 1993     | SCZ           | Denmark                  | Inpatient               | Apr 1970-1987          | 1970-Mar 1988        | NR                            | 9156               | Gen pop            | Age, sex, calendar period                           | Up to 18                                     | CVA, CHD             | P, M, F | SMR             |
| Murray-Thomas, 2013 | SCZ           | UK                       | Community               | 1995-Jan 2011          | 2001-Jan 2011        | 18+                           | 7779               | NR                 | Age, sex, year, GP practice                         | 4.1                                          | CHD                  | P       | RRatio          |
| Newman, 1991        | SCZ           | Canada                   | Community and inpatient | 1976-1985              | 1976-1985            | 9-88, mean 37.3               | 3623               | Gen pop            | Age, sex                                            | 6                                            | CVA, CHD, CVD        | P, M, F | SMR             |
| Nilsson, 1995       | BD            | Sweden                   | Inpatient               | 1970-1977              | 1970-Jul 1991        | Mean 48                       | 362                | Gen pop            | Age, sex                                            | 14.3                                         | CVA, CHD             | P, M, F | SMR             |
| Nordentoft, 2013    | SCZ           | Denmark, Finland, Sweden | Inpatient               | 2000-2006              | 2000-2006            | NR                            | 40970              | Gen pop            | Age, sex                                            | Up to 9                                      | CVD                  | M, F    | SMR             |
| Odegard, 1967       | SCZ           | Norway                   | Inpatient               | 1950-1962              | 1950-1962            | 15+                           | 5200 approx.       | Gen pop            | Age, sex                                            | Up to 12 years of death, but not followed up | CVD                  | M, F    | RRatio          |

| Study, year          | SMI diagnosis | Country     | Setting                 | Period of SMI exposure | Period of outcomes | Age at start of study (years) | Number of cases                                                   | Number of controls | Covariates adjusted for                                                                          | Mean follow-up (years)  | Outcomes (mortality) | Sex     | Type of results |
|----------------------|---------------|-------------|-------------------------|------------------------|--------------------|-------------------------------|-------------------------------------------------------------------|--------------------|--------------------------------------------------------------------------------------------------|-------------------------|----------------------|---------|-----------------|
| Olfson, 2015         | SCZ           | USA         | Community and inpatient | 2001-2007              | 2001-2007          | 20-64                         | 1138853                                                           | Gen pop            | Age, sex, ethnicity/race, geographic region                                                      | 4.2                     | CVA, CHD, CVD        | P, M, F | SMR             |
| Osborn, 2007         | SCZ, BD       | UK          | Community               | June 1987-Apr 2002     | June 1987-Apr 2002 | 18+                           | 29297                                                             | 300246             | Age, sex, calendar period, smoking, social deprivation                                           | SMI: 4.7, controls: 4.3 | CVA, CHD             | P       | HR              |
| Ösby, 2000a          | SCZ           | Sweden      | Inpatient               | 1973-1995              | 1973-1995          | All ages                      | 7784                                                              | Gen pop            | Age, sex, calendar period                                                                        | Up to 23                | CVA, CHD             | P, M, F | SMR             |
| Ösby, 2000b          | SCZ           | Sweden      | Inpatient               | 1976-1995              | 1976-1995          | NR                            | 5802 (first admissions)                                           | Gen pop            | Age, sex, calendar period                                                                        | Up to 20                | CVD                  | M, F    | SMR             |
| Ösby, 2001           | BD            | Sweden      | Inpatient               | 1973-1995              | 1973-1995          | <70, mean 43.1                | 15386                                                             | Gen pop            | Age, sex, calendar period                                                                        | 10.5 (M), 11.5 (F)      | CVA, CHD             | P, M, F | SMR             |
| Ösby, 2016           | SCZ, BD       | Sweden      | Inpatient               | 1987-2010              | 1987-2010          | 15+, mean SCZ: 46.3, BD: 50.9 | 121875 hospitalisations (patients may be included more than once) | Gen pop            | Age, sex, calendar year, length of follow-up                                                     | 2                       | CVA, CHD, CVD        | P       | RRatio          |
| Pan, 2020            | SCZ, BD       | Taiwan      | Community and inpatient | 2005                   | 2005-2008          | Mean 49.95                    | 162878                                                            | Gen pop            | Age, sex, calendar period                                                                        | Up to 3                 | CVD                  | P, M, F | SMR             |
| Park, 2015           | SCZ           | South Korea | Community and inpatient | 1995-2006              | 1995-2009          | 18+                           | NR                                                                | NR                 | Age (sex)                                                                                        | Up to 15                | CVD                  | P       | SMR             |
| Prior, 1996          | SCZ, BD       | UK          | Community and inpatient | 1974-1984              | 1974-1985          | 15-89                         | 1835                                                              | Gen pop            | Age, sex                                                                                         | Up to 11                | CVD                  | P, M, F | SMR             |
| Saku, 1995           | SCZ, BD       | Japan       | Inpatient               | 1948-Mar 1982          | 1948-Aug 1985      | All ages                      | 2455                                                              | Gen pop            | Age, sex, year                                                                                   | Up to 36                | CVA, CHD             | P, M, F | SMR             |
| Salazar-Fraile, 1998 | SCZ           | Spain       | Community               | April-Nov 1986         | 1986-1993          | 16+                           | 186                                                               | 2382               | Age, sex                                                                                         | Up to 11                | CVD                  | P       | HR              |
| Sanchez, 2021        | SCZ           | Spain       | Community               | 2006-2007              | 2008-2011          | 18+, mean 43.4                | 6472                                                              | 94694              | Age, sex, primary care utilisation, alcohol, HT, DM, obesity, dyslipidaemia, smoking (mortality) | Up to 5                 | CVD                  | P       | HR              |

| Study, year         | SMI diagnosis | Country     | Setting                 | Period of SMI exposure | Period of outcomes   | Age at start of study (years) | Number of cases | Number of controls | Covariates adjusted for                                          | Mean follow-up (years) | Outcomes (mortality) | Sex     | Type of results |
|---------------------|---------------|-------------|-------------------------|------------------------|----------------------|-------------------------------|-----------------|--------------------|------------------------------------------------------------------|------------------------|----------------------|---------|-----------------|
|                     |               |             |                         |                        |                      |                               |                 |                    | excludes alcohol, obesity, DM but included cocaine use)          |                        |                      |         |                 |
| Tanskanen, 2018     | SCZ           | Finland     | Inpatient               | 1984-2014              | 1984-2014            | 16+                           | 42343           | 4515838            | Age, sex                                                         | Up to 30               | CVD                  | P       | SMR             |
| Termorshuizen, 2013 | SCZ           | Netherlands | Community and inpatient | 2000-2008              | 2000-2010            | 18-64                         | NR              | NR                 | Age, sex, ethnicity                                              | <2, 2-5, >5            | CVD                  | P       | RRatio          |
| Torniainen, 2015    | SCZ           | Sweden      | Community and inpatient | 1-Jan-2006             | 2006-2010            | 17-65, mean 46                | 21492           | 214920             | Age, sex                                                         | 5                      | CVD                  | P       | HR              |
| Tsuang, 1980        | SCZ, BD       | USA         | Inpatient               | 1934-1944              | 1934-1974            | NR                            | 300             | Gen pop            | Age, sex                                                         | Up to 40               | CVD                  | P, M, F | SMR             |
| Vance, 2019         | SCZ, BD       | USA         | Community               | 2009                   | 2010-2014            | 45-80, mean 61.6              | NR              | NR                 | Age, sex, smoking, race, BP, cholesterol, HDL, HT medication, DM | Up to 5                | CVD                  | M, F    | OR              |
| Weeke, 1986         | BD            | Denmark     | Inpatient               | Apr 1970-Mar 1972      | Apr 1970-Mar 1977    | Mean 50.5                     | 2168            | Gen pop            | Age, sex                                                         | Up to 7                | CVD                  | P, M, F | SMR             |
| Weeke, 1987         | BD            | Denmark     | Inpatient               | 1950-1956, 1969-1976   | 1950-1957, 1969-1977 | Mean 46.1                     | 3431            | Gen pop            | Age                                                              | 4.5                    | CVD                  | M       | SMR             |
| Westman, 2013       | BD            | Sweden      | Inpatient               | 1987-2006              | 1987-2006            | All ages                      | 17101           | 10631208           | Age, sex, calendar year, year of follow-up                       | Up to 20               | CVA, CHD, CVD        | P, M, F | RRatio          |
| Westman, 2017       | SCZ           | Sweden      | Inpatient               | 1987-2010              | 1987-2010            | 15+                           | 46911           | 10631817           | Age, sex, calendar period                                        | Up to 24               | CVA, CHD, CVD, HF    | P, M, F | RRatio          |
| Yung, 2021          | SCZ           | Hong Kong   | Community and inpatient | 2001-2016              | 2006-2016            | 18+                           | 46896           | Gen pop            | Age, sex, calendar year                                          | 8.7                    | CVA, CHD, CVD        | P, M, F | SMR             |
| Zilber, 1989        | SCZ           | Israel      | Inpatient               | 1978                   | 1978-1983            | 10+                           | 8900 (est)      | Gen pop            | Age, sex, year                                                   | 5.15                   | CVD                  | P       | SMR             |

SCZ – schizophrenia, BD – bipolar disorder, NR – not reported, est – estimated, gen pop – general population, DM – diabetes mellitus, HT – hypertension, COPD – chronic obstructive pulmonary disease, TIA – transient ischaemic attack, BMI – body mass index, CVA – cerebrovascular accident, CHD – coronary heart disease, CVD – all circulatory disease, HF – heart failure, P – persons, M – males, F – females, HR – hazard ratio, RRatio – rate ratio, SMR – standardised mortality ratio, HDL – high density lipoprotein cholesterol

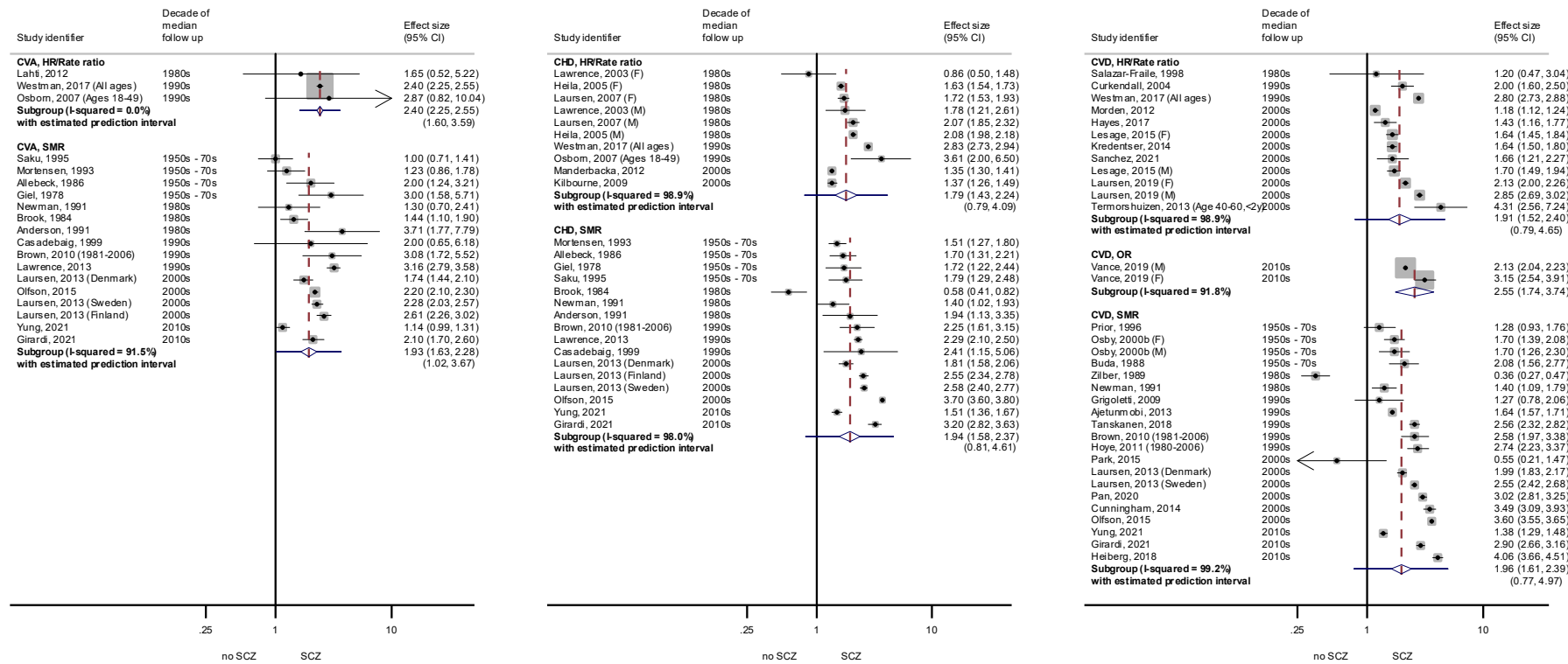
**Table 2.5: Pooled relative risks of cardiovascular mortality by SMI and CVD mortality outcome**

| SMI | Outcome | Measure       | Studies | / | Results | Pooled effect (95% CI)       | p-value | Prediction interval | I <sup>2</sup> | X <sup>2</sup> | df | p-value |
|-----|---------|---------------|---------|---|---------|------------------------------|---------|---------------------|----------------|----------------|----|---------|
| SCZ | CVA     | HR/rate ratio | 3       | / | 3       | <b>2.40</b> ( 2.25 - 2.55 )  | <0.001  | 1.60 - 3.60         | 0.0            | 0.5            | 2  | 0.785   |
| SCZ | CVA     | SMR           | 14      | / | 16      | <b>1.93</b> ( 1.63 - 2.28 )  | <0.001  | 1.02 - 3.67         | 91.5           | 176.3          | 15 | <0.001  |
| SCZ | CHD     | HR/rate ratio | 7       | / | 10      | <b>1.80</b> ( 1.44 - 2.24 )  | <0.001  | 0.79 - 4.09         | 98.9           | 827.1          | 9  | <0.001  |
| SCZ | CHD     | SMR           | 14      | / | 16      | <b>1.94</b> ( 1.58 - 2.37 )  | <0.001  | 0.81 - 4.62         | 98.0           | 733.8          | 15 | <0.001  |
| SCZ | CVD     | HR/rate ratio | 10      | / | 12      | <b>1.91</b> ( 1.52 - 2.41 )  | <0.001  | 0.79 - 4.66         | 98.9           | 979.0          | 11 | <0.001  |
| SCZ | CVD     | OR            | 1       | / | 2       | <b>2.55</b> ( 1.74 - 3.74 )  | <0.001  | .                   | 91.8           | 12.1           | 1  | <0.001  |
| SCZ | CVD     | SMR           | 18      | / | 20      | <b>1.96</b> ( 1.61 - 2.39 )  | <0.001  | 0.77 - 4.97         | 99.2           | 2414.0         | 19 | <0.001  |
| SCZ | HF      | HR/rate ratio | 1       | / | 1       | <b>3.25</b> ( 2.94 - 3.60 )  | <0.001  | .                   | .              | 0.0            | 0  | .       |
| BD  | CVA     | HR/rate ratio | 2       | / | 2       | <b>2.01</b> ( 1.81 - 2.22 )  | <0.001  | .                   | 0.0            | 0.5            | 1  | 0.498   |
| BD  | CVA     | SMR           | 5       | / | 7       | <b>1.55</b> ( 1.33 - 1.81 )  | <0.001  | 0.99 - 2.44         | 74.0           | 23.1           | 6  | 0.001   |
| BD  | CHD     | HR/rate ratio | 5       | / | 7       | <b>1.61</b> ( 1.34 - 1.94 )  | <0.001  | 0.93 - 2.80         | 90.2           | 61.2           | 6  | <0.001  |
| BD  | CHD     | SMR           | 5       | / | 7       | <b>1.67</b> ( 1.54 - 1.82 )  | <0.001  | 1.33 - 2.10         | 57.7           | 14.2           | 6  | 0.028   |
| BD  | CVD     | HR/rate ratio | 2       | / | 2       | 1.52 ( 0.84 - 2.75 )         | 0.162   | .                   | 94.6           | 18.5           | 1  | <0.001  |
| BD  | CVD     | OR            | 1       | / | 2       | <b>1.83</b> ( 1.57 - 2.14 )  | <0.001  | .                   | 65.2           | 2.9            | 1  | 0.090   |
| BD  | CVD     | SMR           | 12      | / | 14      | <b>1.65</b> ( 1.53 - 1.77 )  | <0.001  | 1.29 - 2.10         | 80.4           | 66.4           | 13 | <0.001  |
| SMI | CVA     | SMR           | 1       | / | 1       | 0.80 ( 0.16 - 4.08 )         | 0.788   | .                   | .              | 0.0            | 0  | .       |
| SMI | CHD     | SMR           | 1       | / | 1       | <b>3.70</b> ( 2.47 - 5.55 )  | <0.001  | .                   | .              | 0.0            | 0  | .       |
| SMI | CVD     | HR/rate ratio | 1       | / | 1       | <b>5.41</b> ( 2.40 - 12.20 ) | <0.001  | .                   | .              | 0.0            | 0  | .       |
| SMI | CVD     | SMR           | 4       | / | 5       | <b>2.30</b> ( 1.63 - 3.25 )  | <0.001  | 0.63 - 8.40         | 92.9           | 56.3           | 4  | <0.001  |

SCZ – schizophrenia, BD – bipolar disorder, SMI – mixed schizophrenia and bipolar disorder, HF – heart failure, HR – hazard ratio, OR – odds ratio, RR – risk ratio, SMR – standardised mortality ratio, . – not calculable (insufficient observations). Results where 95% confidence intervals exclude the null highlighted in **bold**

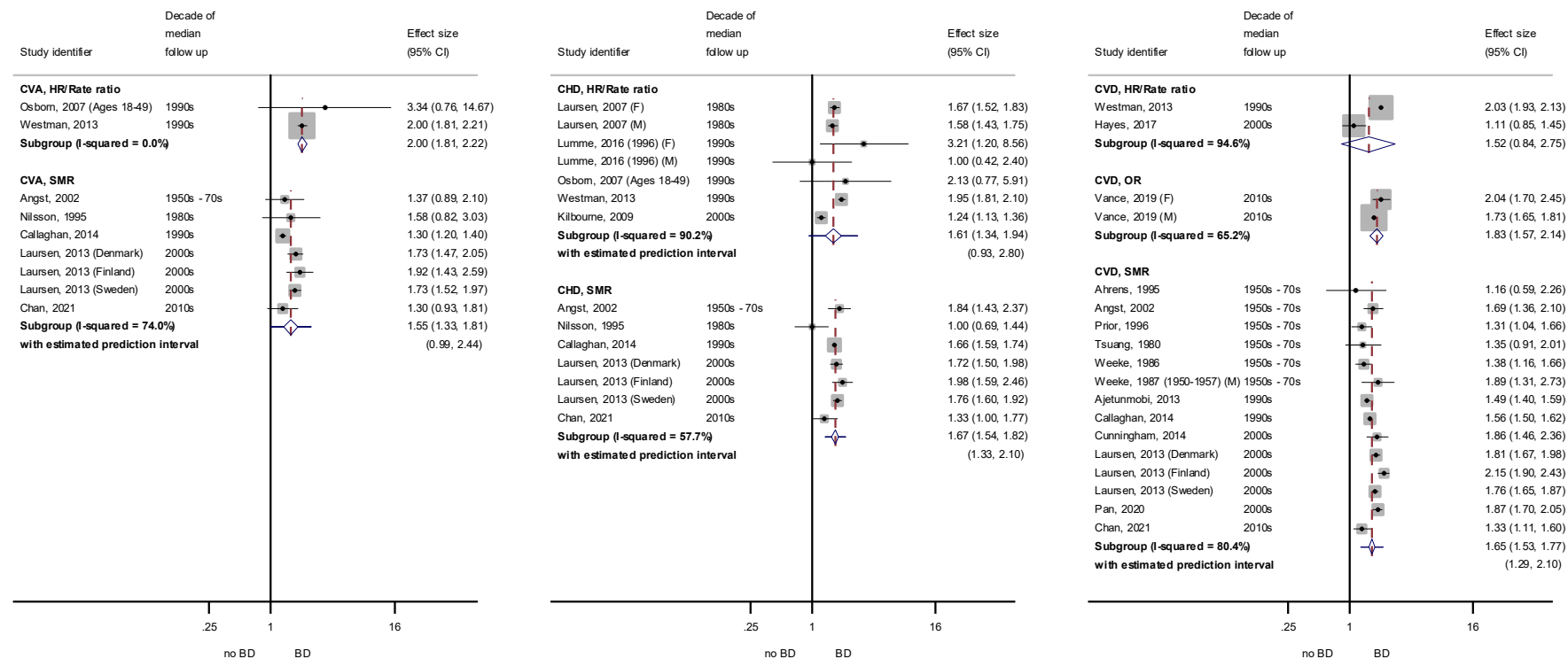
There was significant heterogeneity across all subgroups ( $p < 0.05$  and  $I^2 > 50\%$ ), except for CVA pooled HRs/rate ratios in both schizophrenia and BD and ORs for CVD in BD (the latter based on a single study). Prediction intervals may be informative in describing the likely range of future studies. (109) For schizophrenia, 95% prediction intervals did not overlap unity for CVA and for BD they did not overlap unity for CHD and all circulatory disease SMRs. Thus, for these combinations of SMI and CVD mortality a future study would be expected to report elevated mortality ratios.

Figure 2.2 and Figure 2.3 show forest plots of studies, that were included in meta-analyses, reporting CVD mortality for schizophrenia and BD, respectively. Forest plots of all eligible studies reporting CV mortality are shown in Appendix XI .



Weights are from random effects model. Dashed lines show pooled estimated risks within subgroups. Studies were allocated to decades according to the median year of follow-up. SCZ – schizophrenia, CVA – cerebrovascular accident, CHD – coronary heart disease, CVD – all circulatory disease, HR – hazard ratio, OR – odds ratio, SMR – standardised mortality ratio M – males, F – females

**Figure 2.2: Forest plots showing relative risk of CVD mortality in those with vs without schizophrenia, studies included in meta-analysis**



Weights are from random effects mode. Dashed lines show pooled estimated risks within subgroups. Studies were allocated to decades according to the median year of follow-up. BD – bipolar disorder, CVA – cerebrovascular accident, CHD – coronary heart disease, CVD – all circulatory disease, HR – hazard ratio, OR – odds ratio, SMR – standardised mortality ratio M – males, F – females

**Figure 2.3: Forest plots showing relative risk of CVD mortality in those with vs without bipolar disorder, studies included in meta-analysis**



### 2.3.4 Temporal trends

Results from meta-regression (Table 2.6) showed that for schizophrenia, SMRs for cerebrovascular mortality in the 1990s were two-fold higher than in the 1970s and earlier (SMR: 1.96, (95% CI: 1.02-3.78,  $p=0.044$ )). The earliest decade for which results were available was chosen as the reference group. Pooled HR/rate ratios for CHD were 60% higher in the 1990s compared with the 1980s (HR/rate ratio: 1.61 (95% CI: 1.14-2.28,  $p=0.014$ )). However, the estimated risks for the strength of association between SMI and CVD was lower in the 2000s compared with the 1980s (HR/rate ratio: 0.75 (95% CI: 0.56-1.00,  $p=0.052$ )). BD studies in the 2000s reported SMRs for all circulatory disease higher than those in the 1950s-70s (SMR: 1.27, 95% CI: 1.09-1.47,  $p=0.006$ ).

Heterogeneity between studies was reduced by the inclusion of decade in the case of schizophrenia and CVA ( $I^2=91.5\%$ , residual  $I^2=79.0\%$ ), with decade accounting for a substantial amount of the between study variation (adjusted  $R^2=37.5\%$ ). Similarly, for BD and all CVD mortality, decade reduced heterogeneity and accounted for considerable between study variation ( $I^2=80.4\%$ , residual  $I^2=34.3\%$ , adjusted  $R^2=88.9\%$ ). For schizophrenia and CHD, there was still considerable heterogeneity after the inclusion of decade (residual  $I^2=96.6\%$ , adjusted  $R^2=85.7\%$ ), but the model  $p$ -value of 0.007 indicates some evidence for a relationship between decade and size of association between schizophrenia and CVD mortality.

Figure 2.4 shows the trends in CVD mortality by SMI across decades. For schizophrenia and BD, there appeared to be stronger associations between SMI and both CVD and CHD mortality in studies reporting SMRs occurring during the 1990s and 2000s, compared with

earlier decades, suggesting that, on this measure, the gap between people with SMI and the general population may be widening. In the 2010s SMRs were reduced slightly, but confidence intervals were wider. Pooled HRs and rate ratios appeared to peak in the 1990s. CVA SMRs peaked in the 1990s for schizophrenia and in the 2000s for BD. For most SMI/CVD combinations, increasing the granularity by splitting time into 5-year periods for meta-regression did not add any further information as there were too few studies in each group (Figure 2.5 and Appendix XII ). For those groups that did have sufficient observations, confidence intervals were wide, and most results indicated no increased risk for any 5-year period compared with the reference period. Only for CVA in schizophrenia did the 5-year analysis show higher SMRs for 1995-1999 compared with 1950-1969.

**Table 2.6: Results of meta-regressions: estimates of increased risk relative to the reference category for study-level explanatory variables; exponentiated regression coefficients (95% confidence intervals), p values**

| Explanatory variable<br>(if no. of studies/results ≥10) |                                                                      |                                                                      | Schizophrenia                  |                                |                            | Bipolar disorder               |
|---------------------------------------------------------|----------------------------------------------------------------------|----------------------------------------------------------------------|--------------------------------|--------------------------------|----------------------------|--------------------------------|
|                                                         |                                                                      |                                                                      | CVA                            | CHD                            | CVD                        | CVD                            |
| Decade                                                  | SMR                                                                  | 1950s-70s (ref)                                                      | 1                              | 1                              | 1                          | 1                              |
|                                                         |                                                                      | 1980s                                                                | 1.14 (0.59-2.20), 0.673        | 0.67 (0.36-1.22), 0.169        | 0.43 (0.17-1.06), 0.063    | -                              |
|                                                         |                                                                      | 1990s                                                                | <b>1.96</b> (1.02-3.78), 0.044 | 1.38 (0.75-2.52), 0.267        | 1.26 (0.63-2.53), 0.489    | 1.04 (0.89-1.21), 0.579        |
|                                                         |                                                                      | 2000s                                                                | 1.45 (0.85-2.46), 0.153        | 1.55 (0.92-2.59), 0.089        | 1.51 (0.77-2.96), 0.214    | <b>1.27</b> (1.09-1.47), 0.006 |
|                                                         |                                                                      | 2010s                                                                | 1.01 (0.54-1.89), 0.978        | 1.31 (0.70-2.45), 0.358        | 1.52 (0.70-3.29), 0.271    | 0.91 (0.69-1.18), 0.425        |
|                                                         |                                                                      | <i>Model p-value, residual I<sup>2</sup>, adjusted R<sup>2</sup></i> | <i>0.193, 79.0%, 37.5%</i>     | <i>0.073, 96.6%, 38.3%</i>     | <i>0.059, 98.3%, 39.5%</i> | <i>0.003, 34.3%, 88.9%</i>     |
|                                                         | HR/rate ratio                                                        | 1950s-70s                                                            | Insufficient observations      | -                              | -                          | Insufficient observations      |
|                                                         |                                                                      | 1980s (ref)                                                          |                                | 1                              | 1                          |                                |
|                                                         |                                                                      | 1990s                                                                |                                | <b>1.61</b> (1.14-2.28), 0.014 | 1.99 (0.46-8.60), 0.314    |                                |
|                                                         |                                                                      | 2000s                                                                |                                | 0.75 (0.56-1.00), 0.052        | 1.54 (0.39-6.14), 0.500    |                                |
|                                                         |                                                                      | 2010s                                                                |                                | -                              | -                          |                                |
| Setting                                                 | <i>Model p-value, residual I<sup>2</sup>, adjusted R<sup>2</sup></i> |                                                                      |                                | <i>0.007, 87.0%, 85.7%</i>     | <i>0.487, 98.3%, 2.1%</i>  |                                |
|                                                         | SMRs                                                                 | Community (ref)                                                      | 1                              | 1                              | 1                          | 1                              |
|                                                         |                                                                      | Community and inpatient                                              | 0.62 (0.21-1.81), 0.355        | 1.02 (0.37-2.80), 0.969        | 1.19 (0.43-3.29), 0.728    | 0.96 (0.77-1.19), 0.672        |
|                                                         |                                                                      | Inpatient                                                            | 0.61 (0.21-1.74), 0.325        | 0.76 (0.28-2.03), 0.552        | 0.93 (0.33-2.58), 0.887    | -                              |
|                                                         |                                                                      | <i>Model p-value, residual I<sup>2</sup>, adjusted R<sup>2</sup></i> | <i>0.603, 92.5%, -8.8%</i>     | <i>0.412, 97.4%, -0.9%</i>     | <i>0.699, 98.6%, -5.7%</i> | <i>0.672, 81.5%, -11.1%</i>    |
|                                                         | HR/rate ratio                                                        | Community (ref)                                                      | Insufficient observations      | 1                              | 1                          | Insufficient observations      |
|                                                         |                                                                      | Community and inpatient                                              |                                | 0.67 (0.26-1.76), 0.359        | 1258 (0.79-1.98), 0.292    |                                |
|                                                         |                                                                      | Inpatient                                                            |                                | 0.98 (0.47-2.05), 0.954        | 1.71 (0.79-3.68), 0.150    |                                |
|                                                         | <i>Model p-value, residual I<sup>2</sup>, adjusted R<sup>2</sup></i> |                                                                      |                                | <i>0.524, 99.1%, -18.7%</i>    | <i>0.279, 98.2%, 6.1%</i>  |                                |
| Region                                                  | SMR                                                                  | UK (ref)                                                             | 1                              | 1                              | 1                          | 1                              |
|                                                         |                                                                      | Far East                                                             | <b>0.32</b> (0.15-0.68), 0.007 | 0.78 (0.25-2.38), 0.626        | 0.88 (0.31-2.46), 0.787    | 1.13 (0.79-1.64), 0.451        |
|                                                         |                                                                      | North America                                                        | 0.58 (0.27-1.24), 0.140        | 1.11 (0.36-3.39), 0.836        | 1.26 (0.46-3.42), 0.634    | 1.06 (0.72-1.56), 0.740        |
|                                                         |                                                                      | Oceania                                                              | 0.95 (0.42-2.13), 0.888        | 1.09 (0.29-4.11), 0.887        | 1.98 (0.49-8.07), 0.313    | 1.31 (0.79-2.16), 0.255        |
|                                                         |                                                                      | Other EU/Israel                                                      | 0.58 (0.28-1.19), 0.122        | 0.78 (0.29-2.13), 0.600        | 0.63 (0.23-1.75), 0.351    | 1.11 (0.70-1.75), 0.620        |
|                                                         |                                                                      | Scandinavia                                                          | 0.60 (0.30-1.17), 0.118        | 0.95 (0.37-2.43), 0.897        | 1.35 (0.58-3.15), 0.457    | 1.26 (0.92-1.71), 0.131        |
|                                                         |                                                                      | <i>Model p-value, residual I<sup>2</sup>, adjusted R<sup>2</sup></i> | <i>0.034, 68.5%, 59.9%</i>     | <i>0.942, 94.4%, -37.6%</i>    | <i>0.417, 97.9%, 0.04%</i> | <i>0.586, 73.2%, -17.4%</i>    |

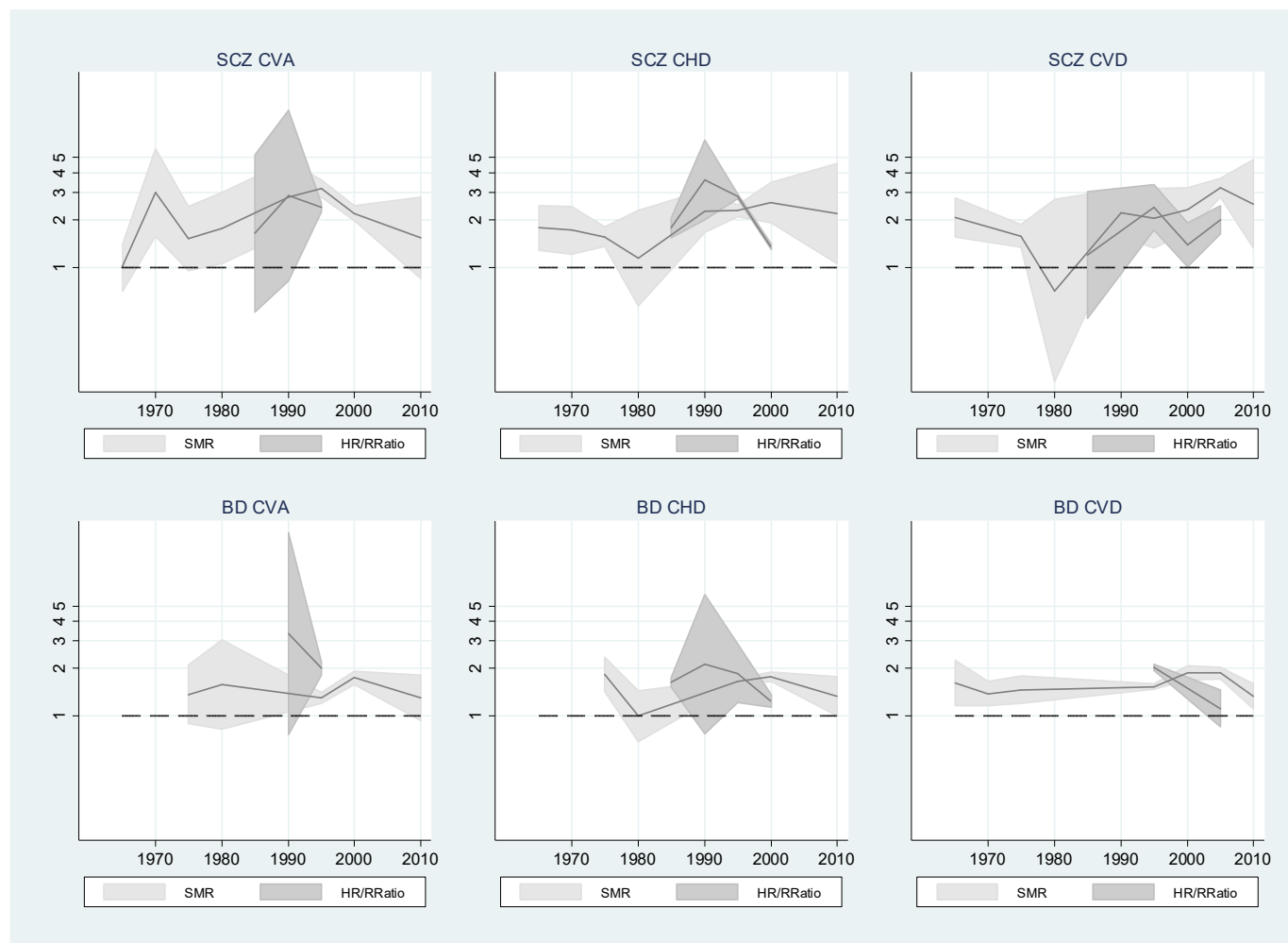
| Explanatory variable<br>(if no. of studies/results ≥10)          |                 | Schizophrenia             |                         |                         | Bipolar disorder          |
|------------------------------------------------------------------|-----------------|---------------------------|-------------------------|-------------------------|---------------------------|
|                                                                  |                 | CVA                       | CHD                     | CVD                     | CVD                       |
| HR/rate ratio                                                    | UK (ref)        | Insufficient observations | 1                       | 1                       | Insufficient observations |
|                                                                  | Far East        |                           | -                       | -                       |                           |
|                                                                  | North America   |                           | 0.38 (0.11-1.30), 0.103 | 1.11 (0.56-2.21), 0.729 |                           |
|                                                                  | Oceania         |                           | 0.36 (0.11-1.21), 0.085 | -                       |                           |
|                                                                  | Other EU/Israel |                           | -                       | 1.51 (0.67-3.42), 0.273 |                           |
|                                                                  | Scandinavia     |                           | 0.52 (0.18-1.51), 0.187 | 1.80 (0.88-3.67), 0.094 |                           |
| Model p-value, residual I <sup>2</sup> , adjusted R <sup>2</sup> |                 |                           | 0.247, 99.2%, 16.6%     | 0.109, 94.8%, 53.8%     |                           |
| Random effects meta-analysis                                     | SMRs            | 91.5%                     | 98.0%                   | 99.2%                   | 80.4%                     |
| I <sup>2</sup>                                                   | HR/rate ratio   |                           | 98.9%                   | 98.9%                   |                           |

CVA – cerebrovascular accident, CHD – coronary heart disease, CVD – all circulatory disease, SMR – standardised mortality ratio, HR – hazard ratio, RR – rate ratio, North America – USA and Canada, Other EU – Western Europe excluding UK and Scandinavia, ref – reference group. Results where 95% confidence intervals exclude the null highlighted in **bold**. Models adjusted for age and sex and minimum number of additional factors



SCZ – schizophrenia, BD – bipolar disorder, CVA – cerebrovascular accident, CHD – coronary heart disease, CVD – all circulatory disease, SMR – standardised mortality ratio, HR – hazard ratio, RRatio – rate ratio. 1970 includes studies with median between 1950 and 1970. y-axes show estimated risks on log scale, shaded areas show 95% confidence intervals for risk estimates

**Figure 2.4: Trend in risk of CVD mortality for severe mental illness compared with control participants, by median decade**

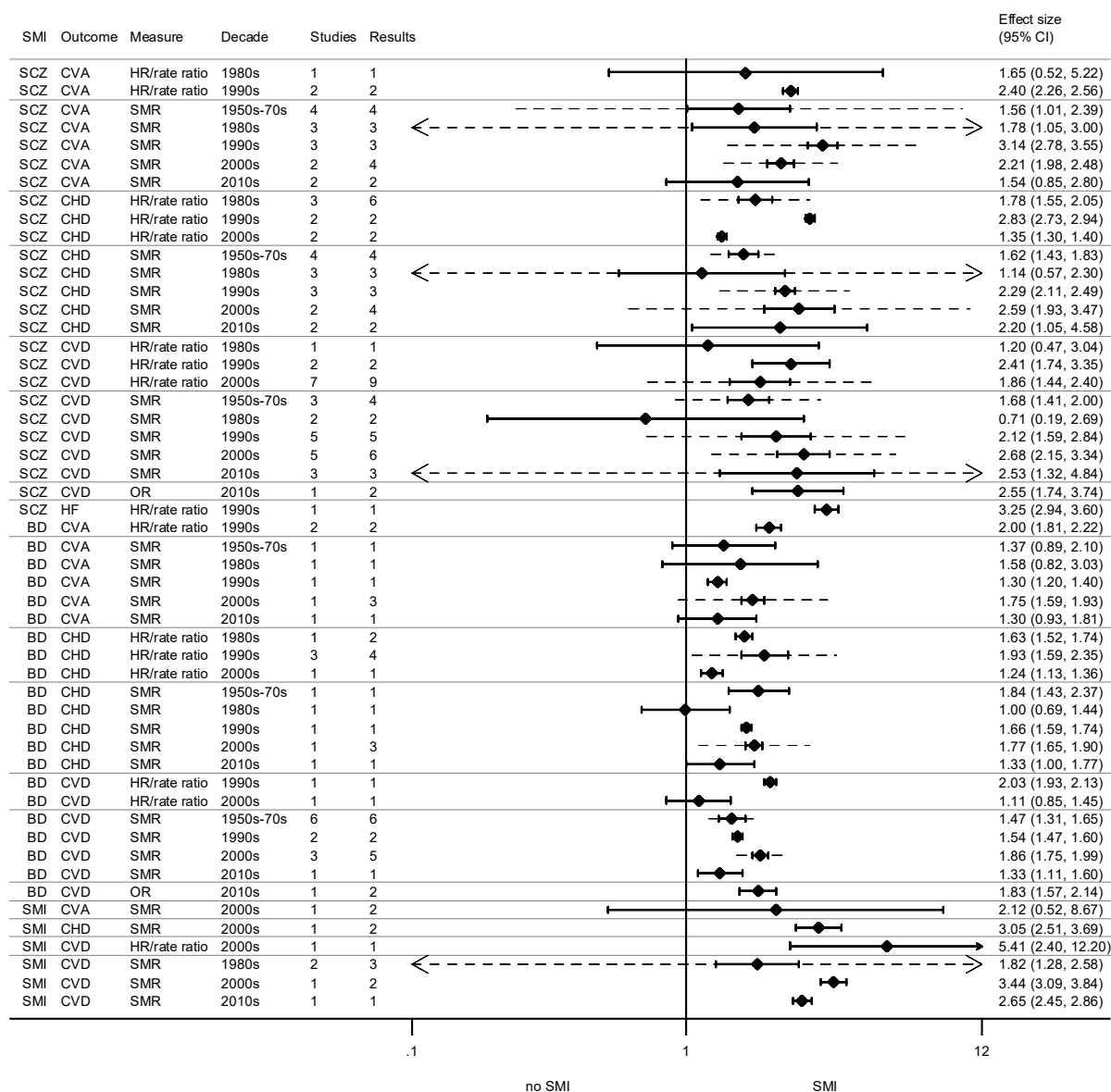


SCZ – schizophrenia, BD – bipolar disorder, CVA – cerebrovascular accident, CHD – coronary heart disease, CVD – all circulatory disease, SMR – standardised mortality ratio, HR – hazard ratio, RRatio – rate ratio. y-axes show estimate of effect size on log scale, shaded areas show 95% confidence intervals for risk estimates

**Figure 2.5: Trend in risk of CVD mortality for severe mental illness compared with controls, by median 5-year calendar period of outcome**

#### 2.3.4.1 Prediction intervals

A summary forest plot of meta-analysis results by SMI, outcome, and decade with the inclusion of prediction intervals is shown in Figure 2.6. Most prediction intervals were wide and included the null, indicating that any future study could potentially show a wide range of potential effects including decreased risk of CVD mortality for SMI compared with control participants. These results are tabulated in Appendix XII .



SCZ – schizophrenia, BD – bipolar disorder, SMI – mixed schizophrenia and bipolar disorder, CHD – coronary heart disease, CVA – cerebrovascular accident, CVD – all circulatory disease, HR – hazard ratio, OR – odds ratio, SMR – standardised mortality ratio. Pooled estimates with 95% confidence intervals (solid lines) and 95% prediction intervals if at least three results (dashed lines)

**Figure 2.6: Forest plot showing pooled estimates of cardiovascular mortality ratios by severe mental illness, outcome, and decade**



### **2.3.5 Subgroup analyses**

#### **2.3.5.1 Age group**

Estimated risks for younger age groups were larger than for older ages in the same study or in the equivalent SMI/outcome/effect type subgroup (Appendix XIII ).

#### **2.3.5.2 Sex**

Confidence intervals of pooled estimates for males and females overlapped for all combinations of SMI and CVD mortality (Appendix XIII ), except for schizophrenia ORs for CVD mortality and pooled HRs/rate ratios for heart failure mortality. Single studies contributed results to these two outcomes. There was a higher reported estimated risk for mortality from heart failure for males compared with females (males: rate ratio: 4.30, 95% CI:3.71-4.98; females: rate ratio: 2.66, 95% CI: 2.32-3.06). However, the OR for circulatory mortality was higher for females than males (males: OR 2.13, 95% CI:2.04-2.23; females: OR 3.15, 95% CI: 2.54-3.91).

#### **2.3.5.3 Location and setting**

Results of meta-regression showed no differences in CVD-related mortality for any region compared with the UK, except for studies reporting SMRs for the Far East, which had a smaller association between schizophrenia and CVD mortality: SMR: 0.32, 95% CI: 0.15-0.68,  $p=0.007$  (Table 2.6). However, there was still considerable residual heterogeneity between studies. The inclusion of region reduced  $I^2$  from 91.5% to 68.5%.

The association between SMI and CVD did not vary for different settings (inpatient, outpatient, and community).

#### **2.3.5.4 Other factors**

No further subgroup analyses by study quality, length of follow-up or confounding factors were completed owing to lack of applicable studies. Only three mortality studies were judged to be of low risk of bias and studies either lacked reported rates for confounding factors in the SMI and control populations or varied in the confounders included.

#### **2.3.6 Sensitivity analysis**

Eighteen mortality studies were excluded from the meta-analysis because overlapping periods of exposure with another included study may have meant that the same participants were double counted if the studies were included. Sensitivity analyses explored the effect of replacing included studies with excluded ones. This made little difference to the findings for CVD mortality, however some pooled estimated risks were increased (Appendix XIV , Appendix table XIV.1). Only one inclusion affected results, increasing the rate ratio of circulatory mortality for BD from HR/rate ratio: 1.52 (95% CI: 0.84-2.75) to 1.78 (95% CI: 1.28-2.47) when the included study (112) was replaced by an alternative that used the same exposed population. (53)

#### **2.3.7 Publication bias and small study effects**

Small study effects were assessed visually by funnel plots (Appendix XV ). Mortality results for SMRs, ORs, HRs and rate ratios were combined for visual assessment. There was some asymmetry in the funnel plots, particularly for CHD and CVD mortality in schizophrenia. Contour funnel plots for these two subgroups showed that some studies with non-significant results may be missing (white areas in the plots). Egger's test was performed for subgroups with more than 10 studies (Appendix XV , Appendix table XV.1). There was evidence of

significant biases for CHD mortality and CVD mortality in schizophrenia studies reporting SMRs. Applying random effects trim-and-fill procedures (108) added five unpublished studies reporting CHD mortality and two reporting all circulatory disease mortality for schizophrenia (Appendix XV , Appendix figure XV.7, Appendix figure XV.8). The resulting pooled random effects estimate changed from SMR=1.94 (95% CI: 1.58-2.37,  $p<0.001$ ) to SMR=1.61 (95% CI: 1.11-2.33,  $p=0.012$ ) for CHD and from SMR=1.96 (95% CI: 1.61-2.38,  $p<0.001$ ) to SMR=1.77 (95% CI: 1.27-2.47,  $p=0.001$ ) for all circulatory disease.

## 2.4 Discussion

This large-scale systematic review has been conducted in a methodologically robust manner and has yielded up-to-date comprehensive evidence on the effects of SMI on mortality from CVD. It has found that the CVD mortality rate for people with SMI is around twice that of the general population. People with schizophrenia are at greater risk than those with BD, however the disparity exists across all types of SMI and both cerebrovascular and cardiac mortality.

Some evidence was found of changes in the risk of CVD over time and results from some studies suggest that the gap between SMI and the general population appears to be widening. The size of the association between SMI and both CHD and all circulatory mortality increased until the 2000s, following this it appeared to decline. Estimated risks of the associations between schizophrenia and CVA mortality were also highest in the 1990s, whereas for BD they were highest for CVA mortality in the 2000s. The apparent increases in CVD risk for people with SMI relative to control participants that the review has found in recent decades are in marked contrast to the reducing rates of CVD experienced by the

general population. Since 1990 there has been a steady decline in the rates of CVD mortality and incidence in the populations of high-income countries. (66) Most European countries have also seen a halving in overall population CHD mortality since the 1980s. (113) Increasing trends in CVD mortality for people with SMI relative to control participants have been noted by other authors. (73-75, 87)

#### **2.4.1 Comparison with previous literature**

Two large systematic reviews and meta-analyses have been published since the current systematic review was conducted. (39, 40) However, these reviews revealed no new primary studies for inclusion in the current systematic review. These reviews are included in the discussions of other literature below.

##### **2.4.1.1 Schizophrenia**

###### **2.4.1.1.1 All circulatory disease**

The pooled results for circulatory mortality in schizophrenia, from 28 studies (HR/rate ratio: 1.91, 95% CI: 1.52-2.41, SMR: 1.96, 95% CI: 1.61-2.39), were slightly smaller than, but in broad agreement with, those of two recent reviews, based on nine and 28 studies, respectively. (40, 54) Sensitivity analysis found that relative risks were increased by the inclusion of one study that had high HRs (114) although this study was also included in the previous reviews. (40, 54) An older review, based on 11 studies reported a lower combined result (SMR=1.04, 95% CI: 1.00-1.08). (86)

#### 2.4.1.1.2 Coronary heart disease

The pooled result for the 14 studies reporting CHD SMRs for schizophrenia, SMR: 1.94 (95% CI: 1.58-2.37), was broadly similar to, but a little lower than the relative risk of 2.21, 95% CI: 1.82-2.67, found in a recent systematic review based on 19 studies. (40) Sensitivity analysis showed that substituting some of the excluded studies could increase the pooled SMR and HR/rate ratio. Small study effects could account for some of this discrepancy; an analysis that accounted for this reduced the effect size (SMR: 1.61, 95% CI: 1.11-2.33). Other, smaller reviews reported effect sizes that were smaller than the current study but in the same direction. (36, 85)

#### 2.4.1.1.3 Cerebrovascular accident

The high pooled CVA relative risk for schizophrenia, (SMR: 1.93, 95% CI: 1.63-2.28) was larger than the relative risk of 1.60, (95% CI: 1.25-2.04) reported by a recent large systematic review and meta-analysis based on 13 studies, (40) and a smaller systematic review based on three studies (relative risk: 1.65, 95% CI: 1.31-2.08). (82) In contrast, other authors reported relative risks in the opposite direction. (36, 85) It is unclear which studies were included in these reviews, but they were relatively small: one only included three studies (median SMR: 0.69, IQR: 0.61-1.30), (36) the other reported an SMR based on 490 deaths (SMR: 0.81, 95% CI: 0.73-0.87). (85)

The current review, however, included 14 studies in the pooled SMR, it was based on 2,800 deaths and all studies showed a higher risk of CVA mortality for people with schizophrenia compared to controls. Pooled HRs and rate ratios were also significantly elevated and were not reduced by the substitution of excluded studies in sensitivity analyses.

#### 2.4.1.2 Bipolar disorder

##### 2.4.1.2.1 All circulatory disease

The pooled SMR of 1.65, 95% CI: 1.53-1.77 for all circulatory mortality in BD, based on 12 studies, is similar to relative risks reported by other authors. (54) (47) However, the combined HR and rate ratio of 1.52, 95% CI: 0.84-2.75 shows a different picture. This result is based on two studies, one of which found no overall excess CVD mortality prior to 2010, although the risk for those with BD compared with the general population became elevated after this time. (72)

##### 2.4.1.2.2 Coronary heart disease

The pooled results for HRs/rate ratios and SMRs (SMR=1.67, 95% CI: 1.54-1.82), based on five studies were broadly similar to those reported by a recent large-scale systematic review and meta-analysis (relative risk: 1.76, 95% CI: 1.53-2.01, 27 studies). (39)

##### 2.4.1.2.3 Cerebrovascular accident

Pooled SMRs for CVA (SMR=1.55, 95% CI: 1.33-1.81) were also based on five studies and were very similar to the findings of a recent large systematic review (relative risk: 1.57, 95% CI: 1.34-1.84, 13 studies). (39)

#### 2.4.1.3 Change over time

There is some evidence that the gap in CVD mortality between people with SMI and the general population appears to be widening. This finding supports the observations in several included studies (72-75) that CVD mortality has increased in recent years for people with SMI relative to the general population. This is likely to be due to several factors. In

developed countries, smoking rates have fallen for the general population over recent decades; from average rates of 33.1% in 1980 to 23.5% in 2012. (115) In England, adult smoking prevalence rates fell from 27% in 1993 to 17% in 2018, (116) whereas people with long-term mental health problems and those on psychotropic medication have not seen a similar decline. (117, 118) Second generation antipsychotic (SGA) medication has been in use since the 1990s. (119, 120) However, their use can result in metabolic problems that increase the risk of CVD. Use of some SGAs, especially clozapine and olanzapine, are likely to result in weight gain, particularly with long-term use. (119) Certain SGAs (particularly clozapine, olanzapine, and quetiapine) are associated with a higher risk of diabetes mellitus than first generation antipsychotic medications (FGA). (121) There is also some evidence of elevated lipid levels with use of clozapine, olanzapine and risperidone compared with FGAs. (122) Differential access to physical health treatments for people with SMI is also an issue. In the UK the number of cardiac revascularisation procedures carried out has increased seven-fold since 1990 but people with schizophrenia who have acute coronary syndrome are much less likely than others to receive this type of treatment. (123)

## **2.4.2 Strengths and limitations**

### **2.4.2.1 Strengths**

The key strengths of this review are its size and scope. Both schizophrenia and BD and a range of cardiovascular outcomes were included. A wide search strategy was used, not limited by language or date of publication. Studies reporting different measures of relative risk were included and changes over time were investigated. Robust methodology including duplicate screening and data extraction was used. Possible sources of heterogeneity

between studies were investigated. Most studies had a follow-up duration of at least 5 years, some considerably longer, and long enough for CVD outcomes to occur. The adequacy of reporting follow-up was generally good. Many of the studies were carried out in Scandinavia which has near complete recording of population health records.

#### 2.4.2.2 Limitations

There are also several limitations to this review. There was significant heterogeneity between studies, which was only partly explained by world region and decade of results. It was difficult to prevent the inclusion of overlapping populations between studies. Although attempts were made to minimise this, it is possible that there may be some double counting of patient populations. This means that the confidence intervals may be slightly narrower than they would have been if all duplicated patients had been excluded. Many of the studies were at high risk of bias as they drew a comparison cohort from general population rates. Most studies did not adjust for cardiovascular risk factors. Furthermore, it was not possible to use reported results that were adjusted for important confounders as there was inconsistency in the confounders reported.

Despite including conference abstracts there was some evidence of publication bias amongst studies reporting CHD and circulatory mortality for schizophrenia. These were studies with a higher risk of bias that used general population mortality rates to report SMRs. However, even after adjustment for possible unpublished studies the risk of excess mortality remained elevated.

Although the literature searches found many papers measuring the association between SMI and the risk of cardiovascular mortality, searching one database for the additional search



term “cause of death” revealed a few additional studies. Thus, a small number of relevant studies may have been missed by failing to include this term in all database searches.

However, any effect on the results is likely to be small due to the large number of included studies.

SMRs were calculated from available information if not reported directly. If only whole numbers of expected deaths were available this may have led to rounding errors. This is unlikely to have had much effect on the results.

#### 2.4.2.2.1 Change over time

Temporal changes were assessed using decade of median year of follow-up. By comparing estimates from different studies from different time periods an ecological analysis is being performed. Studies could have had outcomes spanning multiple decades but would only have been counted against one. This methodology may have reduced the apparent difference in relative risk between decades highlighted in the review. More insight on temporal changes may be gained by considering large, long-term cohort studies, and the use of individual patient data.

#### 2.4.2.2.2 SMI definitions

There was some inconsistency in definitions of SMI diagnosis, which could have accounted for some of the heterogeneity between studies. Most studies used DSM or ICD coding to define SMI, but some defined SMI less robustly as confirmed by psychiatrist or otherwise recorded in notes. (75)

Around half the included studies reporting CVD outcomes for schizophrenia grouped schizoaffective disorder together with schizophrenia. Another study grouped schizoaffective

disorder with BD. (124) Schizophrenia causes more significant disability than BD (125);

schizoaffective disorder has symptoms of both conditions, (126) so its inclusion could have reduced the average severity of schizophrenia exposure or increased it for BD.

Some definitions of schizophrenia (127-134) included schizotypal disorder (a type of non-psychotic personality disorder below the clinical threshold for schizophrenia (135)). Others did not specify either the diagnostic system or the codes used, (101, 136-142) so severity was not able to be determined. The severity of schizophrenia cases could also have been reduced by the exclusion of schizophrenia with substance use disorder. (129)

Three studies were investigations of mortality when on lithium medication. (124, 143, 144)

In these studies, all subjects were treated with lithium, and they included those diagnosed with unipolar depression and other SMI diagnoses that didn't meet inclusion criteria, as well as BD and schizoaffective disorder. It was not possible to exclude the subjects that didn't meet the inclusion criteria so some misclassified patients were included, although numbers were small. Categorisation of SMI in other studies may also be subject to misclassification due to variation in psychiatric diagnostic labelling. (145)

#### 2.4.2.2.3 CVD ascertainment

Most studies did not demonstrate adequately that CVD was not present at the start of the study. Although mortality studies were selected such that SMI was diagnosed before cardiovascular death, presence of diagnosed or undiagnosed CVD prior to death was unknown for most studies.

#### 2.4.2.2.4 Age

Studies were included regardless of the participants' age at death, which was not known for most studies. However, larger associations between SMI and CVD were noted amongst studies that did report relative risks for younger age groups. This could be due to a healthy survivor effect: those with less severe mental illness are more likely to survive to older ages.

#### 2.4.2.2.5 Confounding factors

Not many mortality studies adjusted for confounding factors, other than age and sex, so exploration of the effects of important confounders, such as smoking, ethnicity, deprivation, and other cardiovascular risk factors was not possible. However, some studies noted that antipsychotic medications were associated with higher risks of cardiovascular mortality. (114, 146, 147) More research is needed to assess the effects of confounders on CVD mortality.

#### 2.4.2.2.6 Setting

Included studies were generally representative of persons with SMI. Those that included inpatients only were likely to have missed less severe cases, potentially over-estimating effect sizes, although no significant heterogeneity due to setting was detected.

#### 2.4.2.2.7 Reporting by sex

Results for all persons were included where possible, but for some studies, data were only available separately for males and females. In these cases, results from each sex were included separately in the meta-analyses. However, results for males and females within the

same study are not independent, so the random effects assumption of the meta-analysis could be violated. In practice this is unlikely to have much effect on the conclusions.

## 2.5 Conclusions

The review has found that people with SMI are at increased risk of mortality from CVD compared with the general population and the risk may be increasing over time. It was not possible to explore the effects of confounders such as smoking and obesity, so at least some of the excess risk may be attributable to these factors. There was considerable heterogeneity between studies, partly explained by decade of results, world region and age group. Prediction intervals included unity for some combinations of SMI and CVD mortality, thus a future study may not find an increased risk of CVD mortality for people with SMI. However, this review included results from 82 studies, only seven of which reported effect sizes smaller than one. Any future study is unlikely to materially change the review findings. Deaths from CVD make a large contribution to the inequalities in life expectancy experienced by those with SMI. (55) This highlights the need for targeted interventions to improve the CVD health of people with SMI. Understanding more about the reasons for the higher mortality rates could enable inequalities to be reduced. More research is needed to explore confounders such as smoking and obesity and to understand the role of antipsychotic medication and CVD treatments in excess cardiovascular mortality. More evidence of the association between SMI and CVD morbidity is also required. This will be considered in the next chapter.

## CHAPTER 3 SYSTEMATIC REVIEW OF THE RISK OF CARDIOVASCULAR MORTALITY AND MORBIDITY IN PEOPLE WITH SEVERE MENTAL ILLNESS COMPARED WITH THE GENERAL POPULATION: STUDIES REPORTING INCIDENCE OUTCOMES

### 3.1 Introduction

This chapter presents the second part of the review of risk of cardiovascular mortality and morbidity for people with SMI compared with controls, which is concerned with studies reporting CVD incidence. Recent review evidence for schizophrenia and BD was discussed in sections 2.1.1.1 and 2.1.1.2, respectively, and section 2.1.2 presented the rationale, aims and objectives for this part of the review.

### 3.2 Methods

The search strategy, screening, data extraction and risk of bias assessment for incidence studies were as described for mortality studies in Chapter 2. As for mortality studies, narrative synthesis was conducted for all included studies. Meta-analysis was performed using DerSimonian and Laird random-effects models due to the likelihood of significant heterogeneity between studies. Heterogeneity was measured using  $I^2$  and chi-squared statistics and 95% prediction intervals. (105) Associations from different SMIs, CVD outcomes and type of relative risk measurement were presented in separate subgroups in forest plots. Random-effects meta-analysis was conducted on subgroups that combined results for rate ratios and HRs because they have the same interpretation. ORs and RRs were not combined because even though they can be assumed equivalent where the outcome is rare (under 10%), (148) CVD incidence is likely to be greater than 10% for older age groups.

The decision rules devised for mortality studies (Appendix VI ) were also used for incidence studies to avoid double counting events in the case of overlapping periods of recruitment. Sensitivity analyses were conducted to test the effect of replacing included studies with excluded ones and to test the effect of including different reported results within a study. Case-control studies were combined with cohort studies as there was only one case-control study.

As for mortality, results for all persons were included in the meta-analysis where reported or calculable, otherwise separate results for males and females were used.

There were insufficient studies reporting incidence of CVD to enable exploration of subgroups by meta-regression.

Within each meta-analysis, the potential for the existence of publication bias or small study effects was assessed visually via funnel plots and where there were more than ten studies, formally tested for statistical significance by Egger's test. (106) A random-effects trim-and-fill procedure was applied to estimate the effect of potential unpublished studies if significant bias was identified. (107)

### 3.3 Results

#### 3.3.1 Characteristics of included incidence studies

Of the 108 articles included in the review, incidence was reported by 40: one case-control study and 39 cohort studies. Appendix VIII lists the included studies and Table 3.1 reports the study characteristics. Eleven studies with overlapping periods of recruitment and one with insufficient information were excluded from quantitative analysis, leaving 28 studies, involving  $\geq 401,909$  cases and 14,372,146 controls, that were included in meta-analyses.

Altogether, 29 articles included patients diagnosed with schizophrenia or related conditions while 21 included patients with BD. No studies reported results for mixed SMI. For cardiovascular outcomes, CHD was reported by 28 articles, CVA by 18, heart failure by five and incidence of total CVD events, defined mainly as combined heart disease and stroke, by nine. Rate ratios were reported by 13, HRs by 14, ORs by six, risk ratios were obtained from six studies and one reported standardised incidence ratios (SIRs). Results for both sexes combined were extracted from 33 articles, results for males and females separately from six and males only from one. No studies reported outcomes with a median decade of the 1970s or earlier; six reported results from the 1980s, 11 from the 1990s, 23 from the 2000s and one since 2010. Eighteen of the incidence studies were from Scandinavia; 10 from North America, seven were from the Far East. The others were from the UK, Australia, other Western Europe (excluding Scandinavia and UK) and Israel. Twelve studies were inpatients only, 19 were both inpatients and community and nine were set in the community only. One study (149) did not report confidence intervals or standard errors, so it was not possible to include those results in the meta-analysis.

Full forest plots of all studies reporting CVD incidence included in the study are in Appendix XVI .

### **3.3.2 Risk of bias of included studies**

There was high risk of bias amongst many of the included studies that reported CVD incidence (Appendix XVII ); ascertainment of CVD was good in only seven cohort studies; and there was a lack of clarity regarding presence of CVD at baseline for 32 studies. However, 26

incidence studies adjusted for at least one confounder and adequacy of reporting and duration of follow-up were rated as good for over half of the studies. Overall, twelve incidence studies (52, 53, 150-159) were assessed to have low risk of bias.



**Table 3.1: Characteristics of included incidence studies**

| Study, year        | SMI diagnosis | Country | Setting                 | Period of SMI exposure | Period of outcomes | Age at start of study (years) | Number of cases | Number of controls | Covariates adjusted for                                                              | Mean follow-up (years)                                         | Outcomes      | Sex     | Type of results |
|--------------------|---------------|---------|-------------------------|------------------------|--------------------|-------------------------------|-----------------|--------------------|--------------------------------------------------------------------------------------|----------------------------------------------------------------|---------------|---------|-----------------|
| Bent-Ennakhl, 2018 | SCZ, BD       | Sweden  | Community and inpatient | 1980-2012              | 1980-2012          | 18+, mean SCZ: 42.7, BD: 44   | 4823            | 200486             | Age, sex                                                                             | Up to 32, mean time to event: SCZ 8.95, BD 10.6, controls 5.95 | CVD           | P, M, F | RRatio          |
| Brink, 2018        | SCZ           | Denmark | Inpatient               | 1970-1979              | 1980-2012          | 18-40                         | 4544            | 22597              | Age, sex, year, Charlson score, education, marital status                            | Up to 41                                                       | CVD           | P       | RRatio          |
| Carney, 2006       | SCZ           | USA     | Community and inpatient | 1996-2001              | 1996-2001          | 18-64, mean 40.2              | 1074            | 726262             | Age, sex, urbanisation, healthcare utilisation                                       | (3.3 cases, 2.2 controls)                                      | CVA, CHD, HF  | P       | OR              |
| Chen, 2015         | SCZ           | Taiwan  | Community and inpatient | 2002-2008              | 2002-2011          | Mean 36.5                     | 63913           | 63913              | Age, sex, enrolment time                                                             | 3 to 10                                                        | CVA           | P       | RR              |
| Crump, 2013a       | SCZ           | Sweden  | Community and inpatient | 2001-2002              | 2003-2009          | 25+                           | 8277            | 6097834            | Age, sex, marital status, education, employment status, income                       | 7                                                              | CVA, CHD, CVD | M, F    | HR              |
| Crump, 2013b       | BD            | Sweden  | Community and inpatient | 2001-2002              | 2003-2009          | 20+                           | 6618            | 6587036            | Age, sex, marital status, education, employment status, income                       | 7                                                              | CVA, CHD, CVD | M, F    | HR              |
| Curkendall, 2004   | SCZ           | Canada  | Community               | 1994-1995              | 1996-March 1999    | 18+, mean 49.6                | 2405            | 9175               | Age, sex, >1 of: HT, hyperlipidaemia, DM, CVD, COPD                                  | NR                                                             | CVA, CHD, HF  | P       | RR              |
| Foroughi, 2018     | BD            | USA     | Community               | 1998-2000              | 1998-2018          | Mean 53.8                     | 378             | 23251              | Age, sex, CVD risk                                                                   | 16.1                                                           | CVD           | P       | HR              |
| Foroughi, 2021     | BD            | USA     | Community               | 1998-2003              | 1998- Feb 2016     | Mean 49.8                     | 288             | 35326              | Age, sex, smoking, DM, CKD, HT, alcohol, BMI, HDL, substance abuse, major depression | 16.5 (median), 14.6-17.5 IQR                                   | CVD           | P       | HR              |
| Gale, 2013         | SCZ, BD       | Sweden  | Inpatient               | 1969-1994              | 1969-2004          | Mean 18.3                     | 8527            | 1099304            | Age, sex, parental SES, BMI, DM, BP, intelligence                                    | NR                                                             | CHD           | M       | HR              |
| Goldstein, 2014    | BD            | USA     | Community               | 2001-2002              | 2004-2005          | 18+, mean 36.6                | 1439            | 26266              | Age, sex, race, smoking, HT, obesity, alcohol, drug use                              | 3.08                                                           | CVD           | P       | OR              |
| Gur, 2017          | SCZ           | Israel  | Community and inpatient | 2005-2013              | 2005-2013          | Mean 37.5                     | 1389            | 4095               | Age, sex, SES                                                                        | Up to 9                                                        | CHD, HF       | P       | OR              |

| Study, year       | SMI diagnosis | Country   | Setting                 | Period of SMI exposure | Period of outcomes | Age at start of study (years)               | Number of cases | Number of controls | Covariates adjusted for                                                                                   | Mean follow-up (years)        | Outcomes     | Sex     | Type of results |
|-------------------|---------------|-----------|-------------------------|------------------------|--------------------|---------------------------------------------|-----------------|--------------------|-----------------------------------------------------------------------------------------------------------|-------------------------------|--------------|---------|-----------------|
|                   |               |           |                         |                        |                    | 16+, median<br>SCZ:<br>42.5,<br>BD:<br>42.8 |                 |                    |                                                                                                           |                               |              |         |                 |
| Hayes, 2017       | SCZ, BD       | UK        | Community               | 2000-2014              | 2000-2014          |                                             | 39838           | 219387             | Age, sex, calendar period, deprivation, ethnicity, primary care contacts                                  | median: SCZ 2.47, BD 2.32     | CVD          | P       | HR              |
| Hsu, 2021         | BD            | Taiwan    | Community and inpatient | 2005                   | 2006-2010          | 18+                                         | 5544            | 764579             | Age, sex, income, region, urbanicity                                                                      | 4.3                           | CHD          | P, M, F | RRatio          |
| Jackson, 2020     | SCZ, BD       | UK        | Inpatient               | 1991-2015              | 1991-2015          | 40+                                         | NR              | NR                 | Age, sex                                                                                                  | Up to 25                      | CVA, CHD     | M, F    | RRatio          |
| Jakobsen, 2008    | SCZ           | Denmark   | Inpatient               | 1977-2000              | 1977-2001          | 15+                                         | 15710           | 69447              | Age, sex                                                                                                  | Up to 24                      | CHD          | P       | RRatio          |
| Kessing, 2021     | BD            | Denmark   | Community and inpatient | 1995-2017              | 1995-2017          | Median 44.8                                 | 18981           | 366420             | Age, sex, calendar year, employment                                                                       | Up to 22                      | CHD          | P       | HR              |
| Kugathasan, 2018  | SCZ           | Denmark   | Community and inpatient | 1980-2015              | 1980-2015          | 18+, mean 33.9                              | 36962           | 184810             | Age, sex                                                                                                  | Up to 36 years                | CHD          | P       | RR              |
| Lahti, 2012       | SCZ           | Finland   | Inpatient               | 1969-2004              | 1969-2004          | 25-70, median 35.3                          | 204             | 12735              | Birth year, sex, childhood SES                                                                            | Up to 35                      | CVA, CHD     | P, M, F | HR              |
| Laursen, 2010     | SCZ, BD       | Denmark   | Inpatient               | 1994-2006              | 1994-2006          | 15+                                         | NR              | NR                 | Age, sex                                                                                                  | Up to 13                      | CHD          | P, M, F | RRatio          |
| Laursen, 2011     | SCZ, BD       | Denmark   | Inpatient               | 1995-Jun 2007          | 1995-Jun 2007      | 15-52                                       | 22294           | 2428518            | Age, sex, year                                                                                            | Up to 12.5                    | CVA, CHD, HF | P       | RRatio          |
| Lawrence, 2003    | SCZ           | Australia | Community and inpatient | 1966-1998              | 1980-1998          | NR                                          | NR              | NR                 | Age, sex, year                                                                                            | Up to 18                      | CHD          | M, F    | RRatio          |
| Lin, 2010         | SCZ           | Taiwan    | Community and inpatient | 2000                   | 2000-2006          | 18+                                         | 7353            | 22059              | Age, sex, HT, DM, hyperlipidaemia, income, urbanisation, region                                           | 6                             | CHD          | P       | HR              |
| Manderbacka, 2012 | SCZ           | Finland   | Inpatient               | 1998-2009              | 1998-2009          | 40+                                         | 67659           | Gen pop            | Age, sex, year                                                                                            | Up to 12                      | CHD          | P       | RRatio          |
| McDermott, 2005   | SCZ, BD       | USA       | Community               | 1990-2003              | 1990-2003          | Mean SCZ: 45.6, BD: 43.8                    | 503             | 2083               | Age, sex, race, smoking, HT, obesity, depression, coronary artery disease/congestive HF/TIA, dementia, DM | SCZ 7.9, BD 7.5, controls 6.7 | CVA, CHD, HF | P       | RR              |

| Study, year          | SMI diagnosis | Country | Setting                 | Period of SMI exposure | Period of outcomes   | Age at start of study (years) | Number of cases | Number of controls | Covariates adjusted for                                                                                                                                                                                      | Mean follow-up (years)    | Outcomes          | Sex     | Type of results |
|----------------------|---------------|---------|-------------------------|------------------------|----------------------|-------------------------------|-----------------|--------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------|-------------------|---------|-----------------|
| Momen, 2020          | SCZ           | Denmark | Community and inpatient | 1969-2015              | 2000-2016            | Median 32.1                   | NR              | NR                 | Age, sex, calendar time, other mental disorder                                                                                                                                                               | 14.1                      | CVA, CHD          | P, M, F | HR              |
| Morden, 2012         | SCZ           | USA     | Community and inpatient | Oct 1999 to Sep 2007   | Oct 1999 to Sep 2007 | Mean 53.4                     | 65362           | 65362              | Age, sex, location                                                                                                                                                                                           | Up to 8                   | CHD, CVD          | P       | RRatio          |
| Munk-Jorgensen, 2000 | SCZ           | Denmark | Inpatient               | 1-Jan-78               | 1978-1993            | NR                            | 20495           | 204912             | Age, sex                                                                                                                                                                                                     | Up to 16                  | CVA, CHD          | P       | RRatio          |
| Prieto, 2016         | BD            | USA     | Community and inpatient | 1966-1996              | 1966-2013            | Median 37                     | 334             | 334                | Age, sex, alcohol, HT, DM, smoking                                                                                                                                                                           | 20 (cases), 15 (controls) | CVA, CHD, CVD     | P       | HR              |
| Ramsey, 2010         | BD            | USA     | Community               | 1981-1982              | 1993-1996            | Mean 43.1                     | 58              | 1339               | Age, sex, education, marital status, depression                                                                                                                                                              | 11.5                      | CHD               | P       | OR              |
| Sanchez, 2021        | SCZ           | Spain   | Community               | 2006-2007              | 2008-2011            | 18+, Mean 43.4                | 6472            | 94694              | Age, sex, primary care utilisation, alcohol, HT, DM, obesity, dyslipidaemia, smoking                                                                                                                         | Up to 5                   | CVD               | P       | HR              |
| Sundquist, 2006      | SCZ           | Sweden  | Inpatient               | 1987-2001              | 1987-2001            | 25-64                         | NR              | NR                 | Age, sex, SES, region, time period                                                                                                                                                                           | Up to 15                  | CHD               | M, F    | SIR             |
| Tsai, 2012           | SCZ           | Taiwan  | Community and inpatient | 1999-2003              | 2004-2008            | Mean 56.8                     | 80569           | 241707             | Age, sex, SES diabetes mellitus, hypertension, hyperlipidaemia                                                                                                                                               | Up to 5 years             | CVA               | P       | RR              |
| Vance, 2019          | SCZ, BD       | USA     | Community               | 2009                   | 2010-2014            | 45-80, Mean 61.6              | NR              | NR                 | Age, sex, smoking, race, BP, cholesterol, HDL, HT medication, DM                                                                                                                                             | Up to 5                   | CVD               | M, F    | OR              |
| Westman, 2013        | BD            | Sweden  | Inpatient               | 1987-2006              | 1987-2006            | All ages                      | 17101           | 10631208           | Age, sex, calendar year, year of follow-up                                                                                                                                                                   | Up to 20 years            | CVA, CHD, CVD     | P, M, F | RRatio          |
| Westman, 2017        | SCZ           | Sweden  | Inpatient               | 1987-2010              | 1987-2010            | 15+                           | 46911           | 10631817           | Age, sex, calendar period                                                                                                                                                                                    | Up to 24 years            | CVA, CHD, CVD, HF | P, M, F | RRatio          |
| Wium-Andersen, 2021  | BD            | Denmark | Community and inpatient | 1997-2014              | 1997-2018            | 18+, Median 43.8              | 13725           | 167562             | Age, sex, calendar time, marital status, education, statin, NSAID, acetylsalicylic acid, paracetamol, anticontraception pills, antidepressant medication, antipsychotic medication, lithium, benzodiazepines | 9.5 (range 0-21)          | CVA, CHD          | P       | HR              |

| Study, year         | SMI diagnosis | Country | Setting                 | Period of SMI exposure | Period of outcomes | Age at start of study (years) | Number of cases | Number of controls | Covariates adjusted for                                                                | Mean follow-up (years) | Outcomes | Sex     | Type of results |
|---------------------|---------------|---------|-------------------------|------------------------|--------------------|-------------------------------|-----------------|--------------------|----------------------------------------------------------------------------------------|------------------------|----------|---------|-----------------|
| Wu, 2013            | BD            | Taiwan  | Community and inpatient | 1999-2003              | 2004-2010          | Mean 43.2                     | 16821           | 67284              | Age, sex, DM, HT, hyperlipidaemia, SES, urbanisation, CHD                              | 7                      | CVA      | P       | RR              |
| Wu, 2015            | SCZ, BD       | Taiwan  | Community and inpatient | 1996-2007              | 1996-2007          | 18+                           | 70225           | 207592             | Age, sex, income, urbanisation                                                         | 11                     | CHD      | P, M, F | HR              |
| Yu-Chuan Chiu, 2015 | SCZ, BD       | Taiwan  | Community and inpatient | 1995-2011              | 1998-2011          | 18-45                         | 115             | 10200              | Age, sex, HT, dyslipidaemia, obesity, DM, renal, IHD, arrhythmia, urbanisation, income | Up to 14               | CVA      | P       | OR              |

SCZ – schizophrenia, BD – bipolar disorder, NR – not reported, est – estimated, gen pop – general population, DM – diabetes mellitus, HT – hypertension, COPD – chronic obstructive pulmonary disease, TIA – transient ischaemic attack, BMI – body mass index, SES – socioeconomic status, CVA – cerebrovascular accident, CHD – coronary heart disease, CVD – all circulatory disease, HF – heart failure, P – persons, M – males, F – females, HR – hazard ratio, RRatio – rate ratio, OR – odds ratio, RR – risk ratio, SIR – standardised incidence ratio, HDL – high density lipoprotein cholesterol

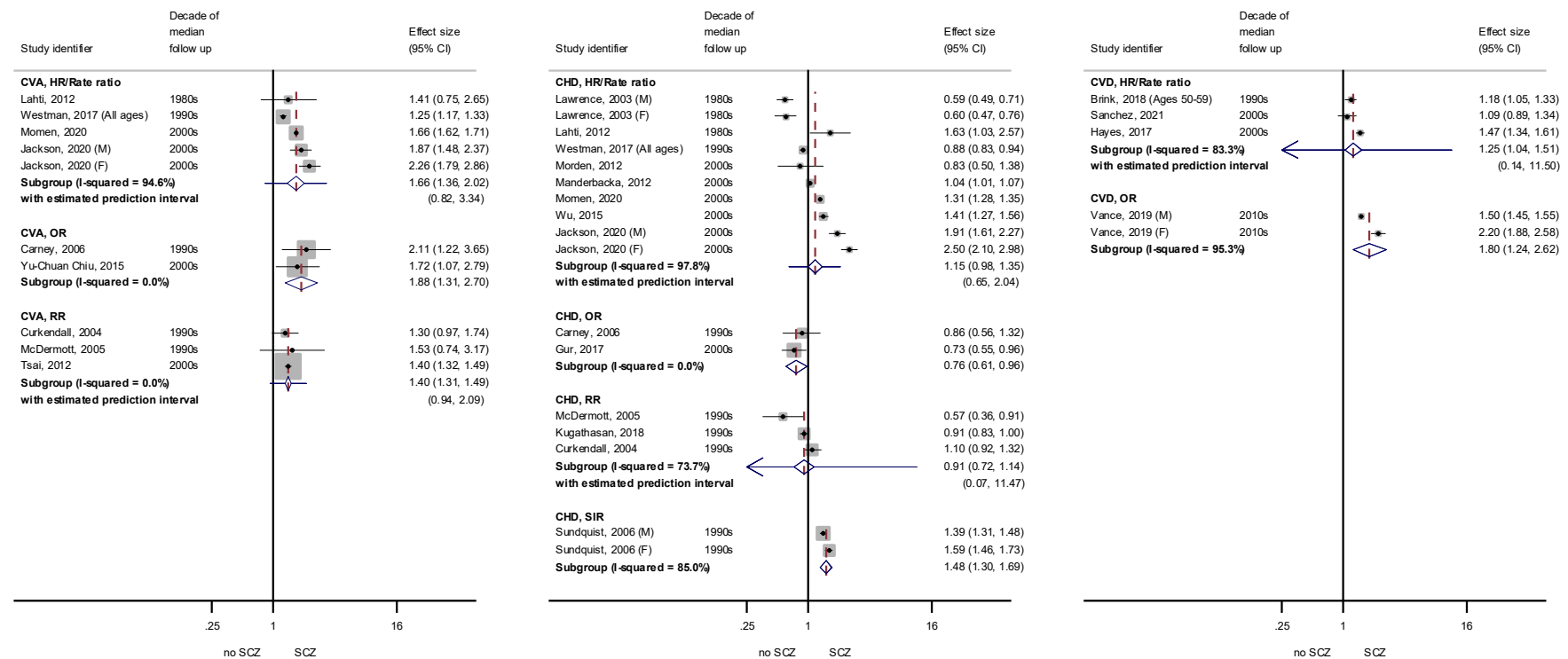
### 3.3.3 Meta-analysis

Results from 28 studies that contributed data on risk of cardiovascular incidence in people with SMI compared with control participants were used in meta-analysis. Some studies contributed more than one result. The number of included participants for studies that did report this information was 401,090 cases and 14,372,146 controls. Pooled results for schizophrenia and BD, for incidence of CVA, CHD, major CVD events and heart failure are shown in Table 3.2. As for mortality, most pooled results involving more than one study indicated an elevated risk of CVD incidence for participants with SMI compared with control participants, with the notable exception of CHD for people with schizophrenia. Pooled ORs indicated a reduced risk of CHD incidence (OR: 0.76, 95% CI: 0.61-0.96,  $p=0.077$ ), whilst RRs and pooled HRs/rate ratios included the null. Risks of CVA, total cardiovascular events and heart failure for both schizophrenia and BD and risk of CHD for BD were in a positive direction for all except two studies, which were not significantly different from unity. (160, 161) In subgroups containing more than one study, there was significant heterogeneity in most groups ( $p<0.1$ ) and  $I^2>50\%$ , except for ORs and RRs for CVA and ORs for CHD and HF in schizophrenia, CVA RRs and CVD HR/rate ratios in BD. Prediction intervals for all subgroups included unity. Forest plots showing meta-analyses for CVD incidence are shown in Figure 3.1 and Figure 3.2.

**Table 3.2: Pooled relative risks of cardiovascular incidence by severe mental illness and cardiovascular outcome**

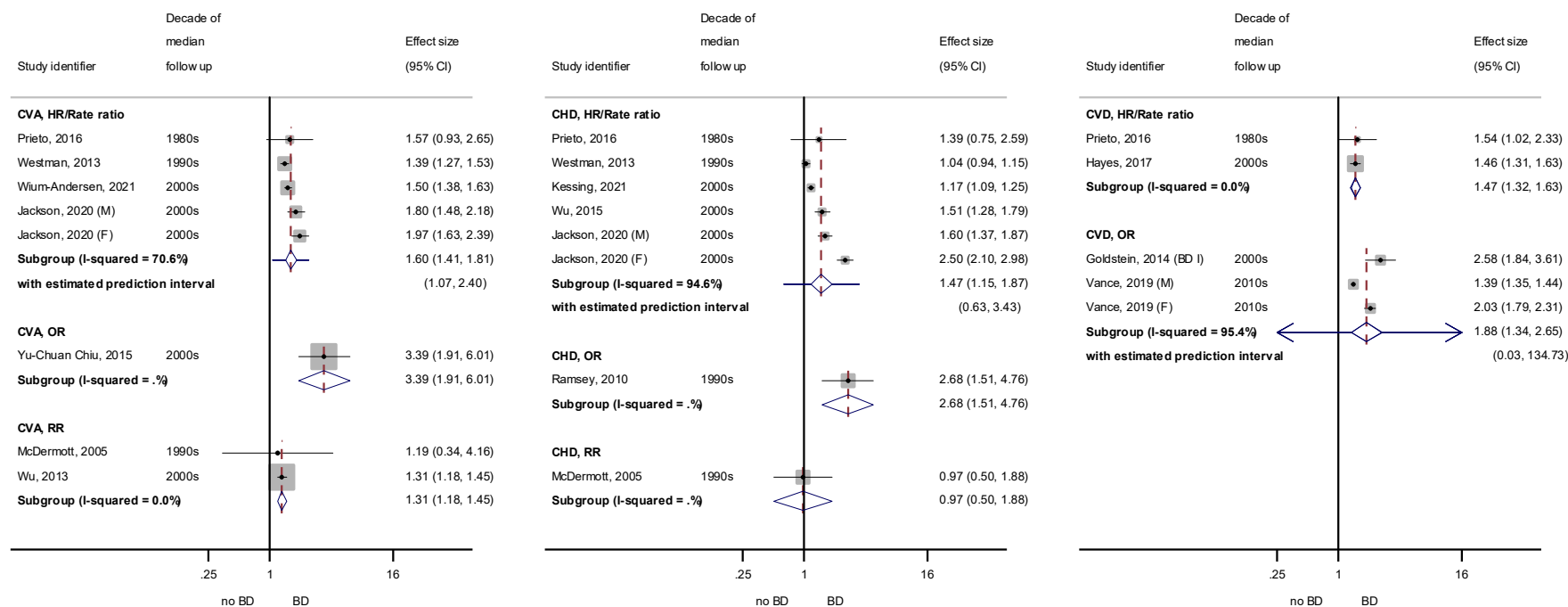
| SMI | Outcome | Measure       | Studies | / | Results | Pooled effect (95% CI)      | p-value | Prediction interval | I <sup>2</sup> | X <sup>2</sup> | df | p-value |
|-----|---------|---------------|---------|---|---------|-----------------------------|---------|---------------------|----------------|----------------|----|---------|
| SCZ | CVA     | HR/rate ratio | 4       | / | 5       | <b>1.66</b> ( 1.36 - 2.02 ) | <0.001  | 0.82 - 3.34         | 94.6           | 74.2           | 4  | <0.001  |
| SCZ | CVA     | OR            | 2       | / | 2       | <b>1.88</b> ( 1.31 - 2.70 ) | 0.001   | .                   | 0.0            | 0.3            | 1  | 0.586   |
| SCZ | CVA     | RR            | 3       | / | 3       | <b>1.40</b> ( 1.31 - 1.49 ) | <0.001  | 0.94 - 2.09         | 0.0            | 0.3            | 2  | 0.861   |
| SCZ | CHD     | HR/rate ratio | 8       | / | 10      | 1.15 ( 0.99 - 1.35 )        | 0.077   | 0.65 - 2.04         | 97.8           | 415.0          | 9  | <0.001  |
| SCZ | CHD     | OR            | 2       | / | 2       | <b>0.76</b> ( 0.61 - 0.96 ) | 0.022   | .                   | 0.0            | 0.4            | 1  | 0.515   |
| SCZ | CHD     | RR            | 3       | / | 3       | 0.91 ( 0.72 - 1.14 )        | 0.403   | 0.07 - 11.47        | 73.7           | 7.6            | 2  | 0.022   |
| SCZ | CHD     | SIR           | 1       | / | 2       | <b>1.48</b> ( 1.30 - 1.69 ) | <0.001  | .                   | 85.0           | 6.7            | 1  | 0.010   |
| SCZ | CVD     | HR/rate ratio | 3       | / | 3       | <b>1.25</b> ( 1.04 - 1.51 ) | 0.016   | 0.14 - 11.50        | 83.3           | 12.0           | 2  | 0.003   |
| SCZ | CVD     | OR            | 1       | / | 2       | <b>1.80</b> ( 1.24 - 2.62 ) | 0.002   | .                   | 95.3           | 21.4           | 1  | <0.001  |
| SCZ | HF      | HR/rate ratio | 1       | / | 1       | <b>3.82</b> ( 3.10 - 4.71 ) | <0.001  | .                   | .              | 0.0            | 0  | .       |
| SCZ | HF      | OR            | 2       | / | 2       | <b>1.79</b> ( 1.04 - 3.07 ) | 0.034   | .                   | 57.3           | 2.3            | 1  | 0.126   |
| SCZ | HF      | RR            | 2       | / | 2       | <b>1.72</b> ( 1.08 - 2.75 ) | 0.023   | .                   | 75.1           | 4.0            | 1  | 0.045   |
| BD  | CVA     | HR/rate ratio | 4       | / | 5       | <b>1.60</b> ( 1.41 - 1.81 ) | <0.001  | 1.07 - 2.40         | 70.6           | 13.6           | 4  | 0.009   |
| BD  | CVA     | OR            | 1       | / | 1       | <b>3.39</b> ( 1.91 - 6.01 ) | <0.001  | .                   | 0.0            | 0.0            | 0  | .       |
| BD  | CVA     | RR            | 2       | / | 2       | <b>1.31</b> ( 1.18 - 1.45 ) | <0.001  | .                   | 0.0            | 0.0            | 1  | 0.882   |
| BD  | CHD     | HR/rate ratio | 5       | / | 6       | <b>1.47</b> ( 1.16 - 1.87 ) | 0.002   | 0.63 - 3.43         | 94.6           | 92.2           | 5  | <0.001  |
| BD  | CHD     | OR            | 1       | / | 1       | <b>2.68</b> ( 1.51 - 4.76 ) | 0.001   | .                   | .              | 0.0            | 0  | .       |
| BD  | CHD     | RR            | 1       | / | 1       | 0.97 ( 0.50 - 1.88 )        | 0.928   | .                   | .              | 0.0            | 0  | .       |
| BD  | CVD     | HR/rate ratio | 2       | / | 2       | <b>1.47</b> ( 1.32 - 1.63 ) | <0.001  | .                   | 0.0            | 0.1            | 1  | 0.807   |
| BD  | CVD     | OR            | 2       | / | 3       | <b>1.88</b> ( 1.34 - 2.66 ) | <0.001  | 0.03 - 134.7        | 95.4           | 43.7           | 2  | <0.001  |
| BD  | HF      | HR/rate ratio | 1       | / | 1       | <b>3.30</b> ( 2.27 - 4.79 ) | <0.001  | .                   | .              | 0.0            | 0  | .       |
| BD  | HF      | RR            | 1       | / | 1       | 1.73 ( 0.88 - 3.40 )        | 0.111   | .                   | .              | 0.0            | 0  | .       |

SCZ – schizophrenia, BD – bipolar disorder, HF – heart failure, HR – hazard ratio, OR – odds ratio, RR – risk ratio, SIR – standardised incidence ratio, . - not calculable (insufficient observations). Results where 95% confidence intervals exclude the null highlighted in **bold**



Weights are from random effects mode. Dashed lines show pooled estimated risks within subgroups. Studies were allocated to decades according to the median year of follow-up. SCZ – schizophrenia, CVA – cerebrovascular accident, CHD – coronary heart disease, CVD – major cardiovascular events, HR – hazard ratio, OR – odds ratio, SIR – standardised incidence ratio, RR – risk ratio, M – males, F – females

**Figure 3.1: Forest plots showing relative risk of CVD incidence in those with vs without schizophrenia, studies included in meta-analysis**



Weights are from random effects mode. Dashed lines show pooled estimated risks within subgroups. Studies were allocated to decades according to the median year of follow-up. BD – bipolar disorder, CVA – cerebrovascular accident, CHD – coronary heart disease, CVD – major cardiovascular events, HR – hazard ratio, OR – odds ratio, RR – risk ratio, M – males, F – females

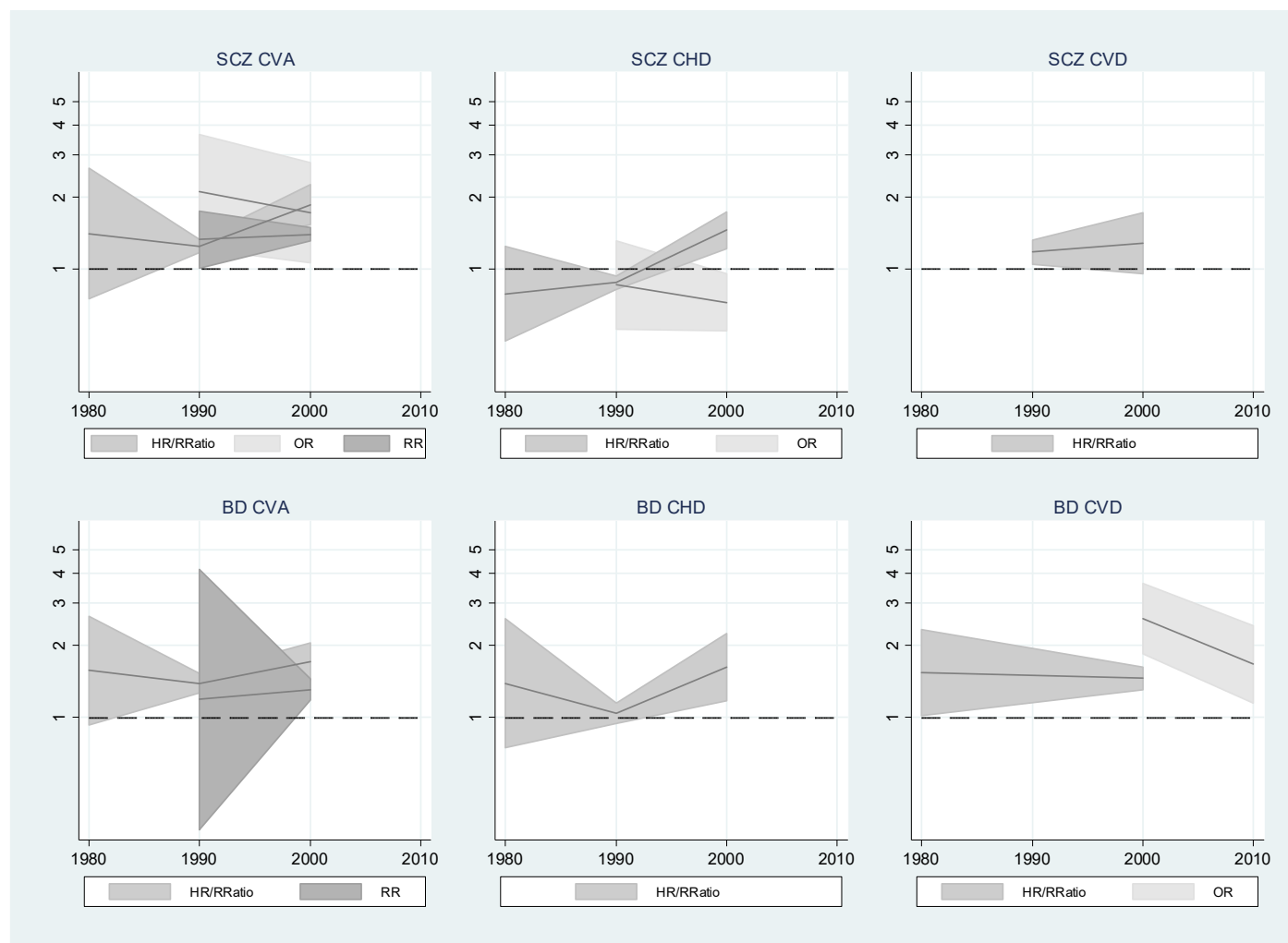
**Figure 3.2: Forest plots showing relative risk of CVD incidence in those with vs without bipolar disorder, studies included in meta-analysis**



### 3.3.4 Temporal trends

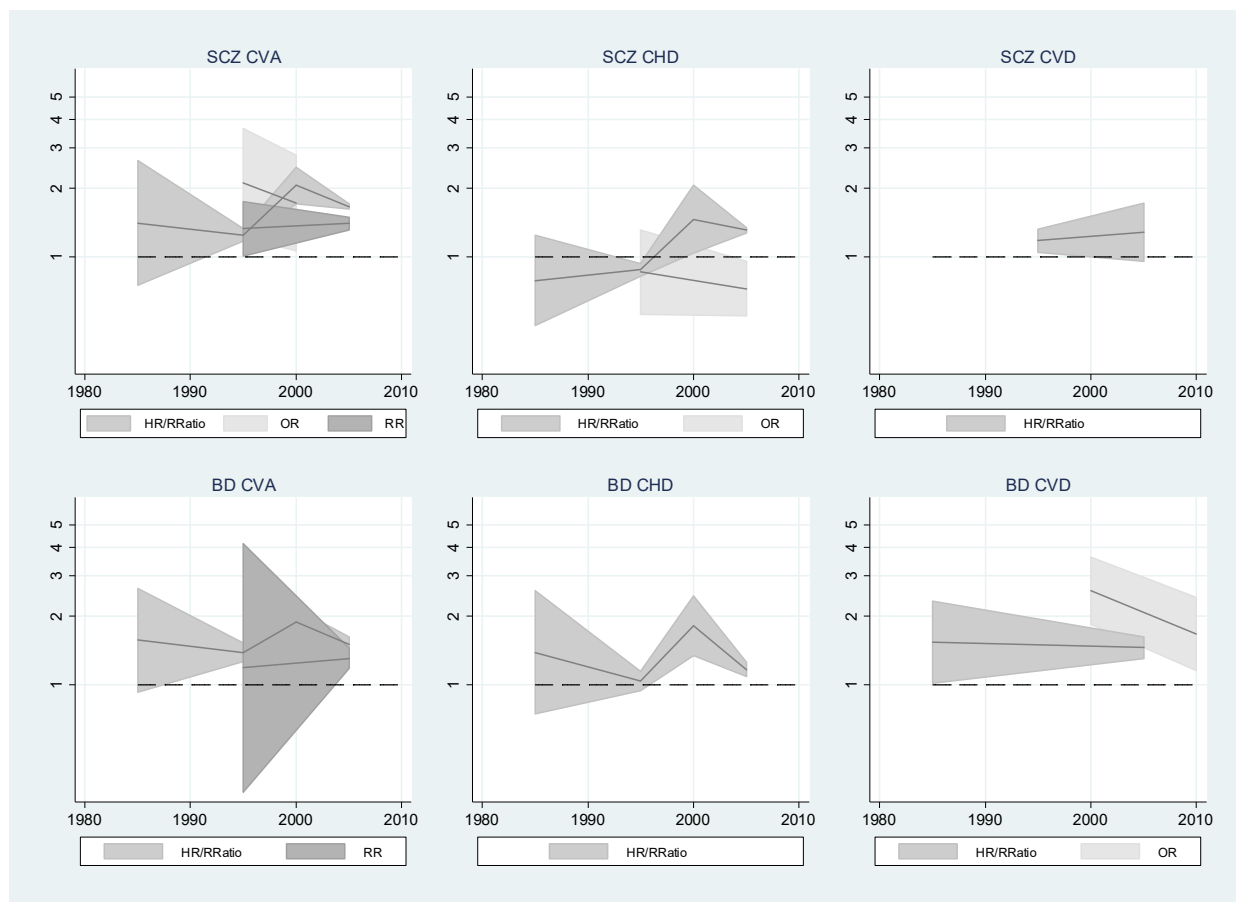
Meta-regression was not performed on cardiovascular incidence data as there were insufficient results in each subgroup. Figure 3.3 shows the trends in CVD incidence by SMI across decades. For schizophrenia and BD, ORs showed decreased effects between the 1990s and later years. However, RRs and pooled HRs and rate ratios increased during the 2000s. No studies reported results on these measures beyond this decade. These measures appear to show a widening gap between people with SMI and the general population. However, when examining the trends by five-year intervals (Figure 3.4), the gap for CHD and CVA appears narrowed during the second part of the decade (2005-09).

A table and summary forest plot of meta-analysis results by SMI, CVD incidence outcome and decade with prediction intervals is shown in Appendix XVIII (Appendix table XVIII.1 and Appendix figure XVIII.1). All prediction intervals that were able to be calculated included the null, indicating that any future study could potentially show a decreased risk of CVD incidence for SMI compared with the general population.



SCZ – schizophrenia, BD – bipolar disorder, CVA – cerebrovascular accident, CHD – coronary heart disease, CVD – major cardiovascular events, HR – hazard ratio, RRatio – rate ratio, OR – odds ratio, RR – risk ratio. y-axes show estimates of effect size on log scale, shaded areas show 95% confidence intervals for risk estimates

**Figure 3.3: Trend in risk of CVD incidence for severe mental illness compared with control participants, by median decade**



SCZ – schizophrenia, BD – bipolar disorder, CVA – cerebrovascular accident, CHD – coronary heart disease, CVD – major cardiovascular events, HR – hazard ratio, RRatio – rate ratio, OR – odds ratio, RR – risk ratio. y-axes show estimates of effect size on log scale, shaded areas show 95% confidence intervals for risk estimates

**Figure 3.4: Trend in risk of CVD incidence for severe mental illness compared with controls, by median 5-year calendar period of outcome**

### **3.3.5 Subgroup analyses**

#### **3.3.5.1 Risk of bias**

Meta-analysis was conducted for the studies assessed to be at low risk of bias (52, 53, 150-159) see section 3.3.2. Pooled relative risks for the low risk of bias studies were similar to results for all included studies (Appendix XIX ) for most SMI/CVD subgroups. One notable exception was incidence of CHD for schizophrenia. The pooled HR/rate ratio for the low risk of bias studies was raised (HR/rate ratio: 1.35, 95% CI: 1.03-1.79,  $p=0.032$ ), whereas the pooled result for all included schizophrenia studies did not exclude the null (HR/rate ratio: 1.15, 95% CI: 0.98-1.35,  $p=0.077$ ).

### **3.3.6 Sensitivity analysis**

Eleven studies were excluded from the meta-analysis because their period of selection for exposed populations overlapped with another included study, meaning the same participants could be double counted if they were included. Sensitivity analyses (Appendix XIV , Appendix table XIV.2: Sensitivity analyses showing effect of replacing included with excluded results, studies reporting incidence outcomes) found that results from these excluded studies presented a similar picture to the meta-analyses for included studies already presented. However, for schizophrenia there were inconsistent results when substituting some of the included studies, particularly for CHD. The pooled HR/rate ratio for CHD was borderline for the studies included in the meta-analysis (HR/rate ratio: 1.15, 95% CI: 0.99-1.35). Sensitivity analysis widened the confidence intervals around the null for some studies but increased the estimated risk away from the null for others.

There were two excluded studies of schizophrenia that it was not able to obtain full texts for, so the methodology could not be confirmed, but they showed similar results for incidence of CHD (162) and heart failure (163) to those presented in Table 3.2. Another study was excluded from the review, because developing countries were included as well as developed countries (164) but this reported similar results for incidence of stroke to those in Table 3.2.

### **3.3.7 Confounding factors**

Results adjusted for age and sex were extracted from incidence studies. Eight studies reported results adjusted by age and sex only. Twenty studies reported models adjusted for up to 18 additional factors, median five factors. Of these, five did not report results adjusted for age and sex alone. Meta-analysis using models adjusted for factors in addition to age and sex made little difference to the direction of results, although effect sizes were reduced for some subgroups (Appendix XIV , Appendix table XIV.3).

Seven incidence studies adjusted for smoking. Seven studies reported rates of antipsychotic use. Subgroup analysis by confounding factors was not possible, because there was too much variability in the confounders adjusted for.

### **3.3.8 Publication bias and small study effects**

Publication bias was assessed visually by funnel plots (Appendix XX ).

Results for HRs, rate ratios, ORs, RRs and SIRs were combined due to small numbers of studies in each group. Egger's test was performed for incidence of CVA and CHD in schizophrenia and all SMI combined, CVD events in all SMI combined, and all CVD outcomes combined for schizophrenia and BD, both separately and combined. Only these subgroups had more than ten studies (Appendix XX , Appendix table XX.1). Significant small study bias

was not found when different SMIs and different outcomes were considered separately, however when results from all BD studies were considered together, publication bias was indicated (Egger's test for bias: 1.94, 95% CI: 0.16 to 3.72,  $p=0.025$ ). However, applying trim and fill methodology did not add any additional unpublished studies, so the effect of publication bias is likely to be small.

### 3.4 Discussion

This review of the association between cardiovascular incidence and SMI found a consistent relationship between SMI and increased incidence of CVA, CVD events and heart failure. The relationship between SMI and CHD was less clear; a positive association only became apparent for high quality studies with low risk of bias.

There appear to have been changes over time. Studies reporting incidence of CVD since the 1990s reported larger associations between SMI and diagnosis of CVA and CHD compared with earlier studies. However, the large associations between those with SMI and the general population noted during the decade 2000-2009 appeared smaller during the second half of that decade compared with the first half. ORs appeared to show the reverse trend, however only five studies contributed results that could be used in this trend analysis.

Some evidence of publication bias was found, suggesting that the results might be biased by small low-quality studies, but only when all studies reporting both types of SMI exposure and all incidence of CVD outcomes were combined. This analysis of publication bias may be flawed as not all results are independent: there may be double counting of population at risk or of outcomes. It may thus violate the random effects assumption. However, the analysis is of value in demonstrating the likely scale of any potential publication bias. Small study bias is

unlikely to account for the increased relative risk of CVD diagnosis found in the review as analysis revealed no likely unpublished studies.

### **3.4.1 Comparison with previous literature**

#### **3.4.1.1 Schizophrenia**

##### **3.4.1.1.1 Total circulatory disease events**

The OR showing increased likelihood of total CVD events in those with schizophrenia (OR=1.80, 95% CI: 1.24-2.62, 1 study) was consistent with the findings of previous systematic reviews, whereas the HR (HR=1.25, 95% CI: 1.04-1.51, 3 studies) was somewhat smaller than other reviews: HR=1.95, 95% CI: 1.41-2.70, 14 studies and relative risk=1.53, 95% CI: 1.27-1.86, 4 studies, respectively. (54, 83) The inclusion criteria for these other reviews used wider definitions of CVD events than the current study.

##### **3.4.1.1.2 Coronary heart disease**

The meta-analysis in this review, which included 14 studies reporting an association between schizophrenia and CHD, found mixed results. There was evidence that people with schizophrenia are less likely than controls to be diagnosed with CHD based on ORs (OR=0.76, 95% CI: 0.61-0.96, 2 studies). RRs found no difference between schizophrenia and controls, whereas HRs/rate ratios found schizophrenia more likely to be associated with CHD diagnosis than controls, although this did not reach statistical significance. Results from other literature has also been mixed. A 2012 systematic review, based on nine studies found no evidence of elevated risk of CHD diagnosis compared with controls: relative risk: 1.20, 95% CI: 0.93-1.53. (83) However, another recent systematic review did find an increased relative risk (HR: 1.59, 95% CI: 1.08-2.35, 5 studies). (54)

Differences between the current study and other systematic reviews may be explained by the differences in included primary studies. One review did not report which studies were included in the meta-analysis of schizophrenia and CHD. (54) However, it reported a significant association only for HRs adjusted for possible confounders; while an unadjusted pooled relative risk based on eight studies was non-significant. Regarding the second review, (83) four of the included primary studies showed a significant association between schizophrenia and increased CHD diagnosis, however, three of these were not included in the current meta-analysis. Two did not meet inclusion criteria due to high prevalence of CVD at baseline (165) and inappropriate study design. (166) The third (153) overlapped with another included study from the same Taiwanese database, (167) so was excluded from the meta-analysis. HRs extracted for the current review from this study (167) and another included study (168) were slightly reduced compared with data selected by the comparator review (83) from two equivalent or similar studies, so partly accounted for the observed reduced pooled relative risk.

Heterogeneity in incidence of CHD could reflect differences in ascertainment. Five schizophrenia studies only included inpatient diagnosis of CHD, (44, 133, 155, 160, 168-170) which could have missed both milder cases treated in the community and deaths from undiagnosed CHD outside of hospital.

#### 3.4.1.1.3 Cerebrovascular accident

The findings of raised risks of the association between schizophrenia and CVA (HR/rate ratio=1.66, 95% CI: 1.36-2.02) correspond with the results of previous reviews: HR=1.57, 95%



CI: 1.09-2.25 (54); relative risk=1.50, 95% CI: 1.25-1.80 (82); relative risk: 1.71, 95% CI: 1.19-2.46. (83)

### 3.4.1.2 Bipolar disorder

#### 3.4.1.2.1 Total CVD disease events

The pooled result for total CVD events in BD (HR=1.47, 95% CI: 1.32-1.63) was similar to that reported by a recent systematic review based on ten studies (HR=1.57, 95% CI: 1.28-1.93). (54)

#### 3.4.1.2.2 Coronary heart disease

The non-significant positive association between CHD and BD shown by the RR was similar to those reported elsewhere: relative risk: 1.09, 95% CI: 0.96-1.24 (81); HR=1.16, 95% CI: 0.76-1.78. (54) In contrast, the positive association between CHD and BD from HRs and ORs was found to be significant in the current review. This may be explained by the inclusion of different primary studies from those included in previous reviews. The current review included one recent study, published after the previous reviews, that reported a strong association between CHD and BD. (171)

#### 3.4.1.2.3 Cerebrovascular accident

Increased risks of stroke as found in the current study (HR/rate ratio=1.60, 95% CI: 1.41-1.81) have also been reported by other reviews: relative risk: 1.74, 95% CI: 1.29-2.35 (81); HR=1.60, 95% CI: 0.99-2.57. (54)

### **3.4.2 Strengths and limitations**

The key strengths of this review of CVD incidence are generally the same as those reported for CVD mortality in section 2.4.2, namely the large size and scope and the robust methodology used. It was also subject to similar limitations:

- Using the median year of study follow-up to assess changes over time meant that the resulting risk estimates were the result of ecological analyses. Stronger evidence of the existence of temporal changes could be gained by long-term cohort studies using patient-level data.
- The potential for double counting study participants due to overlapping periods in different studies and the resulting potential for over precise risk estimates, although attempts were made to minimise this, and sensitivity analysis tested the effects of including different study results.
- The risk of selection or information bias affecting many of the included studies. The risk of CVA diagnosis and total CVD events found for all studies remained elevated amongst the low risk of bias studies. However, risk of CHD diagnosis was elevated only for the low risk of bias studies.
- The lack of adjustment for confounders. Although more incidence studies than mortality studies adjusted for confounders, most did not adjust for important confounders like smoking and comorbidities, and there was inconsistency in the confounders reported for different studies. Using results that were adjusted for confounders made little difference to the results, but it is likely that adjusting for factors such as deprivation, smoking, comorbidities, obesity, or antipsychotic medication use may explain the increased risks.

- The temporal order of SMI and CVD. In incidence studies, although it is likely that SMI diagnosis was made at a younger age than incidence of CVD, it was not possible to be confident that CVD did occur after the start of SMI diagnosis.
- There was evidence of small study bias when all studies were considered together, although trim-and-fill methodology did not reveal any potential unpublished incidence studies.

### 3.5 Conclusions

This review has found that the risk of diagnosis with stroke, heart failure and major cardiovascular events was elevated for people with SMI compared with control participants. However, the association between CHD diagnosis and SMI is unclear, even though the risk of CHD mortality for those with SMI is higher than the general population. A well-designed cohort study, accounting for possible bias in selection of cases and controls, taking more account of comparability through adjustment for potential confounders and minimising potential bias in assessment of outcome could make the picture clearer. Methods of minimising bias include selecting representative, appropriately defined patients with SMI, selecting controls from the same source population, adjusting for age, sex, sociodemographic and other confounders, accurately measuring CVD outcomes and using the same methods to measure for cases and controls and ensuring adequacy of follow-up for patients with and without SMI.

Community settings were under-represented in the review: many of the recruited exposed populations were inpatients. Consequently, the review overrepresents participants with more severe symptoms of exposure and outcome. A lack of patients with relatively mild

symptoms from primary care settings may explain some of the apparent under-diagnosis of CHD seen in the review.

More research is needed to understand the reasons for the higher risk of CVD incidence and to assess why it may have been worsening in recent decades. Such research should include the investigation of the relationship between SMI and cardiovascular risk factors, such as obesity, diabetes mellitus, blood pressure, smoking and antipsychotic medications, and the role of access and adherence to treatments for these risk factors. Cohort studies accounting for these, and other important confounders could help further investigate these factors.

The next chapter reports the results of two cohort studies, using a large primary care dataset which includes data on patients' cardiovascular risk factors as well as cardiovascular outcomes, that explore the effect of SMI on all-cause mortality and cardiovascular incidence and how these have changed over time.

## CHAPTER 4 COHORT STUDIES

### 4.1 Introduction

The systematic review reported in Chapters 2 and 3 confirmed the association between SMI and CVD mortality, and between SMI and incidence of stroke and major CVD events, although the association between SMI and CHD incidence was unclear. This chapter describes two retrospective cohort studies conducted to explore the association of SMI with mortality and CVD using a large primary care dataset. The cohort studies are firstly, a matched open cohort study comparing patients with a first diagnosis of SMI with a matched comparison group without SMI diagnosis, and secondly, an unmatched open cohort study comparing patients with a prevalent or incident recorded diagnosis of SMI, to a comparison group with no recorded diagnosis of SMI. The two types of study could potentially give different results. The unmatched study is larger as it includes all eligible patients with SMI, whereas in the matched study the SMI group is limited to those with a diagnosis date during the study period, thus the start date for follow-up is more reliable.

This chapter will introduce IQVIA Medical Research Data (IMRD), the database that was used for analysis, sets out the rationale for choosing it as a source of primary care data and describes the Read code system of coding used in primary care in the UK. The chapter goes on to discuss the cohort studies in detail and to compare the results with the findings from the two systematic reviews.

## 4.2 Methods

### 4.2.1 Research questions

1. Are people with SMI at increased mortality risk compared with the general population?
2. Are people with SMI at increased risk of cardiovascular disease incidence compared with the general population?
3. Are people with SMI at increased risk of case-fatality after diagnosis with cardiovascular disease compared with the general population?
4. Have the risks changed over time, and do they vary by type of SMI, country, deprivation quintile or cardiovascular risk factors?

### 4.2.2 Cohort study specification

#### 4.2.2.1 The Health Improvement Network (THIN) dataset

IQVIA Medical Research Data (IMRD) incorporates data from THIN, A Cegedim Database.

Reference made to THIN is intended to be descriptive of the data asset licensed by IQVIA.

This work used de-identified data provided by patients as a part of their routine primary care. THIN is an electronic health record primary care database which had, in January 2018, records from 17 million UK patients in 770 general practices that run the Vision software system, (172) and covering over 6% of the UK population. (173) THIN is broadly comparable to the UK population in terms of demography and disease prevalence, including mental health conditions. (174) The database goes back to 1994 (173) but longitudinal data for individual patients is available for many years prior to that. Information is available to researchers on patient demographics, diagnoses, prescriptions, additional health data such as smoking and body mass index (BMI), and socioeconomic status (SES). (172)

#### 4.2.2.2 Read codes

Read codes are a standard coded vocabulary of terms used by clinicians to record details of patient contact. (93, 175) Read version 2 is used in THIN up to and including version THIN1901 (January 2019).

#### 4.2.2.3 Drug codes

A lookup table supplied with THIN allows prescribing information entered by practices to be matched to British National Formulary (BNF) codes. (176) Generic and proprietary names of medications and preparations that are no longer prescribed can be found by reference to annual Prescription Cost Analysis data for England which details all items prescribed in the community in each given year. (177)

#### 4.2.2.4 Additional Health Data (AHD) codes

Information on lifestyle behaviours *e.g.* smoking status, and test results *e.g.* blood pressure, is contained in the AHD part of THIN. A different coding system is used for this dataset.

#### 4.2.2.5 Rationale for choice of THIN

THIN has several advantages (178) which make it suitable for use in the described studies:

- a) Its large size, quality, and comprehensiveness. Even though SMI is a relatively rare condition, affecting only around 1% of the population, in the order of 100,000 patients with SMI would be expected to be recorded in the database
- b) SMI conditions may be managed in primary care after discharge from secondary care mental health services, if symptoms have responded to treatment and remain stable. If not able to be transferred to primary care, then responsibility for physical health

monitoring is shared between secondary and primary care services. (19, 20) Thus, primary care records of patients with SMI should contain relevant clinical and outcomes data

- c) THIN's generalisability to the UK population, meaning that any findings should be representative of the UK
- d) For cohort studies, patients with the exposure of interest can be selected from the same population as the comparator group
- e) It is routinely collected, regularly updated, and reflects "real-life" primary care interactions with patients

However, there are some important limitations that affect not only THIN, but other routinely collected primary care health records, such as Clinical Practice Research Datalink (CPRD).

(179) Primarily, the data were collected for patient management, not research purposes and thus will only contain information related to patient care. (178) This means that not all of the desired information may be available, for example, over-the-counter medication or data not directly relevant to the current consultation, *e.g.* weight, may not be recorded. (178) Routine data collection is also not subject to the same stringent requirements as data collected for research purposes. Therefore, some data will be missing or incorrectly recorded. Patient health records are created when a patient registers with a practice. If the patient then moves to another practice and re-registers a new record is created. There is no way of linking the two records as the information is de-identified. Follow-up is thus limited to the time a patient is registered with a single practice.

Other UK primary care databases are available for research, for example the CPRD and QResearch, (179, 180) however for the current cohort studies THIN had the additional



advantage of its availability to the University of Birmingham research group at the time of data extraction.

Two other potential sources of data containing patient level data were considered but excluded:

- Hospital Episode Statistics (HES): pseudonymised records of hospital admissions, outpatient appointments and accident and emergency (A&E) attendances in England, available from NHS Digital. (181) It may be possible to identify patients with SMI from these data, and to link with health outcomes involving secondary care, but no information is available on covariates of interest, such as medication, lifestyle behaviours or clinical measurements such as BMI or blood pressure.
- Mental Health and Learning Disabilities Dataset: records of patients in contact with secondary care mental health services in England. (182) Patients with SMI are included, however records relating to their care in general practice are absent.

#### 4.2.2.6 Description of the incident and prevalent cohort studies

Approval was gained from the Scientific Review Committee of IQVIA (reference 20SRC020, dated 23/04/2020) for two cohort studies to be conducted:

- a) an open matched cohort study comparing incident patients (first-ever recorded diagnosis) of SMI to a matched comparison group without a recorded diagnosis of SMI. Matching was by sex and age (year of birth within 1 year if a match was available, otherwise within 2 years, and so on up to within 3 years). Up to 3 non-SMI comparators were selected for each patient with SMI. This study was called the “incident cohort” study.

- b) an open unmatched cohort study comparing patients with a prevalent recorded diagnosis of SMI, to a comparison group with no recorded diagnosis of SMI, hereafter called the “prevalent cohort” study. This study included new patients with SMI, diagnosed during the study period as well as historical patients, with a diagnosis date before the start of the study.

#### 4.2.2.7 Study dates and populations

The study period was January 2000 to January 2019, which was the period for which THIN data were available. Patients aged 16-74 years were eligible for inclusion. This was an older age range than that included in the systematic reviews to accommodate outcomes up to age 75 years. Mortality prior to age 75 years is defined as premature by the Office for Health Improvement and Disparities in the UK. (183) Practices were eligible for inclusion in the study from the latest of date of starting to use the Vision software system for data collection + one year, date of acceptable mortality reporting (AMR), and study start date until the earliest of: the study end date and the last collection date for the practice. One year after the Vision date allows enough time for all patients to be captured and baseline comorbidities to be recorded and AMR indicates the date from which a practice’s data is deemed of an acceptable standard. (184)

The start date for each patient was the latest of: practice start date, age 16 years, patient registration date plus 60 days. A period of 60 days after registration was chosen as preliminary analysis suggested this was the best balance between including as many patients as possible (there is a high turnover of SMI patients between practices) and excluding events which might be related to the new registration. The end date for each patient was the

earliest of date of death, date of patient reaching age 75 years, date of patient leaving the practice and the practice last collection date.

For the extraction of the incident cohort, patients in the SMI group were defined by having a Read code indicating a diagnosis of SMI. The date of first recording of a Read code indicating incidence of SMI was the index date for the SMI group. If a first record of SMI was a Read code indicating previous SMI, the patient was assumed to have prevalent SMI and was excluded from the study. People with a Read code indicating a diagnosis of dementia before or within a year of the index date were not eligible to be in the SMI group but were eligible for the non-SMI comparison group. Up to three comparators for each patient with SMI were selected from the pool of patients without SMI at the same general practice who were registered patients at the time of the case index date, matched on sex and year of birth. Patients with SMI defined solely by having a prescription for medications specific to schizophrenia or BD were not eligible to be included in the SMI group, nor were those with a diagnosis of dementia prior to, or within a year of, SMI diagnosis. Patients were followed up until the earliest of death, reaching age 75 years, transferring out of the practice or, for the non-SMI comparison group, a first diagnosis of SMI.

#### 4.2.2.8 Identification of Read code, drug codes and AHD codes required

To specify the extract of THIN data, lists of codes were developed to specify the exposure, outcome, and covariates of interest. The methodologies used to specify Read and drug codes for inclusion is described briefly below. More detail is given on the work carried out to identify SMI, which was the exposure of interest, so was important to specify correctly. Lists

of the Read, drug and AHD codes that were developed are given in Table 4.1. Lists of the final Read codes used are in Appendix XXI to Appendix XXIII .

**Table 4.1: Code lists developed to specify variables required in THIN data extract**

|                   | Read codes                                                                                                                                                                                                                         | Drug codes                                       | AHD codes                                           |
|-------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------|-----------------------------------------------------|
| <b>Exposure</b>   | Schizophrenia<br>Bipolar disorder<br>Other SMI                                                                                                                                                                                     | SMI-specific antipsychotic medication<br>Lithium |                                                     |
| <b>Outcome</b>    | Myocardial infarction<br>Coronary revascularisation<br>Other coronary heart disease<br>Haemorrhagic stroke<br>Non-haemorrhagic stroke<br>Transient ischaemic attack<br>Peripheral arterial disease<br>Other cardiovascular disease |                                                  |                                                     |
| <b>Covariates</b> | Smoking status<br>Obesity<br>Type 1 diabetes mellitus<br>Non-type 1 diabetes mellitus<br>Ethnicity<br>*Charlson index                                                                                                              | *Diabetes mellitus medications<br>*Metformin     | *Smoking<br>*BMI<br>*Blood pressure<br>*Cholesterol |
| <b>Other</b>      | Dementia<br>*PCOS                                                                                                                                                                                                                  |                                                  |                                                     |

AHD – additional health data, SMI – severe mental illness, IHD – ischaemic heart disease, CVD – cardiovascular disease, BMI – body mass index, PCOS – polycystic ovary syndrome. \*All lists developed by AML with input from TM and HMP except for those identified with an asterisk, which were previously created by other members of the research team

#### 4.2.2.8.1 Read codes

The steps used to create lists of appropriate Read codes to specify the data extract used in the cohort studies are outlined here. The Read code dictionary supplied with THIN was used to create a long list of potentially suitable codes for review from chapters and sections identified in the NHS Clinical Terminology browser (185) using version 2 Read codes. The list was extended by adding code lists already developed for the exposures, outcomes and covariates of interest from four sources: codes relating to primary care disease registers from Quality Outcomes Framework (QOF) Business rules, (186) a repository of code lists created by University of Birmingham colleagues involved in developing the Data Extraction

for Epidemiological Research (DExtER) tool, (187) and lists of codes published on two clinical code repository websites: the University of Cambridge Primary Care Unit (188) and the University of Manchester Institute of Population Health repository ClinicalCodes.org. (189) Any missing parent or sibling codes of included codes were also appended. After removal of duplicates and codes that were not version 2 Read codes, the list was reviewed and categorised for inclusion or exclusion by supervisors and others with relevant expertise.

#### 4.2.2.8.2 Drug codes

Medications in THIN data are listed in a drugs dictionary using an encrypted identifier relating to drug product and formulation (drug code), up to three BNF codes (bnfcode1-3) and the drug generic name. (172, 176) The frequency with which each drug code has ever been dispensed is also available. Medications specifying exposures of interest were identified by searching relevant BNF chapters and sections and using Prescription Cost Analysis (PCA) data for England, 2000-2019 (176, 177) to compile lists of drug key words. These sources were referenced against the THIN1901 drugs dictionary to obtain a list of potential medications for review.

#### 4.2.2.9 Description of process used to specify SMI

##### 4.2.2.9.1 Read codes used to define severe mental illness

###### 4.2.2.9.1.1 Methods used for initial identification of Read codes

Preliminary work was carried out in April 2017 to identify Read codes for the exposure of interest: SMI. SMI was defined as a diagnosis of schizophrenia, bipolar affective disorder, and other psychoses. Potential chapters and parts of chapters of the NHS Clinical

Terminology Browser (version 2 Read codes, dated 2016-04-01) (185) containing Read codes relating to mental health diagnoses, symptoms, and processes of care for these conditions were identified (Appendix XXIV ). QOF Business Rules v38.0 (186) were additionally used to ensure inclusion of Read codes identifying patients on mental health registers for payment under the QOF. (190) A full list of Read codes was then created using the Read code dictionary provided with THIN (version THIN1605, May 2016). This long list of codes was reviewed and categorised for inclusion or exclusion. Advice was sought from primary care and psychiatry clinicians and others with expertise in creating case definitions for use in primary care database studies (TM, RR, HP, RJ). The relative number of patients with each of the Read codes identified was quantified using a random 5% sample of patients from each practice contributing to THIN1605. This helped in cases where the decision to include a code was not clear cut. If the code was used only infrequently, then it would make little difference to the analysis if it was included or not.

Several types of SMI were excluded or categorised separately. Organic conditions involving psychosis, for example psychosis in epilepsy, can follow a similar clinical pathway to functional psychoses, however these were excluded as the mental illness was of primary interest. Similarly, Read codes indicating dementia or similar mental health conditions related to older age were excluded. Psychoses with origin in childhood were also excluded. Schizophrenia and BD are typically diagnosed at a young age (teens or twenties), whereas CVD (CHD, stroke, and heart failure) are conditions affecting an older age group. The outcomes of interest are thus likely to only manifest some years after diagnosis. Read codes indicating psychosis and bipolar conditions of a transient or short-term nature were identified separately as it was thought that the presence of these codes in the absence of

any longer-term diagnosis would have only a minimal effect on the outcomes of interest.

These included any of the terms “brief”, “acute”, “transient”, “reactive” or “episode”. Also included in the “transient” category were Read codes indicating psychosis related to pregnancy or the puerperium, or alcohol or drug induced psychoses.

#### 4.2.2.9.1.2 Methods used for updating Read code list

In July 2020, the list of Read codes previously identified in the included and transient categories were checked for accuracy and updates. Firstly, to identify any codes that had previously been missed, by comparing with lists of codes previously developed for SMI from other code list repositories. Secondly, by manually checking the list for inconsistencies and any missed parent or sibling codes. Thirdly, by searching for any new codes by merging with the latest Read code dictionary (THIN1901).

#### 4.2.2.9.1.3 Results of initial Read code identification

The numbers of codes identified by these methods were as follows. Preliminary work on THIN1605 identified 268 Read codes for inclusion and a further 86 were labelled as transient. A total of 1,533 codes were excluded. Of the patients in the THIN 5% sample, a total of 247,493 had any of the Read codes in the initial list of mental health codes potentially defining SMI. Of these, 6,838 had at least one of the included SMI Read codes. 1016 (14.9%) of these also had at least one of the ‘transient’ Read codes. A further 858 patients had at least one transient code, but none of the other Read codes for SMI. 5,595 (81.8%) of patients with a Read code defined as SMI also had at least one of the mental health codes excluded from the SMI group.

Several inferences can be made from analysis of the 5% sample of patients.

- 6,838 had at least one of the Read codes in the included list. Scaling this number up to the full THIN database, the number of patients with exposure to SMI is likely to be in the order of 127,000: a sufficiently large sample size to provide adequate power for data analysis.
- More than half of patients (55%) who had one of the “transient” Read codes, also had one of the codes included as SMI. Only 835 (11%) out of the total number of patients with any of the included or transient Read codes (7,673) had a transient code in the absence of one of the included codes. Thus, the included Read code list is of utility in defining the great majority of patients with the SMI conditions of interest.
- Over 80% of patients with one of the included SMI Read codes also had one of the mental health Read codes that were excluded for the purposes of the proposed cohort studies. This suggests that patients with SMI typically present with other comorbid mental health conditions. The most frequently occurring excluded Read codes were for common mental disorders such as depression and anxiety and it is likely that these conditions will also be prevalent amongst SMI patients.

#### 4.2.2.9.1.4 Results after updating Read code list

After examining THIN1901, code lists from other sources, inconsistencies and further discussion, more Read codes relevant to SMI were added to the list of those already identified. It was decided to exclude the codes classified as transient. These codes were indicative of brief psychosis, which may resolve. If the psychosis turned into a longer-term condition, then it would be captured later in the patient’s record. The codes were reviewed, and the final list comprised 296 codes for definite inclusion and 1,674 codes excluded. The



list of included codes can be found in Appendix XXI . The lists are specific to these studies and exclude mental health and other conditions not of primary interest to the main study questions: to determine the relative risk of mortality and CVD.

#### 4.2.2.9.1.5 Further refinements to Read code list

To enable different SMI diagnoses to be analysed separately, included Read codes were split into three categories: schizophrenia and related conditions (includes schizophrenia, schizoaffective disorder, and other psychoses), BD (includes BD, conditions with mania and depression with psychosis) and other SMI (Read code relating to schizophrenia or BD but not enough information to categorise as individual diagnosis).

The Read code lists were refined further by splitting into codes that could define a new case of SMI, labelled “incident codes” and those that indicated a patient had SMI previously: “prevalent codes”. The reason for this was that the start time for follow-up would be the date of first diagnosis of SMI. If the earliest occurrence of SMI diagnosis was a prevalent code, it was not possible to be certain of the actual date of diagnosis.

#### 4.2.2.9.2 Drug codes used to define severe mental illness

SMI could also be identified in THIN by the presence of a prescription for medication used to treat the condition *e.g.* antipsychotic medication. To obtain a list of medications used to treat SMI, the BNF chapter and section containing medications used in psychoses and related disorders was used (chapter 4, section 2). (176) Next, a list of key words used in the generic and proprietary names of medications in BNF4.2 was compiled. This was done to ensure that any relevant medications in chapters additional to BNF4.2 were captured. PCA data for England, 2000-2019 (177) was used to compile the list of key words of medications

in BNF4.2. PCA data provides annual information on all prescriptions dispensed in the community. Finally, the THIN1901 drugs dictionary was searched, firstly for medications in BNF4.2 in fields bnfcode1-3 and secondly, for medications with any of the keywords from the PCA list. The list of medications was then reviewed to obtain a list of medications used exclusively for treatment of SMI that could be used to identify SMI conditions. These included first and second-generation antipsychotic medications. Lithium was initially included as it is used to treat BD. However, it is also used for treatment resistant depression. In THIN1901 there were a total of 803 medications and 19,404,210 prescriptions ever dispensed that had BNF code or key words relating to medications used to treat SMI. Of these, provisional analysis indicated that 212 drug codes (26.4%) were for the exclusive treatment of SMI, 365 (45.5%) could be used to treat other conditions in addition to SMI, 45 (5.6%) were not for the treatment of SMI and the remaining 181 were unclear. After review, 466 drug codes were defined as specific to the treatment of SMI thus could be used to define SMI, 34 for the treatment of BD only and 432 for the treatment of schizophrenia and other psychoses. Appendix XXV contains lists of the drug codes identified as specific to schizophrenia and BD.

Analysis of a 1% sample of THIN data was performed to check the specificity of using antipsychotic medication codes to identify patients with SMI. 2,180 patients had a prescription for one of the antipsychotic medications identified as specific to SMI. Of these, 1,558 (71%) had no Read code indicating a diagnosis of SMI in their record. Further analysis of the age distribution of patients with SMI defined only by the presence of an SMI-specific drug code revealed that these patients had an older age distribution than would be expected. See Appendix XXVII for more details. Schizophrenia is typically diagnosed in young

adulthood (see Chapter 1 section 1.3). It was hypothesised that the patients who had a prescription for SMI-specific antipsychotic medication, but no SMI Read code could be patients with dementia.

Consideration was given to whether a prescription for lithium could indicate a diagnosis of SMI as lithium is primarily used to treat BD and mania. However, it is also indicated as a treatment for recurrent depression and aggressive or self-harming behaviour.

In summary, as SMI was not well specified by drug codes, it was decided to define SMI only by the presence of a Read code for SMI diagnosis.

#### 4.2.2.9.3 Final inclusion and exclusion criteria for specification of SMI

The final criteria used to specify SMI was schizophrenia, BD, or other psychosis, by Read code for the condition. Diagnosis of dementia, learning disability, depression in the absence of psychosis, puerperal psychosis, alcohol and drug induced psychosis were excluded.

#### 4.2.2.9.4 Severe mental illness as a time-varying covariate

The SMI diagnostic information available in the THIN dataset comprised up to four dates. These were, the earliest occurrence of a Read code indicating i) a new diagnosis of BD (defined as an incident code), ii) a follow-up diagnosis of BD (defined as a prevalent code), iii) a new (incident) diagnosis of schizophrenia and iv) a follow-up (prevalent) diagnosis of schizophrenia. The Read codes corresponding to these four categories are listed in Appendix XXI . A patient with either BD or SCZ could therefore subsequently be diagnosed with the other SMI. In this dataset, no information was available on later BD or schizophrenia diagnoses, therefore, a patient assigned a first diagnosis of BD or SCZ, who was subsequently

diagnosed with the other SMI, could not be reassigned to their first SMI. In other words, in this dataset the SMI diagnosis could only change once. Any SMI diagnosis dates that fell after the end of a patient's period of follow-up were ignored.

Figure 4.1 illustrates how periods with BD and schizophrenia were assigned for five example patients with SMI diagnoses:

- Patient A had a first diagnosis of BD before the start of their follow-up period and a first diagnosis of schizophrenia during their follow-up. They were assigned to BD from their start date until the day before their schizophrenia diagnosis. They were then assigned to schizophrenia from the date of schizophrenia diagnosis until their end date.
- Patient B had a period assigned to no SMI before their period with schizophrenia.
- Patient C had a first diagnosis of BD after the end of their follow-up and were thus assigned to no SMI throughout their study period.
- Patient D was first diagnosed with both BD and schizophrenia during their follow-up. They had a period with no SMI, followed by a period with schizophrenia and finishing with a period with BD.
- Patient E had first diagnoses with both BD and schizophrenia before their follow-up period. They were assigned to the later diagnosis of schizophrenia for the whole of their study period. If the earliest BD diagnosis occurred on the same date as the earliest schizophrenia diagnosis, the period was assigned to schizophrenia, however this only affected a small number of patients (n=111).

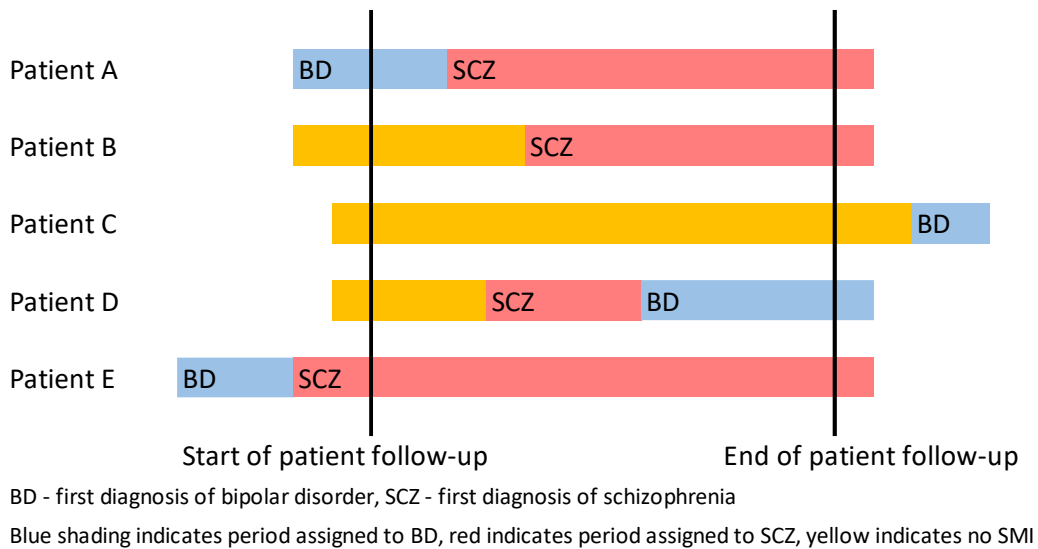


**Figure 4.1** Diagram showing assignment of SMI diagnosis for five example hypothetical patients

Those patients who only had a Read code indicating previous SMI diagnosis (a prevalent code), or with a prevalent Read code prior to an incident one, were assigned to the SMI from date of the prevalent code in initial analyses. This date was defined as their first diagnosis with that SMI. As a prevalent code indicates that the SMI diagnosis on that date is unlikely to be the patient's first occurrence of SMI, this methodology will tend to underestimate the time a patient has SMI. An alternative would be to count the patient as a prevalent, rather than an incident case and to attribute follow-up time to the SMI from the patient's start date. Using this methodology, it was found that around an extra 9,500 person years of follow-up would have been attributable to SMI, an increase of 1.7% (0.02% of the total follow-up). In the final analysis it was decided to exclude patients with a prevalent code prior to an incident as their date of SMI diagnosis was uncertain.

Most patients had a single diagnosis of either BD or schizophrenia. Out of 108,855 patients diagnosed with SMI, a total of 97,984 (90.0%) only ever had one SMI condition (either BD

(n=29,922) or schizophrenia (n=68,062)) recorded. The remaining 10,871 (10.0%) had both BD and schizophrenia diagnoses. The majority of these, 6,996 (64.5%) were both recorded before the start of the patient's study period. 533 (4.9%) of those with both BD and schizophrenia had the two conditions first recorded on the same date (0.5% of the total with SMI). Of the remainder with both conditions, 3,870 (3.6% of the total with SMI, 11.4% of those with BD) switched from BD to schizophrenia and 6,468 (5.9% of the total with SMI, 8.7% of those with SCZ) from schizophrenia to BD. Counting those who changed diagnosis during the study period only, 1,502 (4.8%) of those with BD changed to a schizophrenia diagnosis and 2,262 (3.2%) of those with schizophrenia changed to a diagnosis of BD.

#### 4.2.2.10 Specification of outcomes

##### 4.2.2.10.1 Mortality

The systematic review described in Chapter 2 found strong associations between SMI and CVD mortality. Data fields relating to cause of death were extracted to explore whether it would be possible to use CVD mortality as an outcome. However, the cause of death fields were blank for 83% of patients that had died. Thus, all-cause mortality was used as a primary outcome. A total of 289,222 deaths from all-causes were recorded in the prevalent study data. However, the date of death for 108,298 of these was after the end of the individual's follow-up period. The majority of these were people who died after the age of 75 years, which marked the end of their study period. Nonetheless, excluding patients who died after the age of 75 years and patients who died after they had transferred out of the practice, there remained 6,044 deaths recorded after the end of follow-up. Of these, death dates were recorded one to 3652 days after end of follow-up (median 3 days), with 33% occurring

the day after the end of follow-up. It was not known how many of these were date recording errors. Previous analysis of THIN found that ascertainment of deaths was improved by extending search periods for one day or more after recorded death dates. (191) Deaths recorded within one day of end of follow-up were included, but those recorded after that time were not counted. Deaths recorded one day after the end of follow-up were assumed to have occurred on the end date. Using this methodology 182,999 deaths were included in the analysis of all-cause mortality.

#### 4.2.2.10.2 Case-fatality after cardiovascular diagnosis

As CVD mortality was not an available outcome in the THIN dataset, all-cause mortality after a diagnosis of any CVD was explored as a second primary outcome. Secondary outcomes were mortality after MI or stroke, defined as a first occurrence of a Read code indicating incidence of those conditions (see Appendix XXII for a list of the Read codes used).

A new cohort was formed from the original prevalent cohort to explore case-fatality rates of patients newly diagnosed with CVD and compare those with and without SMI. This case-fatality cohort included only patients with a new diagnosis of any CVD. Those diagnosed with CVD before the start of follow-up were excluded, as were those with a new CVD diagnosis after the end of follow-up. In this analysis patients with a first CVD diagnosis which was identified by a code in one of the CVD prevalent Read code lists were excluded. This was because a prevalent Read code implies previous CVD, therefore the date recorded in the dataset may not have been the actual date of CVD diagnosis. As the date of diagnosis was unclear, these patients were excluded from further analysis. In the prevalent cohort dataset, patients could have up to three periods of follow-up: periods with no SMI, BD and/or

schizophrenia. However, only one period of follow-up for each patient was included in the case-fatality analysis: the period which included their CVD diagnosis. Figure 4.2 shows how follow-up periods are included for four example patients who had a diagnosis of CVD and later died.



|           |     |            |        |     |     |     |        |     |     |       |          |                                                                                    |
|-----------|-----|------------|--------|-----|-----|-----|--------|-----|-----|-------|----------|------------------------------------------------------------------------------------|
| Patient 1 |     | Start date | No SMI |     |     | CVD | No SMI |     | BD  | Death | End date | Follow-up period with BD is right censored, patient did not have outcome           |
| Patient 2 |     | Start date | BD     |     | CVD | BD  |        | SCZ |     | Death | End date | Follow-up period with SCZ is right censored, patient did not have outcome          |
| Patient 3 |     | Start date | No SMI |     | BD  |     | SCZ    | CVD | SCZ | Death | End date | Follow-up periods with no SMI and BD are left censored, patient died in SCZ period |
| Patient 4 | CVD | Start date | No SMI | SCZ |     |     |        |     | BD  | Death | End date | Patient excluded - CVD before start of follow-up                                   |

Shaded area indicates follow-up period after CVD diagnosis for each patient, thick borders indicate separate periods of follow-up with no SMI, BD or SCZ. BD – bipolar disorder, SCZ – schizophrenia, SMI – severe mental illness, CVD – cardiovascular disease

**Figure 4.2: Follow-up for four example patients in the CVD case-fatality cohort**

#### 4.2.2.10.3 Cardiovascular diagnosis

The first occurrence of a diagnosis of CVD was the final primary outcome considered. CVD was defined as i) CHD: MI, revascularisation, other CHD, ii) CVA: haemorrhagic stroke, non-haemorrhagic stroke, transient ischaemic attack (TIA), iii) Peripheral arterial disease (PAD). A diagnosis of heart failure was not included in this outcome as it has a more complicated causal pathway than CHD and CVA and is often diagnosed late or misdiagnosed as respiratory disease. (192)

For each of the included CVD diagnoses, lists of Read codes indicating both new diagnoses of the disease and historic cases of the disease were assembled (Appendix XXII ). Some patients had a diagnosis of historic CVD with no prior record of a new diagnosis of that CVD. The percentage of patients with each type of CVD that this issue applied to are presented in Table 4.2. The number of patients with historic haemorrhagic stroke and no recorded incident haemorrhagic stroke were very small (n=16), so haemorrhagic and non-haemorrhagic were combined. Fisher's exact tests were performed to test for any differences between those with BD, schizophrenia, or no SMI. The p-values in Table 4.2 show no evidence of any differences between those with and without SMI who had recorded historic CVD but no incident CVD. Even though no systematic bias was found, these patients were excluded from further analysis of time to CVD outcome as the exact date of CVD diagnosis could not be determined. Patients with a diagnosis of CVD at baseline were also excluded from this analysis.

**Table 4.2: Number of patients with a diagnosis of historic CVD but no record of prior incident CVD**

| CVD type                                  | BD                                                   |                         |             | Schizophrenia                                        |                         |             | No SMI                                               |                         |             |                      |
|-------------------------------------------|------------------------------------------------------|-------------------------|-------------|------------------------------------------------------|-------------------------|-------------|------------------------------------------------------|-------------------------|-------------|----------------------|
|                                           | Patients with historic CVD but no prior incident CVD | Total patients with CVD | %           | Patients with historic CVD but no prior incident CVD | Total patients with CVD | %           | Patients with historic CVD but no prior incident CVD | Total patients with CVD | %           | p-value <sup>1</sup> |
| Myocardial infarction                     | 3                                                    | 233                     | 1.29        | 3                                                    | 448                     | 1.79        | 721                                                  | 50,519                  | 1.43        | 0.724                |
| Revascularisation                         | 9                                                    | 156                     | 5.77        | 9                                                    | 230                     | 3.91        | 2,189                                                | 45,769                  | 4.78        | 0.676                |
| Other CHD                                 | 7                                                    | 397                     | 1.76        | 12                                                   | 664                     | 1.96        | 1,283                                                | 88,486                  | 1.45        | 0.394                |
| Stroke (haemorrhagic or non-haemorrhagic) | 16                                                   | 458                     | 3.49        | 20                                                   | 829                     | 2.41        | 1,347                                                | 64,317                  | 2.09        | 0.100                |
| Transient ischaemic attack                | 3                                                    | 238                     | 1.26        | 6                                                    | 357                     | 1.68        | 713                                                  | 36,833                  | 1.94        | 0.864                |
| Peripheral arterial disease               | 0                                                    | 149                     | 0.0         | 2                                                    | 328                     | 0.61        | 135                                                  | 31,261                  | 0.43        | 0.819                |
| <b>Any CVD</b>                            | <b>17</b>                                            | <b>1,203</b>            | <b>1.41</b> | <b>41</b>                                            | <b>2,177</b>            | <b>1.88</b> | <b>3,468</b>                                         | <b>216,902</b>          | <b>1.60</b> | <b>0.503</b>         |

CVD – cardiovascular disease, BD – bipolar disorder, CHD – coronary heart disease. <sup>1</sup> p-values from Fisher's exact test for differences between no SMI, BD, and schizophrenia

#### 4.2.2.11 Specification of other covariates

##### 4.2.2.11.1 Temporal trends

Changes over time were explored in two ways: i) using the year of start of follow-up as a continuous variable and ii) using the start year as a categorical variable and dividing the study period into four calendar periods: 2000-2004, 2005-2009, 2010-2014, 2015-2019.

##### 4.2.2.11.2 Country, deprivation and urbanisation

Countries of the UK (England, Wales, Scotland, and Northern Ireland) were included as covariates. Deprivation was defined using the Townsend score (193) of patient's residence, derived from the 2001 Census, divided into quintiles. Patients' area of residence was classified as either urban or non-urban using the Office of National Statistics (ONS) 2004 area classifications for electoral wards. (194) Urban areas were defined as having more than 10,000 residents. However, this classification was only available for England and Wales. Townsend deprivation score and urbanisation were the last recorded values for each patient. These did not change much during follow-up for each patient. If a new value was recorded it could have been either because the patient moved house, or the practice re-entered the patient's details. Using a 1% sample of the dataset, of those patients with recorded data on Townsend score or urbanisation, 87.2% and 90.0%, respectively, had no change in their details during the study period (percentages were slightly lower for those with SMI: 83.4% had no updated Townsend score and 87.0% had no updated urbanisation status.) Of those who did have different Townsend or urbanisation information at the start and end of follow-up, 84.4% stayed in the same deprivation quintile and 98.2% stayed in

either an urban or rural area; for those with SMI, the equivalent percentages were 76.2 and 97.9, respectively. The number of patients who moved to an area that was more deprived was matched by the number moving to a less deprived area. Across the whole sample, 1.0% of patients without SMI and 1.9% with SMI moved to a more deprived area during the study period. Whereas 1.0% without SMI and 2.0% with SMI moved to a less deprived area. Although there was more change in deprivation levels for patients with SMI compared with the general population, it did not affect large numbers of patients and there was no evidence of a systematic drift of patients to either more or less deprived areas. The numbers changing from rural to urban areas or vice versa were very small. Thus, it was decided to use only the latest information on deprivation quintile and urbanisation for each patient.

#### 4.2.2.11.3 Comorbidities

Diabetes mellitus was included as a specific comorbidity due to the association with risk of CVD. Diabetes mellitus was defined by either the presence of a Read code for type 1 or non-type 1 diabetes mellitus or a prescription for medication used to treat diabetes mellitus (excluding metformin when there was a prior diagnosis of polycystic ovary syndrome (PCOS) since metformin is used to treat PCOS).

Other comorbidities were accounted for using the Charlson index, (195) modified to exclude diabetes mellitus (as it was included as a separate covariate), MI, peripheral vascular disease, cerebrovascular disease (as they were included as outcomes). The Charlson index consisted of a score between 0 and 10 applied to each patient at baseline. Scores were calculated by summing weights (between 1 and 6) indicating diagnoses of conditions

associated with mortality. The highest weight of six indicated a diagnosis of either acquired immunodeficiency syndrome (AIDS) or metastatic cancer.

#### 4.2.2.11.4 Additional health data

Smoking status at baseline was defined as never smoked, ex-smoker or current smoker according to the last recorded status in the AHD. However, if a patient's last status was never smoked, but they had a previous value of current or ex-smoking, then they were designated as an ex-smoker.

A patient was defined as having obesity either by the latest recorded BMI  $\geq 30$  kg/m<sup>2</sup> (or 27.5 kg/m<sup>2</sup> if Asian, Black, mixed, Chinese, or other ethnic group) or a Read code indicating obesity. These BMI cut off values categorise someone as living with obesity according to NICE guidance, which was recently updated to include different figures for people of different ethnic backgrounds. (196)

Blood pressure was categorised as normotensive (systolic <140 mmHg and diastolic <90 mmHg) or hypertensive (systolic  $\geq 140$  mmHg or diastolic  $\geq 90$  mmHg), following cut-off values in NICE guidelines for hypertension. (197)

Cholesterol at baseline was categorised based on whether the total to high density lipoprotein (HDL) cholesterol ratio was greater than or less than then median value for the whole cohort. If the total cholesterol: HDL ratio was reported prior to baseline, that value was used. Otherwise, the ratio was calculated from the last reported total cholesterol and HDL values before baseline. A cohort-based cut point was used rather than a diagnostic cut point. A total to HDL ratio above 6.0 is considered high by the British Heart Foundation. (198) In the prevalent cohort, the 94<sup>th</sup> centile of total:HDL ratio values was 6.0. If this

diagnostic cut point was used, only 6% of patients would fall into the “high” category.

Median values from the cohort were thus used to obtain similar numbers of patients in the “high” and “low” categories.

#### 4.2.2.11.5 Ethnicity

Ethnicity was defined by Read code using the last recorded ethnicity code, but the actual date of ethnicity recording was unknown. Ethnicity recording improved during the study period. The percentage with no recorded ethnicity reduced dramatically from 99.4% in 2000 to 35.6% in 2017, which was the year with the smallest percentage of missing values (see Figure 4.3). As there was such a large interaction between calendar period and missing ethnicity, ethnicity was not included in multivariable analysis of time trends.

There were also changes over time in the percentages of patients with unrecorded BMI and smoking status, however these were much smaller than the variations affecting ethnicity (see Figure 4.4 and Figure 4.5).

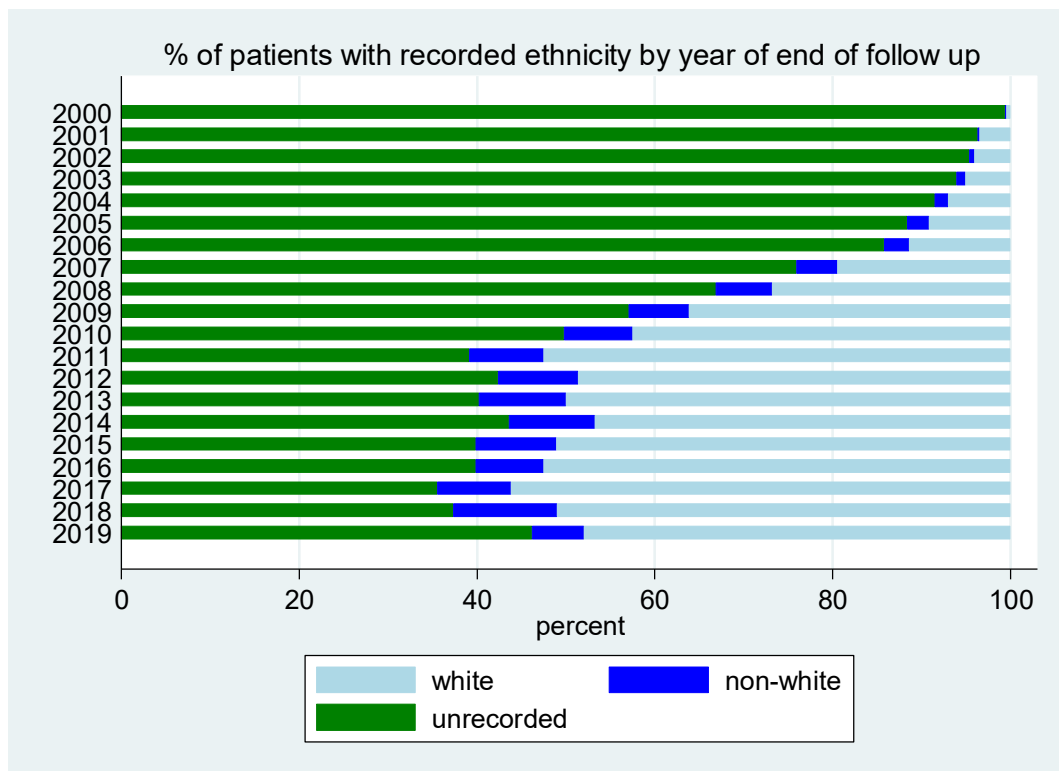


Figure 4.3: Percentage of patients with recorded ethnicity by year of end of follow-up

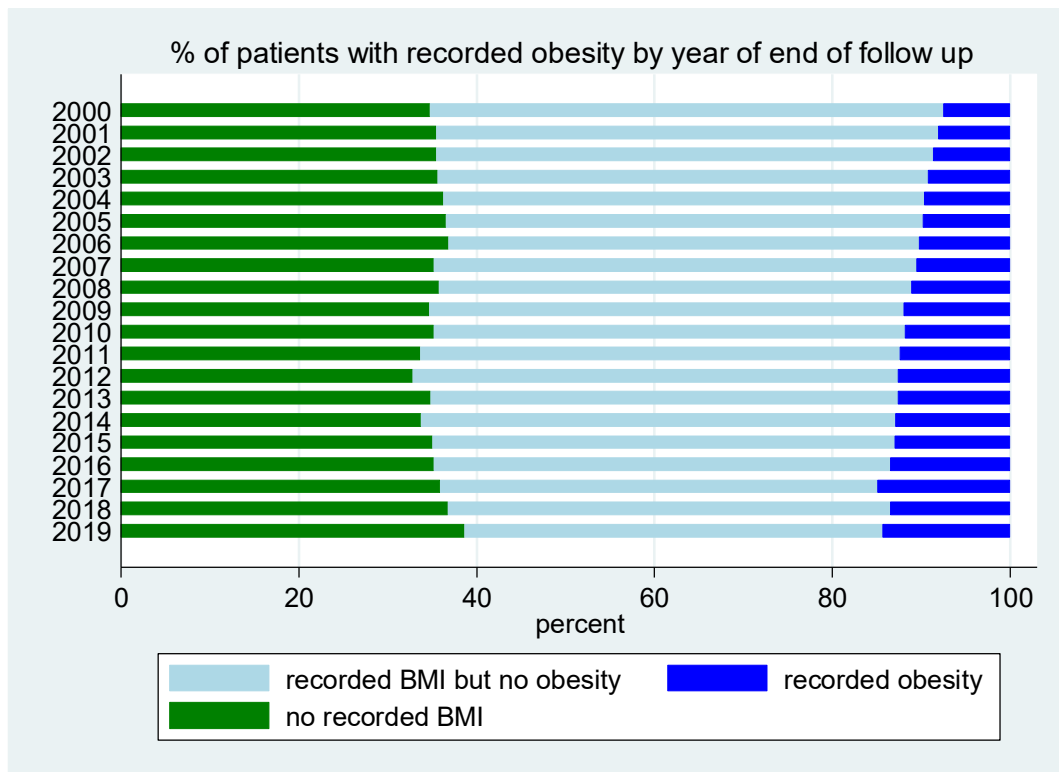


Figure 4.4: Percentage of patients with recorded obesity by year of end of follow-up



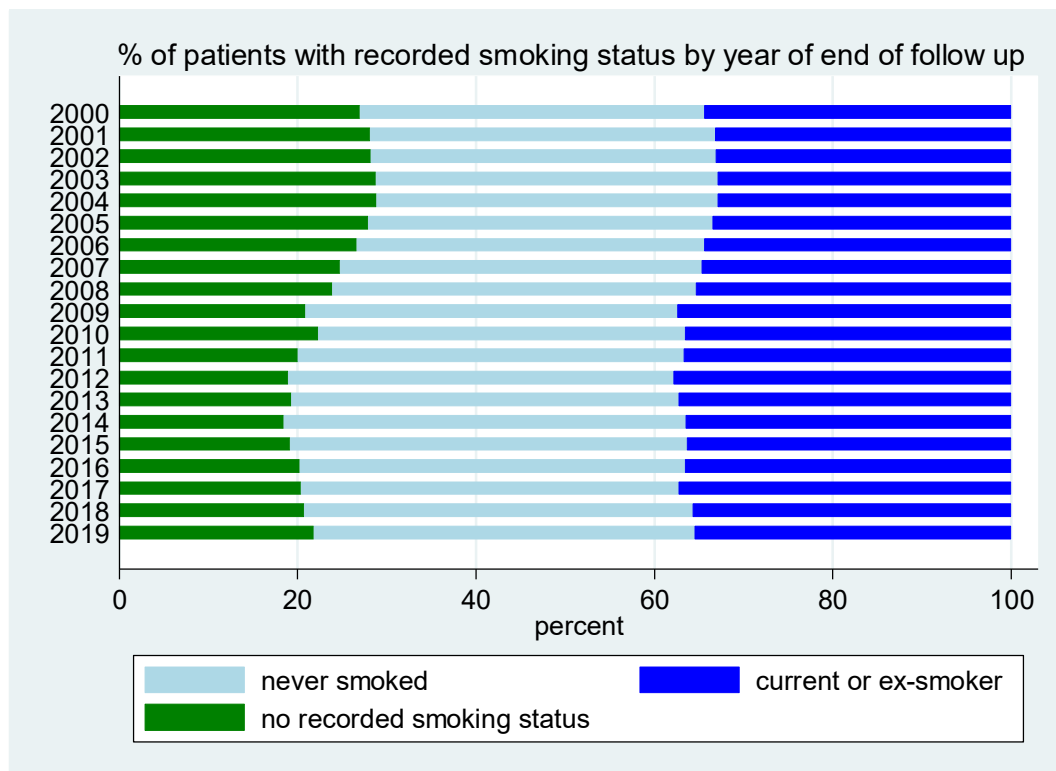


**Figure 4.5: Percentage of patients with recorded smoking status by year of end of follow-up**

### 4.2.3 Statistical analysis

#### 4.2.3.1 Both cohort studies

Descriptive analyses of the prevalent and incident cohorts were conducted initially. Baseline characteristics for patients with BD and schizophrenia were compared with those without SMI using frequencies (n) and percentages for categorical variables; medians and IQRs for continuous variables.

The data were then set as time to event or survival time data using the Stata (version 14.2) `stset` command to compare outcomes for individuals with BD, schizophrenia, and no SMI.

The time variable (or time at risk) was chosen as time since index date in the incident cohort study. In the prevalent cohort study attained age was chosen as the most suitable analysis

time, since the likelihood of each of the outcomes varies dramatically with age. (199) Date of start of follow-up was set as date of entry for the analysis of all-cause mortality and CVD incidence outcomes, whereas date of CVD diagnosis was the date of entry for case-fatality analysis. End of follow-up was the exit date. Death from any cause, death following diagnosis with CVD, MI or stroke, and date of CVD diagnosis were the failure events for the outcomes of all-cause mortality, CVD case-fatality and CVD incidence, respectively.

In the incident cohort study, patients could only have a single SMI diagnosis, but in the prevalent cohort study patients could have periods with both BD and schizophrenia if both diagnoses were recorded during their follow-up.

Crude mortality rates and incidence rates for all-cause mortality and CVD incidence, respectively were calculated. Cox proportional hazards regression analysis was then performed.

#### 4.2.3.1.1 Assessment of proportional hazards

For analyses of both the incident and prevalent cohorts, the assumption of proportional hazards was assessed using log-log plots and chi-squared tests for zero slope of scaled Schoenfeld residuals. In the case of violation of proportional hazards, different methods exist for dealing with non-proportional hazards. (199) These include (i) splitting the follow-up time into different periods, (ii) stratification by a confounder, if it is the confounder that has evidence of non-proportional hazards, (iii) including an exposure X time interaction term. (199)

In the cohort studies different methods were used for different outcomes. In the incident cohort, non-proportional hazards were dealt with by including an interaction between SMI and time. In the prevalent cohort, two other methods were used. For case-fatality outcomes, where the cohort size was relatively smaller, if non-proportionality affected only one or two covariates, rather than the main variable of interest (*i.e.* SMI), stratification on those covariates was used. Otherwise, interactions with time were added for covariates found to exhibit non-proportional hazards. In the analysis of all-cause mortality in the prevalent cohort, where the number of records was already large, to add interactions with time would have meant splitting the data at failure times and thus increasing the size of the dataset even more. In this situation the number of records became too large for the computing resources available. Thus, for all-cause mortality, in the case of non-proportional hazards, the analysis time was split into separate periods with hazards that were more nearly proportional. For CVD incidence in the prevalent cohort a pragmatic strategy was used. With attained age as the time at risk variable there were proportional hazards violations for all covariates. This was improved by using time since baseline. Although the statistical tests still showed lack of proportionality, visually the log-log plots showed hazards that were more nearly proportional. It has been noted that large sample sizes may account for the lack of proportionality in statistical tests, but this may be of little practical significance. (200) The Cox regression models using time since baseline were thus deemed acceptable to explore the association between SMI and CVD incidence. Age at baseline, aggregated into ten-year bands was added as a covariate.

Scaled Schoenfeld residuals were plotted against each covariate included in the final models and global tests for zero slope conducted. Likelihood ratio tests were used to compare the fit of models when adding extra variables. Model fit was also assessed using Akaike's Information Criteria (AIC), with the lower AIC being the preferable model. (201)

#### 4.2.3.2 Incident cohort study

In the matched incident cohort study, Cox regression analysis was performed with time since index date used as the time analysis variable. To preserve the matching by age, sex and general practice, the analysis was stratified on the matching variable. Univariable Cox regression analyses were performed with the following explanatory variables (categories were as for the prevalent cohort study, see below):

- SMI type
- Townsend deprivation score
- Diabetes mellitus at index date
- CVD at index date
- Charlson index at patient start date
- Smoking status at index date
- Obesity at index date
- Blood pressure at index date

Multivariable analyses were also performed. A reduced model included only SMI type and Townsend score, and a full model included all the variables in the univariable analysis. Age, sex, year, and country were not adjusted for in the analysis since these variables were accounted for in the matching.

Changes over time were assessed by splitting follow-up time into four periods: 2000-04, 2005-09, 2010-14, 2015-19. Patients with SMI and non-SMI comparators with an index date within each calendar period only were included in each model.

In the analysis of CVD incidence only new diagnoses of CVD were eligible for inclusion.

Patients whose date of CVD incidence was unclear because they had a Read code indicating previous CVD as their earliest CVD diagnosis were excluded. Patients with a CVD diagnosis prior to the index date were also excluded. Patients in the non-SMI comparison group that matched excluded patients in the SMI group were removed, along with SMI patients that no longer had matching non-SMI comparators.

#### 4.2.3.3 Prevalent cohort study

Basic epidemiological analyses of the prevalent cohort explored age distributions at SMI diagnosis for those with BD and schizophrenia, and incidence and prevalence rates over time and by general practice.

##### 4.2.3.3.1 All-cause mortality

Univariate Cox regression analyses of the unmatched prevalent cohort were performed with the following explanatory variables:

- SMI type: BD, schizophrenia vs no SMI as the reference category
- Sex: males as reference
- Calendar period: 2000-2004 (reference), 2005-2009, 2010-2014, 2015-2019
- Ethnicity: White (reference), Asian, Black, Mixed, Chinese, other, missing

- Townsend deprivation quintile: 1=least deprived (reference), 5=most deprived, plus missing
- Diagnosis of diabetes mellitus at baseline: Read code for type 1 or non-type 1 or prescription for medication used to treat diabetes mellitus (excluding metformin with a diagnosis of PCOS) vs no record of diabetes mellitus (reference)
- Charlson index at baseline, modified to exclude diabetes mellitus and CVD: 0 (reference), 1 or 2+
- CVD diagnosis at baseline: MI, revascularisation, other CHD, haemorrhagic stroke, non-haemorrhagic stroke, TIA, PAD vs no record of CVD (reference)
- Country: England (reference), Wales, Scotland, Northern Ireland
- Urbanisation of patient residence: non-urban (reference), urban, missing. Urbanisation was only available for England and Wales, so Scotland and Northern Ireland were excluded from this analysis.
- Smoking status at baseline: never smoked (reference), ex-smoker, current smoker, missing
- Obesity at baseline: latest recorded BMI below 30 kg/m<sup>2</sup> (or 27.5 kg/m<sup>2</sup> if Asian, Black, Mixed, Chinese, or other ethnic group) (reference) vs latest recorded BMI ≥30/27.5 kg/m<sup>2</sup> or Read code indicating obesity vs no recorded BMI
- Blood pressure at baseline: systolic <140 mmHg and diastolic <90 mmHg (reference), systolic ≥140 mmHg or diastolic ≥90 mmHg, missing
- Cholesterol: total cholesterol:HDL > cohort median (reference), total cholesterol:HDL ≤ cohort median, total cholesterol:HDL missing

Three multivariable Cox regression analyses were then performed. The first (minimally adjusted) included SMI type, sex, and calendar period as explanatory variables. The second Cox regression (partially adjusted) included SMI type, sex, and calendar period, also Townsend deprivation quintile and country. The final, fully adjusted model included all the previously included variables with the addition of diabetes mellitus, Charlson index, diagnosis of any CVD, smoking status at baseline, blood pressure at baseline, and obesity at baseline. Urbanisation was not included in the fully adjusted model as it was correlated with Townsend score and unavailable for Scotland and Northern Ireland. Ethnicity was not included in the fully adjusted model because the completeness increased over time as described in Section 4.2.2.11.5. In addition, the total:HDL cholesterol ratio was not able to be used because of a large amount of missing data.

To assess whether there were any differences between the types of SMI in the trend by year, an interaction term between SMI and year was added.

#### 4.2.3.3.2 Case-fatality

In analysis of case-fatality outcomes, there was evidence of non-proportional hazards for smoking and obesity. As these variables were not of primary interest, in Cox regression the fully adjusted model was stratified by smoking and obesity. A sensitivity analysis was performed including smoking and obesity in a fully adjusted model where they were interacted with time instead of being used for stratification. The models were compared using Akaike's Information Criteria. (201)

Calendar year of CVD diagnosis and age at CVD diagnosis were included as continuous variables. Fractional polynomials of these two variables were explored to assess whether

linear relationships with the hazard were adequate or whether more complex relationships were more appropriate.

The use of fractional polynomials was also explored in the analysis of all-cause mortality to assess the relationship between mortality and single calendar year as a continuous variable. However, these analyses were very computationally intense as the number of observations when split by year was very large. A Cox regression including only SMI found that a linear relationship with year was an inadequate fit and a higher degree, more complex polynomial would be needed. Calendar period as a categorical variable only was thus utilised in analysis of all-cause mortality and CVD incidence outcomes.

#### 4.2.3.3.3 Cardiovascular incidence

In this section, CVD was the outcome of interest. Patients in the prevalent cohort who did not already have a diagnosis of CVD at the start of their follow-up were included in the analysis. Data were set as survival time using Stata V14.2 with separate periods of follow-up for times with no SMI, BD, and schizophrenia. The end of follow-up for each patient was the earliest of attaining age 75 years, leaving the practice or death. The failure event was date of CVD diagnosis. CVD was subdivided into CHD: MI, revascularisation, other CHD; stroke: haemorrhagic and non-haemorrhagic; TIA and PAD.

Cox regression was initially performed with age as the time analysis variable since age is strongly associated with diagnosis of CVD. The earliest of CVD diagnosis, attaining age 75 years or date of transferring out of the practice was the endpoint. Patients who had not been diagnosed with CVD by the end of their study period were censored. The failure event was CVD diagnosis. Records were split into periods with no SMI, BD, and schizophrenia. Date



of start of follow-up was aggregated into calendar periods 2000-04, 2005-09, 2010-14 and 2015-19 to assess changes over time. Included covariates were SMI (BD, schizophrenia, no SMI), sex, calendar period at baseline, Townsend deprivation quintile, country, diabetes mellitus, Charlson index (0, 1 or 2+), smoking status (never, ex-smoker, current smoker, missing), presence of obesity (yes, no, missing) and blood pressure ( $\geq 140/90$  mmHg,  $< 140/90$  mmHg, missing). A small number of records started and ended on the same date (n=118). For these patients, 0.1 was subtracted from their start date so that they could be included in the analysis.

Status of diabetes mellitus, smoking, obesity, and BP were as recorded at baseline for each period of SMI. However, Charlson index was only available for each patient at the start of their follow-up in the prevalent cohort, which for most patients was earlier than their date of CVD diagnosis.

Univariable Cox regression analyses were performed on time from baseline to first CVD diagnosis, with SMI, age band, sex, calendar period, deprivation, country, diabetes mellitus, Charlson index, smoking, obesity, and blood pressure as independent variables.

Multivariable Cox regressions were then conducted on three different models: a minimally adjusted model (adjusted by SMI, age, sex, and calendar period), a partially adjusted model (SMI, age, sex, calendar period, deprivation, and country) and a fully adjusted model (SMI, age, sex, calendar period, deprivation, country, diabetes mellitus, Charlson index, smoking, obesity, and high blood pressure). To test for differences in CVD incidence over time between BD, schizophrenia and the non-SMI comparison group, interactions between SMI

and calendar period were added to the minimal, partial, and full models. Likelihood ratio tests were used to assess whether the interaction significantly improved the model fit.

#### 4.2.3.4 Summary

Section 4.2 has described the methods used in the two cohort studies which are summarised in Table 4.3. The next two sections will describe the results for the incident and prevalent studies separately: the incident study in Section 4.3 and the prevalent study in Section 4.4.

**Table 4.3: Summary of cohort studies analysis**

| Outcome                | Incident cohort                                                                                                                                                                                                                                                                                                                                                                                                      | Prevalent cohort                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
|------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Cohort characteristics | <ul style="list-style-type: none"> <li>Descriptive analyses comparing BD, SCZ and non-SMI</li> </ul>                                                                                                                                                                                                                                                                                                                 | <ul style="list-style-type: none"> <li>Descriptive analyses comparing BD, SCZ and non-SMI</li> <li>Analysis of age distribution at SMI diagnosis</li> <li>Incidence and prevalence of SMI</li> </ul>                                                                                                                                                                                                                                                                                                                                                              |
| All-cause mortality    | <ul style="list-style-type: none"> <li>Crude mortality rates for BD, SCZ, no SMI</li> <li>Cox regression stratified by matching ID (using time since index date for time at risk)</li> <li>Univariable, reduced, fully adjusted models</li> <li>Follow-up time split at one year after index date to correct PH violation</li> <li>Separate Cox regressions by calendar period to assess temporal changes</li> </ul> | <ul style="list-style-type: none"> <li>Crude mortality rates and mortality rate ratios (SMI vs no SMI)</li> <li>Cox regression (using attained age for time at risk, start of follow-up as entry date, end of follow-up as exit date)</li> <li>Univariable, minimally adjusted, partially adjusted, fully adjusted models</li> <li>Age split into ten-year bands to correct PH violations</li> <li>Interaction between SMI and year tested to assess temporal changes</li> </ul>                                                                                  |
| CVD case-fatality      | <ul style="list-style-type: none"> <li>Not applicable to matched incident cohort</li> </ul>                                                                                                                                                                                                                                                                                                                          | <ul style="list-style-type: none"> <li>Descriptive analysis of SMI and non-SMI eligible for inclusion in case-fatality analysis</li> <li>Cox regression (using time since CVD diagnosis for time at risk)</li> <li>Univariable, minimally adjusted, partially adjusted, fully adjusted models</li> <li>Age and calendar year as continuous variables assessed using fractional polynomials</li> <li>Interaction between SMI and year tested to assess temporal changes</li> <li>Interactions with time included for variables exhibiting PH violations</li> </ul> |

| Outcome       | Incident cohort                                                                                                                                                                                                                                                                                                                                                                                                                                      | Prevalent cohort                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
|---------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| CVD incidence | <ul style="list-style-type: none"> <li>• Descriptive analysis of SMI and non-SMI eligible for inclusion in analysis of CVD incidence</li> <li>• Crude CVD incidence rates for BD, SCZ, no SMI</li> <li>• Cox regression stratified by matching ID (using time since index date for time at risk)</li> <li>• Univariable, reduced, fully adjusted models</li> <li>• Separate Cox regressions by calendar period to assess temporal changes</li> </ul> | <ul style="list-style-type: none"> <li>• Descriptive analysis of SMI and non-SMI eligible for inclusion in analysis of CVD incidence</li> <li>• Crude incidence rates and incidence rate ratios (SMI vs no SMI)</li> <li>• Cox regression (using time since baseline for time at risk)</li> <li>• Univariable, minimally adjusted, partially adjusted, fully adjusted models</li> <li>• Interaction between SMI and year tested to assess temporal changes</li> </ul> |

BD – bipolar disorder, SCZ – schizophrenia, SMI – severe mental illness, non-SMI – patients with no diagnosis of BD or SCZ, CVD – cardiovascular disease, PH – proportional hazards

## 4.3 Results – part 1: incident cohort study

### 4.3.1 Cohort characteristics

The matched incident cohort initially comprised 140,972 individuals aged 16-74 years:

35,245 patients with SMI and 105,727 non-SMI comparators (Figure 4.6). Of the patients with SMI, 25,378 had a first diagnosis of BD or schizophrenia, but the remaining 9,867 had a first diagnosis of “other SMI”. As there was found to be a spike in cases of “other SMI” in the prevalent cohort and a likelihood of misclassification (Appendix XXVI ), the 9,867 patients with SMI and matching non-SMI comparators relating to a first diagnosis of “other SMI” were removed from the incident cohort. The omitted SMI patients included 1,182 patients who had an incident diagnosis of BD or schizophrenia after their diagnosis of other SMI.

Unfortunately, it was no longer possible to select non-SMI comparators for these patients, so they were unable to be used in further analysis. The end date for patients in the non-SMI comparison group who had previously ended their follow-up due to a diagnosis of “other

SMI” was reset to be the earlier of the end of their study period or a first diagnosis of BD or schizophrenia.

1,224 SMI patients had diagnoses of both BD and schizophrenia. Of these, 133 had a Read code indicating previous SMI as the earliest episode of their second SMI. These 133 patients, together with their matched non-SMI comparators were excluded from further analysis.

More SMI patients were excluded due to a diagnosis of dementia. There were 257 SMI patients who had dementia either at or within a year of SMI diagnosis. These patients and their matching non-SMI comparators were removed from the cohort. This left 24,988 patients with SMI (8,940 with BD and 16,048 with schizophrenia at earliest SMI diagnosis) and 74,964 non-SMI comparators in the cohort. Patients who had an initial diagnosis of BD and were subsequently diagnosed with schizophrenia (or vice versa) were censored at the date of the second SMI. If both BD and schizophrenia were recorded on the same date, then the patient was deemed to have schizophrenia (85 patients). The patients in the matched comparison group who had no SMI at their index date included 276 patients who later received a diagnosis of BD or schizophrenia and became part of the SMI group.

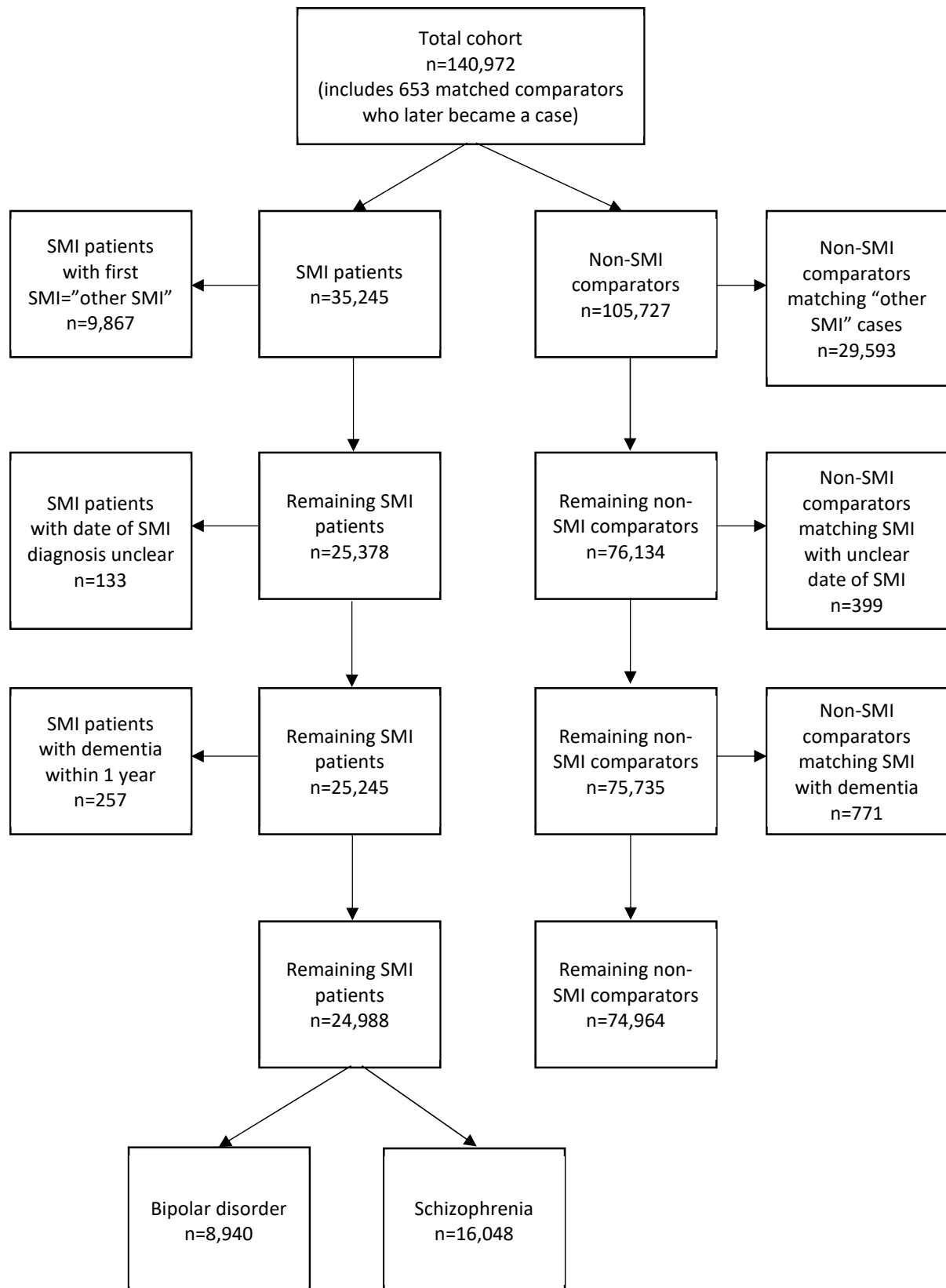


**Figure 4.6: Flow chart showing number of patients included in incident cohort analysis**

Table 4.4 shows the baseline characteristics of the incident cohort. Median follow-up was 3.12 years (IQR: 1.18-6.58) for SMI patients, whereas it was higher for the matched comparison group at 3.83 years (IQR: 1.59-7.48). Males accounted for 51.8% of the cohort. However, there was a higher percentage of females with BD and a higher percentage of males with schizophrenia compared with non-SMI comparators. Mean age at index date was 39.6 years (standard deviation (SD): 14.8); 7.4% were aged 65-74 years at baseline. There were slightly more people of White or Black ethnicity and fewer of Asian ethnicity amongst the SMI group than the matched comparison group, however 50.4% of those with SMI and 53.6% of matched comparators had missing ethnicity. Those with SMI were from more deprived quintiles than those without SMI (21.6% vs 14.5% from the most deprived Townsend quintile) and a slightly higher percentage were from urban areas (58.2% vs 57.2%). A higher percentage of patients with SMI than non-SMI comparators had diabetes mellitus at baseline (6.2% vs 4.5%). 3.9% of patients with SMI and 2.8% of matched non-SMI comparators had a diagnosis of CVD at index date. Those with SMI had more long-term conditions at baseline compared with patients without SMI (modified Charlson score of 2+: 4.2% vs 3.6%). Smoking rates were higher amongst SMI patients compared with the matched comparison group (current smoker: 44.7% vs 25.5%). Mean BMI (last measurement before baseline) was slightly lower for those with SMI compared with those without SMI (26.34 kg/m<sup>2</sup>, SD: 6.13 vs 26.59, SD: 5.80), however 22.8% of SMI patients and 26.3% of the matched non-SMI comparison group had no BMI measurement prior to index date. In contrast, the rate of obesity at index date was higher for those with SMI than non-SMI comparators. The percentage of people with either: last BMI before index date  $\geq 30$  kg/m<sup>2</sup> (27.5 kg/m<sup>2</sup> if non-

White) or, if no valid recorded BMI before index date, a Read code for obesity at baseline, was 18.6% for those with SMI compared with 17.5% for matched comparators. BMI measurements or Read codes for obesity recorded before age 16 years were disregarded. Patients from the matched comparison group were more likely than SMI patients to have missing data for smoking status, BMI, and blood pressure.

There were also some differences between patients with BD and schizophrenia. Compared with BD patients, those with schizophrenia were more likely to be male, younger, non-White, more deprived, smokers and have unrecorded BMI, BP, and smoking status. Fewer comorbidities (diabetes mellitus, obesity and Charlson index) were recorded for those with schizophrenia compared with BD, except for CVD (schizophrenia: 4.0% vs BD: 3.4%).

**Table 4.4: Baseline characteristics of SMI incident cohort and matched comparison group**

|                                                     | <b>Bipolar Disorder<br/>(n=8,940)</b> | <b>Schizophrenia<br/>(n=16,048)</b> | <b>All patients with SMI<br/>(n=24,988)</b> | <b>Comparison group<br/>(no SMI)<br/>(n=74,964)<sup>1</sup></b> |
|-----------------------------------------------------|---------------------------------------|-------------------------------------|---------------------------------------------|-----------------------------------------------------------------|
| Person years of follow-up:                          | 39,393                                | 70,520                              | 109,914                                     | 375,409                                                         |
| Median follow-up, years (IQR):                      | 3.22<br>(1.23-6.55)                   | 3.06<br>(1.16-6.60)                 | 3.12<br>(1.18-6.58)                         | 3.83<br>(1.59-7.48)                                             |
| Male, n (%):                                        | 3,548 (39.7)                          | 9,385 (58.5)                        | 12,933 (51.8)                               | 38,799 (51.8)                                                   |
| Age in years at index date, mean (SD):              | 40.9 (14.1)                           | 38.8 (15.2)                         | 39.6 (14.8)                                 | 39.6 (14.8)                                                     |
| Age in years at index date, 10-year bands, n (%):   |                                       |                                     |                                             |                                                                 |
| 16-24                                               | 1,163 (13.0)                          | 3,457 (21.5)                        | 4,620 (18.5)                                | 13,861 (18.5)                                                   |
| 25-34                                               | 2,144 (24.0)                          | 3,856 (24.0)                        | 6,000 (24.0)                                | 17,999 (24.0)                                                   |
| 35-44                                               | 2,189 (24.5)                          | 3,333 (20.8)                        | 5,522 (22.1)                                | 16,566 (22.1)                                                   |
| 45-54                                               | 1,780 (19.9)                          | 2,589 (16.1)                        | 4,369 (17.5)                                | 13,106 (17.5)                                                   |
| 55-64                                               | 1,042 (11.7)                          | 1,588 (9.9)                         | 2,630 (10.5)                                | 7,891 (10.5)                                                    |
| 65-74                                               | 622 (7.0)                             | 1,225 (7.6)                         | 1,847 (7.4)                                 | 5,541 (7.4)                                                     |
| Ethnicity, n (%):                                   |                                       |                                     |                                             |                                                                 |
| White                                               | 4,261 (47.7)                          | 6,443 (40.2)                        | 10,704 (42.8)                               | 30,062 (40.1)                                                   |
| Asian                                               | 153 (1.7)                             | 469 (2.9)                           | 622 (2.5)                                   | 2,120 (2.8)                                                     |
| Black                                               | 94 (1.1)                              | 532 (3.3)                           | 626 (2.5)                                   | 1,323 (1.8)                                                     |
| Mixed                                               | 52 (0.6)                              | 123 (0.8)                           | 175 (0.7)                                   | 387 (0.5)                                                       |
| Chinese                                             | 13 (0.2)                              | 29 (0.2)                            | 42 (0.2)                                    | 239 (0.3)                                                       |
| Other                                               | 42 (0.5)                              | 172 (1.1)                           | 214 (0.9)                                   | 666 (0.9)                                                       |
| Missing                                             | 4,325 (48.4)                          | 8,280 (51.6)                        | 12,605 (50.4)                               | 40,167 (53.6)                                                   |
| Townsend deprivation quintile <sup>2</sup> , n (%): |                                       |                                     |                                             |                                                                 |
| 1 (least deprived)                                  | 1,362 (15.2)                          | 1,722 (10.7)                        | 3,084 (12.3)                                | 13,235 (17.7)                                                   |

|                                                              | <b>Bipolar Disorder<br/>(n=8,940)</b> | <b>Schizophrenia<br/>(n=16,048)</b> | <b>All patients with SMI<br/>(n=24,988)</b> | <b>Comparison group<br/>(no SMI)<br/>(n=74,964)<sup>1</sup></b> |
|--------------------------------------------------------------|---------------------------------------|-------------------------------------|---------------------------------------------|-----------------------------------------------------------------|
| 2                                                            | 1,309 (14.6)                          | 1,842 (11.5)                        | 3,151 (12.6)                                | 12,317 (16.4)                                                   |
| 3                                                            | 1,627 (18.2)                          | 2,669 (16.6)                        | 4,296 (17.2)                                | 13,522 (18.0)                                                   |
| 4                                                            | 1,758 (19.7)                          | 3,350 (20.9)                        | 5,108 (20.4)                                | 12,971 (17.3)                                                   |
| 5 (most deprived)                                            | 1,436 (16.1)                          | 3,949 (24.6)                        | 5,385 (21.6)                                | 10,903 (14.5)                                                   |
| Missing                                                      | 1,448 (16.2)                          | 2,516 (15.7)                        | 3,964 (15.9)                                | 12,016 (16.0)                                                   |
| Country, n (%):                                              |                                       |                                     |                                             |                                                                 |
| England                                                      | 6,175 (69.1)                          | 11,070 (69.0)                       | 17,245 (69.0)                               | 51,735 (69.0)                                                   |
| Scotland                                                     | 1,316 (14.7)                          | 2,275 (14.2)                        | 3,591 (14.4)                                | 10,773 (14.4)                                                   |
| Wales                                                        | 1,080 (12.1)                          | 1,759 (11.0)                        | 2,839 (11.4)                                | 8,517 (11.4)                                                    |
| Northern Ireland                                             | 369 (4.1)                             | 944 (5.9)                           | 1,313 (5.3)                                 | 3,939 (5.3)                                                     |
| Rurality <sup>2</sup> , n (%):                               |                                       |                                     |                                             |                                                                 |
| Urban                                                        | 5,108 (57.1)                          | 9,435 (58.8)                        | 14,543 (58.2)                               | 42,860 (57.2)                                                   |
| Non-urban                                                    | 917 (10.3)                            | 1,309 (8.2)                         | 2,226 (8.9)                                 | 7,319 (9.8)                                                     |
| Missing                                                      | 2,915 (32.6)                          | 5,304 (33.1)                        | 8,219 (32.9)                                | 24,785 (33.1)                                                   |
| Diabetes mellitus, n (%):                                    |                                       |                                     |                                             |                                                                 |
| Type 1                                                       | 28 (0.3)                              | 59 (0.4)                            | 87 (0.4)                                    | 266 (0.4)                                                       |
| Non-type 1                                                   | 482 (5.4)                             | 786 (4.9)                           | 1,238 (5.1)                                 | 2,744 (3.7)                                                     |
| Type 1, non-type1 or DM prescription <sup>3</sup>            | 612 (6.9)                             | 929 (5.8)                           | 1,541 (6.2)                                 | 3,381 (4.5)                                                     |
| CVD diagnosis, n (%):                                        | 329 (3.4)                             | 638 (4.0)                           | 967 (3.9)                                   | 2,079 (2.8)                                                     |
| Modified Charlson index, n (%):                              |                                       |                                     |                                             |                                                                 |
| 0                                                            | 6,660 (74.5)                          | 12,580 (78.4)                       | 19,240 (77.0)                               | 60,234 (80.4)                                                   |
| 1                                                            | 1,884 (21.1)                          | 2,813 (17.5)                        | 4,697 (18.8)                                | 12,037 (16.1)                                                   |
| 2 or more                                                    | 396 (4.4)                             | 655 (4.1)                           | 1,051 (4.2)                                 | 2,693 (3.6)                                                     |
| Smoking status, n (%):                                       |                                       |                                     |                                             |                                                                 |
| Never smoked                                                 | 2,923 (32.7)                          | 4,865 (30.3)                        | 7,788 (31.2)                                | 34,196 (45.6)                                                   |
| Ex-smoker                                                    | 1,773 (19.8)                          | 2,339 (14.6)                        | 4,112 (16.5)                                | 13,816 (18.4)                                                   |
| Current smoker                                               | 3,787 (42.4)                          | 7,384 (46.0)                        | 11,171 (44.7)                               | 19,104 (25.5)                                                   |
| Missing                                                      | 457 (5.1)                             | 1,460 (9.1)                         | 1,917 (7.7)                                 | 7,848 (10.5)                                                    |
| BMI kg/m <sup>2</sup> , mean (SD):                           | 27.05 (6.23)                          | 25.90 (6.02)                        | 26.34 (6.13)                                | 26.59 (5.80)                                                    |
| Missing, n (%)                                               | 1,521 (17.0)                          | 4,201 (26.2)                        | 5,722 (22.9)                                | 19,775 (26.4)                                                   |
| Obesity, n (%):                                              |                                       |                                     |                                             |                                                                 |
| Defined by BMI <sup>4,5</sup>                                | 1,995 (22.3)                          | 2,639 (16.4)                        | 4,634 (18.5)                                | 13,036 (17.4)                                                   |
| Defined by Read code <sup>5</sup>                            | 542 (6.1)                             | 656 (4.1)                           | 1,198 (4.8)                                 | 3,082 (4.1)                                                     |
| Defined by BMI OR, if no BMI before index date, by Read code | 2,003 (22.4)                          | 2,651 (16.5)                        | 4,654 (18.6)                                | 13,103 (17.5)                                                   |
| No obesity                                                   | 5,424 (60.7)                          | 9,208 (57.4)                        | 14,632 (58.6)                               | 42,153 (56.2)                                                   |
| Missing                                                      | 1,513 (16.9)                          | 4,189 (26.1)                        | 5,702 (22.8)                                | 19,708 (26.3)                                                   |
| Blood pressure, n (%):                                       |                                       |                                     |                                             |                                                                 |
| ≥140/90 mmHg                                                 | 1,797 (20.1)                          | 2,970 (18.5)                        | 4,767 (19.1)                                | 13,878 (18.5)                                                   |
| <140/90 mmHg                                                 | 6,217 (69.35)                         | 10,206 (63.6)                       | 16,423 (65.7)                               | 47,062 (62.8)                                                   |
| BP missing                                                   | 926 (10.4)                            | 2,872 (17.9)                        | 3,798 (15.2)                                | 14,024 (18.7)                                                   |

<sup>1</sup> Includes 276 matched comparators who later became part of SMI group during study period. <sup>2</sup> All variables at baseline except Townsend and rurality, which are last reported. <sup>3</sup> Diabetes mellitus prescription excludes patients prescribed metformin with a prior diagnosis of PCOS. <sup>4</sup> Most recent BMI before index date ≥30 kg/m<sup>2</sup> (27.5kg/m<sup>2</sup> if non-White ethnicity). <sup>5</sup> Disregarded if recorded for patient aged <16 years. IQR – interquartile range, SD – standard deviation, SMI – severe mental illness, DM – diabetes mellitus, PCOS – polycystic ovary symptom, CVD – cardiovascular disease, BMI – body mass index, BP – blood pressure



#### 4.3.2 All-cause mortality

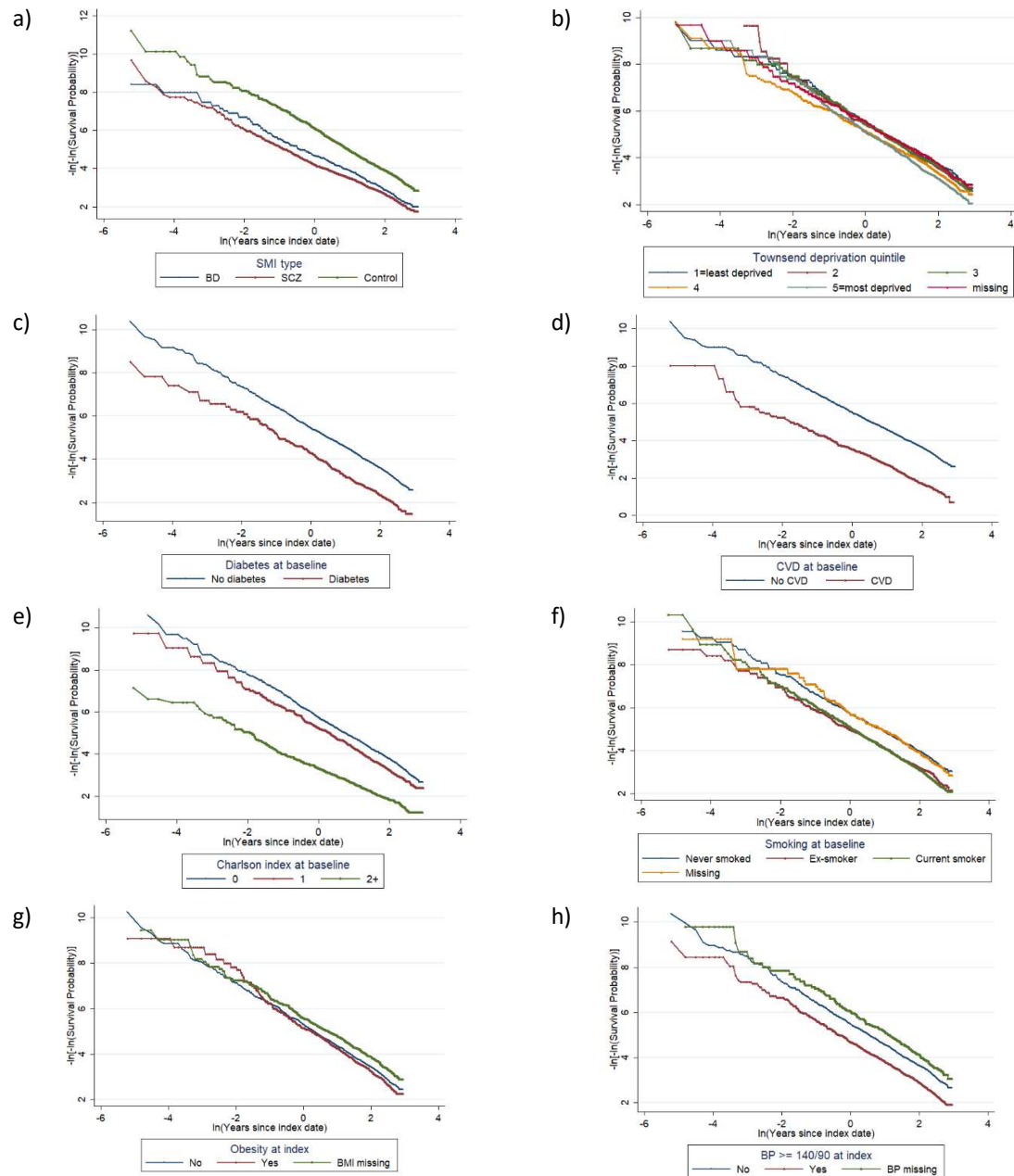
There were 2,089 deaths from all-causes prior to age 75 years during the study period. Crude mortality rates were higher for patients with BD and schizophrenia than matched non-SMI comparators. For BD there were 7.9 deaths per 1,000 person years of follow-up (95% CI: 7.0-8.8). For schizophrenia the rate was 10.3 (95% CI: 9.6-11.1), whereas for the non-SMI group it was 2.8 (95% CI: 2.6-3.0).

Figure 4.7 shows log-log plots for each of the covariates. Although there are crossing lines in the graphs for some of the covariates, formal tests for non-zero slope of the Schoenfeld residuals (Table 4.5) showed that the proportional hazards assumption was violated only by SMI. In Figure 4.7a the lines appeared non-parallel in the early part of the analysis time corresponding to <1 year since index date. This could be due to differential hazards of mortality affecting SMI patients in the first year of diagnosis compared with later years. Risk of suicide is known to be particularly high in patients with SMI within a year of diagnosis. (142, 202, 203) Follow-up time was split at one year after index date and a variable representing the interaction between SMI and time (<1 year,  $\geq 1$  year since index) was added. In a model with SMI and SMI X time interaction a further test of the proportional hazards assumption no longer showed evidence of a violation ( $p=0.978$ ).

Table 4.6 shows HRs from univariable and multivariable Cox regression on time since index date. Both BD and schizophrenia had a large effect on all-cause mortality in the first year since SMI diagnosis. Unadjusted HRs were 5.01, 95% CI: 3.45-7.27 for BD and 6.61, 95% CI: 5.18-8.44 for schizophrenia. The effect of SMI was reduced after the first year of follow-up but was still substantial. Unadjusted HRs were BD: 2.49, 95% CI: 2.07-3.00 and

schizophrenia: 3.56, 95% CI: 3.10-4.08. Adding Townsend quintile made only small differences to these figures. Of the covariates adjusted for in the full model, living in the most deprived two quintiles, being a current or ex-smoker, having CVD, diabetes mellitus, having blood pressure  $\geq 140/90$  mmHg or increasing numbers of other comorbidities were associated with increased mortality. Obesity had no significant effect on mortality. After adjusting for covariates in the full model, the HR remained very high for schizophrenia up to one year after SMI diagnosis (HR: 6.65, 95% CI: 5.13-8.63) but reduced a little for BD (HR: 4.39, 95% CI: 2.93-6.58). Covariates also had an effect on the association between SMI and mortality after the first year since diagnosis. Fully adjusted HRs were reduced to BD: 2.23, 95% CI: 1.83-2.72; schizophrenia: 3.17, 95% CI: 2.73-3.67.

The full model was checked again to ensure the proportional hazards assumption was met. The global test for the final model showed no evidence of proportional hazards violation ( $p=0.780$ ). Log-log plots of SMI, adjusted for the other model covariates showed no lack of proportionality (Figure 4.8). Also, plots of scaled Schoenfeld residuals for each of the covariates (Figure 4.9) showed no patterns indicating lack of model fit.



SMI – severe mental illness, BD – bipolar disorder, SCZ – schizophrenia, CVD – cardiovascular disease

**Figure 4.7: Plots of survival function against time (log scales) to assess proportional hazards assumption for a) SMI, b) deprivation, c) diabetes mellitus, d) CVD, e) Charlson index, f) smoking, g) obesity, h) blood pressure**

**Table 4.5: p-values from tests of proportional hazards assumption in univariate Cox regression analyses, incident cohort**

| Variable                                   | PH test (zero slope of scaled Schoenfeld residuals), p-value |
|--------------------------------------------|--------------------------------------------------------------|
| SMI (vs matched non-SMI comparison group): |                                                              |
| BD                                         | 0.022                                                        |
| Schizophrenia                              | 0.018                                                        |
| <i>Global PH test for SMI</i>              | <i>0.004</i>                                                 |
| Townsend quintile (vs 1=least deprived):   |                                                              |
| 2                                          | 0.520                                                        |
| 3                                          | 0.796                                                        |
| 4                                          | 0.581                                                        |
| 5                                          | 0.424                                                        |
| Missing                                    | 0.386                                                        |
| <i>Global PH test for Townsend</i>         | <i>0.673</i>                                                 |
| Diabetes mellitus at baseline:             | 0.748                                                        |
| CVD at baseline:                           | 0.622                                                        |
| Charlson index at baseline (vs 0)          |                                                              |
| 1                                          | 0.841                                                        |
| 2+                                         | 0.102                                                        |
| <i>Global PH test for Charlson</i>         | <i>0.226</i>                                                 |
| Smoking at baseline (vs never smoked):     |                                                              |
| Ex-smoker                                  | 0.806                                                        |
| Current smoker                             | 0.426                                                        |
| Missing                                    | 0.331                                                        |
| <i>Global PH test for smoking</i>          | <i>0.742</i>                                                 |
| Obesity at baseline (vs no obesity):       |                                                              |
| Has obesity                                | 0.361                                                        |
| BMI missing                                | 0.208                                                        |
| <i>Global PH test for obesity</i>          | <i>0.215</i>                                                 |
| Blood pressure at baseline:                |                                                              |
| ≥ 140/90 mmHg                              | 0.038                                                        |
| BP missing                                 | 0.978                                                        |
| <i>Global PH test for BP</i>               | <i>0.106</i>                                                 |

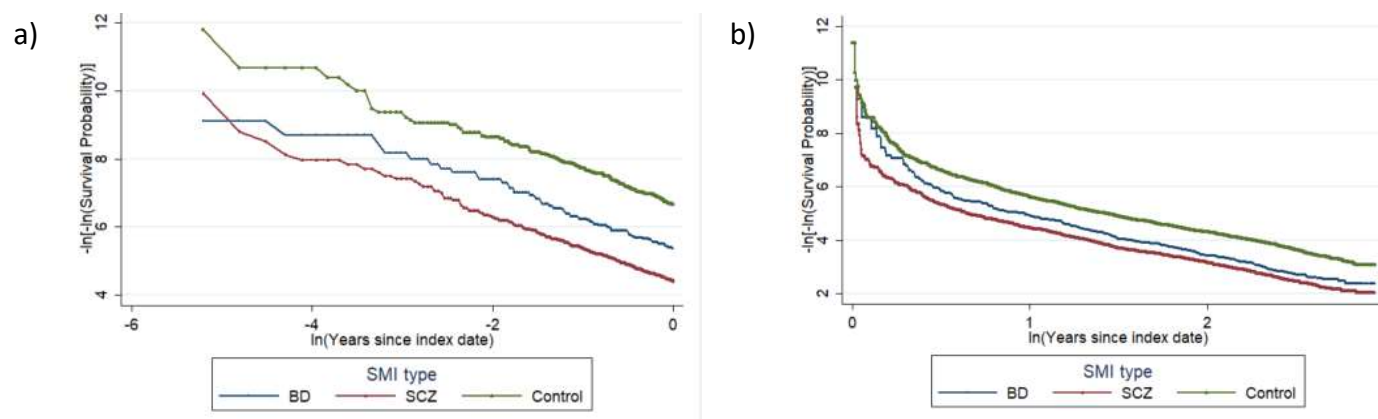
SMI – severe mental illness, BD – bipolar disorder, CVD – cardiovascular disease, BP – blood pressure, PH – proportional hazards

**Table 4.6: Hazard ratios for all-cause mortality in univariable and multivariable Cox regression analyses, incident cohort**

| Variable                         | Univariable (unadjusted) |        |      |      | Reduced model <sup>1</sup> |        |      |      | Full model <sup>2</sup> |        |      |      |
|----------------------------------|--------------------------|--------|------|------|----------------------------|--------|------|------|-------------------------|--------|------|------|
|                                  | HR                       | p      | lcl  | ucl  | HR                         | p      | lcl  | ucl  | HR                      | P      | lcl  | ucl  |
| SMI (<1 year after index):       |                          |        |      |      |                            |        |      |      |                         |        |      |      |
| No SMI (ref)                     | 1                        |        |      |      | 1                          |        |      |      | 1                       |        |      |      |
| BD                               | <b>5.01</b>              | <0.001 | 3.45 | 7.27 | <b>4.96</b>                | <0.001 | 3.41 | 7.22 | <b>4.39</b>             | <0.001 | 2.93 | 6.58 |
| SCZ                              | <b>6.61</b>              | <0.001 | 5.18 | 8.44 | <b>6.32</b>                | <0.001 | 4.94 | 8.09 | <b>6.65</b>             | <0.001 | 5.13 | 8.63 |
| SMI (≥1 year after index):       |                          |        |      |      |                            |        |      |      |                         |        |      |      |
| No SMI (ref)                     | 1                        |        |      |      | 1                          |        |      |      | 1                       |        |      |      |
| BD                               | <b>2.49</b>              | <0.001 | 2.07 | 3.00 | <b>2.38</b>                | <0.001 | 1.97 | 2.87 | <b>2.23</b>             | <0.001 | 1.83 | 2.72 |
| SCZ                              | <b>3.56</b>              | <0.001 | 3.10 | 4.08 | <b>3.30</b>                | <0.001 | 2.87 | 3.80 | <b>3.17</b>             | <0.001 | 2.73 | 3.67 |
| Townsend:                        |                          |        |      |      |                            |        |      |      |                         |        |      |      |
| 1 (least deprived)               | 1                        |        |      |      | 1                          |        |      |      | 1                       |        |      |      |
| 2                                | <b>1.26</b>              | 0.020  | 1.04 | 1.52 | <b>1.24</b>                | 0.041  | 1.01 | 1.53 | <b>1.21</b>             | 0.091  | 0.97 | 1.50 |
| 3                                | <b>1.40</b>              | 0.001  | 1.16 | 1.70 | <b>1.29</b>                | 0.019  | 1.04 | 1.59 | <b>1.17</b>             | 0.168  | 0.94 | 1.45 |
| 4                                | <b>2.14</b>              | <0.001 | 1.76 | 2.60 | <b>1.80</b>                | <0.001 | 1.46 | 2.23 | <b>1.59</b>             | <0.001 | 1.27 | 1.99 |
| 5 (most deprived)                | <b>2.94</b>              | <0.001 | 2.38 | 3.62 | <b>2.14</b>                | <0.001 | 1.71 | 2.69 | <b>1.76</b>             | <0.001 | 1.38 | 2.24 |
| Missing                          | <b>1.90</b>              | 0.002  | 1.28 | 2.83 | 1.48                       | 0.075  | 0.96 | 2.28 | 1.32                    | 0.227  | 0.84 | 2.08 |
| Diabetes mellitus <sup>3</sup> : | <b>1.80</b>              | <0.001 | 1.51 | 2.12 |                            |        |      |      | <b>1.37</b>             | 0.003  | 1.11 | 1.69 |
| CVD:                             | <b>2.45</b>              | <0.001 | 2.05 | 2.92 |                            |        |      |      | <b>2.01</b>             | <0.001 | 1.63 | 2.47 |
| Charlson index:                  |                          |        |      |      |                            |        |      |      |                         |        |      |      |
| 0                                | 1                        |        |      |      |                            |        |      |      | 1                       |        |      |      |
| 1                                | <b>1.71</b>              | <0.001 | 1.48 | 1.96 |                            |        |      |      | <b>1.60</b>             | <0.001 | 1.37 | 1.88 |
| 2+                               | <b>3.76</b>              | <0.001 | 3.15 | 4.47 |                            |        |      |      | <b>3.90</b>             | <0.001 | 3.19 | 4.78 |
| Smoking status:                  |                          |        |      |      |                            |        |      |      |                         |        |      |      |
| Never smoked                     | 1                        |        |      |      |                            |        |      |      | 1                       |        |      |      |
| Ex-smoker                        | <b>1.53</b>              | <0.001 | 1.31 | 1.79 |                            |        |      |      | <b>1.27</b>             | 0.007  | 1.07 | 1.52 |
| Current smoker                   | <b>2.59</b>              | <0.001 | 2.27 | 2.96 |                            |        |      |      | <b>1.99</b>             | <0.001 | 1.71 | 2.32 |
| Missing                          | 1.21                     | 0.096  | 0.97 | 1.52 |                            |        |      |      | 1.29                    | 0.092  | 0.96 | 1.75 |
| Obesity at baseline:             |                          |        |      |      |                            |        |      |      |                         |        |      |      |
| No                               | 1                        |        |      |      |                            |        |      |      | 1                       |        |      |      |
| Yes                              | 1.04                     | 0.514  | 0.92 | 1.19 |                            |        |      |      | 0.93                    | 0.380  | 0.80 | 1.09 |

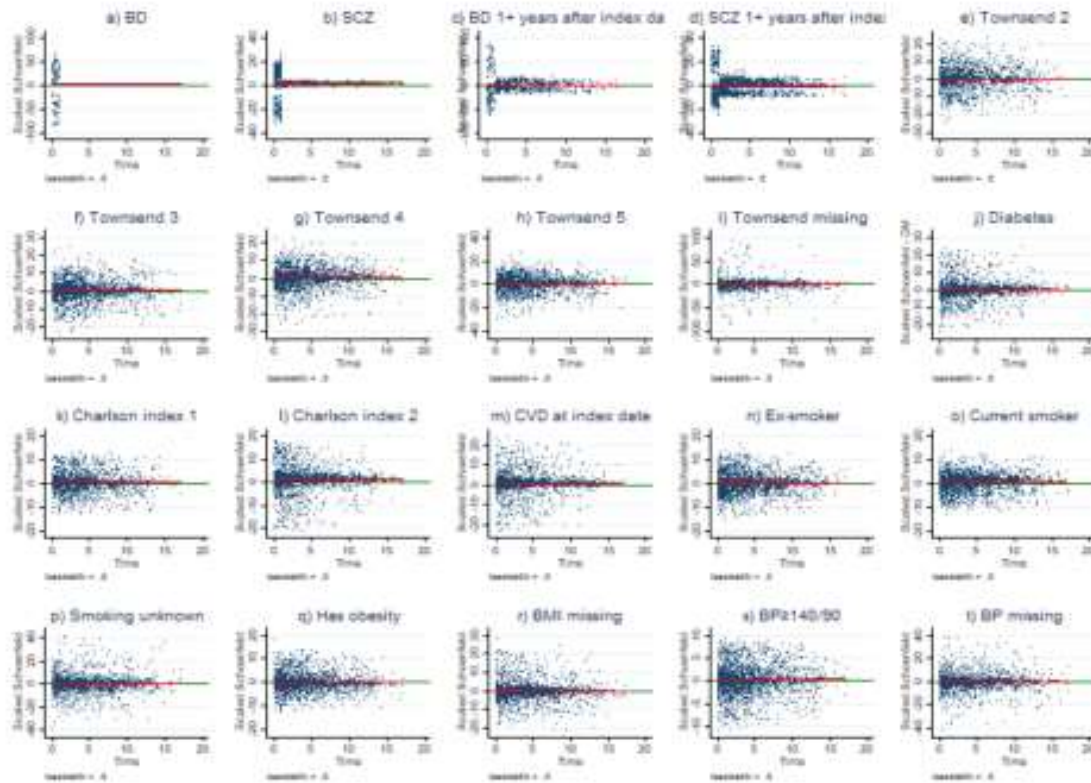
| Variable                    | Univariable (unadjusted) |       |      |      | Reduced model <sup>1</sup> |   |     |     | Full model <sup>2</sup> |       |      |      |
|-----------------------------|--------------------------|-------|------|------|----------------------------|---|-----|-----|-------------------------|-------|------|------|
|                             | HR                       | p     | lcl  | ucl  | HR                         | p | lcl | ucl | HR                      | P     | lcl  | ucl  |
| Unrecorded                  | 0.90                     | 0.166 | 0.77 | 1.05 |                            |   |     |     | 1.13                    | 0.236 | 0.92 | 1.39 |
| Blood pressure at baseline: |                          |       |      |      |                            |   |     |     |                         |       |      |      |
| <140/90 mmHg                | 1                        |       |      |      |                            |   |     |     | 1                       |       |      |      |
| ≥ 140/90 mmHg               | <b>1.12</b>              | 0.05  | 1.00 | 1.26 |                            |   |     |     | <b>1.25</b>             | 0.001 | 1.09 | 1.43 |
| BP missing                  | 0.85                     | 0.12  | 0.70 | 1.04 |                            |   |     |     | 1.01                    | 0.929 | 0.77 | 1.33 |

<sup>1</sup> adjusted for SMI and deprivation, <sup>2</sup> adjusted for SMI, deprivation, diabetes mellitus, Charlson index, CVD, smoking, obesity, blood pressure, <sup>3</sup> Type 1, non-type 1 or DM prescription, excluding patients prescribed metformin with a prior diagnosis of PCOS. SMI – severe mental illness, BD – bipolar disorder, SCZ – schizophrenia, CVD – cardiovascular disease, BP – blood pressure, HR – hazard ratio, lcl – lower 95% confidence limit, ucl – upper 95% confidence limit, DM – diabetes mellitus, PCOS – polycystic ovary syndrome. Analyses stratified by variable matching on age, sex, and general practice. Values that exclude the null highlighted in **bold**



SMI – severe mental illness, BD – bipolar disorder, SCZ – schizophrenia. Model adjusted for deprivation, diabetes mellitus, CVD, Charlson index, smoking, obesity, blood pressure. Stratified by age, sex, general practice

**Figure 4.8: Plots of survival function against time (log scales) to assess proportional hazards assumption for SMI a) <1 year after index date, b) 1 year or more after index date**

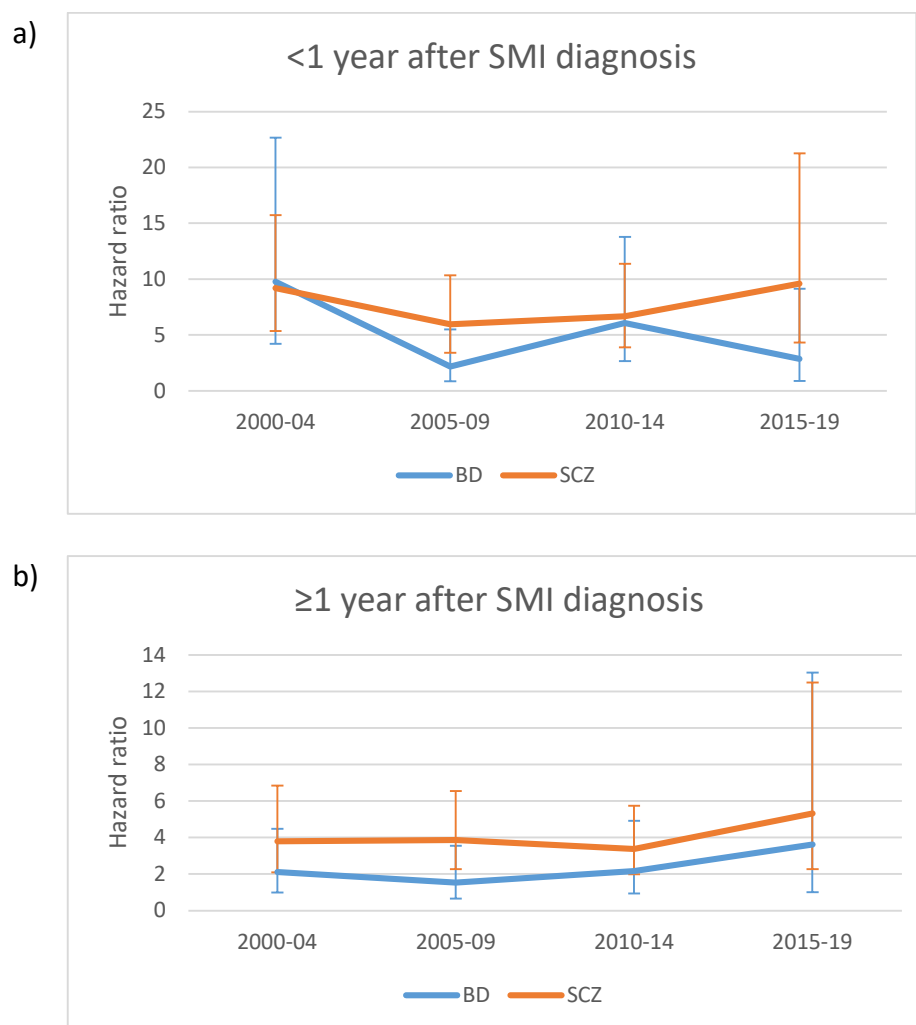


BD – bipolar disorder, SCZ – schizophrenia, CVD – cardiovascular disease. Model stratified by age, sex, general practice. If hazards are proportional, smoothed line through residuals (shown in red) should have slope of zero.

**Figure 4.9: Scaled Schoenfeld residuals for a) BD <1 year after index, b) schizophrenia <1 year after index, c) BD ≥ 1 year after index, d) schizophrenia ≥1 year after index, e-i) Townsend quintiles 2-5,missing, j) diabetes mellitus, k) Charlson index 1, l) Charlson index 2+, m) CVD, n) ex-smoker, o) current smoker, p) smoking status unknown, q) has obesity, r) BMI missing, s) BP ≥ 140/90 mmHg, t) BP missing, from multivariable Cox regression analysis of all-cause mortality**

### 4.3.2.1 Trend in all-cause mortality

To assess changes in mortality by SMI over time, separate multivariable Cox regression models were applied to records split by 5-year calendar period (Table 4.7). As can be seen in Figure 4.10, confidence intervals were wide and there was no strong trend by calendar period.



HRs predicted by Cox regression models for separate calendar periods: a) <1 year after SMI diagnosis, b) ≥1 year after SMI diagnosis. Analyses stratified by variable matching on age, sex, and general practice. Models adjusted by deprivation, diabetes mellitus, CVD, Charlson index, smoking, obesity. SMI – severe mental illness, BD – bipolar disorder, SCZ – schizophrenia, HR – hazard ratio.

**Figure 4.10: Trend in hazard ratios by SMI compared with matched non-SMI comparators for a) <1 year since diagnosis, b) ≥1 year since SMI diagnosis, incident cohort**



**Table 4.7: Hazard ratios for all-cause mortality in multivariable Cox regression analyses by five-year calendar period, incident cohort, <1 year after SMI diagnosis, ≥1 year after SMI diagnosis**

| Variable                   | 2000-04     |        |      |       | 2005-09     |        |      |       | 2010-14     |        |      |       | 2015-19     |        |      |       |
|----------------------------|-------------|--------|------|-------|-------------|--------|------|-------|-------------|--------|------|-------|-------------|--------|------|-------|
|                            | HR          | p      | lcl  | ucl   | HR          | p      | lcl  | ucl   | HR          | p      | lcl  | ucl   | HR          | p      | lcl  | ucl   |
| SMI (<1 year after index): |             |        |      |       |             |        |      |       |             |        |      |       |             |        |      |       |
| No SMI (ref)               | 1           |        |      |       | 1           |        |      |       | 1           |        |      |       | 1           |        |      |       |
| <b>BD</b>                  | <b>9.76</b> | <0.001 | 4.20 | 22.69 | 2.18        | 0.098  | 0.86 | 5.51  | <b>6.06</b> | <0.001 | 2.66 | 13.80 | 2.86        | 0.077  | 0.89 | 9.14  |
| <b>SCZ</b>                 | <b>9.19</b> | <0.001 | 5.37 | 15.74 | <b>5.95</b> | <0.001 | 3.42 | 10.34 | <b>6.67</b> | <0.001 | 3.91 | 11.37 | <b>9.60</b> | <0.001 | 4.33 | 21.28 |
| SMI (≥1 year after index): |             |        |      |       |             |        |      |       |             |        |      |       |             |        |      |       |
| No SMI (ref)               | 1           |        |      |       | 1           |        |      |       | 1           |        |      |       | 1           |        |      |       |
| <b>BD</b>                  | <b>2.12</b> | 0.050  | 1.00 | 4.48  | 1.54        | 0.308  | 0.67 | 3.50  | 2.16        | 0.066  | 0.95 | 4.92  | <b>3.63</b> | 0.048  | 1.01 | 13.04 |
| <b>SCZ</b>                 | <b>3.80</b> | <0.001 | 2.11 | 6.86  | <b>3.86</b> | <0.001 | 2.27 | 6.56  | <b>3.38</b> | <0.001 | 1.99 | 5.75  | <b>5.32</b> | <0.001 | 2.27 | 12.49 |

SMI – severe mental illness, BD – bipolar disorder, SCZ – schizophrenia, HR – hazard ratio, lcl – lower 95% confidence limit, ucl – upper 95% confidence limit. Adjusted by deprivation, diabetes mellitus, CVD, Charlson index, smoking, obesity, blood pressure. Analyses stratified by variable matching on age, sex, and general practice. Values that exclude the null highlighted in **bold**

### 4.3.3 Incidence of cardiovascular disease

Figure 4.11 shows the numbers of SMI patients and matched non-SMI comparators included in the analysis. The cohort for the incident CVD analysis included 23,992 patients with SMI (BD: 8,600; schizophrenia: 15,392) and 70,300 matched comparators (Table 4.8). Patients with SMI and non-SMI comparators were slightly less well matched than for the whole incident cohort. The mean age of those with SMI was 38.7 years (SD: 14.3) vs 38.2 years (SD: 14.0) for the non-SMI comparison group and the percentage of males was 51.6 vs 51.5 for SMI and non-SMI, respectively. Table 4.8 shows that after excluding patients with CVD at baseline, the incident CVD cohort had fewer patients with comorbidities (diabetes mellitus, obesity and Charlson index of 2+) and fewer ex-smokers than the main cohort.

In total, 1,638 patients had a first diagnosis of CVD during their period of follow-up. Crude CVD incidence rates were higher for patients with BD and schizophrenia than the matched comparison group. BD: 5.2 per 1,000 person years at risk (PYAR) (95% CI: 4.5-6.0); schizophrenia: 4.7 per 1,000 PYAR (95% CI: 4.2-5.3), whereas for non-SMI comparators the incidence rate was 3.2 per 1,000 PYAR (95% CI: 3.0-3.4).

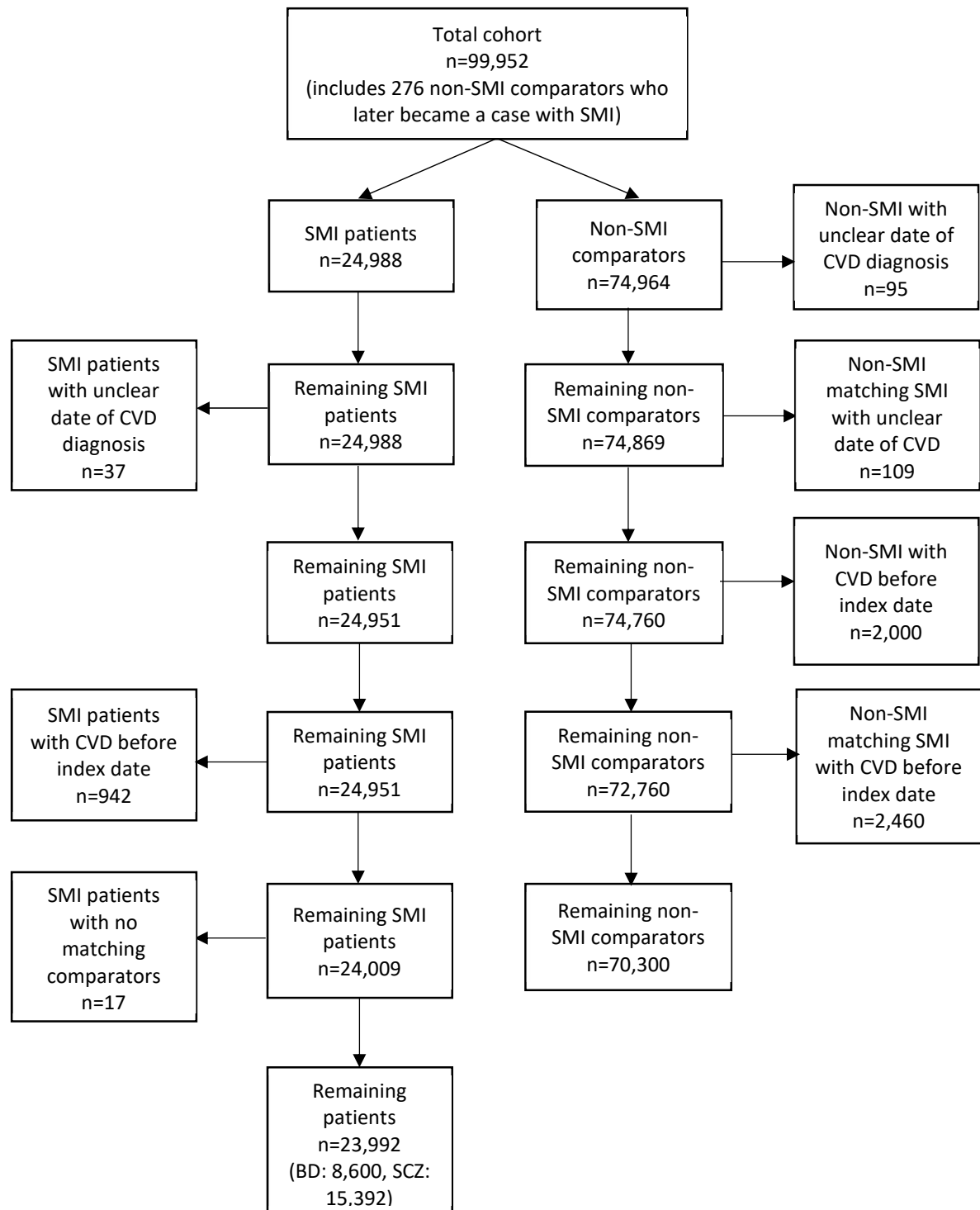


**Figure 4.11: Flow chart showing incident cohort cases and controls included in analysis of CVD incidence**

There was no substantial violation of the proportional hazards assumption for any of the covariates, (see Figure 4.12, Table 4.9), with the exception of Charlson index, which had some evidence of non-proportionality ( $p=0.03$ ). Proportionality was improved by categorising the Charlson index into four groups instead of three (0,1,2,3+), however in a multivariable Cox regression a more granular grouping for Charlson index made little difference to the HRs for the other variables. As the Charlson index was not the main variable of interest, the variable was categorised into only three groups to simplify the model.

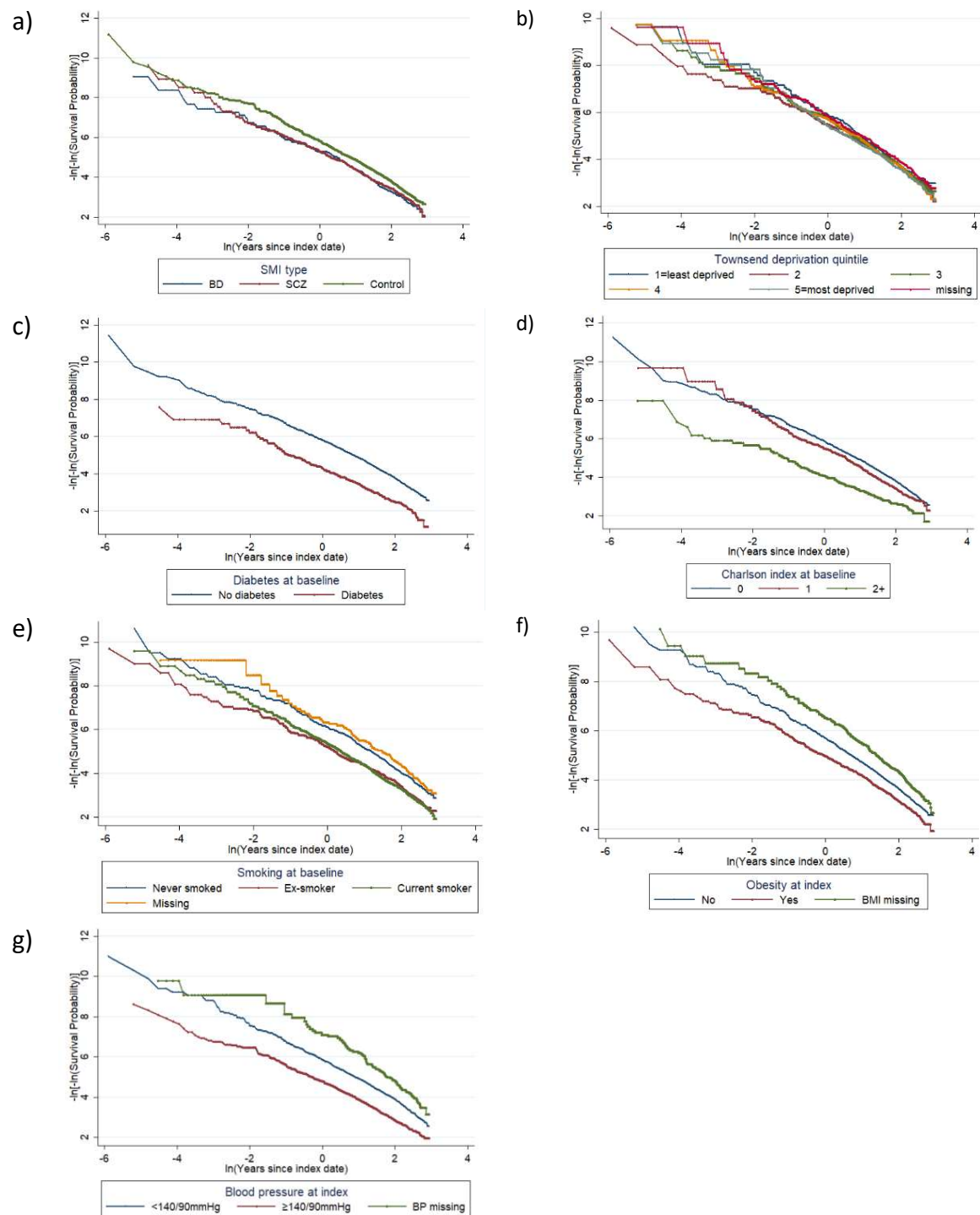
Table 4.10 shows HRs from univariable and multivariable Cox regression on time to CVD diagnosis since index date. In unadjusted analyses, BD and schizophrenia were associated with around a 50% increase in CVD incidence compared with the non-SMI comparison group (BD: HR=1.63, 95% CI: 1.35-1.97; schizophrenia: HR=1.45, 95% CI: 1.25-1.67). The largest association with CVD incidence was current smoking (HR=2.54, 95% CI: 2.18-2.95), followed by diabetes mellitus (HR=2.21, 95% CI: 1.77-2.74), although ex-smoking, deprivation, Charlson comorbidity and obesity were also associated with 40%-60% increases in CVD incidence. Unrecorded blood pressure was associated with a 37% lower risk of CVD incidence, although this became non-significant after adjusting for other covariates. Unrecorded obesity status was associated with a 22% decrease in CVD incidence. After adjusting for all covariates included in the univariable analysis, HRs for SMI were reduced to BD: HR=1.41, 95% CI: 1.16-1.72, schizophrenia: HR=1.30, 95% CI: 1.11-1.51.

Scaled Schoenfeld residuals showed no evidence of proportional hazards violations in the full model, either visually (Figure 4.13) or in a global test for non-zero slope ( $p=0.70$ ).

**Table 4.8: Baseline characteristics of SMI patients and matched non-SMI comparison group for incident CVD analysis**

|                                                     | <b>Bipolar Disorder<br/>(n=8,600)</b> | <b>Schizophrenia<br/>(n=15,392)</b> | <b>All patients with SMI<br/>(n=23,992)</b> | <b>Comparators (no SMI)<br/>(n=70,300)<sup>1</sup></b> |
|-----------------------------------------------------|---------------------------------------|-------------------------------------|---------------------------------------------|--------------------------------------------------------|
| Person years of follow-up:                          | 38,063                                | 68,299                              | 106,362                                     | 353,592                                                |
| Median follow-up, years (IQR):                      | 3.2<br>(1.2-6.6)                      | 3.1<br>(1.2-6.7)                    | 3.2<br>(1.2-6.6)                            | 3.8<br>(1.6-7.5)                                       |
| Male, n (%):                                        | 3,355 (39.0)                          | 9,026 (58.6)                        | 12,381 (51.6)                               | 36,197 (51.5)                                          |
| Age at index date (years), mean (SD):               | 40.2 (13.6)                           | 37.8 (14.6)                         | 38.7 (14.3)                                 | 38.2 (14.0)                                            |
| Townsend deprivation quintile <sup>2</sup> , n (%): |                                       |                                     |                                             |                                                        |
| 1 (least deprived)                                  | 1,316 (15.3)                          | 1,652 (10.7)                        | 2,968 (12.4)                                | 12,377 (17.6)                                          |
| 2                                                   | 1,241 (14.4)                          | 1,754 (11.4)                        | 2,995 (12.5)                                | 11,495 (16.4)                                          |
| 3                                                   | 1,561 (18.2)                          | 2,563 (16.7)                        | 4,124 (17.2)                                | 12,697 (18.1)                                          |
| 4                                                   | 1,701 (19.8)                          | 3,217 (20.9)                        | 4,918 (20.5)                                | 12,191 (17.3)                                          |
| 5 (most deprived)                                   | 1,379 (16.0)                          | 3,783 (24.6)                        | 5,162 (21.5)                                | 10,167 (14.5)                                          |
| Missing                                             | 1,402 (16.3)                          | 2,423 (15.7)                        | 3,825 (15.9)                                | 11,373 (16.2)                                          |
| Diabetes mellitus <sup>3</sup> , n (%):             | 535 (6.2)                             | 784 (5.1)                           | 1,319 (5.5)                                 | 2,656 (3.8)                                            |
| Modified Charlson index, n (%):                     |                                       |                                     |                                             |                                                        |
| 0                                                   | 6,468 (75.2)                          | 12,214 (79.4)                       | 18,682 (77.9)                               | 57,078 (81.2)                                          |
| 1                                                   | 1,794 (20.9)                          | 2,679 (17.4)                        | 4,473 (18.6)                                | 11,150 (15.9)                                          |
| 2 or more                                           | 338 (3.9)                             | 499 (3.2)                           | 837 (3.5)                                   | 2,072 (3.0)                                            |
| Smoking status, n (%):                              |                                       |                                     |                                             |                                                        |
| Never smoked                                        | 2,825 (32.9)                          | 4,690 (30.5)                        | 7,515 (31.3)                                | 32,542 (46.3)                                          |
| Ex-smoker                                           | 1,670 (19.4)                          | 2,127 (13.8)                        | 3,797 (15.8)                                | 12,164 (17.3)                                          |
| Current smoker                                      | 3,654 (42.5)                          | 7,127 (46.3)                        | 10,781 (44.9)                               | 17,967 (25.6)                                          |
| Missing                                             | 451 (5.2)                             | 1,448 (9.4)                         | 1,899 (7.9)                                 | 7,627 (10.9)                                           |
| BMI, mean (SD):                                     | 26.97 (6.22)                          | 25.80 (6.00)                        | 26.35 (6.11)                                | 26.44 (5.77)                                           |
| Missing, n (%):                                     | 1,491 (17.3)                          | 4,131 (26.8)                        | 5,622 (23.4)                                | 19,256 (27.4)                                          |
| Obesity, n (%):                                     |                                       |                                     |                                             |                                                        |
| Has obesity <sup>4</sup>                            | 1,881 (21.9)                          | 2,456 (16.0)                        | 4,337 (18.1)                                | 11,708 (16.7)                                          |
| No obesity                                          | 5,235 (60.9)                          | 8,815 (57.3)                        | 14,050 (58.6)                               | 39,400 (56.1)                                          |
| Missing                                             | 1,484 (17.3)                          | 4,121 (26.8)                        | 5,605 (23.4)                                | 19,192 (27.3)                                          |
| Blood pressure, n (%):                              |                                       |                                     |                                             |                                                        |
| ≥140/90 mmHg                                        | 1,664 (19.4)                          | 2,752 (17.9)                        | 4,416 (18.4)                                | 12,110 (17.2)                                          |
| <140/90 mmHg                                        | 6,018 (70.0)                          | 9,780 (63.5)                        | 15,798 (65.9)                               | 44,396 (63.2)                                          |
| BP missing                                          | 918 (10.7)                            | 2,860 (18.6)                        | 3,778 (15.8)                                | 13,794 (19.6)                                          |

<sup>1</sup> Includes 256 matched comparators who later became part of SMI group during study period. <sup>2</sup> All variables at baseline except Townsend and rurality, which are last reported. <sup>3</sup> Diabetes mellitus includes type 1, non-type 1, and DM prescription (excluding patients prescribed metformin with a prior diagnosis of PCOS). <sup>4</sup> Defined by BMI ≥30kg/m<sup>2</sup> (27.5kg/m<sup>2</sup> if non-White ethnicity) OR, if no BMI before index date, by Read code; disregarded if BMI or obesity Read code recorded for patient aged <16 years. IQR – interquartile range, SD – standard deviation, SMI – severe mental illness, DM – diabetes mellitus, PCOS – polycystic ovary symptom, CVD – cardiovascular disease, BMI – body mass index, BP – blood pressure



SMI – severe mental illness, BD – bipolar disorder, SCZ – schizophrenia, CVD – cardiovascular disease

**Figure 4.12: Plots of survival function against time (log scales) to assess proportional hazards assumption for a) SMI, b) deprivation, c) diabetes mellitus, d) Charlson index, e) smoking, f) obesity, g) blood pressure, incident cohort, CVD incidence**

**Table 4.9: p-values from tests of proportional hazards assumption in univariate Cox regression analyses, incident cohort, CVD incidence**

| Variable                                    | PH test (zero slope of scaled Schoenfeld residuals), p-value |
|---------------------------------------------|--------------------------------------------------------------|
| SMI (vs non-SMI comparison group):          |                                                              |
| <b>BD</b>                                   | 0.294                                                        |
| <b>Schizophrenia</b>                        | 0.924                                                        |
| <i>Global PH test for SMI</i>               | <i>0.573</i>                                                 |
| Townsend quintile (vs 1=least deprived):    |                                                              |
| 2                                           | 0.490                                                        |
| 3                                           | 0.527                                                        |
| 4                                           | 0.968                                                        |
| 5                                           | 0.678                                                        |
| Missing                                     | 0.546                                                        |
| <i>Global PH test for Townsend</i>          | <i>0.941</i>                                                 |
| Diabetes mellitus at baseline:              | 0.841                                                        |
| Charlson index at baseline, 3 groups (vs 0) |                                                              |
| 1                                           | 0.183                                                        |
| 2+                                          | 0.013                                                        |
| <i>Global PH test for Charlson</i>          | <i>0.030</i>                                                 |
| Charlson index at baseline, 4 groups (vs 0) |                                                              |
| 1                                           | 0.181                                                        |
| 2                                           | 0.071                                                        |
| 3+                                          | 0.040                                                        |
| <i>Global PH test for Charlson</i>          | <i>0.051</i>                                                 |
| Smoking at index date (vs never smoked):    |                                                              |
| Ex-smoker                                   | 0.544                                                        |
| Current smoker                              | 0.148                                                        |
| Missing                                     | 0.760                                                        |
| <i>Global PH test for smoking</i>           | <i>0.446</i>                                                 |
| Obesity at index date (vs no obesity):      |                                                              |
| Has obesity                                 | 0.145                                                        |
| BMI missing                                 | 0.810                                                        |
| <i>Global PH test for obesity</i>           | <i>0.293</i>                                                 |
| Blood pressure at index date:               |                                                              |
| ≥ 140/90 mmHg                               | 0.282                                                        |
| BP missing                                  | 0.699                                                        |
| <i>Global PH test for BP</i>                | <i>0.461</i>                                                 |

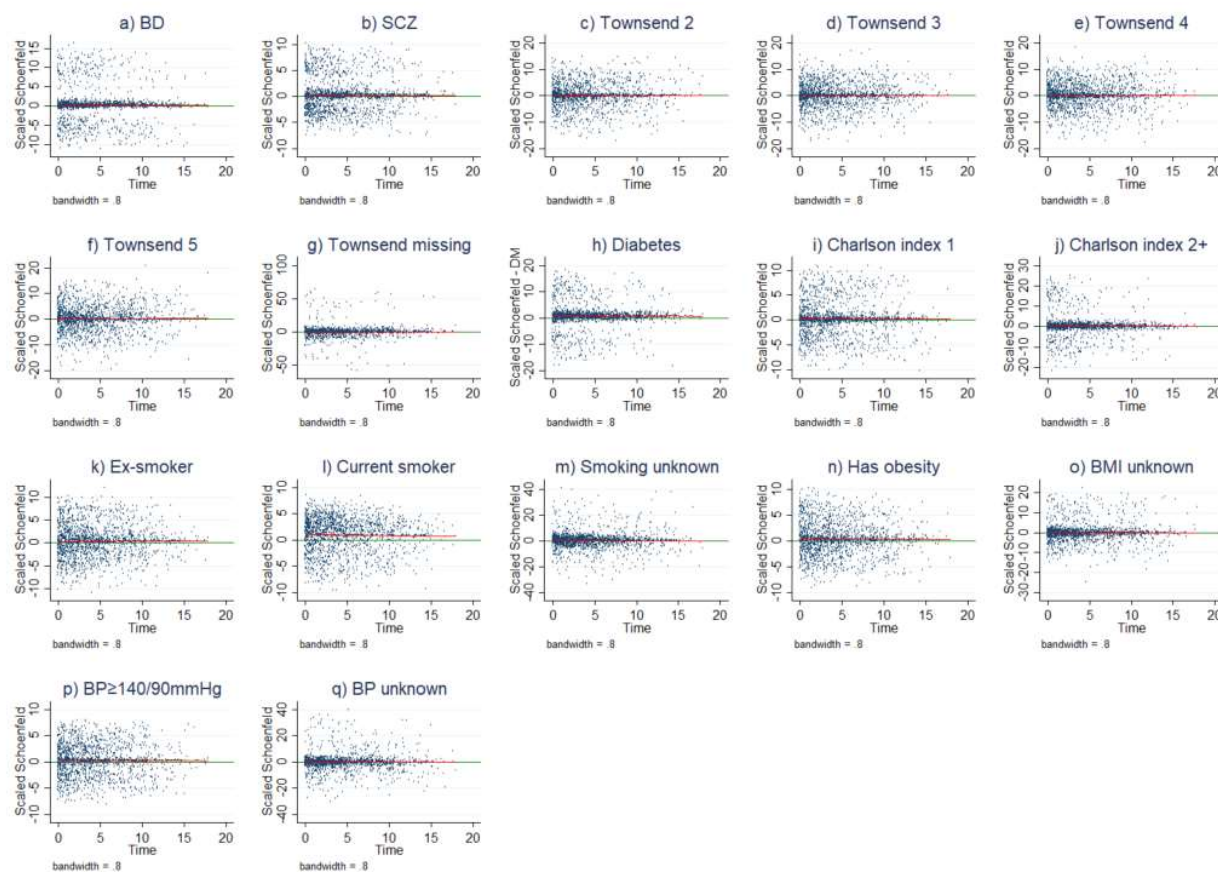
SMI – severe mental illness, BD – bipolar disorder, PH – proportional hazards, BMI – body mass index, BP – blood pressure

**Table 4.10: Hazard ratios for CVD incidence in univariable and multivariable Cox regression analyses, incident cohort**

| Variable                         |                    | Univariable (unadjusted) |        |      |      | Reduced model <sup>1</sup> |        |      |      | Full model <sup>2</sup> |        |      |      |
|----------------------------------|--------------------|--------------------------|--------|------|------|----------------------------|--------|------|------|-------------------------|--------|------|------|
|                                  |                    | HR                       | p      | lcl  | ucl  | HR                         | p      | lcl  | ucl  | HR                      | p      | lcl  | ucl  |
| SMI:                             | No SMI (ref)       | 1                        |        |      |      | 1                          |        |      |      | 1                       |        |      |      |
|                                  | BD                 | <b>1.63</b>              | <0.001 | 1.35 | 1.97 | <b>1.61</b>                | <0.001 | 1.33 | 1.95 | <b>1.41</b>             | 0.001  | 1.16 | 1.72 |
|                                  | SCZ                | <b>1.45</b>              | <0.001 | 1.25 | 1.67 | <b>1.40</b>                | <0.001 | 1.21 | 1.62 | <b>1.30</b>             | 0.001  | 1.11 | 1.51 |
| Townsend:                        | 1 (least deprived) | 1                        |        |      |      | 1                          |        |      |      | 1                       |        |      |      |
|                                  | 2                  | 1.20                     | 0.082  | 0.98 | 1.48 | 1.19                       | 0.107  | 0.96 | 1.47 | 1.12                    | 0.321  | 0.90 | 1.39 |
|                                  | 3                  | <b>1.36</b>              | 0.005  | 1.10 | 1.68 | <b>1.32</b>                | 0.012  | 1.06 | 1.64 | 1.21                    | 0.098  | 0.97 | 1.51 |
|                                  | 4                  | <b>1.62</b>              | <0.001 | 1.30 | 2.02 | <b>1.54</b>                | <0.001 | 1.12 | 1.92 | 1.21                    | 0.110  | 0.96 | 1.53 |
|                                  | 5 (most deprived)  | <b>1.59</b>              | <0.001 | 1.26 | 2.02 | <b>1.44</b>                | 0.003  | 1.13 | 1.83 | 1.16                    | 0.266  | 0.90 | 1.49 |
|                                  | Missing            | 1.16                     | 0.490  | 0.76 | 1.77 | 1.09                       | 0.673  | 0.72 | 1.67 | 0.85                    | 0.462  | 0.54 | 1.32 |
| Diabetes mellitus <sup>3</sup> : |                    | <b>2.21</b>              | <0.001 | 1.77 | 2.74 |                            |        |      |      | <b>1.99</b>             | <0.001 | 1.58 | 2.51 |
| Charlson index:                  | 0                  | 1                        |        |      |      |                            |        |      |      | 1                       |        |      |      |
|                                  | 1                  | <b>1.45</b>              | <0.001 | 1.24 | 1.69 |                            |        |      |      | <b>1.28</b>             | 0.004  | 1.08 | 1.51 |
|                                  | 2+                 | <b>1.39</b>              | 0.007  | 1.10 | 1.77 |                            |        |      |      | 1.25                    | 0.083  | 0.97 | 1.61 |
| Smoking status:                  | Never smoked       | 1                        |        |      |      |                            |        |      |      | 1                       |        |      |      |
|                                  | Ex-smoker          | <b>1.48</b>              | <0.001 | 1.24 | 1.76 |                            |        |      |      | <b>1.39</b>             | <0.001 | 1.16 | 1.65 |
|                                  | Current smoker     | <b>2.54</b>              | <0.001 | 2.18 | 2.95 |                            |        |      |      | <b>2.47</b>             | <0.001 | 2.10 | 2.90 |
|                                  | Missing            | 1.02                     | 0.883  | 0.78 | 1.34 |                            |        |      |      | <b>1.46</b>             | 0.030  | 1.04 | 2.05 |
| Obesity at baseline:             | No                 | 1                        |        |      |      |                            |        |      |      | 1                       |        |      |      |
|                                  | Yes                | <b>1.40</b>              | <0.001 | 1.21 | 1.62 |                            |        |      |      | <b>1.35</b>             | <0.001 | 1.16 | 1.58 |
|                                  | Unrecorded         | <b>0.78</b>              | 0.009  | 0.65 | 0.94 |                            |        |      |      | 0.92                    | 0.485  | 0.73 | 1.16 |
| Blood pressure at baseline:      |                    |                          |        |      |      |                            |        |      |      |                         |        |      |      |
|                                  | <140/90 mmHg       | 1                        |        |      |      |                            |        |      |      | 1                       |        |      |      |
|                                  | ≥ 140/90 mmHg      | <b>1.28</b>              | <0.001 | 1.12 | 1.47 |                            |        |      |      | <b>1.27</b>             | 0.001  | 1.10 | 1.46 |
|                                  | BP missing         | <b>0.63</b>              | <0.001 | 0.48 | 0.82 |                            |        |      |      | 0.76                    | 0.097  | 0.54 | 1.05 |

SMI – severe mental illness, BD – bipolar disorder, SCZ – schizophrenia, CVD – cardiovascular disease, DM – diabetes mellitus, HR – hazard ratio, lcl – lower 95% confidence limit, ucl – upper 95% confidence limit. Analyses stratified by variable matching on age, sex, and general practice. <sup>1</sup> adjusted for SMI and deprivation, <sup>2</sup> adjusted for SMI, deprivation, diabetes mellitus, Charlson index, smoking, obesity, blood pressure, <sup>3</sup> Includes type 1, non-type 1, and DM prescription (excluding patients prescribed metformin with a prior diagnosis of PCOS). Values that exclude the null highlighted in **bold**





BD – bipolar disorder, SCZ – schizophrenia, CVD – cardiovascular disease. Model stratified by age, sex, general practice. If hazards are proportional, smoothed line through residuals (shown in red) should have slope of zero.

**Figure 4.13: Scaled Schoenfeld residuals for a) BD, b) schizophrenia, c-g) Townsend quintiles 2-5, missing, h) diabetes mellitus, i) Charlson index 1, j) Charlson index 2+, k) ex-smoker, l) current smoker, m) smoking status unknown, n) has obesity, o) BMI unknown, p) BP $\geq$ 140/90 mmHg, q) BP unknown, from multivariable Cox regression analysis of CVD incidence, incident cohort**

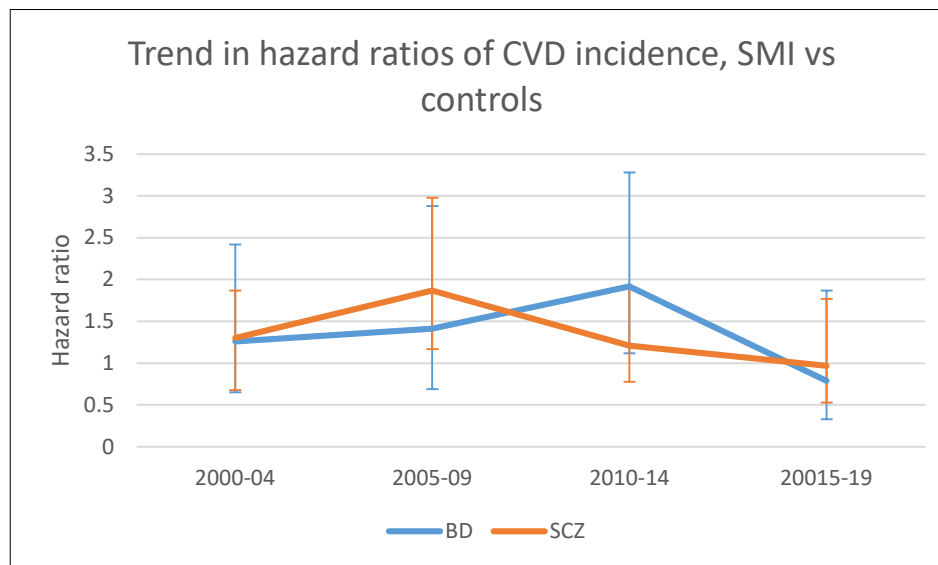
#### 4.3.3.1 Trend in cardiovascular incidence

To explore changes in the association between SMI and CVD incidence over time, separate Cox regression models were applied to records split by 5-year calendar period (Table 4.11). They were adjusted by deprivation, diabetes mellitus, Charlson index, smoking status, obesity, and blood pressure. SMI patients and matched non-SMI comparators with an index date within each calendar period only were included in each model. Figure 4.14 shows the risk of CVD incidence increased for schizophrenia compared with non-SMI comparators between 2000-04 and 2005-09 (the confidence interval excluded one) but decreased thereafter. Whereas for BD, the risk of CVD incidence was higher than matched comparators only in the period 2010-14.

**Table 4.11: Hazard ratios for CVD incidence in multivariable Cox regression analyses by five year calendar period, incident cohort**

| Variable     | 2000-04 |       |      |      | 2005-09     |       |      |      | 2010-14     |       |      |      | 2015-19 |       |      |      |
|--------------|---------|-------|------|------|-------------|-------|------|------|-------------|-------|------|------|---------|-------|------|------|
|              | HR      | p     | lcl  | ucl  | HR          | p     | lcl  | ucl  | HR          | p     | lcl  | ucl  | HR      | p     | lcl  | ucl  |
| SMI:         |         |       |      |      |             |       |      |      |             |       |      |      |         |       |      |      |
| No SMI (ref) | 1       |       |      |      | 1           |       |      |      | 1           |       |      |      | 1       |       |      |      |
| BD           | 1.26    | 0.489 | 0.66 | 2.42 | 1.41        | 0.346 | 0.69 | 2.88 | <b>1.92</b> | 0.017 | 1.12 | 3.28 | 0.79    | 0.588 | 0.33 | 1.87 |
| SCZ          | 1.13    | 0.646 | 0.68 | 1.87 | <b>1.87</b> | 0.009 | 1.17 | 2.98 | 1.21        | 0.393 | 0.78 | 1.90 | 0.97    | 0.915 | 0.53 | 1.77 |

SMI – severe mental illness, BD – bipolar disorder, SCZ – schizophrenia, HR – hazard ratio, lcl – lower 95% confidence limit, ucl – upper 95% confidence limit. Adjusted by deprivation, diabetes mellitus, Charlson index, smoking status, obesity, and blood pressure. Analyses stratified by variable matching on age, sex, and general practice. Values that exclude the null highlighted in **bold**



SMI – severe mental illness, BD – bipolar disorder, SCZ – schizophrenia, CVD – cardiovascular disease, HR – hazard ratio. HRs predicted by Cox regression models adjusted by deprivation, diabetes mellitus, Charlson index, smoking status, obesity, and blood pressure. Analyses stratified by variable matching on age, sex, and general practice.

**Figure 4.14: Trend in hazard ratios for CVD incidence, SMI compared with non-SMI comparison group, incident cohort**

## 4.4 Results – part 2: prevalent cohort study

### 4.4.1 Prevalent cohort characteristics

The cohort comprised 9,243,001 participants aged 16-74 years, including 109,570 (1.2%) with a diagnosis of SMI. Of these, 2,741 (2.5%) had a Read code indicating previous SMI with no prior Read code, indicating a new SMI diagnosis. The date of SMI incidence was thus unclear, and these patients were excluded from further analysis. Patients with SMI who were diagnosed with dementia either before or within a year of their SMI diagnosis (n=542) were excluded, as their SMI could be mis-diagnosed early dementia. Of the remaining 106,287 with SMI, 27,078 (25.5%) were new cases, with an incident diagnosis during follow-up. The other 79,209 (74.5%) were historic or prevalent cases, having a first SMI diagnosis occurring before the start of follow-up. The patients with SMI, together with 9,133,431 without SMI made up a cohort of 9,239,718 patients who were included in further analysis (Figure 4.15).

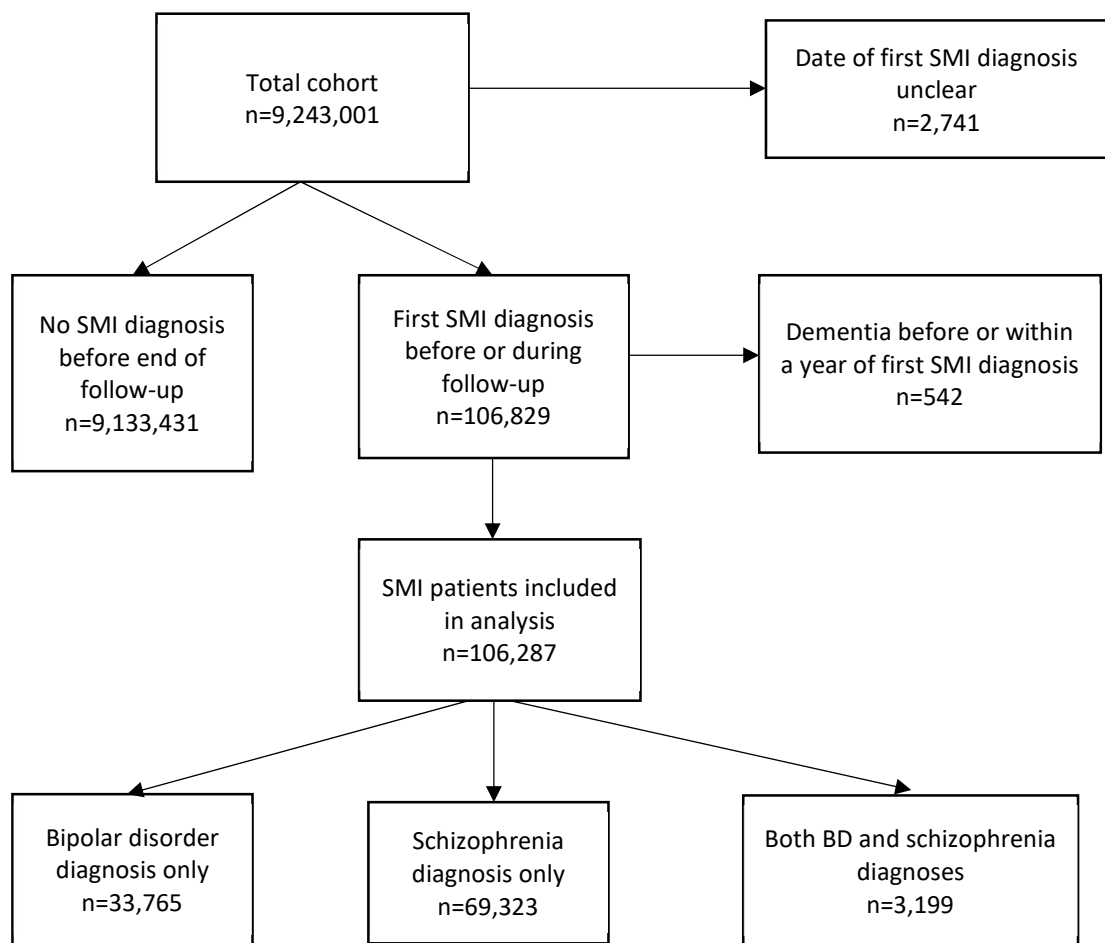


**Figure 4.15: Flow chart showing patients included in prevalent cohort analysis**

Table 4.12 shows the baseline characteristics for the cohort. The cohort was followed up for a total of 57,864,332 person years, with shorter follow-up for those with SMI than without SMI. 49.0% were males (including 60.1% of those with schizophrenia and 41.0% of those with BD). Median age at start of follow-up for patients with no SMI was 34.9 years (IQR: 24.4 – 49.5) but was older for people with SMI (BD: median: 44.2, IQR: 33.6 – 56.0, schizophrenia: 41.7, IQR: 31.3-54.0).

Fewer patients with SMI had missing ethnicity than those without SMI (BD: 45.9%, SCZ: 47.5%, no SMI: 52.5%). Of those with ethnicity recorded, those with a BD diagnosis had a higher percentage than the other groups recorded as White, patients with schizophrenia had a higher percentage recorded as Black and those without SMI had a higher percentage recorded as Asian. Patients with schizophrenia had higher percentages in the most deprived quintiles than those with BD or with no SMI. Fewer patients with SMI lived in England compared with those without SMI. The percentage of people with schizophrenia was higher in urban areas than the other groups. Diabetes mellitus was more common amongst patients with SMI than those without SMI (7.3% vs 3.1%), as was a diagnosis of CVD (BD: 5.0%, SCZ: 4.6%, no SMI: 2.9%). People with SMI also had higher Charlson indices compared with those without SMI. Smoking rates were higher amongst those with SMI. 49.1% of people with schizophrenia and 42.4% with BD were current smokers compared with 22.2% of the unmatched comparison group. People with SMI were more likely to have a recorded BMI than non-SMI comparators and had higher rates of obesity (BD: 24.0%, SCZ: 20.8%, no SMI: 12.5%). There were also higher rates of recorded blood pressure (BP) and total:HDL cholesterol ratios amongst those with SMI compared with those without SMI. The percentage of those with high BP (systolic  $\geq 140$  mmHg or diastolic  $\geq 90$  mmHg) or high

cholesterol (total:HDL ratio above the median for the whole cohort) was higher for patients with SMI than patients without SMI. However, across the whole cohort, 90.1% did not have total:HDL cholesterol ratio recorded at baseline. Cholesterol measurements were thus not able to be used in further analysis.

**Table 4.12: Baseline characteristics, prevalent cohort**

|                                                                                        | <b>BD<sup>1</sup><br/>(n=36,964)</b> | <b>SCZ<sup>1</sup><br/>(n=72,522)</b> | <b>No SMI<sup>1</sup><br/>(n=9,160,509)</b> |
|----------------------------------------------------------------------------------------|--------------------------------------|---------------------------------------|---------------------------------------------|
| Person years of follow-up:                                                             | 180,104                              | 354,699                               | 57,329,529                                  |
| Median follow-up, years (IQR):                                                         | 3.4 (1.3-7.3)                        | 3.3 (1.2-7.3)                         | 4.7 (1.9-9.9)                               |
| Male, n (%):                                                                           | 15,150 (41.0)                        | 43,547 (60.1)                         | 4,487,286 (49.0)                            |
| Age at baseline, years: median (IQR):                                                  | 44.2 (33.6-56.0)                     | 41.7 (31.3-54.0)                      | 34.9 (24.4-49.5)                            |
| Ethnicity, n (%)                                                                       |                                      |                                       |                                             |
| White                                                                                  | 18,326 (49.6)                        | 32,461 (44.8)                         | 3,728,345 (40.7)                            |
| Asian                                                                                  | 673 (1.8)                            | 1,864 (2.6)                           | 274,741 (3.0)                               |
| Black                                                                                  | 506 (1.4)                            | 2,393 (3.3)                           | 154,702 (1.7)                               |
| Chinese                                                                                | 51 (0.1)                             | 113 (0.2)                             | 42,596 (0.5)                                |
| Mixed                                                                                  | 242 (0.7)                            | 650 (0.9)                             | 52,404 (0.6)                                |
| Other                                                                                  | 204 (0.6)                            | 613 (0.9)                             | 97,333 (1.1)                                |
| Missing                                                                                | 16,962 (45.9)                        | 34,428 (47.5)                         | 4,810,388 (52.5)                            |
| Townsend deprivation quintile <sup>2</sup> , n (%):                                    |                                      |                                       |                                             |
| 1 (least deprived)                                                                     | 4,872 (13.2)                         | 6,670 (9.2)                           | 1,667,569 (18.2)                            |
| 2                                                                                      | 5,227 (14.1)                         | 7,976 (11.0)                          | 1,515,636 (16.6)                            |
| 3                                                                                      | 6,595 (17.8)                         | 11,509 (15.9)                         | 1,613,300 (17.6)                            |
| 4                                                                                      | 7,277 (19.7)                         | 15,476 (21.3)                         | 1,502,557 (16.4)                            |
| 5 (most deprived)                                                                      | 6,199 (16.8)                         | 17,311 (23.9)                         | 1,114,075 (12.2)                            |
| Missing                                                                                | 6,794 (18.4)                         | 13,580 (18.7)                         | 1,747,372 (19.1)                            |
| Country, n (%):                                                                        |                                      |                                       |                                             |
| England                                                                                | 25,031 (67.7)                        | 49,561 (68.3)                         | 6,476,042 (70.7)                            |
| Scotland                                                                               | 6,235 (16.9)                         | 10,669 (14.7)                         | 1,287,573 (14.1)                            |
| Wales                                                                                  | 4,401 (11.9)                         | 9,081 (12.5)                          | 1,064,576 (11.6)                            |
| Northern Ireland                                                                       | 1,297 (3.5)                          | 3,211 (4.4)                           | 332,318 (3.6)                               |
| Rurality <sup>2</sup> , n (%):                                                         |                                      |                                       |                                             |
| Urban                                                                                  | 20,040 (54.2)                        | 41,463 (57.2)                         | 5,026,857 (54.9)                            |
| Non-urban                                                                              | 3,838 (10.4)                         | 6,030 (8.3)                           | 1,045,905 (11.4)                            |
| Missing                                                                                | 13,086 (35.4)                        | 25,029 (34.5)                         | 3,087,747 (33.7)                            |
| Diabetes mellitus at baseline, n (%):                                                  |                                      |                                       |                                             |
| Type 1 (Read code)                                                                     | 105 (0.3)                            | 215 (0.3)                             | 26,440 (0.3)                                |
| Non-type 1 (Read code)                                                                 | 2,263 (6.1)                          | 4,626 (6.4)                           | 230,678 (2.5)                               |
| Diabetes mellitus (Type 1, non-type 1, or diabetes mellitus prescription) <sup>3</sup> | 2,706 (7.3)                          | 5,285 (7.3)                           | 285,574 (3.1)                               |
| CVD diagnosis at baseline, n (%):                                                      | 1,859 (5.0)                          | 3,355 (4.6)                           | 263,488 (2.9)                               |
| Modified Charlson index <sup>4</sup> , n (%):                                          |                                      |                                       |                                             |
| 0                                                                                      | 28,249 (76.4)                        | 57,672 (79.5)                         | 7,677,023 (83.8)                            |
| 1                                                                                      | 6,714 (18.2)                         | 11,877 (16.4)                         | 1,256,630 (13.7)                            |
| 2 or more                                                                              | 2,001 (5.4)                          | 2,973 (4.1)                           | 226,856 (2.5)                               |
| Smoking status at baseline, n (%):                                                     |                                      |                                       |                                             |
| Never smoked                                                                           | 11,430 (30.9)                        | 18,376 (25.3)                         | 3,888,158 (42.4)                            |

|                                                     | <b>BD<sup>1</sup></b><br><b>(n=36,964)</b> | <b>SCZ<sup>1</sup></b><br><b>(n=72,522)</b> | <b>No SMI<sup>1</sup></b><br><b>(n=9,160,509)</b> |
|-----------------------------------------------------|--------------------------------------------|---------------------------------------------|---------------------------------------------------|
| Ex-smoker                                           | 6,574 (17.8)                               | 9,362 (12.9)                                | 1,227,872 (13.4)                                  |
| Current smoker                                      | 15,681 (42.4)                              | 35,616 (49.1)                               | 2,030,113 (22.2)                                  |
| Missing                                             | 3,279 (8.9)                                | 9,168 (12.6)                                | 2,014,366 (22.0)                                  |
| BMI kg/m <sup>2</sup> at baseline, mean (SD):       | 27.4 (6.1)                                 | 26.9 (6.1)                                  | 25.9 (5.3)                                        |
| Missing, n (%)                                      | 7,250 (19.6)                               | 18,437 (25.4)                               | 3,322,206 (36.3)                                  |
| Obesity at baseline, n (%):                         |                                            |                                             |                                                   |
| Defined by BMI <sup>5,6</sup>                       | 8,745 (23.7)                               | 14,811 (20.4)                               | 1,129,458 (12.3)                                  |
| Defined by Read code <sup>6</sup>                   | 2,318 (6.3)                                | 3,431 (4.7)                                 | 217,373 (2.4)                                     |
| Defined by BMI (OR Read code if no BMI at baseline) | 8,861 (24.0)                               | 15,046 (20.8)                               | 1,143,758 (12.5)                                  |
| No obesity                                          | 20,969 (56.7)                              | 39,274 (54.2)                               | 4,708,845 (51.4)                                  |
| Missing                                             | 7,134 (19.3)                               | 18,202 (25.1)                               | 3,307,906 (36.1)                                  |
| Blood pressure at baseline, n (%):                  |                                            |                                             |                                                   |
| ≥ 140/90 mmHg                                       | 7,820 (21.2)                               | 14,141 (19.5)                               | 1,516,157 (16.6)                                  |
| <140/90 mmHg                                        | 23,303 (63.0)                              | 43,134 (59.5)                               | 4,700,589 (51.3)                                  |
| BP missing                                          | 5,841 (15.8)                               | 15,247 (21.0)                               | 2,943,763 (32.1)                                  |
| Cholesterol at baseline, n (%):                     |                                            |                                             |                                                   |
| Total:HDL ratio>cohort median                       | 4,666 (12.6)                               | 7,728 (10.7)                                | 432,204 (4.7)                                     |
| Total:HDL ratio≤cohort median                       | 4,795 (13.0)                               | 6,953 (9.6)                                 | 469,632 (5.1)                                     |
| Total:HDL ratio missing                             | 27,503 (74.4)                              | 57,841 (80.0)                               | 8,258,670 (90.2)                                  |

<sup>1</sup> Patients may have periods of follow-up in more than one category. <sup>2</sup> All variables at baseline except Townsend and rurality, which are last reported. <sup>3</sup> Diabetes mellitus prescription excludes patients prescribed metformin with a prior diagnosis of PCOS.

<sup>4</sup> Recorded at start date for each patient. <sup>5</sup> Most recent BMI before index date ≥30 kg/m<sup>2</sup> (27.5kg/m<sup>2</sup> if non-White ethnicity).

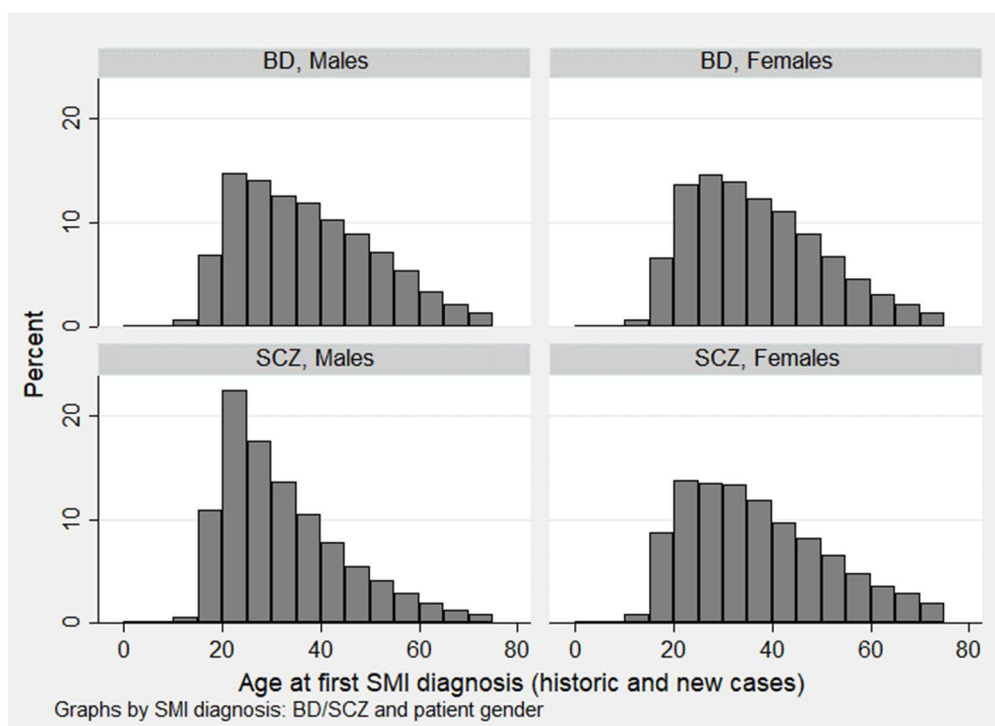
<sup>6</sup> Disregarded if recorded for patient aged<16 years, IQR – interquartile range, SD – standard deviation, SMI – severe mental illness, PCOS – polycystic ovary symptom, CVD – cardiovascular disease, BMI – body mass index, mmHg – millimetres of mercury, HDL – high density lipoprotein cholesterol

## 4.4.2 Age at diagnosis of severe mental illness

### 4.4.2.1 All severe mental illness

Median age at first occurrence of SMI diagnosis was 32.5 years (IQR: 24.5–44.0) for all people with SMI. The age at first mention of schizophrenia diagnosis was younger for men than women (median 29.5, IQR: 22.8 – 39.5 for males; median 34.8, IQR: 25.5– 46.9 for females). The sexes were similar for age at first diagnosis of BD. Age at first SMI diagnosis peaked at ages 20-24 years for men with both BD and schizophrenia, although more dramatically for the latter condition. However, for women, typical age at first diagnosis was broadly spread between ages 20 to 40 years (Figure 4.16).



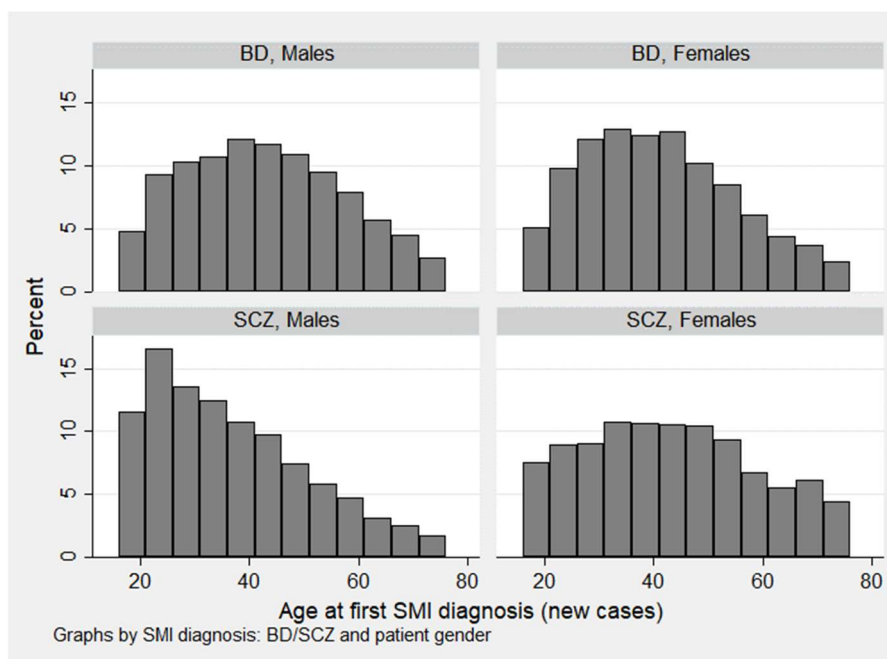


SMI – severe mental illness, BD – bipolar disorder, SCZ - schizophrenia

**Figure 4.16: Age in years at first mention of SMI diagnosis (prevalent and incident patients): males, females**

#### 4.4.2.2 New cases

The age at first diagnosis was slightly older for those with a first mention of SMI diagnosis during follow-up (median 39.1 years, IQR: 28.2 – 51.0), with a broader spread by age group (Figure 4.17).



SMI – severe mental illness, BD – bipolar disorder, SCZ - schizophrenia

**Figure 4.17: Age in years at first mention of SMI diagnosis (new cases): males, females**

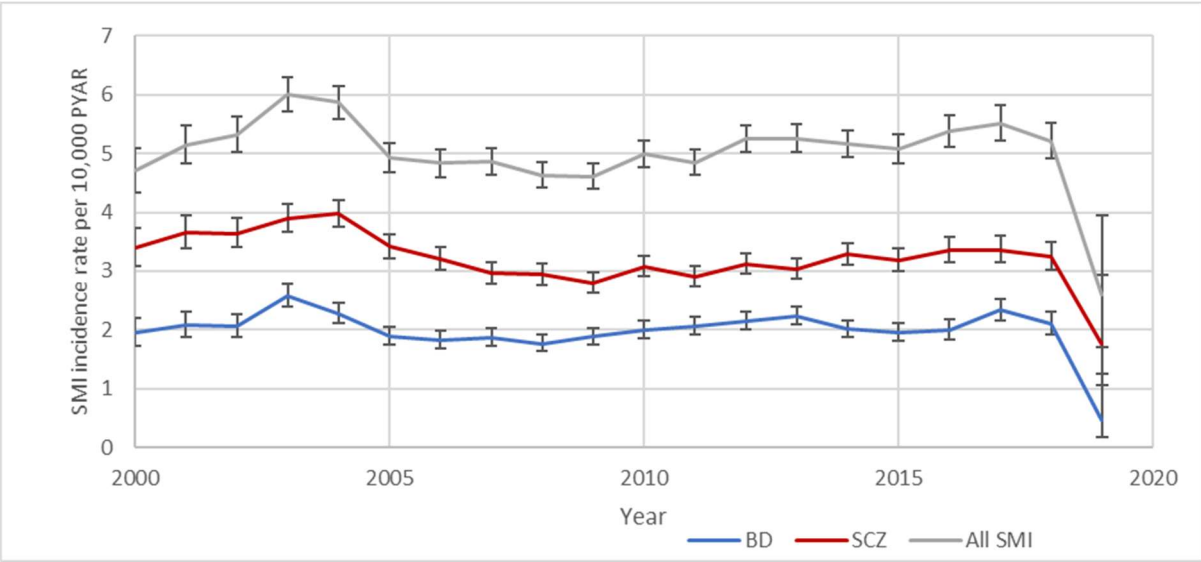
#### 4.4.3 Severe mental illness incidence

During the study period 27,078 patients had a new diagnosis of SMI. Of these, 11,775 had a diagnosis of BD and 18,596 of schizophrenia, with 3,293 being diagnosed with both conditions. The crude SMI incidence rate was 4.72 per 10,000 PYAR, (95% CI: 4.67-4.78).

Incidence rates for BD and schizophrenia were 2.04 (95% CI: 2.01-2.08) and 3.24 (95% CI: 3.19-3.28) PYAR, respectively. Figure 4.18 shows the trend in rates during the study period.

Rates peaked in 2003 for BD and in 2004 for schizophrenia. After 2004 rates for schizophrenia remained steady, whereas for BD they increased slightly over the study period. The dataset was extracted in January 2019, so there were relatively few patients contributing data in 2019 calendar year when incidence rates appear to reduce. The peaks approximately coincide with the introduction of the QOF in England in 2004. (190) Under this framework general practitioners (GPs) were remunerated for maintaining a register of

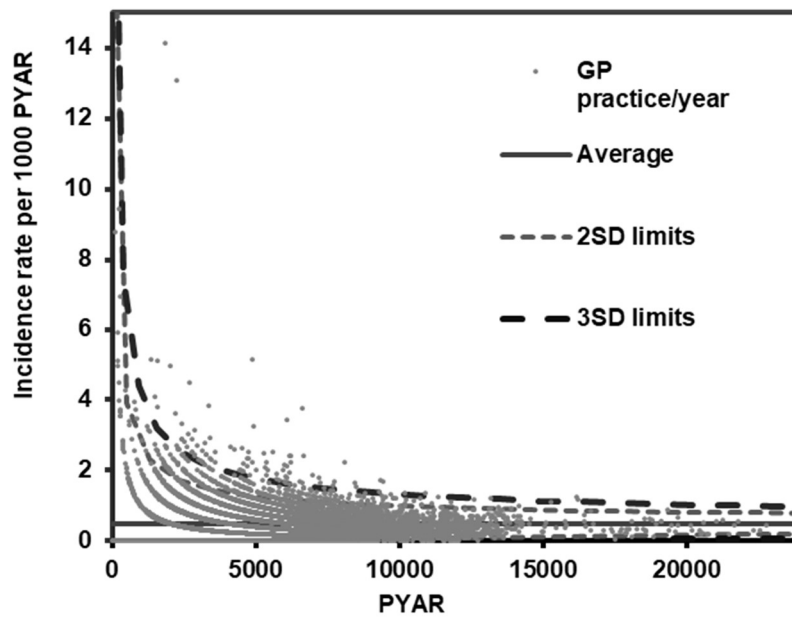
people with SMI and providing particular care activities to them. This change in policy could account for an increase in cases as GPs sought to maximise QOF payments by ensuring that known SMI patients were included on the register. Figure 4.19 shows a funnel plot of SMI incidence rates for practices in each calendar year they contributed data, produced from the funnel plot tool for rates developed by Public Health England. (204) Funnel plots are a type of control chart with control limits that indicate whether data points in a system are due to “common cause” (within the limits) or “special cause” (outside the limits). (205-207) 99.1% of data points were within 3SD control limits, meaning that <1% of values for practices over the study period had SMI incidence higher than expected, which could be due to “special causes” within those particular practices. Figure 4.20 shows the trend in practice SMI incidence rates by year. The most extreme outliers had rates of 14.1 and 13.1 per 1,000 PYAR in 2017 and 2005, respectively, compared with the median of 0.42 for all years and practices.



BD – bipolar disorder, SCZ – schizophrenia, SMI – severe mental illness

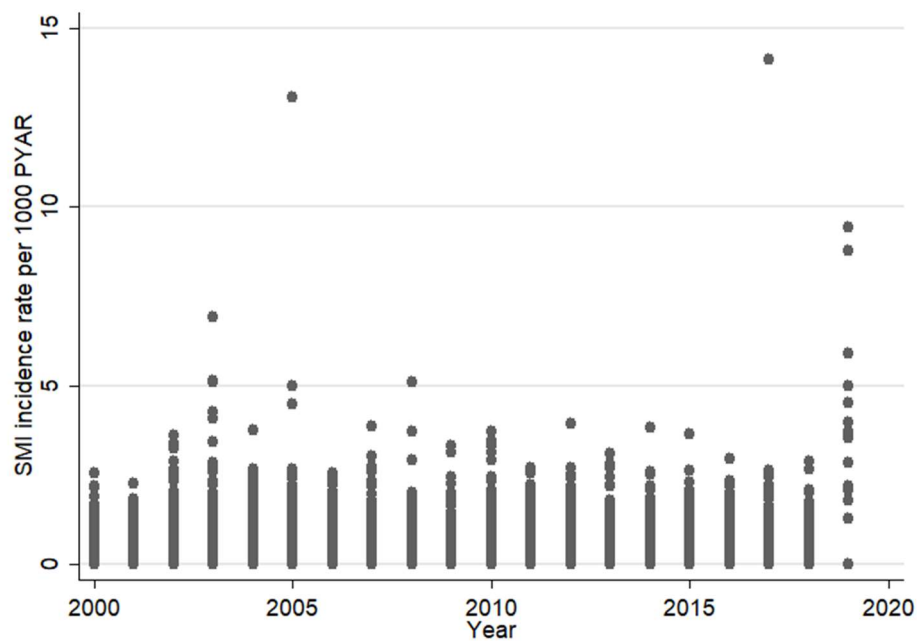
**Figure 4.18: Trend in SMI incidence: rate of new cases per 10,000 person years at risk**

**SMI incidence rate per 1000 person years at risk**



SMI – severe mental illness, PYAR – person years at risk, SD – standard deviation. Chart produced from the funnel plot tool for rates developed by Public Health England [accessed 19 May 2022]. Available from: <https://fingertips.phe.org.uk/profile/guidance/supporting-information/PH-methods> (204)

**Figure 4.19: Funnel plot showing SMI incidence rates per 1000 person years at risk for general practices by calendar year**

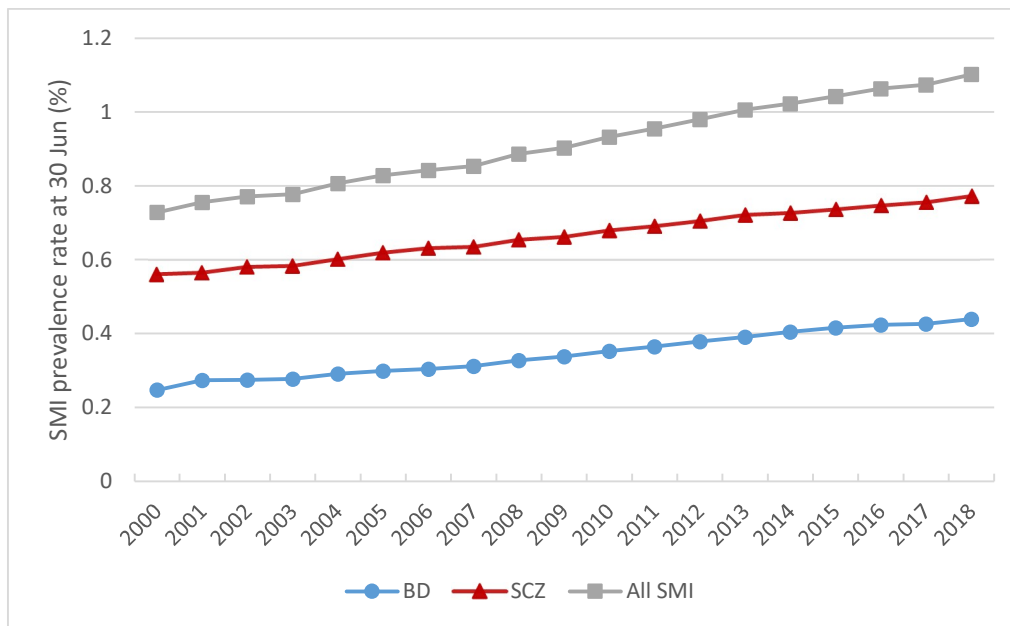


SMI – severe mental illness, PYAR – person years at risk

**Figure 4.20: Incidence rate of SMI per 1000 person years at risk, by general practice and year**

#### 4.4.4 Severe mental illness prevalence

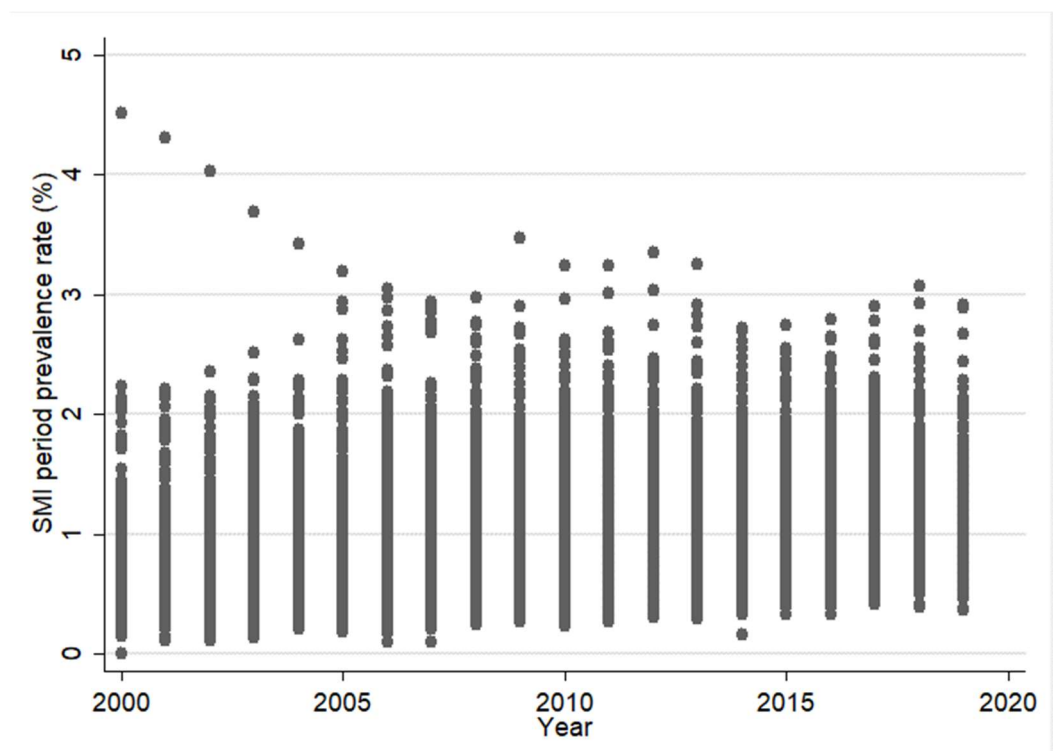
The overall prevalence rate of SMI during 2000-2019 was 1.15% (BD: 0.40%, schizophrenia: 0.78%). The annual mid-year point prevalence rate increased steadily for both BD and schizophrenia over the study period. The overall SMI rates increased from 0.73% in 2000 to 1.10% in 2018 (Figure 4.21).



BD – bipolar disorder, SCZ – schizophrenia, SMI – severe mental illness

**Figure 4.21: Trend in SMI prevalence rates: number of people with SMI as a percentage of mid-year population**

Annual SMI period prevalence rates for each general practice are shown in Figure 4.22. The median rate was 0.92% (IQR: 0.70-1.21) with some variability between practices. However, in two English practices, patients with SMI consistently accounted for between 3 and 4.5% of the registered population.



SMI – severe mental illness

**Figure 4.22: Prevalence rate of SMI: total cases of SMI as a percentage of annual practice population, by general practice and year**

#### 4.4.5 All-cause mortality

The overall crude mortality rate per thousand PYAR was 3.16 (95% CI: 3.15-3.18). For those with SMI, rates were 12.08 (95% CI: 11.72-12.44) for those with schizophrenia and 10.03 (95% CI: 9.57-10.50) for those with BD. The mortality rate for people without SMI was much lower, at 3.09 (95% CI: 3.07-3.10). Crude MRRs were 3.25 (95% CI: 3.10-3.40) for BD and 3.91 (95% CI: 3.80-4.03) for schizophrenia. These were reduced to 2.60 (95% CI: 2.49-2.73) and 3.45 (95% CI: 3.35-3.56), respectively, when adjusted by age and sex.

Table 4.13 shows that the HRs for all-cause mortality for each SMI diagnosis were raised compared to no SMI. Unadjusted HRs (which accounted for age as age was chosen for analysis time variable) for schizophrenia were higher than BD (schizophrenia: HR=3.45, 95%

CI: 3.35-3.56 vs BD: HR=2.50, 95% CI: 2.39-2.62). Schizophrenia results were similar when adjusted for sex and calendar period, but values were reduced when deprivation, country and comorbidities were included in the model (HR=2.68, 95% CI: 2.60-2.76). For BD, adjustment for deprivation and country reduced HRs compared with the minimally adjusted model and the addition of comorbidities reduced values further (HR=2.07, 95% CI: 1.98-2.17). HRs were reduced for females compared with males (HR: 0.67, 95% CI: 0.67-0.68). Results for sex were similar after adjustment for covariates. For calendar period, HRs showed that compared with 2000-04, there was a reducing gradient over time. The effect size was reduced, however, after full adjustment. Compared to those with White ethnicity, non-White ethnic groups had reduced HRs, whereas those with missing ethnicity had increased HRs. The HRs for non-missing values of Townsend score increased with increasing levels of deprivation in both adjusted and unadjusted models, although the effect size was smaller in the fully adjusted model. The effect of comorbidities (diabetes mellitus, any CVD diagnosis and Charlson index) was to increase HRs. However, the values of HRs were reduced when all these factors were included. Compared with England, HRs were increased for Scotland and Wales in the unadjusted analysis but were reduced for Scotland and Northern Ireland compared with England in the fully adjusted model. HRs were also raised for patients in urban areas. Patients recorded as current or ex-smokers and those with unknown smoking status at baseline had higher HRs than those who had never smoked. Similarly, patients with a record of obesity at baseline and those with unrecorded BMI both had a higher hazard of mortality than those with baseline BMI below 30 kg/m<sup>2</sup> (or 27.5 kg/m<sup>2</sup> if non-White ethnicity).

**Table 4.13: Hazard ratios for all-cause mortality in univariable and multivariable Cox regression analyses, prevalent cohort**

|                    | Univariable (unadjusted) |        |      |      | Minimally adjusted <sup>1</sup> |        |      |      | Partially adjusted <sup>2</sup> |        |      |      | Fully adjusted <sup>3</sup> |        |      |      |
|--------------------|--------------------------|--------|------|------|---------------------------------|--------|------|------|---------------------------------|--------|------|------|-----------------------------|--------|------|------|
| Variable           | HR                       | p      | lcl  | ucl  | HR                              | p      | lcl  | ucl  | HR                              | p      | lcl  | ucl  | HR                          | p      | lcl  | ucl  |
| SMI:               |                          |        |      |      |                                 |        |      |      |                                 |        |      |      |                             |        |      |      |
| No SMI (ref)       | 1                        |        |      |      | 1                               |        |      |      | 1                               |        |      |      | 1                           |        |      |      |
| BD                 | <b>2.50</b>              | <0.001 | 2.39 | 2.62 | <b>2.63</b>                     | <0.001 | 2.51 | 2.75 | <b>2.45</b>                     | <0.001 | 2.34 | 2.57 | <b>2.07</b>                 | <0.001 | 1.98 | 2.17 |
| SCZ                | <b>3.45</b>              | <0.001 | 3.35 | 3.56 | <b>3.49</b>                     | <0.001 | 3.38 | 3.60 | <b>3.06</b>                     | <0.001 | 2.97 | 3.15 | <b>2.68</b>                 | <0.001 | 2.60 | 2.76 |
| Sex:               |                          |        |      |      |                                 |        |      |      |                                 |        |      |      |                             |        |      |      |
| Males (ref)        | 1                        |        |      |      | 1                               |        |      |      | 1                               |        |      |      | 1                           |        |      |      |
| Females            | <b>0.67</b>              | <0.001 | 0.67 | 0.68 | <b>0.67</b>                     | <0.001 | 0.67 | 0.68 | <b>0.67</b>                     | <0.001 | 0.67 | 0.68 | <b>0.73</b>                 | <0.001 | 0.73 | 0.74 |
| Calendar period:   |                          |        |      |      |                                 |        |      |      |                                 |        |      |      |                             |        |      |      |
| 2000-04 (ref)      | 1                        |        |      |      | 1                               |        |      |      | 1                               |        |      |      | 1                           |        |      |      |
| 2005-09            | <b>0.96</b>              | <0.001 | 0.95 | 0.98 | <b>0.96</b>                     | <0.001 | 0.95 | 0.97 | <b>0.96</b>                     | <0.001 | 0.95 | 0.98 | 1.01                        | 0.297  | 0.99 | 1.02 |
| 2010-14            | <b>0.85</b>              | <0.001 | 0.84 | 0.86 | <b>0.85</b>                     | <0.001 | 0.84 | 0.86 | <b>0.84</b>                     | <0.001 | 0.83 | 0.86 | <b>0.91</b>                 | <0.001 | 0.90 | 0.93 |
| 2015-19            | <b>0.84</b>              | <0.001 | 0.82 | 0.85 | <b>0.83</b>                     | <0.001 | 0.82 | 0.84 | <b>0.82</b>                     | <0.001 | 0.80 | 0.83 | <b>0.92</b>                 | <0.001 | 0.90 | 0.93 |
| Ethnicity:         |                          |        |      |      |                                 |        |      |      |                                 |        |      |      |                             |        |      |      |
| White(ref)         | 1                        |        |      |      |                                 |        |      |      |                                 |        |      |      |                             |        |      |      |
| Asian              | <b>0.81</b>              | <0.001 | 0.77 | 0.86 |                                 |        |      |      |                                 |        |      |      |                             |        |      |      |
| Black              | 0.94                     | 0.070  | 0.88 | 1.01 |                                 |        |      |      |                                 |        |      |      |                             |        |      |      |
| Mixed              | <b>0.82</b>              | 0.008  | 0.71 | 0.95 |                                 |        |      |      |                                 |        |      |      |                             |        |      |      |
| Other              | <b>0.72</b>              | <0.001 | 0.64 | 0.80 |                                 |        |      |      |                                 |        |      |      |                             |        |      |      |
| Chinese            | <b>0.50</b>              | <0.001 | 0.41 | 0.62 |                                 |        |      |      |                                 |        |      |      |                             |        |      |      |
| Missing            | <b>2.00</b>              | <0.001 | 1.98 | 2.02 |                                 |        |      |      |                                 |        |      |      |                             |        |      |      |
| Townsend:          |                          |        |      |      |                                 |        |      |      |                                 |        |      |      |                             |        |      |      |
| 1 (least deprived) | 1                        |        |      |      |                                 |        |      |      | 1                               |        |      |      | 1                           |        |      |      |
| 2                  | <b>1.14</b>              | <0.001 | 1.13 | 1.16 |                                 |        |      |      | <b>1.14</b>                     | <0.001 | 1.13 | 1.16 | <b>1.09</b>                 | <0.001 | 1.08 | 1.11 |
| 3                  | <b>1.40</b>              | <0.001 | 1.38 | 1.42 |                                 |        |      |      | <b>1.39</b>                     | <0.001 | 1.37 | 1.42 | <b>1.24</b>                 | <0.001 | 1.22 | 1.26 |
| 4                  | <b>1.80</b>              | <0.001 | 1.77 | 1.83 |                                 |        |      |      | <b>1.78</b>                     | <0.001 | 1.75 | 1.81 | <b>1.46</b>                 | <0.001 | 1.44 | 1.48 |
| 5 (most deprived)  | <b>2.32</b>              | <0.001 | 2.28 | 2.35 |                                 |        |      |      | <b>2.27</b>                     | <0.001 | 2.23 | 2.30 | <b>1.72</b>                 | <0.001 | 1.69 | 1.75 |
| Missing            | <b>1.28</b>              | <0.001 | 1.26 | 1.30 |                                 |        |      |      | <b>1.27</b>                     | <0.001 | 1.25 | 1.30 | <b>1.15</b>                 | <0.001 | 1.13 | 1.17 |
| Country:           |                          |        |      |      |                                 |        |      |      |                                 |        |      |      |                             |        |      |      |
| England            | 1                        |        |      |      |                                 |        |      |      | 1                               |        |      |      | 1                           |        |      |      |
| Scotland           | <b>1.07</b>              | <0.001 | 1.05 | 1.08 |                                 |        |      |      | 1.01                            | 0.339  | 0.99 | 1.02 | <b>0.91</b>                 | <0.001 | 0.89 | 0.92 |
| Wales              | <b>1.06</b>              | <0.001 | 1.04 | 1.07 |                                 |        |      |      | <b>1.10</b>                     | <0.001 | 1.09 | 1.12 | 1.01                        | 0.115  | 1.00 | 1.03 |
| Northern Ireland   | 0.99                     | 0.278  | 0.97 | 1.01 |                                 |        |      |      | <b>0.93</b>                     | <0.001 | 0.91 | 0.96 | <b>0.92</b>                 | <0.001 | 0.90 | 0.94 |



|                                  | Univariable (unadjusted) |        |      |      | Minimally adjusted <sup>1</sup> |   |     |     | Partially adjusted <sup>2</sup> |   |     |     | Fully adjusted <sup>3</sup> |        |      |      |
|----------------------------------|--------------------------|--------|------|------|---------------------------------|---|-----|-----|---------------------------------|---|-----|-----|-----------------------------|--------|------|------|
| Variable                         | HR                       | p      | lcl  | ucl  | HR                              | p | lcl | ucl | HR                              | p | lcl | ucl | HR                          | p      | lcl  | ucl  |
| Urbanisation (E&W only):         |                          |        |      |      |                                 |   |     |     |                                 |   |     |     |                             |        |      |      |
| Non-urban                        | 1                        |        |      |      |                                 |   |     |     |                                 |   |     |     |                             |        |      |      |
| Urban                            | <b>1.15</b>              | <0.001 | 1.14 | 1.17 |                                 |   |     |     |                                 |   |     |     |                             |        |      |      |
| Missing                          | <b>0.96</b>              | <0.001 | 0.95 | 0.98 |                                 |   |     |     |                                 |   |     |     |                             |        |      |      |
| Diabetes mellitus <sup>4</sup> : | <b>2.23</b>              | <0.001 | 2.20 | 2.27 |                                 |   |     |     |                                 |   |     |     | <b>1.77</b>                 | <0.001 | 1.74 | 1.80 |
| Charlson index:                  |                          |        |      |      |                                 |   |     |     |                                 |   |     |     |                             |        |      |      |
| 0                                | 1                        |        |      |      |                                 |   |     |     |                                 |   |     |     | 1                           |        |      |      |
| 1                                | <b>1.63</b>              | <0.001 | 1.61 | 1.65 |                                 |   |     |     |                                 |   |     |     | <b>1.51</b>                 | <0.001 | 1.49 | 1.53 |
| 2+                               | <b>3.63</b>              | <0.001 | 3.58 | 3.68 |                                 |   |     |     |                                 |   |     |     | <b>3.34</b>                 | <0.001 | 3.30 | 3.39 |
| Any CVD:                         | <b>2.42</b>              | <0.001 | 2.39 | 2.45 |                                 |   |     |     |                                 |   |     |     | <b>1.71</b>                 | <0.001 | 1.68 | 1.73 |
| Smoking status:                  |                          |        |      |      |                                 |   |     |     |                                 |   |     |     |                             |        |      |      |
| Never smoked                     | 1                        |        |      |      |                                 |   |     |     |                                 |   |     |     | 1                           |        |      |      |
| Ex-smoker                        | <b>1.59</b>              | <0.001 | 1.56 | 1.61 |                                 |   |     |     |                                 |   |     |     | <b>1.28</b>                 | <0.001 | 1.26 | 1.30 |
| Current smoker                   | <b>2.79</b>              | <0.001 | 2.76 | 2.82 |                                 |   |     |     |                                 |   |     |     | <b>2.35</b>                 | <0.001 | 2.32 | 2.38 |
| Missing                          | <b>1.57</b>              | <0.001 | 1.55 | 1.60 |                                 |   |     |     |                                 |   |     |     | <b>1.30</b>                 | <0.001 | 1.27 | 1.32 |
| Obesity at baseline:             |                          |        |      |      |                                 |   |     |     |                                 |   |     |     |                             |        |      |      |
| No                               | 1                        |        |      |      |                                 |   |     |     |                                 |   |     |     | 1                           |        |      |      |
| Yes                              | <b>1.17</b>              | <0.001 | 1.16 | 1.19 |                                 |   |     |     |                                 |   |     |     | <b>1.02</b>                 | 0.017  | 1.00 | 1.03 |
| Unrecorded                       | <b>1.19</b>              | <0.001 | 1.18 | 1.21 |                                 |   |     |     |                                 |   |     |     | <b>1.28</b>                 | <0.001 | 1.26 | 1.29 |
| Blood pressure at baseline:      |                          |        |      |      |                                 |   |     |     |                                 |   |     |     |                             |        |      |      |
| <140/90 mmHg                     | 1                        |        |      |      |                                 |   |     |     |                                 |   |     |     | 1                           |        |      |      |
| ≥140/90 mmHg                     | <b>1.18</b>              | <0.001 | 1.17 | 1.20 |                                 |   |     |     |                                 |   |     |     | <b>1.16</b>                 | <0.001 | 1.15 | 1.17 |
| Missing                          | <b>1.16</b>              | <0.001 | 1.14 | 1.17 |                                 |   |     |     |                                 |   |     |     | <b>1.14</b>                 | <0.001 | 1.12 | 1.16 |

SMI – severe mental illness, BD – bipolar disorder, SCZ – schizophrenia, CVD – cardiovascular disease, ref – reference category, E&W – England & Wales, HR – hazard ratio, lcl – lower 95% confidence limit, ucl – upper 95% confidence. <sup>1</sup> adjusted for sex, calendar period. <sup>2</sup> adjusted for sex, calendar period, deprivation, country. <sup>3</sup> adjusted for sex, calendar period, deprivation, country, diabetes mellitus, CVD, Charlson index, smoking, obesity, blood pressure. <sup>4</sup> includes type 1, non-type 1 and diabetes mellitus prescription (excluding patients prescribed metformin with a prior diagnosis of polycystic ovary syndrome). Values that exclude the null highlighted in **bold**

#### 4.4.5.1 Interactions

The relationship between SMI and calendar period was explored by adding an interaction term to the partially and fully adjusted models. Likelihood ratio tests for interaction showed that the interaction had no additional effect for the reduced model ( $p=0.593$ ), nor for the full model ( $p=0.720$ ). The lack of interaction between SMI and calendar period suggests that the hazard of all-cause mortality for people with SMI has not worsened over the study period, however, neither unfortunately, has it improved.

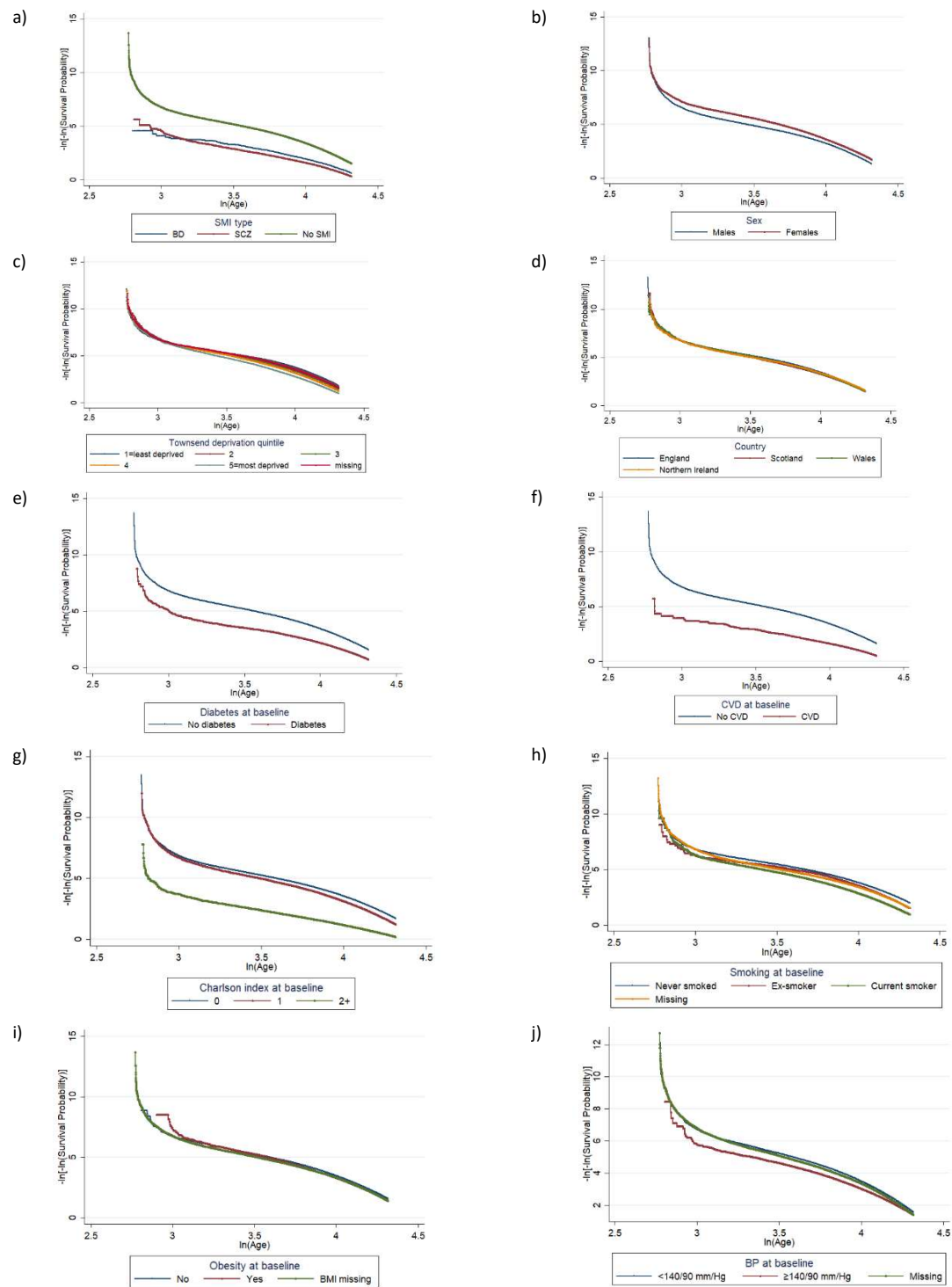
#### 4.4.5.2 Testing the proportional hazards assumption

There were violations of the assumption of proportional hazards for all covariates according to statistical tests (Table 4.14), whereas the plots in Figure 4.23 do not appear to suggest substantial proportional hazards violations for most of the covariates as the lines are either parallel or very close together. However, for SMI, which is the main covariate of interest, the lines for BD and schizophrenia are not only non-parallel, but they also cross over, suggesting an interaction between SMI type and analysis time (age at death in this model). Thus, the Cox regression model may not adequately summarise the effect of SMI at all ages of death. For all-cause mortality, non-proportional hazards were dealt with by splitting the follow-up time (*i.e.* attained age) into different periods. Figure 4.24 shows log-log plots by SMI for 10-year age bands. The lines in these plots are more nearly parallel than the lines in Figure 4.23, particularly for older ages. Thus, the analysis was repeated, splitting analysis time into 10-year age bands. Status of diabetes mellitus, CVD, smoking, obesity, and blood pressure were updated to baseline values at the start of each age band and calendar period.

**Table 4.14: Statistical tests for proportional hazards from univariate Cox regression analyses of all-cause mortality, prevalent cohort**

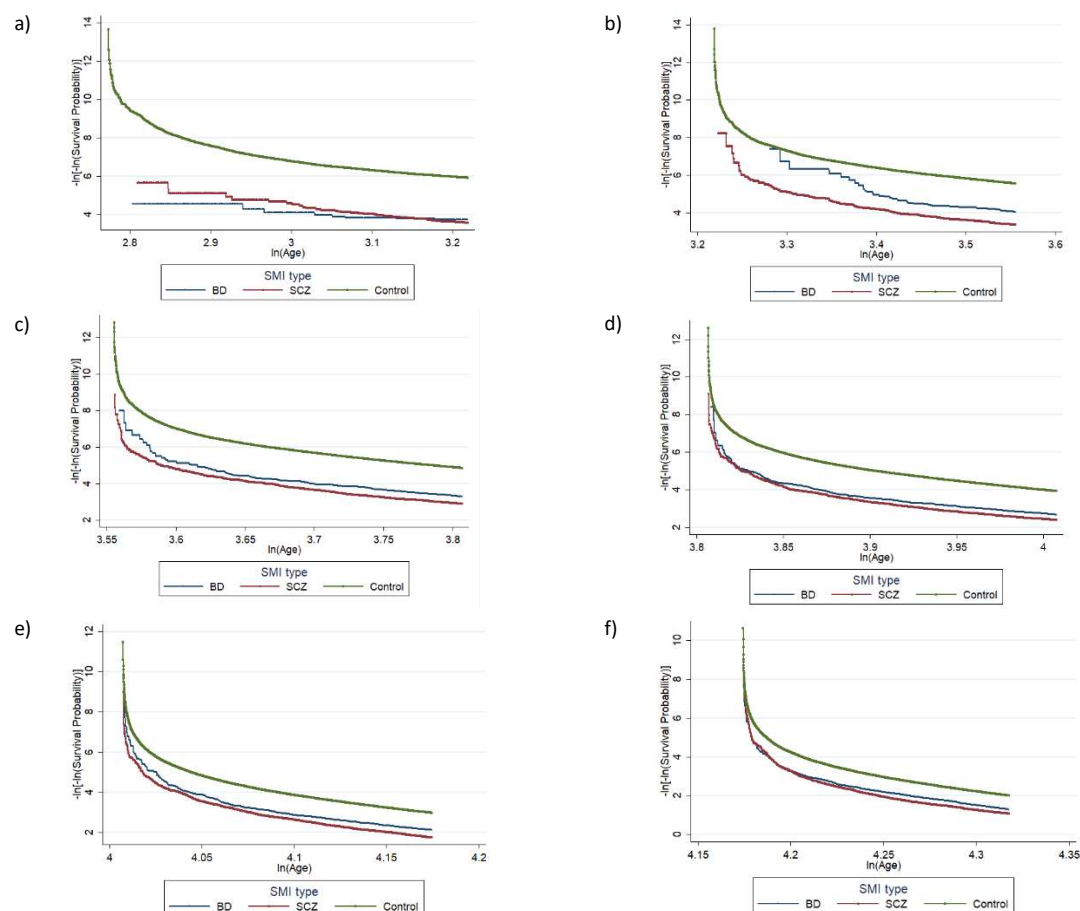
| Variable                                    |                                    | PH test (zero slope of scaled Schoenfeld residuals), p-value |
|---------------------------------------------|------------------------------------|--------------------------------------------------------------|
| SMI:                                        | No SMI                             | 1                                                            |
|                                             | <b>Bipolar disorder</b>            | <0.001                                                       |
|                                             | <b>Schizophrenia</b>               | <0.001                                                       |
|                                             | <i>Global PH test for SMI</i>      | <0.001                                                       |
| Sex:                                        | Males                              | 1                                                            |
|                                             | Females                            | 0.342                                                        |
| Calendar period:                            | 2000-04                            | 1                                                            |
|                                             | 2005-09                            | <0.001                                                       |
|                                             | 2010-14                            | <0.001                                                       |
|                                             | 2015-19                            | <0.001                                                       |
|                                             | <i>Global PH test for period</i>   | <0.001                                                       |
| Townsend:                                   | 1 (least deprived)                 | 1                                                            |
|                                             | 2                                  | 0.636                                                        |
|                                             | 3                                  | 0.031                                                        |
|                                             | 4                                  | 0.022                                                        |
|                                             | 5 (most deprived)                  | <0.001                                                       |
|                                             | Missing                            | 0.465                                                        |
|                                             | <i>Global PH test for Townsend</i> | <0.001                                                       |
| Country:                                    | England                            | 1                                                            |
|                                             | Scotland                           | <0.001                                                       |
|                                             | Wales                              | <0.001                                                       |
|                                             | Northern Ireland                   | <0.001                                                       |
|                                             | <i>Global PH test for country</i>  | <0.001                                                       |
| Diabetes mellitus <sup>1</sup> at baseline: |                                    | <0.001                                                       |
| Charlson index:                             | 0                                  | 1                                                            |
|                                             | 1                                  | <0.001                                                       |
|                                             | 2+                                 | <0.001                                                       |
|                                             | <i>Global PH test for Charlson</i> | <0.001                                                       |
| CVD at baseline:                            |                                    | <0.001                                                       |
| Smoking at baseline:                        |                                    |                                                              |
|                                             | Never smoked                       | 1                                                            |
|                                             | Ex-smoker                          | <0.001                                                       |
|                                             | Current smoker                     | <0.001                                                       |
|                                             | Missing                            | 0.098                                                        |
|                                             | <i>Global PH test for smoking</i>  | <0.001                                                       |
| Obesity at baseline:                        | No                                 | 1                                                            |
|                                             | Yes                                | <0.001                                                       |
|                                             | Unrecorded                         | 0.057                                                        |
|                                             | <i>Global PH test for obesity</i>  | <0.001                                                       |
| BP at baseline:                             | <140/90 mmHg                       | 1                                                            |
|                                             | ≥140/90 mmHg                       | <0.001                                                       |
|                                             | Missing                            | 0.159                                                        |
|                                             | <i>Global test for BP</i>          | <0.001                                                       |

<sup>1</sup> includes type 1, non-type 1 and diabetes mellitus prescription except for metformin if prior polycystic ovary syndrome. PH – proportional hazards, SMI – severe mental illness, CVD – cardiovascular disease, BP – blood pressure



SMI – severe mental illness, BD – bipolar disorder, SCZ – schizophrenia, CVD – cardiovascular disease, BP – blood pressure

**Figure 4.23: Plots of survival function against time (log scales) to assess proportional hazards assumption for a) SMI type, b) sex, c) deprivation quintile, d) country, e) diabetes mellitus at baseline, f) CVD at baseline, g) Charlson index at patient start date, h) smoking at baseline, i) obesity at baseline, j) blood pressure at baseline; prevalent cohort**



SMI – severe mental illness, BD – bipolar disorder, SCZ – schizophrenia

**Figure 4.24: Plots of survival function against time (log scales) to assess proportional hazards assumption for severe mental illness for ages a) 15-24, b) 25-34, c) 35-44, d) 45-54, e) 55-64, f) 65-74 years; prevalent cohort**

#### 4.4.5.3 Splitting follow-up time

Table 4.15 to Table 4.20 show HRs for univariable and minimally, partially, and fully adjusted multivariable Cox regression models, split into 10-year age bands. SMI had a large effect on the hazard of all-cause mortality, particularly in younger ages. Schizophrenia, ages 15-24 years: unadjusted HR=11.00; 95% CI: 8.39-14.41, ages 65-74 years: HR=2.56; 95% CI: 2.44-2.69; BD, ages 15-24 years: HR= 5.00, 95% CI: 2.50-10.02, ages 65-74 years: HR=2.08, 95% CI: 1.95-2.23. Across all age groups, HRs were larger for males, those with diabetes mellitus, CVD and higher Charlson indices at baseline. Effects of comorbidities were very high in

younger age groups, although the effect sizes decreased with increasing age. There was a socioeconomic gradient with higher HRs in the most deprived areas compared with the least deprived. HRs for current smokers, and patients with unrecorded smoking status were higher than patients who had never smoked across all age groups. HRs for both current and ex-smoking increased with increasing age. HRs were raised for patients with unrecorded BMI across all age groups. For age groups 35 years and over, HRs were also elevated for patients with obesity at baseline compared to those with a recorded BMI below 30 kg/m<sup>2</sup> (27.5 kg/m<sup>2</sup> for non-White ethnicity). However, after adjusting for smoking, other comorbidities and blood pressure, the HRs for having recorded obesity were reduced compared with patients with BMI < 30/27.5 kg/m<sup>2</sup>. Recorded blood pressure over 140/90 mmHg was associated with higher mortality in all age groups except ages 65-74 years. HRs for countries were inconsistent.

HRs for calendar period were lower from 2010 onwards, particularly in ages 15-24 years and ages over 45 years. Thus, across the whole cohort, the trend was for an improvement in mortality rates in these age groups. To determine whether the improvement applied equally to patients with and without SMI, Cox regression analyses including interaction terms for SMI X calendar period were performed. Table 4.21 shows the results of likelihood-ratio tests for the additional effect of adding an interaction to the partially adjusted model (including SMI, sex, age, Townsend, and country) and the fully adjusted model (additionally adjusted for comorbidities, smoking, obesity, and blood pressure). After full adjustment for covariates, there was only weak evidence for an interaction between SMI and calendar period in ages 25-34 years (p=0.058) and 35-44 years (p=0.047). Table 4.22 and

Table 4.23 show HRs for the interaction terms added to both the partially and fully adjusted models, respectively, for each age group over 25 years. In ages 25-34 years, results from the fully adjusted model showed that, compared with 2000-04, mortality rates were reduced for BD in 2015-19, and for schizophrenia in 2010-14. The HR for BD in 2015-19 was 0.22 times the HR in 2000-04 (95% CI: 0.06-0.79,  $p=0.021$ ) and the HR for schizophrenia in 2010-14 was 0.61 times that in 2000-04 (95% CI: 0.41-0.93,  $p=0.021$ ). For ages 35-44 years, HRs for schizophrenia after 2005 were lower than in 2000-04 and for ages 55-64 years HRs for schizophrenia were also reduced after 2010 compared with 2000-04.

Figure 4.25 shows a graphical representation of the interaction between calendar period and SMI for each age group. Although there are some reductions in the HRs for BD and schizophrenia for some time periods, there is no consistent trend over time and mortality remains high compared with the general population.

**Table 4.15: Hazard ratios for all-cause mortality in univariable and multivariable Cox regression analyses, ages 15-24 years, prevalent cohort**

| Variable                         |                    | Univariable (unadjusted) |        |      |       | Minimally adjusted <sup>1</sup> |        |      |      | Partially adjusted <sup>2</sup> |        |      |      | Fully adjusted <sup>3</sup> |        |      |      |
|----------------------------------|--------------------|--------------------------|--------|------|-------|---------------------------------|--------|------|------|---------------------------------|--------|------|------|-----------------------------|--------|------|------|
|                                  |                    | HR                       | p      | lcl  | ucl   | HR                              | p      | lcl  | ucl  | HR                              | p      | lcl  | ucl  | HR                          | p      | lcl  | ucl  |
| SMI:                             |                    |                          |        |      |       |                                 |        |      |      |                                 |        |      |      |                             |        |      |      |
|                                  | No SMI             | 1                        |        |      |       | 1                               |        |      |      | 1                               |        |      |      | 1                           |        |      |      |
|                                  | BD                 | <b>5.00</b>              | <0.001 | 2.50 | 10.02 | <b>5.54</b>                     | <0.001 | 2.77 | 11.1 | <b>5.49</b>                     | <0.001 | 2.74 | 11.0 | <b>4.91</b>                 | <0.001 | 2.45 | 9.84 |
|                                  | SCZ                | <b>11.00</b>             | <0.001 | 8.39 | 14.41 | <b>9.84</b>                     | <0.001 | 7.51 | 12.9 | <b>9.62</b>                     | <0.001 | 7.33 | 12.6 | <b>7.71</b>                 | <0.001 | 5.86 | 10.1 |
| Sex:                             |                    |                          |        |      |       |                                 |        |      |      |                                 |        |      |      |                             |        |      |      |
|                                  | Males              | 1                        |        |      |       | 1                               |        |      |      | 1                               |        |      |      | 1                           |        |      |      |
|                                  | Females            | <b>0.50</b>              | <0.001 | 0.46 | 0.54  | <b>0.50</b>                     | <0.001 | 0.46 | 0.55 | <b>0.50</b>                     | <0.001 | 0.46 | 0.55 | <b>0.51</b>                 | <0.001 | 0.47 | 0.56 |
| Calendar period:                 |                    |                          |        |      |       |                                 |        |      |      |                                 |        |      |      |                             |        |      |      |
|                                  | 2000-04            | 1                        |        |      |       | 1                               |        |      |      | 1                               |        |      |      | 1                           |        |      |      |
|                                  | 2005-09            | 0.96                     | 0.430  | 0.86 | 1.07  | 0.96                            | 0.423  | 0.86 | 1.07 | 0.95                            | 0.397  | 0.85 | 1.06 | 0.92                        | 0.120  | 0.82 | 1.02 |
|                                  | 2010-14            | <b>0.70</b>              | <0.001 | 0.62 | 0.78  | <b>0.70</b>                     | <0.001 | 0.62 | 0.78 | <b>0.69</b>                     | <0.001 | 0.62 | 0.78 | <b>0.66</b>                 | <0.001 | 0.58 | 0.74 |
|                                  | 2015-19            | <b>0.70</b>              | <0.001 | 0.61 | 0.80  | <b>0.70</b>                     | <0.001 | 0.61 | 0.80 | <b>0.69</b>                     | <0.001 | 0.60 | 0.79 | <b>0.64</b>                 | <0.001 | 0.56 | 0.74 |
| Townsend:                        |                    |                          |        |      |       |                                 |        |      |      |                                 |        |      |      |                             |        |      |      |
|                                  | 1 (least deprived) | 1                        |        |      |       |                                 |        |      |      | 1                               |        |      |      | 1                           |        |      |      |
|                                  | 2                  | 0.98                     | 0.731  | 0.85 | 1.12  |                                 |        |      |      | 0.97                            | 0.720  | 0.85 | 1.12 | 0.97                        | 0.691  | 0.84 | 1.12 |
|                                  | 3                  | 1.01                     | 0.857  | 0.88 | 1.16  |                                 |        |      |      | 1.01                            | 0.854  | 0.89 | 1.16 | 1.00                        | 0.944  | 0.87 | 1.14 |
|                                  | 4                  | 1.07                     | 0.292  | 0.94 | 1.23  |                                 |        |      |      | 1.08                            | 0.259  | 0.95 | 1.24 | 1.06                        | 0.405  | 0.93 | 1.21 |
|                                  | 5 (most deprived)  | <b>1.24</b>              | 0.002  | 1.09 | 1.43  |                                 |        |      |      | <b>1.23</b>                     | 0.003  | 1.08 | 1.41 | <b>1.19</b>                 | 0.015  | 1.03 | 1.37 |
|                                  | Missing            | 0.92                     | 0.230  | 0.79 | 1.06  |                                 |        |      |      | 0.94                            | 0.418  | 0.82 | 1.09 | 0.96                        | 0.552  | 0.83 | 1.11 |
| Country:                         |                    |                          |        |      |       |                                 |        |      |      |                                 |        |      |      |                             |        |      |      |
|                                  | England            | 1                        |        |      |       |                                 |        |      |      | 1                               |        |      |      | 1                           |        |      |      |
|                                  | Scotland           | 1.01                     | 0.919  | 0.89 | 1.13  |                                 |        |      |      | 1.08                            | 0.204  | 0.96 | 1.22 | 1.07                        | 0.260  | 0.95 | 1.21 |
|                                  | Wales              | 0.98                     | 0.795  | 0.87 | 1.11  |                                 |        |      |      | 1.08                            | 0.240  | 0.95 | 1.22 | 1.08                        | 0.206  | 0.96 | 1.23 |
|                                  | Northern Ireland   | 1.11                     | 0.208  | 0.94 | 1.32  |                                 |        |      |      | 1.13                            | 0.145  | 0.96 | 1.34 | 1.13                        | 0.160  | 0.95 | 1.34 |
| Diabetes mellitus <sup>4</sup> : |                    | <b>6.01</b>              | <0.001 | 4.99 | 7.24  |                                 |        |      |      |                                 |        |      |      | <b>5.26</b>                 | <0.001 | 4.34 | 6.38 |
| Charlson index:                  |                    |                          |        |      |       |                                 |        |      |      |                                 |        |      |      |                             |        |      |      |
|                                  | 0                  | 1                        |        |      |       |                                 |        |      |      |                                 |        |      |      | 1                           |        |      |      |
|                                  | 1                  | <b>1.24</b>              | <0.001 | 1.13 | 1.37  |                                 |        |      |      |                                 |        |      |      | <b>1.17</b>                 | 0.002  | 1.06 | 1.29 |
|                                  | 2+                 | <b>19.39</b>             | <0.001 | 16.2 | 23.18 |                                 |        |      |      |                                 |        |      |      | <b>15.11</b>                | <0.001 | 12.6 | 18.2 |
| Any CVD:                         |                    | <b>10.31</b>             | <0.001 | 5.85 | 18.19 |                                 |        |      |      |                                 |        |      |      | <b>3.69</b>                 | <0.001 | 2.07 | 6.58 |
| Smoking status:                  |                    |                          |        |      |       |                                 |        |      |      |                                 |        |      |      |                             |        |      |      |



| Variable       | Univariable (unadjusted) |        |      |      | Minimally adjusted <sup>1</sup> |   |     |     | Partially adjusted <sup>2</sup> |   |     |     | Fully adjusted <sup>3</sup> |        |      |      |
|----------------|--------------------------|--------|------|------|---------------------------------|---|-----|-----|---------------------------------|---|-----|-----|-----------------------------|--------|------|------|
|                | HR                       | p      | lcl  | ucl  | HR                              | p | lcl | ucl | HR                              | p | lcl | ucl | HR                          | p      | lcl  | ucl  |
| Never smoked   | 1                        |        |      |      |                                 |   |     |     |                                 |   |     |     | 1                           |        |      |      |
| Ex-smoker      | 1.13                     | 0.264  | 0.91 | 1.39 |                                 |   |     |     |                                 |   |     |     | <b>1.24</b>                 | 0.047  | 1.00 | 1.53 |
| Current smoker | <b>1.73</b>              | <0.001 | 1.55 | 1.92 |                                 |   |     |     |                                 |   |     |     | <b>1.70</b>                 | <0.001 | 1.52 | 1.90 |
| Missing        | <b>1.25</b>              | <0.001 | 1.14 | 1.38 |                                 |   |     |     |                                 |   |     |     | 1.01                        | 0.865  | 0.90 | 1.13 |
| Obesity:       |                          |        |      |      |                                 |   |     |     |                                 |   |     |     |                             |        |      |      |
| No             | 1                        |        |      |      |                                 |   |     |     |                                 |   |     |     | 1                           |        |      |      |
| Yes            | 1.16                     | 0.160  | 0.94 | 1.42 |                                 |   |     |     |                                 |   |     |     | 1.09                        | 0.418  | 0.89 | 1.34 |
| Unrecorded     | <b>1.31</b>              | <0.001 | 1.19 | 1.45 |                                 |   |     |     |                                 |   |     |     | <b>1.35</b>                 | <0.001 | 1.20 | 1.51 |
| BP:            |                          |        |      |      |                                 |   |     |     |                                 |   |     |     |                             |        |      |      |
| <140/90 mmHg   | 1                        |        |      |      |                                 |   |     |     |                                 |   |     |     | 1                           |        |      |      |
| ≥140/90 mmHg   | <b>1.77</b>              | <0.001 | 1.44 | 2.16 |                                 |   |     |     |                                 |   |     |     | <b>1.41</b>                 | 0.001  | 1.15 | 1.73 |
| Missing        | <b>1.11</b>              | 0.014  | 1.02 | 1.21 |                                 |   |     |     |                                 |   |     |     | 0.96                        | 0.484  | 0.87 | 1.07 |

SMI – severe mental illness, BD – bipolar disorder, SCZ – schizophrenia, CVD – cardiovascular disease, BP – blood pressure, HR – hazard ratio, lcl – lower 95% confidence limit, ucl – upper 95% confidence limit. <sup>1</sup> adjusted for sex, calendar period. <sup>2</sup> adjusted for sex, calendar period, deprivation, country. <sup>3</sup> adjusted for sex, calendar period, deprivation, country, diabetes mellitus, CVD, Charlson index, smoking, obesity, blood pressure. <sup>4</sup> includes type 1, non-type 1 and diabetes mellitus prescription except for metformin if prior polycystic ovary syndrome. Values that exclude the null highlighted in **bold**

**Table 4.16: Hazard ratios for all-cause mortality in univariable and multivariable Cox regression analyses, ages 25-34 years, prevalent cohort**

| Variable         |                    | Univariable (unadjusted) |        |      |       | Minimally adjusted <sup>1</sup> |        |      |      | Partially adjusted <sup>2</sup> |        |      |      | Fully adjusted <sup>3</sup> |        |      |      |
|------------------|--------------------|--------------------------|--------|------|-------|---------------------------------|--------|------|------|---------------------------------|--------|------|------|-----------------------------|--------|------|------|
|                  |                    | HR                       | p      | lcl  | ucl   | HR                              | p      | lcl  | ucl  | HR                              | p      | lcl  | ucl  | HR                          | p      | lcl  | ucl  |
| SMI:             | No SMI             | 1                        |        |      |       | 1                               |        |      |      | 1                               |        |      |      | 1                           |        |      |      |
|                  | BD                 | <b>4.78</b>              | <0.001 | 3.53 | 6.48  | <b>5.10</b>                     | <0.001 | 3.77 | 6.92 | <b>4.84</b>                     | <0.001 | 3.57 | 6.57 | <b>3.93</b>                 | <0.001 | 2.89 | 5.33 |
|                  | SCZ                | <b>8.97</b>              | <0.001 | 7.77 | 10.35 | <b>7.95</b>                     | <0.001 | 6.88 | 9.17 | <b>7.20</b>                     | <0.001 | 6.23 | 8.31 | <b>5.66</b>                 | <0.001 | 4.89 | 6.54 |
| Sex:             | Males              | 1                        |        |      |       | 1                               |        |      |      | 1                               |        |      |      | 1                           |        |      |      |
|                  | Females            | <b>0.51</b>              | <0.001 | 0.48 | 0.55  | <b>0.53</b>                     | <0.001 | 0.49 | 0.56 | <b>0.53</b>                     | <0.001 | 0.50 | 0.57 | <b>0.56</b>                 | <0.001 | 0.53 | 0.60 |
| Calendar period: | 2000-04            | 1                        |        |      |       | 1                               |        |      |      | 1                               |        |      |      | 1                           |        |      |      |
|                  | 2005-09            | <b>1.12</b>              | 0.008  | 1.03 | 1.22  | <b>1.12</b>                     | 0.012  | 1.02 | 1.22 | <b>1.09</b>                     | 0.042  | 1.00 | 1.19 | <b>1.10</b>                 | 0.033  | 1.01 | 1.20 |
|                  | 2010-14            | 0.95                     | 0.264  | 0.87 | 1.04  | 0.94                            | 0.200  | 0.87 | 1.03 | <b>0.89</b>                     | 0.013  | 0.82 | 0.98 | <b>0.91</b>                 | 0.036  | 0.83 | 0.99 |
|                  | 2015-19            | 0.94                     | 0.227  | 0.85 | 1.04  | 0.93                            | 0.176  | 0.85 | 1.03 | <b>0.86</b>                     | 0.003  | 0.77 | 0.95 | <b>0.86</b>                 | 0.006  | 0.78 | 0.96 |
| Townsend:        | 1 (least deprived) | 1                        |        |      |       |                                 |        |      |      | 1                               |        |      |      | 1                           |        |      |      |
|                  | 2                  | 1.05                     | 0.400  | 0.93 | 1.19  |                                 |        |      |      | 1.03                            | 0.581  | 0.92 | 1.17 | 1.02                        | 0.765  | 0.90 | 1.15 |
|                  | 3                  | <b>1.23</b>              | <0.001 | 1.10 | 1.37  |                                 |        |      |      | <b>1.19</b>                     | 0.002  | 1.07 | 1.33 | <b>1.15</b>                 | 0.016  | 1.03 | 1.28 |
|                  | 4                  | <b>1.47</b>              | <0.001 | 1.32 | 1.64  |                                 |        |      |      | <b>1.41</b>                     | <0.001 | 1.27 | 1.57 | <b>1.32</b>                 | <0.001 | 1.18 | 1.47 |
|                  | 5 (most deprived)  | <b>2.15</b>              | <0.001 | 1.93 | 2.39  |                                 |        |      |      | <b>1.97</b>                     | <0.001 | 1.77 | 2.20 | <b>1.79</b>                 | <0.001 | 1.61 | 1.99 |
|                  | Missing            | 1.09                     | 0.144  | 0.97 | 1.22  |                                 |        |      |      | 1.06                            | 0.296  | 0.95 | 1.20 | 1.06                        | 0.327  | 0.94 | 1.19 |

| Variable                         |                  | Univariable (unadjusted) |        |      |       | Minimally adjusted <sup>1</sup> |   |     |     | Partially adjusted <sup>2</sup> |        |      |      | Fully adjusted <sup>3</sup> |        |      |      |
|----------------------------------|------------------|--------------------------|--------|------|-------|---------------------------------|---|-----|-----|---------------------------------|--------|------|------|-----------------------------|--------|------|------|
|                                  |                  | HR                       | p      | lcl  | ucl   | HR                              | p | lcl | ucl | HR                              | p      | lcl  | ucl  | HR                          | p      | lcl  | ucl  |
| Country:                         | England          | 1                        |        |      |       |                                 |   |     |     | 1                               |        |      |      | 1                           |        |      |      |
|                                  | Scotland         | <b>1.31</b>              | <0.001 | 1.20 | 1.42  |                                 |   |     |     | <b>1.25</b>                     | <0.001 | 1.15 | 1.37 | <b>1.23</b>                 | <0.001 | 1.13 | 1.34 |
|                                  | Wales            | <b>1.13</b>              | 0.013  | 1.03 | 1.23  |                                 |   |     |     | <b>1.19</b>                     | <0.001 | 1.08 | 1.31 | <b>1.17</b>                 | 0.001  | 1.06 | 1.29 |
|                                  | Northern Ireland | <b>1.27</b>              | <0.001 | 1.11 | 1.44  |                                 |   |     |     | <b>1.22</b>                     | 0.002  | 1.07 | 1.39 | <b>1.21</b>                 | 0.004  | 1.06 | 1.38 |
| Diabetes mellitus <sup>4</sup> : |                  | <b>3.51</b>              | <0.001 | 4.99 | 7.24  |                                 |   |     |     |                                 |        |      |      | <b>3.37</b>                 | <0.001 | 2.94 | 3.87 |
| Charlson index:                  | 0                | 1                        |        |      |       |                                 |   |     |     |                                 |        |      |      | 1                           |        |      |      |
|                                  | 1                | <b>1.39</b>              | <0.001 | 1.28 | 1.50  |                                 |   |     |     |                                 |        |      |      | <b>1.36</b>                 | <0.001 | 1.26 | 1.47 |
|                                  | 2+               | <b>15.30</b>             | <0.001 | 13.6 | 17.26 |                                 |   |     |     |                                 |        |      |      | <b>13.1</b>                 | <0.001 | 11.5 | 14.8 |
| Any CVD:                         |                  | <b>7.94</b>              | <0.001 | 5.83 | 10.79 |                                 |   |     |     |                                 |        |      |      | <b>3.74</b>                 | <0.001 | 2.73 | 5.11 |
| Smoking status:                  | Never smoked     | 1                        |        |      |       |                                 |   |     |     |                                 |        |      |      | 1                           |        |      |      |
|                                  | Ex-smoker        | <b>1.15</b>              | 0.009  | 1.04 | 1.28  |                                 |   |     |     |                                 |        |      |      | <b>1.16</b>                 | 0.008  | 1.04 | 1.29 |
|                                  | Current smoker   | <b>2.24</b>              | <0.001 | 2.09 | 2.40  |                                 |   |     |     |                                 |        |      |      | <b>1.91</b>                 | <0.001 | 1.77 | 2.05 |
|                                  | Missing          | <b>1.63</b>              | <0.001 | 1.49 | 1.80  |                                 |   |     |     |                                 |        |      |      | <b>1.38</b>                 | <0.001 | 1.23 | 1.55 |
| Obesity:                         | No               | 1                        |        |      |       |                                 |   |     |     |                                 |        |      |      | 1                           |        |      |      |
|                                  | Yes              | 1.08                     | 0.117  | 0.98 | 1.19  |                                 |   |     |     |                                 |        |      |      | 0.96                        | 0.477  | 0.87 | 1.06 |
|                                  | Unrecorded       | <b>1.26</b>              | <0.001 | 1.18 | 1.35  |                                 |   |     |     |                                 |        |      |      | <b>1.20</b>                 | <0.001 | 1.11 | 1.31 |
| BP:                              | <140/90 mmHg     | 1                        |        |      |       |                                 |   |     |     |                                 |        |      |      | 1                           |        |      |      |
|                                  | ≥140/90 mmHg     | <b>1.63</b>              | <0.001 | 1.49 | 1.79  |                                 |   |     |     |                                 |        |      |      | <b>1.33</b>                 | <0.001 | 1.21 | 1.46 |
|                                  | Missing          | <b>1.16</b>              | <0.001 | 1.08 | 1.25  |                                 |   |     |     |                                 |        |      |      | 0.92                        | 0.054  | 0.84 | 1.00 |

SMI – severe mental illness, BD – bipolar disorder, SCZ – schizophrenia, CVD – cardiovascular disease, BP – blood pressure, HR – hazard ratio, lcl – lower 95% confidence limit, ucl – upper 95% confidence limit. <sup>1</sup> adjusted for sex, calendar period. <sup>2</sup> adjusted for sex, calendar period, deprivation, country. <sup>3</sup> adjusted for sex, calendar period, deprivation, country, diabetes mellitus, CVD, Charlson index, smoking, obesity, blood pressure. <sup>4</sup> includes type 1, non-type 1 and diabetes mellitus prescription except for metformin if prior polycystic ovary syndrome. Values that exclude the null highlighted in **bold**

**Table 4.17: Hazard ratios for all-cause mortality in univariable and multivariable Cox regression analyses, ages 35-44 years, prevalent cohort**

| Variable         |            | Univariable (unadjusted) |        |      |      | Minimally adjusted <sup>1</sup> |        |      |      | Partially adjusted <sup>2</sup> |        |      |      | Fully adjusted <sup>3</sup> |        |      |      |
|------------------|------------|--------------------------|--------|------|------|---------------------------------|--------|------|------|---------------------------------|--------|------|------|-----------------------------|--------|------|------|
|                  |            | HR                       | p      | lcl  | ucl  | HR                              | p      | lcl  | ucl  | HR                              | p      | lcl  | ucl  | HR                          | p      | lcl  | ucl  |
| SMI:             | No SMI     | 1                        |        |      |      | 1                               |        |      |      | 1                               |        |      |      | 1                           |        |      |      |
|                  | <b>BD</b>  | <b>4.77</b>              | <0.001 | 4.04 | 5.63 | <b>4.95</b>                     | <0.001 | 4.19 | 5.84 | <b>4.41</b>                     | <0.001 | 3.74 | 5.21 | <b>3.48</b>                 | <0.001 | 2.95 | 4.11 |
|                  | <b>SCZ</b> | <b>7.06</b>              | <0.001 | 6.42 | 7.77 | <b>6.72</b>                     | <0.001 | 6.11 | 7.39 | <b>5.53</b>                     | <0.001 | 5.03 | 6.09 | <b>4.19</b>                 | <0.001 | 3.81 | 4.62 |
| Sex:             | Males      | 1                        |        |      |      | 1                               |        |      |      | 1                               |        |      |      | 1                           |        |      |      |
|                  | Females    | <b>0.68</b>              | <0.001 | 0.65 | 0.71 | <b>0.69</b>                     | <0.001 | 0.67 | 0.72 | <b>0.71</b>                     | <0.001 | 0.68 | 0.73 | <b>0.76</b>                 | <0.001 | 0.73 | 0.79 |
| Calendar period: | 2000-04    | 1                        |        |      |      | 1                               |        |      |      | 1                               |        |      |      | 1                           |        |      |      |
|                  | 2005-09    | <b>1.06</b>              | 0.050  | 1.00 | 1.12 | 1.05                            | 0.090  | 0.99 | 1.11 | 1.03                            | 0.322  | 0.97 | 1.09 | 1.03                        | 0.243  | 0.98 | 1.10 |
|                  | 2010-14    | 0.98                     | 0.462  | 0.92 | 1.04 | 0.96                            | 0.214  | 0.91 | 1.02 | <b>0.91</b>                     | 0.002  | 0.86 | 0.97 | <b>0.93</b>                 | 0.022  | 0.88 | 0.99 |
|                  | 2015-19    | 1.02                     | 0.496  | 0.96 | 1.09 | 1.00                            | 0.934  | 0.94 | 1.07 | <b>0.91</b>                     | 0.007  | 0.85 | 0.97 | 0.94                        | 0.065  | 0.87 | 1.00 |

| Variable                         |                    | Univariable (unadjusted) |        |      |      | Minimally adjusted <sup>1</sup> |   |     |     | Partially adjusted <sup>2</sup> |        |      |      | Fully adjusted <sup>3</sup> |        |      |      |
|----------------------------------|--------------------|--------------------------|--------|------|------|---------------------------------|---|-----|-----|---------------------------------|--------|------|------|-----------------------------|--------|------|------|
|                                  |                    | HR                       | p      | lcl  | ucl  | HR                              | p | lcl | ucl | HR                              | p      | lcl  | ucl  | HR                          | p      | lcl  | ucl  |
| Townsend:                        | 1 (least deprived) | 1                        |        |      |      |                                 |   |     |     | 1                               |        |      |      | 1                           |        |      |      |
|                                  | 2                  | <b>1.18</b>              | <0.001 | 1.09 | 1.27 |                                 |   |     |     | <b>1.15</b>                     | <0.001 | 1.07 | 1.25 | <b>1.10</b>                 | 0.012  | 1.02 | 1.19 |
|                                  | 3                  | <b>1.56</b>              | <0.001 | 1.45 | 1.67 |                                 |   |     |     | <b>1.50</b>                     | <0.001 | 1.40 | 1.62 | <b>1.35</b>                 | <0.001 | 1.26 | 1.46 |
|                                  | 4                  | <b>2.12</b>              | <0.001 | 1.98 | 2.28 |                                 |   |     |     | <b>1.99</b>                     | <0.001 | 1.86 | 2.14 | <b>1.66</b>                 | <0.001 | 1.55 | 1.79 |
|                                  | 5 (most deprived)  | <b>3.02</b>              | <0.001 | 2.82 | 3.24 |                                 |   |     |     | <b>2.73</b>                     | <0.001 | 2.54 | 2.93 | <b>2.12</b>                 | <0.001 | 1.97 | 2.28 |
|                                  | Missing            | <b>1.38</b>              | <0.001 | 1.28 | 1.49 |                                 |   |     |     | <b>1.31</b>                     | <0.001 | 1.21 | 1.41 | <b>1.23</b>                 | <0.001 | 1.13 | 1.32 |
| Country:                         | England            | 1                        |        |      |      |                                 |   |     |     | 1                               |        |      |      | 1                           |        |      |      |
|                                  | Scotland           | <b>1.32</b>              | <0.001 | 1.25 | 1.40 |                                 |   |     |     | <b>1.19</b>                     | <0.001 | 1.12 | 1.26 | <b>1.14</b>                 | <0.001 | 1.08 | 1.21 |
|                                  | Wales              | <b>1.20</b>              | <0.001 | 1.13 | 1.28 |                                 |   |     |     | <b>1.25</b>                     | <0.001 | 1.17 | 1.33 | <b>1.18</b>                 | <0.001 | 1.10 | 1.26 |
|                                  | Northern Ireland   | <b>1.11</b>              | 0.033  | 1.01 | 1.21 |                                 |   |     |     | 1.03                            | 0.552  | 0.94 | 1.13 | 1.04                        | 0.433  | 0.95 | 1.14 |
| Diabetes mellitus <sup>4</sup> : |                    | <b>3.01</b>              | <0.001 | 2.80 | 3.24 |                                 |   |     |     |                                 |        |      |      | <b>2.58</b>                 | <0.001 | 2.39 | 2.79 |
| Charlson index:                  | 0                  | 1                        |        |      |      |                                 |   |     |     |                                 |        |      |      | 1                           |        |      |      |
|                                  | 1                  | <b>1.49</b>              | <0.001 | 1.41 | 1.58 |                                 |   |     |     |                                 |        |      |      | <b>1.42</b>                 | <0.001 | 1.34 | 1.51 |
|                                  | 2+                 | <b>11.61</b>             | <0.001 | 10.8 | 12.4 |                                 |   |     |     |                                 |        |      |      | <b>9.79</b>                 | <0.001 | 9.13 | 10.5 |
| Any CVD:                         |                    | <b>6.86</b>              | <0.001 | 6.11 | 7.71 |                                 |   |     |     |                                 |        |      |      | <b>3.36</b>                 | <0.001 | 2.98 | 3.79 |
| Smoking status:                  | Never smoked       | 1                        |        |      |      |                                 |   |     |     |                                 |        |      |      | 1                           |        |      |      |
|                                  | Ex-smoker          | <b>1.19</b>              | <0.001 | 1.11 | 1.27 |                                 |   |     |     |                                 |        |      |      | <b>1.11</b>                 | 0.002  | 1.04 | 1.19 |
|                                  | Current smoker     | <b>2.72</b>              | <0.001 | 2.60 | 2.85 |                                 |   |     |     |                                 |        |      |      | <b>2.19</b>                 | <0.001 | 2.09 | 2.30 |
|                                  | Missing            | <b>1.46</b>              | <0.001 | 1.36 | 1.57 |                                 |   |     |     |                                 |        |      |      | <b>1.22</b>                 | <0.001 | 1.12 | 1.34 |
| Obesity:                         | No                 | 1                        |        |      |      |                                 |   |     |     |                                 |        |      |      | 1                           |        |      |      |
|                                  | Yes                | <b>1.23</b>              | <0.001 | 1.17 | 1.30 |                                 |   |     |     |                                 |        |      |      | 1.01                        | 0.817  | 0.95 | 1.06 |
|                                  | Unrecorded         | <b>1.23</b>              | <0.001 | 1.17 | 1.29 |                                 |   |     |     |                                 |        |      |      | <b>1.31</b>                 | <0.001 | 1.24 | 1.40 |
| BP:                              | <140/90 mmHg       | 1                        |        |      |      |                                 |   |     |     |                                 |        |      |      | 1                           |        |      |      |
|                                  | ≥140/90 mmHg       | <b>1.59</b>              | <0.001 | 1.52 | 1.68 |                                 |   |     |     |                                 |        |      |      | <b>1.40</b>                 | <0.001 | 1.33 | 1.47 |
|                                  | Missing            | <b>1.11</b>              | <0.001 | 1.05 | 1.17 |                                 |   |     |     |                                 |        |      |      | 0.99                        | 0.745  | 0.92 | 1.06 |

SMI – severe mental illness, BD – bipolar disorder, SCZ – schizophrenia, CVD – cardiovascular disease, BP – blood pressure, HR – hazard ratio, lcl – lower 95% confidence limit, ucl – upper 95% confidence limit. <sup>1</sup> adjusted for sex, calendar period. <sup>2</sup> adjusted for sex, calendar period, deprivation, country. <sup>3</sup> adjusted for sex, calendar period, deprivation, country, diabetes mellitus, CVD, Charlson index, smoking, obesity, blood pressure. <sup>4</sup> includes type 1, non-type 1 and diabetes mellitus prescription except for metformin if prior polycystic ovary syndrome. Values that exclude the null highlighted in **bold**

**Table 4.18: Hazard ratios for all-cause mortality in univariable and multivariable Cox regression analyses, ages 45-54 years, prevalent cohort**

| Variable                         |                    | Univariable (unadjusted) |        |      |      | Minimally adjusted <sup>1</sup> |        |      |      | Partially adjusted <sup>2</sup> |        |      |      | Fully adjusted <sup>3</sup> |        |      |      |
|----------------------------------|--------------------|--------------------------|--------|------|------|---------------------------------|--------|------|------|---------------------------------|--------|------|------|-----------------------------|--------|------|------|
|                                  |                    | HR                       | p      | lcl  | ucl  | HR                              | p      | lcl  | ucl  | HR                              | p      | lcl  | ucl  | HR                          | p      | lcl  | ucl  |
| SMI:                             | No SMI             | 1                        |        |      |      | 1                               |        |      |      | 1                               |        |      |      | 1                           |        |      |      |
|                                  | BD                 | <b>3.54</b>              | <0.001 | 3.16 | 3.95 | <b>3.67</b>                     | <0.001 | 3.28 | 4.11 | <b>3.28</b>                     | <0.001 | 2.93 | 3.67 | <b>2.58</b>                 | <0.001 | 2.31 | 2.89 |
|                                  | SCZ                | <b>4.69</b>              | <0.001 | 4.36 | 5.04 | <b>4.63</b>                     | <0.001 | 4.31 | 4.98 | <b>3.81</b>                     | <0.001 | 3.54 | 4.10 | <b>3.03</b>                 | <0.001 | 2.81 | 3.26 |
| Sex:                             | Males              | 1                        |        |      |      | 1                               |        |      |      | 1                               |        |      |      | 1                           |        |      |      |
|                                  | Females            | <b>0.75</b>              | <0.001 | 0.73 | 0.77 | <b>0.75</b>                     | <0.001 | 0.73 | 0.77 | <b>0.76</b>                     | <0.001 | 0.74 | 0.78 | <b>0.80</b>                 | <0.001 | 0.78 | 0.83 |
| Calendar period:                 | 2000-04            | 1                        |        |      |      | 1                               |        |      |      | 1                               |        |      |      | 1                           |        |      |      |
|                                  | 2005-09            | <b>0.96</b>              | 0.039  | 0.93 | 1.00 | <b>0.96</b>                     | 0.021  | 0.92 | 0.99 | <b>0.94</b>                     | 0.002  | 0.91 | 0.98 | <b>0.96</b>                 | 0.021  | 0.92 | 0.99 |
|                                  | 2010-14            | <b>0.85</b>              | <0.001 | 0.82 | 0.89 | <b>0.85</b>                     | <0.001 | 0.81 | 0.88 | <b>0.82</b>                     | <0.001 | 0.79 | 0.85 | <b>0.85</b>                 | <0.001 | 0.82 | 0.88 |
|                                  | 2015-19            | <b>0.89</b>              | <0.001 | 0.86 | 0.93 | <b>0.88</b>                     | <0.001 | 0.84 | 0.92 | <b>0.83</b>                     | <0.001 | 0.79 | 0.87 | <b>0.88</b>                 | <0.001 | 0.84 | 0.92 |
| Townsend:                        | 1 (least deprived) | 1                        |        |      |      |                                 |        |      |      | 1                               |        |      |      | 1                           |        |      |      |
|                                  | 2                  | <b>1.18</b>              | <0.001 | 1.12 | 1.24 |                                 |        |      |      | <b>1.17</b>                     | <0.001 | 1.12 | 1.23 | <b>1.11</b>                 | <0.001 | 1.06 | 1.16 |
|                                  | 3                  | <b>1.52</b>              | <0.001 | 1.45 | 1.59 |                                 |        |      |      | <b>1.50</b>                     | <0.001 | 1.43 | 1.57 | <b>1.31</b>                 | <0.001 | 1.25 | 1.37 |
|                                  | 4                  | <b>2.00</b>              | <0.001 | 1.91 | 2.09 |                                 |        |      |      | <b>1.94</b>                     | <0.001 | 1.86 | 2.03 | <b>1.54</b>                 | <0.001 | 1.47 | 1.61 |
|                                  | 5 (most deprived)  | <b>2.86</b>              | <0.001 | 2.74 | 2.99 |                                 |        |      |      | <b>2.71</b>                     | <0.001 | 2.59 | 2.84 | <b>1.94</b>                 | <0.001 | 1.85 | 2.03 |
|                                  | Missing            | <b>1.39</b>              | <0.001 | 1.33 | 1.46 |                                 |        |      |      | <b>1.36</b>                     | <0.001 | 1.30 | 1.43 | <b>1.21</b>                 | <0.001 | 1.16 | 1.28 |
| Country:                         | England            | 1                        |        |      |      |                                 |        |      |      | 1                               |        |      |      | 1                           |        |      |      |
|                                  | Scotland           | <b>1.14</b>              | <0.001 | 1.10 | 1.19 |                                 |        |      |      | <b>1.05</b>                     | 0.018  | 1.01 | 1.09 | 0.98                        | 0.319  | 0.94 | 1.02 |
|                                  | Wales              | <b>1.09</b>              | <0.001 | 1.05 | 1.14 |                                 |        |      |      | <b>1.13</b>                     | <0.001 | 1.09 | 1.18 | <b>1.06</b>                 | 0.008  | 1.01 | 1.10 |
|                                  | Northern Ireland   | 1.05                     | 0.116  | 0.99 | 1.12 |                                 |        |      |      | 0.97                            | 0.396  | 0.92 | 1.04 | 0.98                        | 0.554  | 0.92 | 1.04 |
| Diabetes mellitus <sup>4</sup> : |                    | <b>2.58</b>              | <0.001 | 2.47 | 2.69 |                                 |        |      |      |                                 |        |      |      | <b>2.07</b>                 | <0.001 | 1.98 | 2.16 |
| Charlson index:                  | 0                  | 1                        |        |      |      |                                 |        |      |      |                                 |        |      |      | 1                           |        |      |      |
|                                  | 1                  | <b>1.60</b>              | <0.001 | 1.54 | 1.66 |                                 |        |      |      |                                 |        |      |      | <b>1.48</b>                 | <0.001 | 1.42 | 1.53 |
|                                  | 2+                 | <b>7.52</b>              | <0.001 | 7.23 | 7.84 |                                 |        |      |      |                                 |        |      |      | <b>6.51</b>                 | <0.001 | 6.25 | 6.79 |
| Any CVD:                         |                    | <b>3.87</b>              | <0.001 | 3.69 | 4.07 |                                 |        |      |      |                                 |        |      |      | <b>2.29</b>                 | <0.001 | 2.18 | 2.41 |
| Smoking status:                  | Never smoked       | 1                        |        |      |      |                                 |        |      |      |                                 |        |      |      | 1                           |        |      |      |
|                                  | Ex-smoker          | <b>1.41</b>              | <0.001 | 1.36 | 1.47 |                                 |        |      |      |                                 |        |      |      | <b>1.25</b>                 | <0.001 | 1.20 | 1.30 |
|                                  | Current smoker     | <b>2.87</b>              | <0.001 | 2.78 | 2.96 |                                 |        |      |      |                                 |        |      |      | <b>2.29</b>                 | <0.001 | 2.22 | 2.37 |
|                                  | Missing            | <b>1.36</b>              | <0.001 | 1.29 | 1.44 |                                 |        |      |      |                                 |        |      |      | <b>1.11</b>                 | 0.002  | 1.04 | 1.19 |
| Obesity:                         | No                 | 1                        |        |      |      |                                 |        |      |      |                                 |        |      |      | 1                           |        |      |      |
|                                  | Yes                | <b>1.10</b>              | <0.001 | 1.06 | 1.14 |                                 |        |      |      |                                 |        |      |      | <b>0.91</b>                 | <0.001 | 0.88 | 0.94 |
|                                  | Unrecorded         | <b>1.11</b>              | <0.001 | 1.07 | 1.14 |                                 |        |      |      |                                 |        |      |      | <b>1.23</b>                 | <0.001 | 1.18 | 1.28 |
| BP:                              | <140/90 mmHg       | 1                        |        |      |      |                                 |        |      |      |                                 |        |      |      | 1                           |        |      |      |
|                                  | ≥140/90 mmHg       | <b>1.31</b>              | <0.001 | 1.28 | 1.35 |                                 |        |      |      |                                 |        |      |      | <b>1.25</b>                 | <0.001 | 1.21 | 1.29 |
|                                  | Missing            | 1.04                     | 0.104  | 0.99 | 1.08 |                                 |        |      |      |                                 |        |      |      | <b>1.06</b>                 | 0.039  | 1.00 | 1.12 |

SMI – severe mental illness, BD – bipolar disorder, SCZ – schizophrenia, CVD – cardiovascular disease, BP – blood pressure, HR – hazard ratio, lcl – lower 95% confidence limit, ucl – upper 95% confidence limit. <sup>1</sup> adjusted for sex, calendar period. <sup>2</sup> adjusted for sex, calendar period, deprivation, country. <sup>3</sup> adjusted for sex, calendar period, deprivation, country, diabetes mellitus, CVD, Charlson index, smoking, obesity, blood pressure. <sup>4</sup> includes type 1, non-type 1 and diabetes mellitus prescription except for metformin if prior polycystic ovary syndrome. Values that exclude the null highlighted in **bold**

**Table 4.19: Hazard ratios for all-cause mortality in univariable and multivariable Cox regression analyses, ages 55-64 years, prevalent cohort**

| Variable                         |                    | Univariable (unadjusted) |        |      |      | Minimally adjusted <sup>1</sup> |        |      |      | Partially adjusted <sup>2</sup> |        |      |      | Fully adjusted <sup>3</sup> |        |      |      |
|----------------------------------|--------------------|--------------------------|--------|------|------|---------------------------------|--------|------|------|---------------------------------|--------|------|------|-----------------------------|--------|------|------|
|                                  |                    | HR                       | p      | lcl  | ucl  | HR                              | p      | lcl  | ucl  | HR                              | p      | lcl  | ucl  | HR                          | p      | lcl  | ucl  |
| SMI:                             | No SMI             | 1                        |        |      |      | 1                               |        |      |      | 1                               |        |      |      | 1                           |        |      |      |
|                                  | BD                 | <b>2.40</b>              | <0.001 | 2.19 | 2.62 | <b>2.51</b>                     | <0.001 | 2.29 | 2.74 | <b>2.31</b>                     | <0.001 | 2.11 | 2.53 | <b>1.89</b>                 | <0.001 | 1.73 | 2.07 |
|                                  | SCZ                | <b>3.42</b>              | <0.001 | 3.23 | 3.62 | <b>3.43</b>                     | <0.001 | 3.24 | 3.64 | <b>2.93</b>                     | <0.001 | 2.76 | 3.10 | <b>2.48</b>                 | <0.001 | 2.34 | 2.63 |
| Sex:                             | Males              | 1                        |        |      |      | 1                               |        |      |      | 1                               |        |      |      | 1                           |        |      |      |
|                                  | Females            | <b>0.69</b>              | <0.001 | 0.68 | 0.71 | <b>0.69</b>                     | <0.001 | 0.68 | 0.71 | <b>0.70</b>                     | <0.001 | 0.68 | 0.71 | <b>0.76</b>                 | <0.001 | 0.74 | 0.77 |
| Calendar period:                 | 2000-04            | 1                        |        |      |      | 1                               |        |      |      | 1                               |        |      |      | 1                           |        |      |      |
|                                  | 2005-09            | 0.98                     | 0.079  | 0.95 | 1.00 | 0.98                            | 0.065  | 0.95 | 1.00 | 0.98                            | 0.072  | 0.95 | 1.00 | 1.01                        | 0.610  | 0.98 | 1.03 |
|                                  | 2010-14            | <b>0.88</b>              | <0.001 | 0.85 | 0.90 | <b>0.87</b>                     | <0.001 | 0.85 | 0.90 | <b>0.86</b>                     | <0.001 | 0.84 | 0.89 | <b>0.92</b>                 | <0.001 | 0.90 | 0.95 |
|                                  | 2015-19            | <b>0.86</b>              | <0.001 | 0.84 | 0.89 | <b>0.86</b>                     | <0.001 | 0.83 | 0.88 | <b>0.83</b>                     | <0.001 | 0.81 | 0.86 | <b>0.91</b>                 | <0.001 | 0.88 | 0.94 |
| Townsend:                        | 1 (least deprived) | 1                        |        |      |      |                                 |        |      |      | 1                               |        |      |      | 1                           |        |      |      |
|                                  | 2                  | <b>1.14</b>              | <0.001 | 1.10 | 1.17 |                                 |        |      |      | <b>1.14</b>                     | <0.001 | 1.10 | 1.17 | <b>1.08</b>                 | <0.001 | 1.05 | 1.11 |
|                                  | 3                  | <b>1.44</b>              | <0.001 | 1.40 | 1.49 |                                 |        |      |      | <b>1.44</b>                     | <0.001 | 1.40 | 1.49 | <b>1.26</b>                 | <0.001 | 1.22 | 1.29 |
|                                  | 4                  | <b>1.89</b>              | <0.001 | 1.83 | 1.95 |                                 |        |      |      | <b>1.87</b>                     | <0.001 | 1.81 | 1.92 | <b>1.47</b>                 | <0.001 | 1.42 | 1.51 |
|                                  | 5 (most deprived)  | <b>2.46</b>              | <0.001 | 2.39 | 2.54 |                                 |        |      |      | <b>2.41</b>                     | <0.001 | 2.33 | 2.49 | <b>1.70</b>                 | <0.001 | 1.65 | 1.76 |
|                                  | Missing            | <b>1.31</b>              | <0.001 | 1.26 | 1.35 |                                 |        |      |      | <b>1.29</b>                     | <0.001 | 1.25 | 1.34 | <b>1.15</b>                 | <0.001 | 1.11 | 1.19 |
| Country:                         | England            | 1                        |        |      |      |                                 |        |      |      | 1                               |        |      |      | 1                           |        |      |      |
|                                  | Scotland           | <b>1.06</b>              | <0.001 | 1.03 | 1.09 |                                 |        |      |      | 0.99                            | 0.387  | 0.96 | 1.02 | <b>0.90</b>                 | <0.001 | 0.88 | 0.93 |
|                                  | Wales              | <b>1.07</b>              | <0.001 | 1.04 | 1.10 |                                 |        |      |      | <b>1.11</b>                     | <0.001 | 1.08 | 1.14 | 1.02                        | 0.142  | 0.99 | 1.05 |
|                                  | Northern Ireland   | <b>0.95</b>              | 0.027  | 0.91 | 0.99 |                                 |        |      |      | <b>0.89</b>                     | <0.001 | 0.85 | 0.93 | <b>0.88</b>                 | <0.001 | 0.84 | 0.92 |
| Diabetes mellitus <sup>4</sup> : |                    | <b>2.18</b>              | <0.001 | 2.13 | 2.23 |                                 |        |      |      |                                 |        |      |      | <b>1.81</b>                 | <0.001 | 1.76 | 1.85 |
| Charlson index:                  | 0                  | 1                        |        |      |      |                                 |        |      |      |                                 |        |      |      | 1                           |        |      |      |
|                                  | 1                  | <b>1.62</b>              | <0.001 | 1.58 | 1.66 |                                 |        |      |      |                                 |        |      |      | <b>1.48</b>                 | <0.001 | 1.44 | 1.51 |
|                                  | 2+                 | <b>4.52</b>              | <0.001 | 4.40 | 4.63 |                                 |        |      |      |                                 |        |      |      | <b>4.14</b>                 | <0.001 | 4.03 | 4.25 |
| Any CVD:                         |                    | <b>2.71</b>              | <0.001 | 2.64 | 2.77 |                                 |        |      |      |                                 |        |      |      | <b>1.86</b>                 | <0.001 | 1.81 | 1.90 |
| Smoking status:                  | Never smoked       | 1                        |        |      |      |                                 |        |      |      |                                 |        |      |      | 1                           |        |      |      |
|                                  | Ex-smoker          | <b>1.62</b>              | <0.001 | 1.58 | 1.66 |                                 |        |      |      |                                 |        |      |      | <b>1.37</b>                 | <0.001 | 1.34 | 1.41 |
|                                  | Current smoker     | <b>2.98</b>              | <0.001 | 2.92 | 3.05 |                                 |        |      |      |                                 |        |      |      | <b>2.38</b>                 | <0.001 | 2.33 | 2.44 |
|                                  | Missing            | <b>1.55</b>              | <0.001 | 1.49 | 1.61 |                                 |        |      |      |                                 |        |      |      | <b>1.17</b>                 | <0.001 | 1.11 | 1.23 |
| Obesity:                         | No                 | 1                        |        |      |      |                                 |        |      |      |                                 |        |      |      | 1                           |        |      |      |
|                                  | Yes                | <b>1.07</b>              | <0.001 | 1.05 | 1.09 |                                 |        |      |      |                                 |        |      |      | <b>0.91</b>                 | <0.001 | 0.89 | 0.93 |

| Variable     | Univariable (unadjusted) |        |      |      | Minimally adjusted <sup>1</sup> |   |     |     | Partially adjusted <sup>2</sup> |   |     |     | Fully adjusted <sup>3</sup> |        |      |      |
|--------------|--------------------------|--------|------|------|---------------------------------|---|-----|-----|---------------------------------|---|-----|-----|-----------------------------|--------|------|------|
|              | HR                       | p      | lcl  | ucl  | HR                              | p | lcl | ucl | HR                              | p | lcl | ucl | HR                          | p      | lcl  | ucl  |
| Unrecorded   | <b>1.21</b>              | <0.001 | 1.18 | 1.24 |                                 |   |     |     |                                 |   |     |     | <b>1.38</b>                 | <0.001 | 1.34 | 1.42 |
| BP:          |                          |        |      |      |                                 |   |     |     |                                 |   |     |     |                             |        |      |      |
| <140/90 mmHg | 1                        |        |      |      |                                 |   |     |     |                                 |   |     |     | 1                           |        |      |      |
| ≥140/90 mmHg | <b>1.11</b>              | <0.001 | 1.09 | 1.13 |                                 |   |     |     |                                 |   |     |     | <b>1.10</b>                 | <0.001 | 1.08 | 1.12 |
| Missing      | <b>1.07</b>              | <0.001 | 1.03 | 1.11 |                                 |   |     |     |                                 |   |     |     | <b>1.05</b>                 | 0.033  | 1.00 | 1.10 |

SMI – severe mental illness, BD – bipolar disorder, SCZ – schizophrenia, CVD – cardiovascular disease, BP – blood pressure, HR – hazard ratio, lcl – lower 95% confidence limit, ucl – upper 95% confidence limit. <sup>1</sup> adjusted for sex, calendar period. <sup>2</sup> adjusted for sex, calendar period, deprivation, country. <sup>3</sup> adjusted for sex, calendar period, deprivation, country, diabetes mellitus, CVD, Charlson index, smoking, obesity, blood pressure. <sup>4</sup> includes type 1, non-type 1 and diabetes mellitus prescription except for metformin if prior polycystic ovary syndrome Values that exclude the null highlighted in **bold**

**Table 4.20: Hazard ratios for all-cause mortality in univariable and multivariable Cox regression analyses, ages 65-74 years, prevalent cohort**

| Variable                         | Univariable (unadjusted) |        |      |      | Minimally adjusted <sup>1</sup> |        |      |      | Partially adjusted <sup>2</sup> |        |      |      | Fully adjusted <sup>3</sup> |        |      |      |
|----------------------------------|--------------------------|--------|------|------|---------------------------------|--------|------|------|---------------------------------|--------|------|------|-----------------------------|--------|------|------|
|                                  | HR                       | p      | lcl  | ucl  | HR                              | p      | lcl  | ucl  | HR                              | p      | lcl  | ucl  | HR                          | p      | lcl  | ucl  |
| SMI:                             |                          |        |      |      |                                 |        |      |      |                                 |        |      |      |                             |        |      |      |
| No SMI                           | 1                        |        |      |      | 1                               |        |      |      | 1                               |        |      |      | 1                           |        |      |      |
| BD                               | <b>2.08</b>              | <0.001 | 1.95 | 2.23 | <b>2.20</b>                     | <0.001 | 2.05 | 2.35 | <b>2.09</b>                     | <0.001 | 1.95 | 2.24 | <b>1.79</b>                 | <0.001 | 1.67 | 1.92 |
| SCZ                              | <b>2.56</b>              | <0.001 | 2.44 | 2.69 | <b>2.64</b>                     | <0.001 | 2.51 | 2.77 | <b>2.39</b>                     | <0.001 | 2.27 | 2.50 | <b>2.14</b>                 | <0.001 | 2.04 | 2.24 |
| Sex:                             |                          |        |      |      |                                 |        |      |      |                                 |        |      |      |                             |        |      |      |
| Males                            | 1                        |        |      |      | 1                               |        |      |      | 1                               |        |      |      | 1                           |        |      |      |
| Females                          | <b>0.66</b>              | <0.001 | 0.65 | 0.67 | <b>0.66</b>                     | <0.001 | 0.65 | 0.66 | <b>0.65</b>                     | <0.001 | 0.64 | 0.66 | <b>0.75</b>                 | <0.001 | 0.74 | 0.76 |
| Calendar period:                 |                          |        |      |      |                                 |        |      |      |                                 |        |      |      |                             |        |      |      |
| 2000-04                          | 1                        |        |      |      | 1                               |        |      |      | 1                               |        |      |      | 1                           |        |      |      |
| 2005-09                          | <b>0.94</b>              | <0.001 | 0.92 | 0.96 | <b>0.94</b>                     | <0.001 | 0.92 | 0.96 | <b>0.95</b>                     | <0.001 | 0.93 | 0.97 | <b>0.97</b>                 | 0.001  | 0.95 | 0.99 |
| 2010-14                          | <b>0.83</b>              | <0.001 | 0.81 | 0.84 | <b>0.82</b>                     | <0.001 | 0.81 | 0.84 | <b>0.83</b>                     | <0.001 | 0.82 | 0.85 | <b>0.87</b>                 | <0.001 | 0.86 | 0.89 |
| 2015-19                          | <b>0.80</b>              | <0.001 | 0.78 | 0.81 | <b>0.79</b>                     | <0.001 | 0.78 | 0.81 | <b>0.80</b>                     | <0.001 | 0.78 | 0.81 | <b>0.85</b>                 | <0.001 | 0.84 | 0.87 |
| Townsend:                        |                          |        |      |      |                                 |        |      |      |                                 |        |      |      |                             |        |      |      |
| 1 (least deprived)               | 1                        |        |      |      |                                 |        |      |      | 1                               |        |      |      | 1                           |        |      |      |
| 2                                | <b>1.14</b>              | <0.001 | 1.12 | 1.17 |                                 |        |      |      | <b>1.15</b>                     | <0.001 | 1.12 | 1.17 | <b>1.10</b>                 | <0.001 | 1.07 | 1.12 |
| 3                                | <b>1.35</b>              | <0.001 | 1.32 | 1.38 |                                 |        |      |      | <b>1.36</b>                     | <0.001 | 1.33 | 1.39 | <b>1.21</b>                 | <0.001 | 1.19 | 1.24 |
| 4                                | <b>1.73</b>              | <0.001 | 1.69 | 1.76 |                                 |        |      |      | <b>1.73</b>                     | <0.001 | 1.69 | 1.77 | <b>1.41</b>                 | <0.001 | 1.38 | 1.44 |
| 5 (most deprived)                | <b>2.10</b>              | <0.001 | 2.06 | 2.15 |                                 |        |      |      | <b>2.09</b>                     | <0.001 | 2.05 | 2.14 | <b>1.57</b>                 | <0.001 | 1.53 | 1.61 |
| Missing                          | <b>1.25</b>              | <0.001 | 1.22 | 1.28 |                                 |        |      |      | <b>1.26</b>                     | <0.001 | 1.23 | 1.29 | <b>1.14</b>                 | <0.001 | 1.11 | 1.16 |
| Country:                         |                          |        |      |      |                                 |        |      |      |                                 |        |      |      |                             |        |      |      |
| England                          | 1                        |        |      |      |                                 |        |      |      | 1                               |        |      |      | 1                           |        |      |      |
| Scotland                         | <b>1.02</b>              | 0.018  | 1.00 | 1.04 |                                 |        |      |      | <b>0.98</b>                     | 0.026  | 0.96 | 1.00 | <b>0.87</b>                 | <0.001 | 0.85 | 0.89 |
| Wales                            | <b>1.03</b>              | 0.003  | 1.01 | 1.05 |                                 |        |      |      | <b>1.07</b>                     | <0.001 | 1.05 | 1.10 | 0.98                        | 0.093  | 0.96 | 1.00 |
| Northern Ireland                 | <b>0.96</b>              | 0.017  | 0.93 | 0.99 |                                 |        |      |      | <b>0.92</b>                     | <0.001 | 0.90 | 0.95 | <b>0.90</b>                 | <0.001 | 0.87 | 0.93 |
| Diabetes mellitus <sup>4</sup> : | <b>1.84</b>              | <0.001 | 1.82 | 1.87 |                                 |        |      |      |                                 |        |      |      | <b>1.60</b>                 | <0.001 | 1.58 | 1.63 |
| Charlson index:                  |                          |        |      |      |                                 |        |      |      |                                 |        |      |      |                             |        |      |      |
| 0                                | 1                        |        |      |      |                                 |        |      |      |                                 |        |      |      | 1                           |        |      |      |
| 1                                | <b>1.66</b>              | <0.001 | 1.63 | 1.68 |                                 |        |      |      |                                 |        |      |      | <b>1.50</b>                 | <0.001 | 1.48 | 1.53 |
| 2+                               | <b>2.88</b>              | <0.001 | 2.83 | 2.93 |                                 |        |      |      |                                 |        |      |      | <b>2.66</b>                 | <0.001 | 2.62 | 2.71 |
| Any CVD:                         | <b>2.21</b>              | <0.001 | 2.18 | 2.25 |                                 |        |      |      |                                 |        |      |      | <b>1.71</b>                 | <0.001 | 1.68 | 1.73 |

| Variable        |                | Univariable (unadjusted) |        |      |      | Minimally adjusted <sup>1</sup> |   |     |     | Partially adjusted <sup>2</sup> |   |     |     | Fully adjusted <sup>3</sup> |        |      |      |
|-----------------|----------------|--------------------------|--------|------|------|---------------------------------|---|-----|-----|---------------------------------|---|-----|-----|-----------------------------|--------|------|------|
|                 |                | HR                       | p      | lcl  | ucl  | HR                              | p | lcl | ucl | HR                              | p | lcl | ucl | HR                          | p      | lcl  | ucl  |
| Smoking status: | Never smoked   | 1                        |        |      |      |                                 |   |     |     |                                 |   |     |     | 1                           |        |      |      |
|                 | Ex-smoker      | <b>1.71</b>              | <0.001 | 1.68 | 1.74 |                                 |   |     |     |                                 |   |     |     | <b>1.43</b>                 | <0.001 | 1.41 | 1.46 |
|                 | Current smoker | <b>2.92</b>              | <0.001 | 2.87 | 2.97 |                                 |   |     |     |                                 |   |     |     | <b>2.36</b>                 | <0.001 | 2.32 | 2.40 |
|                 | Missing        | <b>1.81</b>              | <0.001 | 1.76 | 1.87 |                                 |   |     |     |                                 |   |     |     | <b>1.21</b>                 | <0.001 | 1.16 | 1.25 |
| Obesity:        | No             | 1                        |        |      |      |                                 |   |     |     |                                 |   |     |     | 1                           |        |      |      |
|                 | Yes            | <b>1.04</b>              | <0.001 | 1.02 | 1.06 |                                 |   |     |     |                                 |   |     |     | <b>0.92</b>                 | <0.001 | 0.90 | 0.93 |
|                 | Unrecorded     | <b>1.34</b>              | <0.001 | 1.32 | 1.37 |                                 |   |     |     |                                 |   |     |     | <b>1.49</b>                 | <0.001 | 1.45 | 1.52 |
| BP:             | <140/90 mmHg   | 1                        |        |      |      |                                 |   |     |     |                                 |   |     |     | 1                           |        |      |      |
|                 | ≥140/90 mmHg   | <b>0.94</b>              | <0.001 | 0.93 | 0.96 |                                 |   |     |     |                                 |   |     |     | <b>0.98</b>                 | <0.001 | 0.96 | 0.99 |
|                 | Missing        | <b>1.21</b>              | <0.001 | 1.17 | 1.24 |                                 |   |     |     |                                 |   |     |     | <b>1.14</b>                 | <0.001 | 1.10 | 1.18 |

SMI – severe mental illness, BD – bipolar disorder, SCZ – schizophrenia, CVD – cardiovascular disease, BP – blood pressure, HR – hazard ratio, lcl – lower 95% confidence limit, ucl – upper 95% confidence limit. <sup>1</sup> adjusted for sex, calendar period. <sup>2</sup> adjusted for sex, calendar period, deprivation, country. <sup>3</sup> adjusted for sex, calendar period, deprivation, country, diabetes mellitus, CVD, Charlson index, smoking, obesity, blood pressure. <sup>4</sup> includes type 1, non-type 1 and diabetes mellitus prescription except for metformin if prior polycystic ovary syndrome. Values that exclude the null highlighted in **bold**

**Table 4.21: Results of likelihood-ratio tests for the additional effect of SMI X period interaction, prevalent cohort, all-cause mortality**

| Age group (years) | Reduced model <sup>1</sup> |       | Full model <sup>2</sup>  |       |
|-------------------|----------------------------|-------|--------------------------|-------|
|                   | LR test statistic (6 df)   | p     | LR test statistic (6 df) | p     |
| 15-24             | 5.42                       | 0.491 | 4.91                     | 0.556 |
| 25-34             | 9.60                       | 0.143 | 12.21                    | 0.058 |
| 35-44             | 7.37                       | 0.288 | <b>12.76</b>             | 0.047 |
| 45-54             | <b>13.76</b>               | 0.032 | 7.47                     | 0.279 |
| 55-64             | 4.88                       | 0.559 | 8.26                     | 0.220 |
| 65-74             | 9.48                       | 0.149 | 8.18                     | 0.225 |

LR – likelihood-ratio, df – degrees of freedom, SMI – severe mental illness, CVD – cardiovascular disease <sup>1</sup> Includes SMI, sex, calendar period, deprivation, country. <sup>2</sup> includes above covariates plus diabetes mellitus, Charlson index, CVD, smoking, obesity, blood pressure. Values that exclude the null highlighted in **bold**

**Table 4.22: Hazard ratios for all-cause mortality in multivariable Cox regression analyses, partially adjusted model with SMI X period interaction, ages 25 years+**

| Variable                  | Ages 25-34  |        |      |       | Ages 35-44  |        |      |      | Ages 45-54  |        |      |      | Ages 55-64  |        |      |      | Ages 65-74  |        |      |      |
|---------------------------|-------------|--------|------|-------|-------------|--------|------|------|-------------|--------|------|------|-------------|--------|------|------|-------------|--------|------|------|
|                           | HR          | p      | lcl  | ucl   | HR          | p      | lcl  | ucl  | HR          | p      | lcl  | ucl  | HR          | p      | lcl  | ucl  | HR          | p      | lcl  | ucl  |
| SMI: No SMI               | 1           |        |      |       | 1           |        |      |      | 1           |        |      |      | 1           |        |      |      | 1           |        |      |      |
| BD                        | <b>7.25</b> | <0.001 | 3.89 | 13.54 | <b>3.94</b> | <0.001 | 2.51 | 6.19 | <b>3.38</b> | <0.001 | 2.55 | 4.48 | <b>2.05</b> | <0.001 | 1.61 | 2.60 | <b>2.21</b> | <0.001 | 1.88 | 2.59 |
| SCZ                       | <b>8.70</b> | <0.001 | 6.38 | 11.88 | <b>6.99</b> | <0.001 | 5.67 | 8.62 | <b>3.33</b> | <0.001 | 2.75 | 4.03 | <b>3.17</b> | <0.001 | 2.77 | 3.62 | <b>2.13</b> | <0.001 | 1.89 | 2.40 |
| Sex: Males                | 1           |        |      |       | 1           |        |      |      | 1           |        |      |      | 1           |        |      |      | 1           |        |      |      |
| Females                   | <b>0.53</b> | <0.001 | 0.50 | 0.57  | <b>0.70</b> | <0.001 | 0.68 | 0.73 | <b>0.76</b> | <0.001 | 0.74 | 0.78 | <b>0.70</b> | <0.001 | 0.68 | 0.71 | <b>0.65</b> | <0.001 | 0.64 | 0.66 |
| Calendar period: 2000-04  | 1           |        |      |       | 1           |        |      |      | 1           |        |      |      | 1           |        |      |      | 1           |        |      |      |
| 2005-09                   | <b>1.11</b> | 0.024  | 1.01 | 1.21  | 1.04        | 0.147  | 0.98 | 1.11 | <b>0.94</b> | 0.004  | 0.91 | 0.98 | 0.98        | 0.090  | 0.95 | 1.00 | <b>0.95</b> | <0.001 | 0.93 | 0.96 |
| 2010-14                   | <b>0.91</b> | 0.043  | 0.83 | 1.00  | <b>0.92</b> | 0.007  | 0.87 | 0.98 | <b>0.81</b> | <0.001 | 0.78 | 0.84 | <b>0.86</b> | <0.001 | 0.84 | 0.89 | <b>0.83</b> | <0.001 | 0.82 | 0.85 |
| 2015-19                   | <b>0.87</b> | 0.010  | 0.78 | 0.97  | <b>0.92</b> | 0.018  | 0.85 | 0.99 | <b>0.82</b> | <0.001 | 0.79 | 0.86 | <b>0.83</b> | <0.001 | 0.81 | 0.86 | <b>0.80</b> | <0.001 | 0.78 | 0.81 |
| Townsend <sup>1</sup> : 1 | 1           |        |      |       | 1           |        |      |      | 1           |        |      |      | 1           |        |      |      | 1           |        |      |      |
| 2                         | 1.03        | 0.585  | 0.92 | 1.17  | <b>1.15</b> | <0.001 | 1.07 | 1.25 | <b>1.17</b> | <0.001 | 1.12 | 1.23 | <b>1.14</b> | <0.001 | 1.10 | 1.17 | <b>1.15</b> | <0.001 | 1.12 | 1.17 |
| 3                         | <b>1.19</b> | 0.002  | 1.07 | 1.33  | <b>1.50</b> | <0.001 | 1.40 | 1.62 | <b>1.50</b> | <0.001 | 1.43 | 1.57 | <b>1.44</b> | <0.001 | 1.40 | 1.49 | <b>1.36</b> | <0.001 | 1.33 | 1.39 |
| 4                         | <b>1.41</b> | <0.001 | 1.26 | 1.57  | <b>1.99</b> | <0.001 | 1.86 | 2.14 | <b>1.94</b> | <0.001 | 1.86 | 2.03 | <b>1.87</b> | <0.001 | 1.81 | 1.92 | <b>1.73</b> | <0.001 | 1.69 | 1.77 |
| 5                         | <b>1.97</b> | <0.001 | 1.77 | 2.19  | <b>2.73</b> | <0.001 | 2.54 | 2.93 | <b>2.71</b> | <0.001 | 2.59 | 2.84 | <b>2.41</b> | <0.001 | 2.34 | 2.49 | <b>2.09</b> | <0.001 | 2.05 | 2.14 |
| Missing                   | 1.06        | 0.302  | 0.95 | 1.20  | <b>1.31</b> | <0.001 | 1.21 | 1.41 | <b>1.36</b> | <0.001 | 1.30 | 1.43 | <b>1.29</b> | <0.001 | 1.25 | 1.34 | <b>1.26</b> | <0.001 | 1.23 | 1.29 |
| Country: England          | 1           |        |      |       | 1           |        |      |      | 1           |        |      |      | 1           |        |      |      | 1           |        |      |      |
| Scotland                  | <b>1.25</b> | <0.001 | 1.15 | 1.37  | <b>1.19</b> | <0.001 | 1.12 | 1.26 | <b>1.05</b> | 0.018  | 1.01 | 1.09 | 0.99        | 0.384  | 0.96 | 1.01 | <b>0.98</b> | 0.026  | 0.96 | 1.00 |
| Wales                     | <b>1.19</b> | <0.001 | 1.08 | 1.31  | <b>1.25</b> | <0.001 | 1.17 | 1.33 | <b>1.14</b> | <0.001 | 1.09 | 1.18 | <b>1.11</b> | <0.001 | 1.08 | 1.14 | <b>1.07</b> | <0.001 | 1.05 | 1.10 |
| N. Ireland                | <b>1.22</b> | 0.002  | 1.07 | 1.39  | 1.03        | 0.554  | 0.94 | 1.13 | 0.97        | 0.395  | 0.92 | 1.04 | <b>0.89</b> | <0.001 | 0.85 | 0.93 | <b>0.92</b> | <0.001 | 0.90 | 0.95 |
| SMI X period: BD 2000-04  | 1           |        |      |       | 1           |        |      |      | 1           |        |      |      | 1           |        |      |      | 1           |        |      |      |
| BD 2005-09                | 0.68        | 0.365  | 0.30 | 1.56  | 1.02        | 0.949  | 0.59 | 1.76 | 0.84        | 0.339  | 0.58 | 1.20 | 1.16        | 0.301  | 0.87 | 1.55 | 0.87        | 0.186  | 0.70 | 1.07 |
| BD 2010-14                | 0.77        | 0.522  | 0.35 | 1.71  | 1.16        | 0.578  | 0.68 | 1.98 | 1.10        | 0.595  | 0.78 | 1.53 | 1.18        | 0.248  | 0.89 | 1.57 | 0.94        | 0.559  | 0.77 | 1.15 |
| BD 2015-19                | <b>0.23</b> | 0.025  | 0.06 | 0.83  | 1.29        | 0.378  | 0.73 | 2.28 | 0.94        | 0.724  | 0.65 | 1.35 | 1.09        | 0.603  | 0.80 | 1.48 | 1.01        | 0.936  | 0.81 | 1.25 |
| SCZ 2000-04               | 1           |        |      |       | 1           |        |      |      | 1           |        |      |      | 1           |        |      |      | 1           |        |      |      |
| SCZ 2005-09               | 0.83        | 0.350  | 0.56 | 1.23  | <b>0.71</b> | 0.016  | 0.54 | 0.94 | 1.00        | 0.992  | 0.79 | 1.27 | 0.91        | 0.266  | 0.77 | 1.08 | 1.15        | 0.055  | 1.00 | 1.34 |
| SCZ 2010-14               | 0.71        | 0.099  | 0.47 | 1.07  | 0.78        | 0.074  | 0.60 | 1.02 | 1.22        | 0.090  | 0.97 | 1.53 | 0.87        | 0.108  | 0.73 | 1.03 | <b>1.19</b> | 0.019  | 1.03 | 1.37 |
| SCZ 2015-19               | 0.87        | 0.550  | 0.55 | 1.37  | 0.76        | 0.074  | 0.56 | 1.03 | <b>1.33</b> | 0.020  | 1.05 | 1.69 | 0.97        | 0.706  | 0.80 | 1.16 | 1.07        | 0.403  | 0.91 | 1.26 |

<sup>1</sup> Townsend deprivation score (1=least deprived, 5= most deprived). SMI – severe mental illness, BD – bipolar disorder, SCZ – schizophrenia, CVD – cardiovascular disease, ref – reference category, HR – hazard ratio, lcl – lower 95% confidence limit, ucl – upper 95% confidence limit. Models adjusted for all listed variables. Values that exclude the null highlighted in **bold**

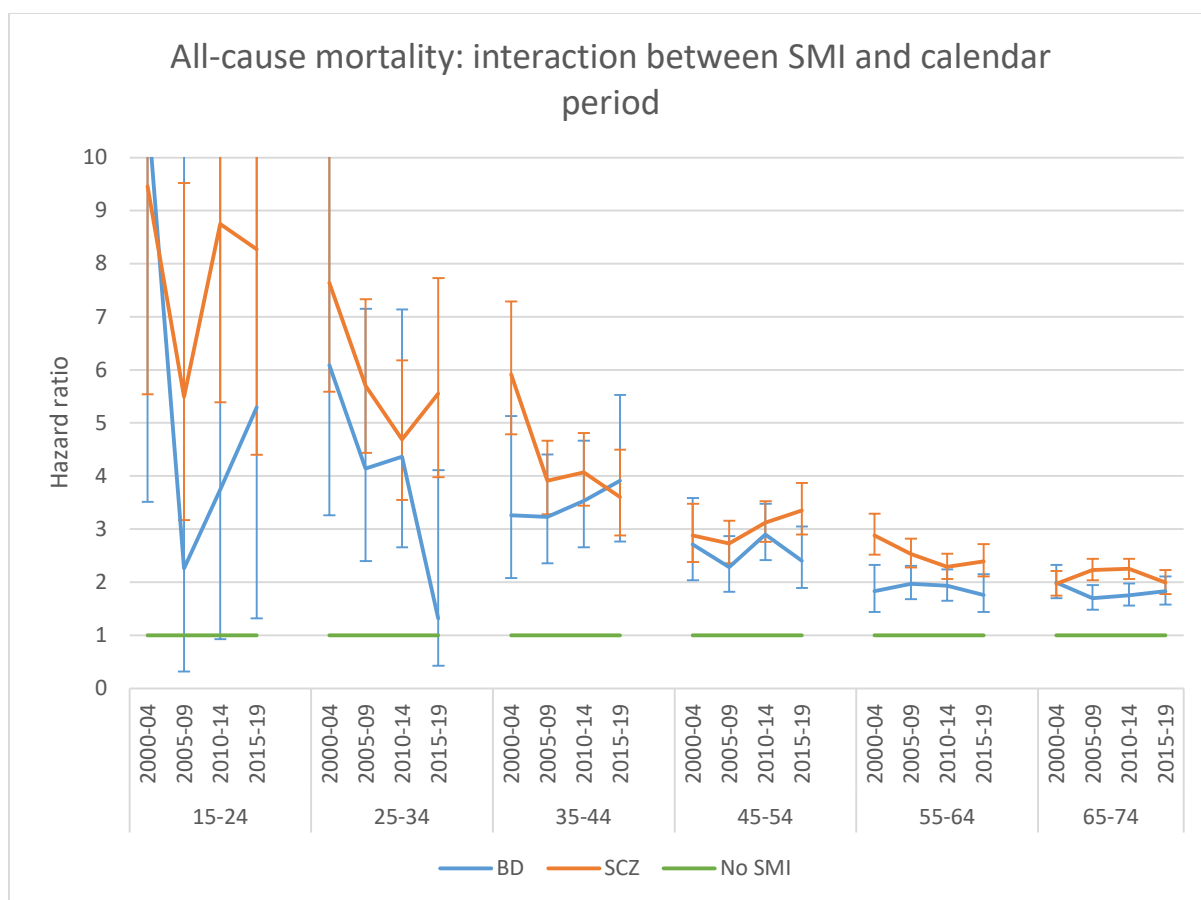


**Table 4.23: Hazard ratios for all-cause mortality in multivariable Cox regression analyses, fully adjusted model with SMI X period interaction, ages 25 years+**

| Variable           |         | Ages 25-34  |        |      |       | Ages 35-44  |        |      |      | Ages 45-54  |        |      |      | Ages 55-64  |        |      |      | Ages 65-74  |        |      |      |
|--------------------|---------|-------------|--------|------|-------|-------------|--------|------|------|-------------|--------|------|------|-------------|--------|------|------|-------------|--------|------|------|
|                    |         | HR          | p      | lcl  | ucl   | HR          | p      | lcl  | ucl  | HR          | p      | lcl  | ucl  | HR          | p      | lcl  | ucl  | HR          | p      | lcl  | ucl  |
| SMI:               | No SMI  | 1           |        |      |       | 1           |        |      |      | 1           |        |      |      | 1           |        |      |      | 1           |        |      |      |
|                    | BD      | <b>6.09</b> | <0.001 | 3.26 | 11.37 | <b>3.26</b> | <0.001 | 2.08 | 5.13 | <b>2.71</b> | <0.001 | 2.04 | 3.59 | <b>1.83</b> | <0.001 | 1.44 | 2.33 | <b>1.99</b> | <0.001 | 1.70 | 2.33 |
|                    | SCZ     | <b>7.64</b> | <0.001 | 5.59 | 10.42 | <b>5.91</b> | <0.001 | 4.79 | 7.29 | <b>2.88</b> | <0.001 | 2.38 | 3.48 | <b>2.88</b> | <0.001 | 2.52 | 3.29 | <b>1.97</b> | <0.001 | 1.75 | 2.21 |
| Sex:               | Males   | 1           |        |      |       | 1           |        |      |      | 1           |        |      |      | 1           |        |      |      | 1           |        |      |      |
|                    | Females | <b>0.56</b> | <0.001 | 0.53 | 0.60  | <b>0.76</b> | <0.001 | 0.73 | 0.79 | <b>0.80</b> | <0.001 | 0.78 | 0.83 | <b>0.76</b> | <0.001 | 0.74 | 0.77 | <b>0.75</b> | <0.001 | 0.74 | 0.76 |
| Calendar period:   |         |             |        |      |       |             |        |      |      |             |        |      |      |             |        |      |      |             |        |      |      |
| 2000-04            |         | 1           |        |      |       | 1           |        |      |      | 1           |        |      |      | 1           |        |      |      | 1           |        |      |      |
| 2005-09            |         | <b>1.12</b> | 0.015  | 1.02 | 1.22  | 1.05        | 0.086  | 0.99 | 1.12 | <b>0.96</b> | 0.037  | 0.92 | 1.00 | 1.01        | 0.507  | 0.98 | 1.04 | <b>0.97</b> | <0.001 | 0.95 | 0.99 |
| 2010-14            |         | 0.93        | 0.132  | 0.85 | 1.02  | 0.95        | 0.079  | 0.89 | 1.01 | <b>0.85</b> | <0.001 | 0.81 | 0.88 | <b>0.93</b> | <0.001 | 0.90 | 0.95 | <b>0.87</b> | <0.001 | 0.86 | 0.89 |
| 2015-19            |         | <b>0.89</b> | 0.029  | 0.79 | 0.99  | 0.95        | 0.208  | 0.89 | 1.03 | <b>0.87</b> | <0.001 | 0.83 | 0.91 | <b>0.91</b> | <0.001 | 0.88 | 0.94 | <b>0.86</b> | <0.001 | 0.84 | 0.87 |
| Townsend:          |         |             |        |      |       |             |        |      |      |             |        |      |      |             |        |      |      |             |        |      |      |
| 1 (least deprived) |         | 1           |        |      |       | 1           |        |      |      | 1           |        |      |      | 1           |        |      |      | 1           |        |      |      |
| 2                  |         | 1.02        | 0.771  | 0.90 | 1.15  | <b>1.10</b> | 0.012  | 1.02 | 1.19 | <b>1.11</b> | <0.001 | 1.06 | 1.16 | <b>1.08</b> | <0.001 | 1.05 | 1.11 | <b>1.10</b> | <0.001 | 1.07 | 1.12 |
| 3                  |         | <b>1.15</b> | 0.016  | 1.03 | 1.28  | <b>1.35</b> | <0.001 | 1.26 | 1.45 | <b>1.31</b> | <0.001 | 1.25 | 1.37 | <b>1.26</b> | <0.001 | 1.22 | 1.29 | <b>1.21</b> | <0.001 | 1.19 | 1.24 |
| 4                  |         | <b>1.32</b> | <0.001 | 1.18 | 1.47  | <b>1.66</b> | <0.001 | 1.55 | 1.79 | <b>1.54</b> | <0.001 | 1.47 | 1.61 | <b>1.47</b> | <0.001 | 1.42 | 1.51 | <b>1.41</b> | <0.001 | 1.38 | 1.44 |
| 5 (most deprived)  |         | <b>1.78</b> | <0.001 | 1.60 | 1.99  | <b>2.12</b> | <0.001 | 1.97 | 2.28 | <b>1.94</b> | <0.001 | 1.85 | 2.03 | <b>1.70</b> | <0.001 | 1.65 | 1.76 | <b>1.57</b> | <0.001 | 1.53 | 1.61 |
| Missing            |         | 1.06        | 0.338  | 0.94 | 1.19  | <b>1.22</b> | <0.001 | 1.13 | 1.32 | <b>1.21</b> | <0.001 | 1.16 | 1.28 | <b>1.15</b> | <0.001 | 1.11 | 1.19 | <b>1.14</b> | <0.001 | 1.11 | 1.16 |
| Country:           |         |             |        |      |       |             |        |      |      |             |        |      |      |             |        |      |      |             |        |      |      |
| England            |         | 1           |        |      |       | 1           |        |      |      | 1           |        |      |      | 1           |        |      |      | 1           |        |      |      |
| Scotland           |         | <b>1.23</b> | <0.001 | 1.13 | 1.34  | <b>1.14</b> | <0.001 | 1.08 | 1.21 | 0.98        | 0.317  | 0.94 | 1.02 | <b>0.70</b> | <0.001 | 0.88 | 0.93 | <b>0.87</b> | <0.001 | 0.85 | 0.89 |
| Wales              |         | <b>1.17</b> | 0.001  | 1.06 | 1.29  | <b>1.18</b> | <0.001 | 1.10 | 1.26 | <b>1.06</b> | 0.009  | 1.01 | 1.10 | 1.02        | 0.144  | 0.99 | 1.05 | 0.98        | 0.093  | 0.96 | 1.00 |
| Northern Ireland   |         | <b>1.21</b> | 0.004  | 1.06 | 1.37  | 1.04        | 0.436  | 0.95 | 1.14 | 0.98        | 0.552  | 0.92 | 1.04 | <b>0.88</b> | <0.001 | 0.84 | 0.92 | <b>0.90</b> | <0.001 | 0.87 | 0.93 |
| Diabetes mellitus: |         | <b>3.38</b> | <0.001 | 2.95 | 3.88  | <b>2.59</b> | <0.001 | 2.40 | 2.79 | <b>2.06</b> | <0.001 | 1.97 | 2.16 | <b>1.81</b> | <0.001 | 1.76 | 1.85 | <b>1.60</b> | <0.001 | 1.58 | 1.63 |
| Charlson index: 0  |         | 1           |        |      |       | 1           |        |      |      | 1           |        |      |      | 1           |        |      |      | 1           |        |      |      |
| 1                  |         | <b>1.36</b> | <0.001 | 1.26 | 1.47  | <b>1.42</b> | <0.001 | 1.34 | 1.51 | <b>1.48</b> | <0.001 | 1.42 | 1.53 | <b>1.48</b> | <0.001 | 1.44 | 1.51 | <b>1.50</b> | <0.001 | 1.48 | 1.53 |
| 2+                 |         | <b>13.1</b> | <0.001 | 11.6 | 14.78 | <b>9.80</b> | <0.001 | 9.14 | 10.5 | <b>6.51</b> | <0.001 | 6.25 | 6.78 | <b>4.14</b> | <0.001 | 4.03 | 4.25 | <b>2.66</b> | <0.001 | 2.62 | 2.71 |
| Any CVD:           |         | <b>3.76</b> | <0.001 | 2.75 | 5.15  | <b>3.36</b> | <0.001 | 2.98 | 3.79 | <b>2.29</b> | <0.001 | 2.18 | 2.41 | <b>1.86</b> | <0.001 | 1.81 | 1.90 | <b>1.71</b> | <0.001 | 1.68 | 1.73 |
| Smoking status:    |         |             |        |      |       |             |        |      |      |             |        |      |      |             |        |      |      |             |        |      |      |
| Never smoked       |         | 1           |        |      |       | 1           |        |      |      | 1           |        |      |      | 1           |        |      |      | 1           |        |      |      |
| Ex-smoker          |         | <b>1.16</b> | 0.008  | 1.04 | 1.29  | <b>1.11</b> | 0.002  | 1.04 | 1.19 | <b>1.25</b> | <0.001 | 1.20 | 1.30 | <b>1.37</b> | <0.001 | 1.34 | 1.41 | <b>1.43</b> | <0.001 | 1.41 | 1.46 |
| Current smoker     |         | <b>1.91</b> | <0.001 | 1.78 | 2.05  | <b>2.19</b> | <0.001 | 2.09 | 2.30 | <b>2.29</b> | <0.001 | 2.22 | 2.37 | <b>2.38</b> | <0.001 | 2.33 | 2.44 | <b>2.36</b> | <0.001 | 2.32 | 2.40 |
| Missing            |         | <b>1.39</b> | <0.001 | 1.24 | 1.56  | <b>1.23</b> | <0.001 | 1.12 | 1.34 | <b>1.11</b> | 0.003  | 1.04 | 1.18 | <b>1.17</b> | <0.001 | 1.11 | 1.23 | <b>1.21</b> | <0.001 | 1.16 | 1.25 |
| Obesity:           |         |             |        |      |       |             |        |      |      |             |        |      |      |             |        |      |      |             |        |      |      |
| No                 |         | 1           |        |      |       | 1           |        |      |      | 1           |        |      |      | 1           |        |      |      | 1           |        |      |      |
| Yes                |         | 0.97        | 0.510  | 0.88 | 1.07  | 1.01        | 0.799  | 0.95 | 1.07 | <b>0.91</b> | <0.001 | 0.88 | 0.94 | <b>0.91</b> | <0.001 | 0.89 | 0.93 | <b>0.92</b> | <0.001 | 0.90 | 0.93 |
| Unrecorded         |         | <b>1.20</b> | 0.001  | 1.11 | 1.31  | <b>1.31</b> | <0.001 | 1.24 | 1.39 | <b>1.23</b> | <0.001 | 1.18 | 1.28 | <b>1.38</b> | <0.001 | 1.34 | 1.42 | <b>1.49</b> | <0.001 | 1.45 | 1.52 |

| Variable      | Ages 25-34  |        |      |      | Ages 35-44  |        |      |      | Ages 45-54  |        |      |      | Ages 55-64  |        |      |      | Ages 65-74  |        |      |      |
|---------------|-------------|--------|------|------|-------------|--------|------|------|-------------|--------|------|------|-------------|--------|------|------|-------------|--------|------|------|
|               | HR          | p      | lcl  | ucl  | HR          | p      | lcl  | ucl  | HR          | p      | lcl  | ucl  | HR          | p      | lcl  | ucl  | HR          | p      | lcl  | ucl  |
| BP:           |             |        |      |      |             |        |      |      |             |        |      |      |             |        |      |      |             |        |      |      |
| <140/90 mmHg  | 1           |        |      |      | 1           |        |      |      | 1           |        |      |      | 1           |        |      |      | 1           |        |      |      |
| ≥140/90 mmHg  | <b>1.33</b> | <0.001 | 1.21 | 1.46 | <b>1.40</b> | <0.001 | 1.33 | 1.47 | <b>1.25</b> | <0.001 | 1.21 | 1.29 | <b>1.10</b> | <0.001 | 1.08 | 1.12 | <b>0.97</b> | <0.001 | 0.96 | 0.99 |
| Missing       | 0.91        | 0.051  | 0.84 | 1.00 | 0.99        | 0.733  | 0.92 | 1.06 | <b>1.06</b> | 0.039  | 1.00 | 1.12 | <b>1.05</b> | 0.034  | 1.00 | 1.10 | <b>1.14</b> | <0.001 | 1.10 | 1.18 |
| SMI X period: |             |        |      |      |             |        |      |      |             |        |      |      |             |        |      |      |             |        |      |      |
| BD 2000-04    | 1           |        |      |      | 1           |        |      |      | 1           |        |      |      | 1           |        |      |      | 1           |        |      |      |
| BD 2005-09    | 0.68        | 0.361  | 0.30 | 1.56 | 0.99        | 0.966  | 0.57 | 1.71 | 0.84        | 0.354  | 0.59 | 1.21 | 1.07        | 0.630  | 0.80 | 1.43 | 0.85        | 0.141  | 0.69 | 1.05 |
| BD 2010-14    | 0.72        | 0.409  | 0.32 | 1.58 | 1.08        | 0.777  | 0.63 | 1.84 | 1.07        | 0.690  | 0.77 | 1.50 | 1.05        | 0.733  | 0.79 | 1.39 | 0.88        | 0.216  | 0.72 | 1.08 |
| BD 2015-19    | <b>0.22</b> | 0.021  | 0.06 | 0.79 | 1.20        | 0.532  | 0.68 | 2.12 | 0.89        | 0.522  | 0.61 | 1.28 | 0.96        | 0.786  | 0.70 | 1.31 | 0.92        | 0.423  | 0.74 | 1.14 |
| SCZ 2000-04   | 1           |        |      |      | 1           |        |      |      | 1           |        |      |      | 1           |        |      |      | 1           |        |      |      |
| SCZ 2005-09   | 0.75        | 0.151  | 0.50 | 1.11 | <b>0.66</b> | 0.003  | 0.50 | 0.87 | 0.95        | 0.666  | 0.75 | 1.21 | 0.88        | 0.143  | 0.74 | 1.04 | 1.13        | 0.092  | 0.98 | 1.31 |
| SCZ 2010-14   | <b>0.61</b> | 0.021  | 0.41 | 0.93 | <b>0.69</b> | 0.006  | 0.53 | 0.90 | 1.09        | 0.478  | 0.87 | 1.36 | <b>0.80</b> | 0.008  | 0.67 | 0.94 | 1.14        | 0.071  | 0.99 | 1.32 |
| SCZ 2015-19   | 0.73        | 0.167  | 0.46 | 1.14 | <b>0.61</b> | 0.002  | 0.45 | 0.83 | 1.16        | 0.216  | 0.92 | 1.48 | <b>0.83</b> | 0.050  | 0.69 | 1.00 | 1.01        | 0.884  | 0.86 | 1.19 |

SMI – severe mental illness, BD – bipolar disorder, SCZ – schizophrenia, CVD – cardiovascular disease, ref – reference category, HR – hazard ratio, lcl – lower 95% confidence limit, ucl – upper 95% confidence limit. Models adjusted for all listed variables. Values that exclude the null highlighted in **bold**



SMI – severe mental illness, BD – bipolar disorder, SCZ – schizophrenia. Hazard ratios from model adjusted for SMI, sex, calendar period, deprivation, country, diabetes mellitus, Charlson index, CVD, smoking, obesity, blood pressure, SMI X period interaction

**Figure 4.25: Charts showing the interaction between SMI and calendar period, by age group, fully adjusted model**

#### 4.4.6 Case-fatality

##### 4.4.6.1 All cardiovascular disease

Figure 4.26 shows a flow chart for patients included in the case-fatality cohort (for comparison the flow chart for the full prevalent cohort is shown in Figure 4.15). Of the total prevalent cohort, 215,270 patients were included in the analysis of CVD case-fatality, 1,145 (0.53%) with BD and 2,035 (0.95%) with schizophrenia. Table 4.24 shows the baseline characteristics of the CVD case-fatality cohort. Overall, patients were followed-up for a median of 3.7 years (IQR 1.5-6.9); the median age at CVD diagnosis was 62.0 years (IQR 55.0-69.0) and 61.9% were males. Broadly, those with BD and schizophrenia had, on average, shorter periods of follow-up, were more likely to be female (in the case of BD), had higher levels of deprivation, diabetes mellitus and other comorbidities and were more likely to be smokers and have obesity. The shorter periods of follow-up for those with SMI were due to both higher rates of death and higher rates of changing GP. Higher mortality had more of an effect in reducing follow-up for BD compared to those without SMI, whereas for those with schizophrenia transferring GP practice contributed more to the reduced follow-up.

There were 17,632 deaths after a diagnosis of CVD. Of those with BD, 150 (13.1%) died during their period of follow-up; also 299 (14.7%) of those with schizophrenia and 17,183 (8.1%) of patients with no SMI.

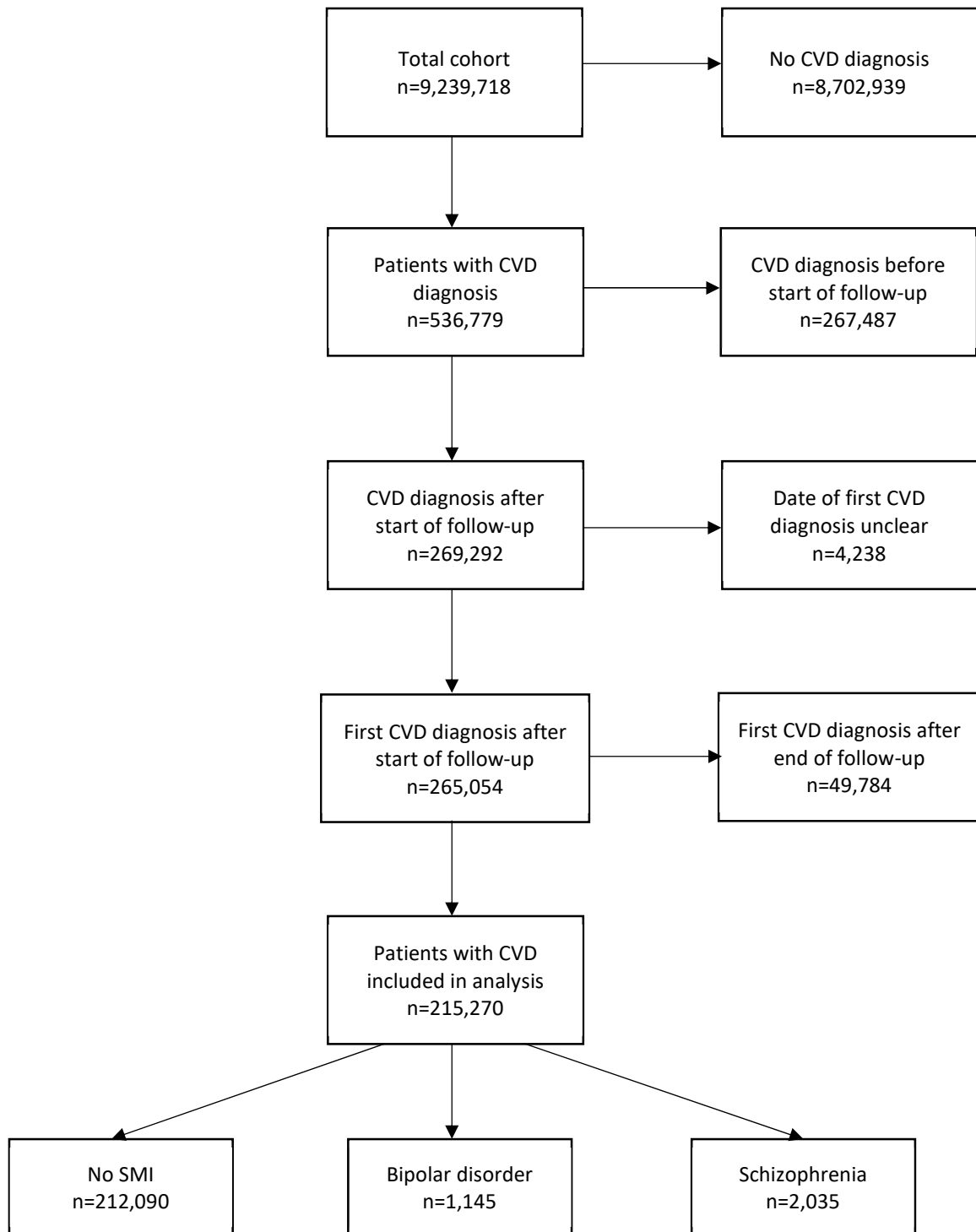


**Figure 4.26: Flow chart showing number of patients included in CVD case-fatality analysis**

**Table 4.24: Characteristics of CVD case-fatality cohort at baseline (date of CVD diagnosis)**

|                                                                | <b>BD<br/>(n=1,145)</b> | <b>Schizophrenia<br/>(n=2,035)</b> | <b>No SMI<br/>(n=212,090)</b> |
|----------------------------------------------------------------|-------------------------|------------------------------------|-------------------------------|
| Median follow-up, years (IQR):                                 | 3.0 (1.2-6.0)           | 2.8 (1.1-5.8)                      | 3.7 (1.5-6.9)                 |
| Male, n (%):                                                   | 546 (47.7)              | 1,183 (58.1)                       | 131,600 (62.1)                |
| Age at baseline, years: median (IQR):                          | 62.0<br>(54.0-68.0)     | 60.0<br>(52.0-67.0)                | 62.0<br>(55.0-69.0)           |
| Townsend deprivation quintile, n (%):                          |                         |                                    |                               |
| 1 (least deprived)                                             | 146 (12.8)              | 182 (8.9)                          | 41,759 (19.7)                 |
| 2                                                              | 175 (15.3)              | 228 (11.2)                         | 39,576 (18.7)                 |
| 3                                                              | 225 (19.7)              | 330 (16.2)                         | 38,964 (18.4)                 |
| 4                                                              | 230 (20.1)              | 472 (23.2)                         | 35,663 (16.8)                 |
| 5 (most deprived)                                              | 205 (17.9)              | 509 (25.0)                         | 27,658 (13.0)                 |
| Missing                                                        | 164 (14.3)              | 314 (15.4)                         | 28,470 (13.4)                 |
| Country, n (%):                                                |                         |                                    |                               |
| England                                                        | 735 (64.2)              | 1,289 (63.3)                       | 141,641 (66.8)                |
| Scotland                                                       | 226 (19.7)              | 361 (17.7)                         | 34,256 (16.2)                 |
| Wales                                                          | 128 (11.2)              | 266 (13.1)                         | 25,248 (11.9)                 |
| Northern Ireland                                               | 56 (4.9)                | 119 (5.9)                          | 10,945 (5.2)                  |
| Diabetes mellitus <sup>1</sup> , n (%):                        | 258 (22.5)              | 499 (24.5)                         | 35,501 (16.7)                 |
| Modified Charlson index <sup>2</sup> , n (%):                  |                         |                                    |                               |
| 0                                                              | 807 (70.5)              | 1,517 (74.6)                       | 165,279 (77.9)                |
| 1                                                              | 235 (20.5)              | 382 (18.8)                         | 34,814 (16.4)                 |
| 2 or more                                                      | 103 (9.0)               | 136 (6.7)                          | 11,997 (5.7)                  |
| Smoking status, n (%):                                         |                         |                                    |                               |
| Never smoked                                                   | 277 (24.2)              | 440 (21.6)                         | 66,410 (31.3)                 |
| Ex-smoker                                                      | 309 (27.0)              | 462 (22.7)                         | 69,039 (32.6)                 |
| Current smoker                                                 | 542 (47.3)              | 1,080 (53.1)                       | 70,266 (33.1)                 |
| Missing                                                        | 17 (1.5)                | 53 (2.6)                           | 6,375 (30.1)                  |
| Obesity at baseline <sup>3</sup> , n (%):                      |                         |                                    |                               |
| No obesity (BMI < 30 (27.5 if non-White))                      | 673 (58.8)              | 1,182 (58.1)                       | 128,128 (60.4)                |
| Has obesity (BMI ≥30 (27.5 if non-White) or obesity Read code) | 405 (35.4)              | 672 (33.0)                         | 61,378 (28.9)                 |
| Missing BMI                                                    | 67 (5.9)                | 181 (8.9)                          | 22,584 (10.7)                 |

<sup>1</sup> Includes type 1, non-type 1, and diabetes mellitus prescription (excluding patients prescribed metformin with a prior diagnosis of polycystic ovary syndrome). <sup>2</sup> Recorded at start date for each patient. <sup>3</sup> Obesity disregarded if recorded at age<16 years. BD – bipolar disorder, SMI – severe mental illness, BMI – body mass index

Analysis of fractional polynomials for scaled and centred age at CVD diagnosis found that a second-degree polynomial (FP2) containing cubic terms ( $\text{age}^3 + \log(\text{age}) \times \text{age}^3$ ) was a better fit compared with a first-degree polynomial (FP1) with a squared term ( $\text{age}^2$ ) and compared with a model with just a linear term for age. This was true for a minimally adjusted model (adjusted by SMI and sex only), a partially adjusted model (adjusted by SMI, sex, Townsend quintile and country) and a fully adjusted model (adjusted by SMI, sex, Townsend quintile,

country, diabetes mellitus, Charlson index, smoking, obesity, and year of CVD diagnosis). P-values for testing the improvement of fit of the FP2 compared with the FP1 model were 0.071, 0.020 and 0.008 for the minimally adjusted, partially adjusted, and fully adjusted models, respectively. There was also some evidence for an FP3 model being a better fit than the FP2:  $p=0.055$ , 0.043, 0.018 for the minimally adjusted, partially adjusted, and fully adjusted models, respectively. However, the FP3 was more complicated, having age terms with different sets of powers in the three adjusted models. The choice of age term had a negligible effect on the HRs for the other covariates in the model and there was virtually no difference in the AIC for the fully adjusted model with either the FP2 or FP3, so the simpler FP2 age term model was used.

For calendar year there was no evidence to reject year as a linear term in favour of a higher order fractional polynomial in any of the adjusted models (FP1 compared with linear term:  $p=0.270, 0.299, 1.000$  in minimally, partially, and fully adjusted models, respectively).

Figure 4.27 shows log-log plots of the covariates included in univariable Cox regression.

There are proportional hazards violations for several of the variables as the lines cross at various points on the time axis. Table 4.25 shows p-values from statistical tests of the proportional hazards assumption. There was evidence of non-proportional hazards for age, sex, year, Townsend quintile, country, diabetes mellitus, smoking and obesity, meaning that there is an association between the coefficients of these variables and time from CVD diagnosis to death. Table 4.26 shows results of Cox multivariable regression that include interactions with time for all the variables exhibiting lack of proportionality. The main effects part of the table shows the HRs at time=0, *i.e.* the hazard of death at diagnosis of CVD. The time-varying coefficient part of the table gives the adjustment for the HRs after one unit of

time since CVD diagnosis (*i.e.* one year). For example, the HR for diabetes mellitus at time=0 was 1.64, but after one year this increased to 1.67 ( $1.64 \times 1.02$ ).

The unadjusted HR for BD was 1.85 (95% CI: 1.58-2.18) and for schizophrenia was 2.12 (95% CI: 1.89-2.38). The associations increased after adjustment for age, sex, and calendar year.

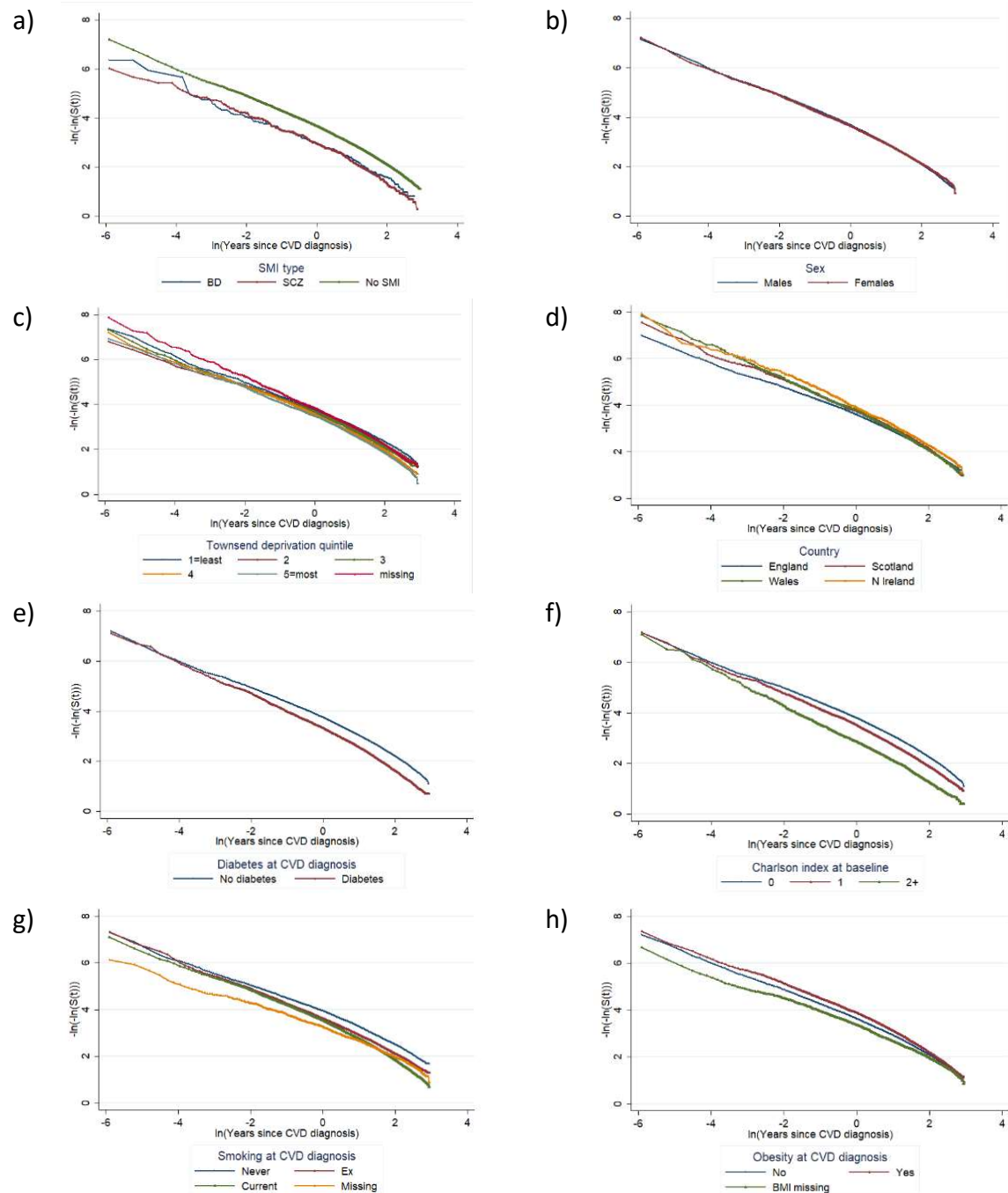
However, after further adjustment by deprivation and country, then additionally by diabetes mellitus, Charlson index, smoking and obesity, and after adding time varying components to the coefficients that were found to vary over time, HRs reduced to HR: 1.67, 95% CI: 1.42-

1.96 for BD and HR: 1.97, 95% CI: 1.75-2.21 for schizophrenia. CVD case-fatality HRs

increased over time since CVD diagnosis for those in the most deprived Townsend quintiles and for those with unrecorded deprivation, those in Scotland, Wales and Northern Ireland vs England, patients with diabetes mellitus, current smokers, and those with obesity, whereas for females and those with unrecorded BMI, HRs reduced over time since CVD diagnosis.

HRs reduced by 2% each year over the study period (HR: 0.98, 95% CI: 0.97-0.99). Model fit was not improved by adding an interaction between SMI and calendar period (likelihood ratio test for minimally, partially, and fully adjusted models:  $p=0.365$ ,  $0.345$ ,  $0.430$ , respectively).





SMI – severe mental illness, BD – bipolar disorder, SCZ – schizophrenia, CVD – cardiovascular disease

**Figure 4.27: Plots of survival function against time since CVD diagnosis (log scales) to assess proportional hazards assumption for a) SMI type, b) sex, c) deprivation quintile, d) country, e) diabetes mellitus, f) Charlson index, g) smoking, h) obesity**

**Table 4.25: Hazard ratios for all-cause mortality after CVD diagnosis from univariable Cox regression analysis**

| Variable                                                               | HR          | p      | lcl  | ucl  | PH test (zero slope of scaled Schoenfeld residuals), p-value |
|------------------------------------------------------------------------|-------------|--------|------|------|--------------------------------------------------------------|
| SMI: No SMI                                                            | 1           |        |      |      |                                                              |
| BD                                                                     | <b>1.85</b> | <0.001 | 1.58 | 2.18 | 0.846                                                        |
| SCZ                                                                    | <b>2.12</b> | <0.001 | 1.89 | 2.38 | 0.387                                                        |
| <i>Global PH test for SMI</i>                                          |             |        |      |      | <i>0.673</i>                                                 |
| Sex: Males                                                             | 1           |        |      |      |                                                              |
| Females                                                                | 0.97        | 0.085  | 0.94 | 1.00 | <0.001                                                       |
| Age at CVD diagnosis (scaled and centred fractional polynomial terms): |             |        |      |      |                                                              |
| Age <sup>3</sup>                                                       | <b>1.04</b> | <0.001 | 1.03 | 1.04 | 0.010                                                        |
| Age <sup>3</sup> X log(age)                                            | <b>0.99</b> | <0.001 | 0.98 | 0.99 | 0.015                                                        |
| <i>Global PH test for age</i>                                          |             |        |      |      | <i>0.002</i>                                                 |
| Calendar year (linear term):                                           | <b>0.98</b> | <0.001 | 0.97 | 0.98 | 0.001                                                        |
| Townsend:                                                              |             |        |      |      |                                                              |
| 1 (least deprived)                                                     | 1           |        |      |      |                                                              |
| 2                                                                      | <b>1.15</b> | <0.001 | 1.10 | 1.21 | 0.650                                                        |
| 3                                                                      | <b>1.25</b> | <0.001 | 1.19 | 1.31 | 0.050                                                        |
| 4                                                                      | <b>1.48</b> | <0.001 | 1.41 | 1.55 | <0.001                                                       |
| 5 (most deprived)                                                      | <b>1.61</b> | <0.001 | 1.53 | 1.70 | <0.001                                                       |
| Missing                                                                | <b>1.13</b> | <0.001 | 1.07 | 1.20 | <0.001                                                       |
| <i>Global PH test for Townsend</i>                                     |             |        |      |      | <i>&lt;0.001</i>                                             |
| Country:                                                               |             |        |      |      |                                                              |
| England                                                                | 1           |        |      |      |                                                              |
| Scotland                                                               | <b>0.96</b> | 0.036  | 0.92 | 1.00 | <0.001                                                       |
| Wales                                                                  | 0.98        | 0.410  | 0.94 | 1.03 | <0.001                                                       |
| Northern Ireland                                                       | <b>0.81</b> | <0.001 | 0.75 | 0.87 | 0.152                                                        |
| <i>Global PH test for country</i>                                      |             |        |      |      | <i>&lt;0.001</i>                                             |
| Diabetes mellitus <sup>1</sup> at CVD:                                 | <b>1.73</b> | <0.001 | 1.67 | 1.79 | <0.001                                                       |
| Charlson index at baseline:                                            |             |        |      |      |                                                              |
| 0                                                                      | 1           |        |      |      |                                                              |
| 1                                                                      | <b>1.43</b> | <0.001 | 1.37 | 1.48 | 0.893                                                        |
| 2+                                                                     | <b>2.60</b> | <0.001 | 2.48 | 2.73 | 0.406                                                        |
| <i>Global PH test for Charlson</i>                                     |             |        |      |      | <i>0.680</i>                                                 |
| Smoking at CVD:                                                        |             |        |      |      |                                                              |
| Never smoked                                                           | 1           |        |      |      |                                                              |
| Ex-smoker                                                              | <b>1.45</b> | <0.001 | 1.39 | 1.51 | 0.117                                                        |
| Current smoker                                                         | <b>1.89</b> | <0.001 | 1.82 | 1.97 | <0.001                                                       |
| Missing                                                                | <b>1.67</b> | <0.001 | 1.55 | 1.81 | 0.014                                                        |
| <i>Global PH test for smoking</i>                                      |             |        |      |      | <i>&lt;0.001</i>                                             |
| Obesity at CVD:                                                        |             |        |      |      |                                                              |
| No                                                                     | 1           |        |      |      |                                                              |
| Yes                                                                    | <b>0.89</b> | <0.001 | 0.86 | 0.92 | <0.001                                                       |
| Unrecorded                                                             | <b>1.15</b> | <0.001 | 1.10 | 1.20 | <0.001                                                       |
| <i>Global PH test for obesity</i>                                      |             |        |      |      | <i>&lt;0.001</i>                                             |

SMI – severe mental illness, BD – bipolar disorder, SCZ – schizophrenia, CVD – cardiovascular disease, PH- proportional hazards. <sup>1</sup> Includes type 1, non-type 1, and diabetes mellitus prescription (excluding patients prescribed metformin with a prior diagnosis of polycystic ovary syndrome). Values that exclude the null highlighted in **bold**

**Table 4.26: Hazard ratios for all-cause mortality after CVD diagnosis from multivariable Cox regression analysis**

| Variable                                                               |                             | Minimally adjusted model <sup>1</sup> |        |      |      | Partially adjusted model <sup>2</sup> |        |      |      | Fully adjusted model <sup>3</sup> |        |      |      |
|------------------------------------------------------------------------|-----------------------------|---------------------------------------|--------|------|------|---------------------------------------|--------|------|------|-----------------------------------|--------|------|------|
|                                                                        |                             | HR                                    | p      | lcl  | ucl  | HR                                    | p      | lcl  | ucl  | HR                                | p      | lcl  | ucl  |
| <b>Main effects</b>                                                    |                             |                                       |        |      |      |                                       |        |      |      |                                   |        |      |      |
| SMI:                                                                   | No SMI                      | 1                                     |        |      |      | 1                                     |        |      |      | 1                                 |        |      |      |
|                                                                        | BD                          | <b>1.95</b>                           | <0.001 | 1.66 | 2.28 | <b>1.87</b>                           | <0.001 | 1.59 | 2.19 | <b>1.67</b>                       | <0.001 | 1.42 | 1.96 |
|                                                                        | SCZ                         | <b>2.37</b>                           | <0.001 | 2.12 | 2.66 | <b>2.19</b>                           | <0.001 | 1.95 | 2.45 | <b>1.97</b>                       | <0.001 | 1.75 | 2.21 |
| Sex:                                                                   | Females                     | <b>0.95</b>                           | 0.016  | 0.91 | 0.99 | <b>0.94</b>                           | 0.005  | 0.90 | 0.98 | 0.97                              | 0.144  | 0.92 | 1.01 |
| Age at CVD diagnosis (scaled and centred fractional polynomial terms): |                             |                                       |        |      |      |                                       |        |      |      |                                   |        |      |      |
|                                                                        | Age <sup>3</sup>            | <b>1.03</b>                           | <0.001 | 1.02 | 1.04 | <b>1.03</b>                           | <0.001 | 1.02 | 1.04 | <b>1.03</b>                       | <0.001 | 1.02 | 1.04 |
|                                                                        | Age <sup>3</sup> X log(age) | <b>0.99</b>                           | <0.001 | 0.99 | 1.00 | <b>0.99</b>                           | <0.001 | 0.98 | 0.99 | <b>0.99</b>                       | <0.001 | 0.98 | 0.99 |
| Calendar year (linear term):                                           |                             | <b>0.97</b>                           | <0.001 | 0.97 | 0.98 | <b>0.98</b>                           | <0.001 | 0.97 | 0.98 | <b>0.98</b>                       | <0.001 | 0.97 | 0.99 |
| Townsend:                                                              | 1 (least deprived)          |                                       |        |      |      | 1                                     |        |      |      | 1                                 |        |      |      |
|                                                                        | 2                           |                                       |        |      |      | <b>1.16</b>                           | <0.001 | 1.08 | 1.25 | <b>1.13</b>                       | 0.001  | 1.05 | 1.22 |
|                                                                        | 3                           |                                       |        |      |      | <b>1.26</b>                           | <0.001 | 1.17 | 1.35 | <b>1.17</b>                       | <0.001 | 1.09 | 1.26 |
|                                                                        | 4                           |                                       |        |      |      | <b>1.45</b>                           | <0.001 | 1.35 | 1.56 | <b>1.28</b>                       | <0.001 | 1.19 | 1.37 |
|                                                                        | 5 (most deprived)           |                                       |        |      |      | <b>1.64</b>                           | <0.001 | 1.52 | 1.77 | <b>1.39</b>                       | <0.001 | 1.29 | 1.50 |
|                                                                        | Missing                     |                                       |        |      |      | <b>1.09</b>                           | 0.045  | 1.00 | 1.18 | 1.01                              | 0.797  | 0.93 | 1.10 |
| Country:                                                               | England                     |                                       |        |      |      | 1                                     |        |      |      | 1                                 |        |      |      |
|                                                                        | Scotland                    |                                       |        |      |      | <b>0.88</b>                           | <0.001 | 0.83 | 0.94 | <b>0.86</b>                       | <0.001 | 0.80 | 0.91 |
|                                                                        | Wales                       |                                       |        |      |      | 0.97                                  | 0.446  | 0.91 | 1.04 | <b>0.93</b>                       | 0.035  | 0.87 | 0.99 |
|                                                                        | Northern Ireland            |                                       |        |      |      | <b>0.81</b>                           | <0.001 | 0.73 | 0.89 | <b>0.80</b>                       | <0.001 | 0.72 | 0.89 |
| Diabetes mellitus at CVD:                                              |                             |                                       |        |      |      |                                       |        |      |      | <b>1.64</b>                       | <0.001 | 1.55 | 1.72 |
| Charlson index at baseline:                                            | 0                           |                                       |        |      |      |                                       |        |      |      | 1                                 |        |      |      |
|                                                                        | 1                           |                                       |        |      |      |                                       |        |      |      | <b>1.34</b>                       | <0.001 | 1.29 | 1.39 |
|                                                                        | 2+                          |                                       |        |      |      |                                       |        |      |      | <b>2.20</b>                       | <0.001 | 2.09 | 2.31 |
| Smoking at CVD:                                                        | Never smoked                |                                       |        |      |      |                                       |        |      |      | 1                                 |        |      |      |
|                                                                        | Ex-smoker                   |                                       |        |      |      |                                       |        |      |      | <b>1.29</b>                       | <0.001 | 1.21 | 1.37 |
|                                                                        | Current smoker              |                                       |        |      |      |                                       |        |      |      | <b>1.77</b>                       | <0.001 | 1.67 | 1.88 |
|                                                                        | Missing                     |                                       |        |      |      |                                       |        |      |      | <b>1.40</b>                       | <0.001 | 1.24 | 1.58 |
| Obesity at CVD:                                                        | No                          |                                       |        |      |      |                                       |        |      |      | 1                                 |        |      |      |
|                                                                        | Yes                         |                                       |        |      |      |                                       |        |      |      | <b>0.81</b>                       | <0.001 | 0.77 | 0.85 |
|                                                                        | Unrecorded                  |                                       |        |      |      |                                       |        |      |      | <b>1.42</b>                       | <0.001 | 1.32 | 1.52 |
| <b>Time varying effects</b>                                            |                             |                                       |        |      |      |                                       |        |      |      |                                   |        |      |      |
| Sex:                                                                   | Females                     | <b>0.99</b>                           | 0.006  | 0.98 | 1.00 | <b>0.98</b>                           | 0.001  | 0.98 | 0.99 | <b>0.98</b>                       | <0.001 | 0.97 | 0.99 |
| Age at CVD diagnosis (scaled and centred fractional polynomial terms): |                             |                                       |        |      |      |                                       |        |      |      |                                   |        |      |      |
|                                                                        | Age <sup>3</sup>            | 1.00                                  | 0.558  | 1.00 | 1.00 | 1.00                                  | 0.399  | 1.00 | 1.00 | 1.00                              | 0.535  | 1.00 | 1.00 |

| Variable        |                                        | Minimally adjusted model <sup>1</sup> |        |      |      | Partially adjusted model <sup>2</sup> |        |      |      | Fully adjusted model <sup>3</sup> |        |      |      |
|-----------------|----------------------------------------|---------------------------------------|--------|------|------|---------------------------------------|--------|------|------|-----------------------------------|--------|------|------|
|                 |                                        | HR                                    | p      | lcl  | ucl  | HR                                    | p      | lcl  | ucl  | HR                                | p      | lcl  | ucl  |
|                 | Age <sup>3</sup> X log(age)            | 1.00                                  | 0.764  | 1.00 | 1.00 | 1.00                                  | 0.598  | 1.00 | 1.00 | 1.00                              | 0.851  | 1.00 | 1.00 |
|                 | Calendar year (linear term):           | <b>1.00</b>                           | <0.001 | 1.00 | 1.00 | <b>1.00</b>                           | 0.006  | 1.00 | 1.00 | <b>1.00</b>                       | 0.019  | 1.00 | 1.00 |
| Townsend:       | 1 (least deprived)                     |                                       |        |      |      | 1                                     |        |      |      | 1                                 |        |      |      |
|                 | 2                                      |                                       |        |      |      | 1.00                                  | 0.882  | 0.99 | 1.02 | 1.00                              | 0.878  | 0.98 | 1.01 |
|                 | 3                                      |                                       |        |      |      | 1.01                                  | 0.073  | 1.00 | 1.03 | 1.01                              | 0.348  | 0.99 | 1.02 |
|                 | 4                                      |                                       |        |      |      | <b>1.03</b>                           | <0.001 | 1.02 | 1.05 | <b>1.02</b>                       | 0.007  | 1.01 | 1.04 |
|                 | 5 (most deprived)                      |                                       |        |      |      | <b>1.04</b>                           | <0.001 | 1.02 | 1.05 | <b>1.03</b>                       | 0.002  | 1.01 | 1.04 |
|                 | Missing                                |                                       |        |      |      | <b>1.03</b>                           | <0.001 | 1.02 | 1.05 | <b>1.03</b>                       | 0.002  | 1.01 | 1.04 |
| Country:        | England                                |                                       |        |      |      | 1                                     |        |      |      | 1                                 |        |      |      |
|                 | Scotland                               |                                       |        |      |      | <b>1.02</b>                           | 0.001  | 1.01 | 1.03 | <b>1.02</b>                       | 0.003  | 1.01 | 1.03 |
|                 | Wales                                  |                                       |        |      |      | <b>1.02</b>                           | 0.014  | 1.00 | 1.03 | <b>1.02</b>                       | 0.009  | 1.00 | 1.03 |
|                 | Northern Ireland                       |                                       |        |      |      | 1.00                                  | 0.724  | 0.99 | 1.02 | 1.00                              | 0.724  | 0.99 | 1.02 |
|                 | Diabetes mellitus <sup>4</sup> at CVD: |                                       |        |      |      |                                       |        |      |      | <b>1.02</b>                       | <0.001 | 1.01 | 1.04 |
| Smoking at CVD: | Never smoked                           |                                       |        |      |      |                                       |        |      |      | 1                                 |        |      |      |
|                 | Ex-smoker                              |                                       |        |      |      |                                       |        |      |      | 1.00                              | 0.968  | 0.99 | 1.01 |
|                 | Current smoker                         |                                       |        |      |      |                                       |        |      |      | <b>1.04</b>                       | <0.001 | 1.03 | 1.06 |
|                 | Missing                                |                                       |        |      |      |                                       |        |      |      | 1.02                              | 0.066  | 1.00 | 1.04 |
| Obesity at CVD: | No                                     |                                       |        |      |      |                                       |        |      |      | 1                                 |        |      |      |
|                 | Yes                                    |                                       |        |      |      |                                       |        |      |      | <b>1.03</b>                       | <0.001 | 1.02 | 1.04 |
|                 | Unrecorded                             |                                       |        |      |      |                                       |        |      |      | <b>0.97</b>                       | <0.001 | 0.96 | 0.99 |

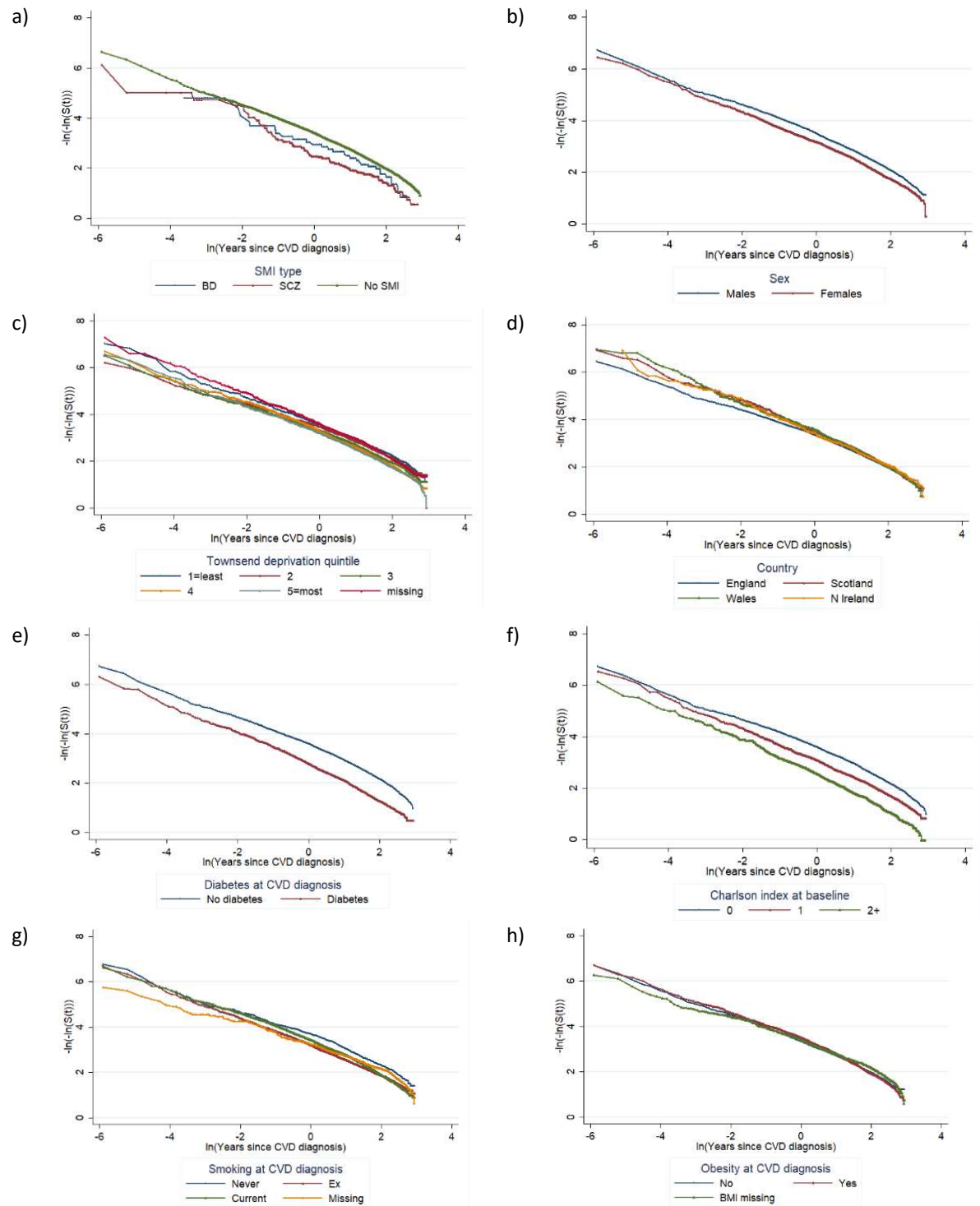
<sup>1</sup> adjusted for SMI, age, sex, and calendar year, <sup>2</sup> adjusted for SMI, age, sex, calendar year, deprivation, and country, <sup>3</sup> adjusted for SMI, age, sex, calendar year, deprivation, country, diabetes mellitus, Charlson index, smoking, obesity, <sup>4</sup> Includes type 1, non-type 1, and diabetes mellitus prescription (excluding patients prescribed metformin with a prior diagnosis of polycystic ovary syndrome). SMI – severe mental illness, BD – bipolar disorder, SCZ – schizophrenia, CVD – cardiovascular disease. Values that exclude the null highlighted in **bold**

#### 4.4.6.2 Myocardial infarction

Section 4.4.6.1 explored case-fatality after a diagnosis of any CVD. In this section, CVD was restricted to MI only. 55,110 patients were included in this analysis and there were 5,231 deaths. Fractional polynomials for age and calendar year found that a squared term for age and linear year adequately described the relationships with hazard of mortality after MI. According to log-log plots (Figure 4.28) and tests of the proportional hazards assumption (Table 4.27) there was evidence of non-proportional hazards for smoking and obesity only, these variables were used for stratification in the fully adjusted model.

In univariable analysis (Table 4.27), there was an association between SMI and mortality after MI for both BD and schizophrenia (BD: HR=1.53, 95% CI: 1.08-2.17; schizophrenia: HR=1.95, 95% CI: 1.55-2.45). HRs were similar for schizophrenia in the fully adjusted model (HR: 1.93, 95% CI: 1.53-2.43), however, after adjustment the association disappeared for BD (HR: 1.26, 95% CI: 0.89-1.79). As for case-fatality after any CVD, the hazard increased with increasing age and increasing Charlson index. HRs also reduced over the study period (HR: 0.98, 95% CI: 0.97-0.99). This means that the hazard was reduced by 2% for each year after 2000. HRs were higher for females and for patients with diabetes mellitus. There was no evidence of an interaction between SMI and calendar year in the minimally, partially, or fully adjusted models (likelihood ratio (LR) test:  $p=0.782$ ,  $0.758$ ,  $0.648$ , respectively). In sensitivity analysis, the replacement of stratification variables smoking and obesity with time-varying coefficients made only negligible differences to the other model coefficients, but the model fit was worse (AIC: 104085 vs 83082).

The fully adjusted multivariable model included SMI, age, sex, calendar year, Townsend deprivation score, country, diabetes mellitus and Charlson index (Table 4.28). For this model, plots of the scaled Schoenfeld residuals (Figure 4.29) showed no evidence of non-proportional hazards.



SMI – severe mental illness, BD – bipolar disorder, SCZ – schizophrenia, CVD – cardiovascular disease, MI – myocardial infarction

**Figure 4.28: Plots of survival function against time since MI diagnosis (log scales) to assess proportional hazards assumption for a) SMI type, b) sex, c) deprivation quintile, d) country, e) diabetes mellitus, f) Charlson index, g) smoking, h) obesity**

**Table 4.27: Hazard ratios for all-cause mortality after myocardial infarction from univariable Cox regression analysis**

| Variable                               | HR          | p      | lcl  | ucl  | PH test (zero slope of scaled Schoenfeld residuals), p-value |
|----------------------------------------|-------------|--------|------|------|--------------------------------------------------------------|
| SMI: No SMI                            | 1           |        |      |      |                                                              |
| BD                                     | <b>1.53</b> | 0.016  | 1.08 | 2.17 | 0.119                                                        |
| SCZ                                    | <b>1.95</b> | <0.001 | 1.55 | 2.45 | 0.605                                                        |
| <i>Global PH test for SMI</i>          |             |        |      |      | <i>0.258</i>                                                 |
| Sex: Males                             | 1           |        |      |      |                                                              |
| Females                                | <b>1.38</b> | <0.001 | 1.30 | 1.46 | 0.396                                                        |
| Age (squared term):                    | <b>1.09</b> | <0.001 | 1.09 | 1.09 | 0.402                                                        |
| Calendar year (linear):                | <b>0.97</b> | <0.001 | 0.97 | 0.98 | 0.151                                                        |
| Townsend: 1 (least deprived)           | 1           |        |      |      |                                                              |
| 2                                      | 1.09        | 0.072  | 0.99 | 1.21 | 0.591                                                        |
| 3                                      | <b>1.30</b> | <0.001 | 1.19 | 1.43 | 0.933                                                        |
| 4                                      | <b>1.51</b> | <0.001 | 1.38 | 1.65 | 0.159                                                        |
| 5 (most deprived)                      | <b>1.57</b> | <0.001 | 1.43 | 1.73 | 0.324                                                        |
| Missing                                | 1.08        | 0.147  | 0.97 | 1.20 | 0.127                                                        |
| <i>Global PH test for Townsend</i>     |             |        |      |      | <i>0.167</i>                                                 |
| Country: England                       | 1           |        |      |      |                                                              |
| Scotland                               | <b>0.92</b> | 0.036  | 0.86 | 0.99 | 0.043                                                        |
| Wales                                  | 0.93        | 0.125  | 0.86 | 1.02 | 0.049                                                        |
| Northern Ireland                       | 0.91        | 0.120  | 0.81 | 1.02 | 0.647                                                        |
| <i>Global PH test for country</i>      |             |        |      |      | <i>0.055</i>                                                 |
| Diabetes mellitus <sup>1</sup> at CVD: | <b>2.35</b> | <0.001 | 2.21 | 2.49 | 0.743                                                        |
| Charlson index at baseline: 0          | 1           |        |      |      |                                                              |
| 1                                      | <b>1.62</b> | <0.001 | 1.51 | 1.73 | 0.154                                                        |
| 2+                                     | <b>3.04</b> | <0.001 | 2.79 | 3.31 | 0.511                                                        |
| <i>Global PH test for Charlson</i>     |             |        |      |      | <i>0.231</i>                                                 |
| Smoking at CVD: Never smoked           | 1           |        |      |      |                                                              |
| Ex-smoker                              | <b>1.58</b> | <0.001 | 1.46 | 1.71 | 0.264                                                        |
| Current smoker                         | <b>1.48</b> | <0.001 | 1.38 | 1.60 | 0.001                                                        |
| Missing                                | <b>1.26</b> | 0.002  | 1.09 | 1.45 | 0.927                                                        |
| <i>Global PH test for smoking</i>      |             |        |      |      | <i>&lt;0.001</i>                                             |
| Obesity at CVD: No                     | 1           |        |      |      |                                                              |
| Yes                                    | 1.01        | 0.640  | 0.95 | 1.08 | <0.001                                                       |
| Unrecorded                             | <b>0.87</b> | 0.001  | 0.80 | 0.95 | 0.829                                                        |
| <i>Global PH test for obesity</i>      |             |        |      |      | <i>&lt;0.001</i>                                             |

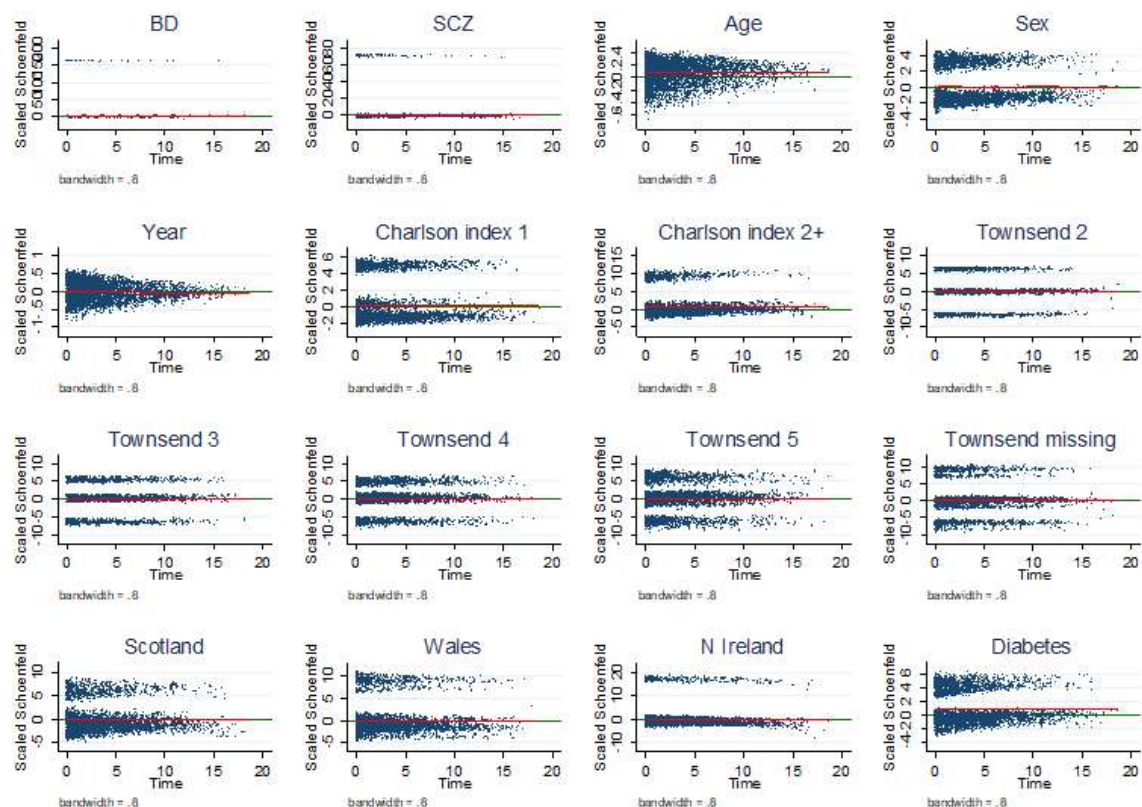
SMI – severe mental illness, BD – bipolar disorder, SCZ – schizophrenia, CVD – cardiovascular disease, PH- proportional hazards. <sup>1</sup> Includes type 1, non-type 1, and diabetes mellitus prescription (excluding patients prescribed metformin with a prior diagnosis of polycystic ovary syndrome). Values that exclude the null highlighted in **bold**



**Table 4.28: Hazard ratios for all-cause mortality after myocardial infarction from multivariable Cox regression analysis**

| Variable                               |                    | Minimally adjusted model <sup>1</sup> |        |      |      | Partially adjusted model <sup>2</sup> |        |      |      | Fully adjusted model <sup>3</sup> |        |      |      |
|----------------------------------------|--------------------|---------------------------------------|--------|------|------|---------------------------------------|--------|------|------|-----------------------------------|--------|------|------|
| Main effects                           |                    | HR                                    | p      | lcl  | ucl  | HR                                    | p      | lcl  | ucl  | HR                                | p      | lcl  | ucl  |
| SMI:                                   | No SMI             | 1                                     |        |      |      | 1                                     |        |      |      | 1                                 |        |      |      |
|                                        | BD                 | 1.38                                  | 0.067  | 0.98 | 1.96 | 1.36                                  | 0.081  | 0.96 | 1.93 | 1.26                              | 0.193  | 0.89 | 1.79 |
|                                        | SCZ                | <b>2.14</b>                           | <0.001 | 1.70 | 2.69 | <b>2.04</b>                           | <0.001 | 1.62 | 2.57 | <b>1.93</b>                       | <0.001 | 1.53 | 2.43 |
| Sex:                                   | Females            | <b>1.17</b>                           | <0.001 | 1.10 | 1.24 | <b>1.14</b>                           | <0.001 | 1.07 | 1.21 | <b>1.09</b>                       | 0.007  | 1.02 | 1.15 |
| Age (squared):                         |                    | <b>1.03</b>                           | <0.001 | 1.02 | 1.04 | <b>1.03</b>                           | <0.001 | 1.02 | 1.04 | <b>1.09</b>                       | <0.001 | 1.08 | 1.09 |
| Calendar year (linear term):           |                    | <b>0.97</b>                           | <0.001 | 0.97 | 0.98 | <b>0.98</b>                           | <0.001 | 0.97 | 0.98 | <b>0.98</b>                       | <0.001 | 0.97 | 0.99 |
| Townsend:                              | 1 (least deprived) |                                       |        |      |      | 1                                     |        |      |      | 1                                 |        |      |      |
|                                        | 2                  |                                       |        |      |      | 1.07                                  | 0.174  | 0.97 | 1.18 | 1.06                              | 0.218  | 0.96 | 1.17 |
|                                        | 3                  |                                       |        |      |      | <b>1.28</b>                           | <0.001 | 1.17 | 1.41 | <b>1.25</b>                       | <0.001 | 1.14 | 1.37 |
|                                        | 4                  |                                       |        |      |      | <b>1.48</b>                           | <0.001 | 1.35 | 1.62 | <b>1.39</b>                       | <0.001 | 1.26 | 1.52 |
|                                        | 5 (most deprived)  |                                       |        |      |      | <b>1.58</b>                           | <0.001 | 1.43 | 1.74 | <b>1.47</b>                       | <0.001 | 1.43 | 1.62 |
|                                        | Missing            |                                       |        |      |      | 1.11                                  | 0.068  | 0.99 | 1.23 | 1.07                              | 0.238  | 0.96 | 1.19 |
| Country:                               | England            |                                       |        |      |      | 1                                     |        |      |      | 1                                 |        |      |      |
|                                        | Scotland           |                                       |        |      |      | <b>0.92</b>                           | 0.031  | 0.85 | 0.99 | <b>0.91</b>                       | 0.020  | 0.84 | 0.99 |
|                                        | Wales              |                                       |        |      |      | 0.99                                  | 0.651  | 0.90 | 1.07 | 0.96                              | 0.438  | 0.88 | 1.06 |
|                                        | Northern Ireland   |                                       |        |      |      | 0.90                                  | 0.078  | 0.80 | 1.01 | 0.89                              | 0.056  | 0.79 | 0.99 |
| Diabetes mellitus <sup>4</sup> at CVD: |                    |                                       |        |      |      |                                       |        |      |      | <b>2.14</b>                       | <0.001 | 2.01 | 2.28 |
| Charlson index at baseline:            | 0                  |                                       |        |      |      |                                       |        |      |      | 1                                 |        |      |      |
|                                        | 1                  |                                       |        |      |      |                                       |        |      |      | <b>1.40</b>                       | <0.001 | 1.31 | 1.50 |
|                                        | 2+                 |                                       |        |      |      |                                       |        |      |      | <b>2.17</b>                       | <0.001 | 1.99 | 2.37 |

SMI – severe mental illness, BD – bipolar disorder, SCZ – schizophrenia, CVD – cardiovascular disease. Models stratified by smoking and obesity. <sup>1</sup> adjusted for SMI, age, sex, and calendar year, <sup>2</sup> adjusted for SMI, age, sex, calendar year, deprivation, and country, <sup>3</sup> adjusted for SMI, age, sex, calendar year, deprivation, country, diabetes mellitus, Charlson index, <sup>4</sup> Includes type 1, non-type 1, and diabetes mellitus prescription (excluding patients prescribed metformin with a prior diagnosis of polycystic ovary syndrome). Values that exclude the null highlighted in **bold**



BD – bipolar disorder, SCZ – schizophrenia. Model stratified by deprivation, country, smoking, obesity. If hazards are proportional, smoothed line through residuals (shown in red) should have slope of zero.

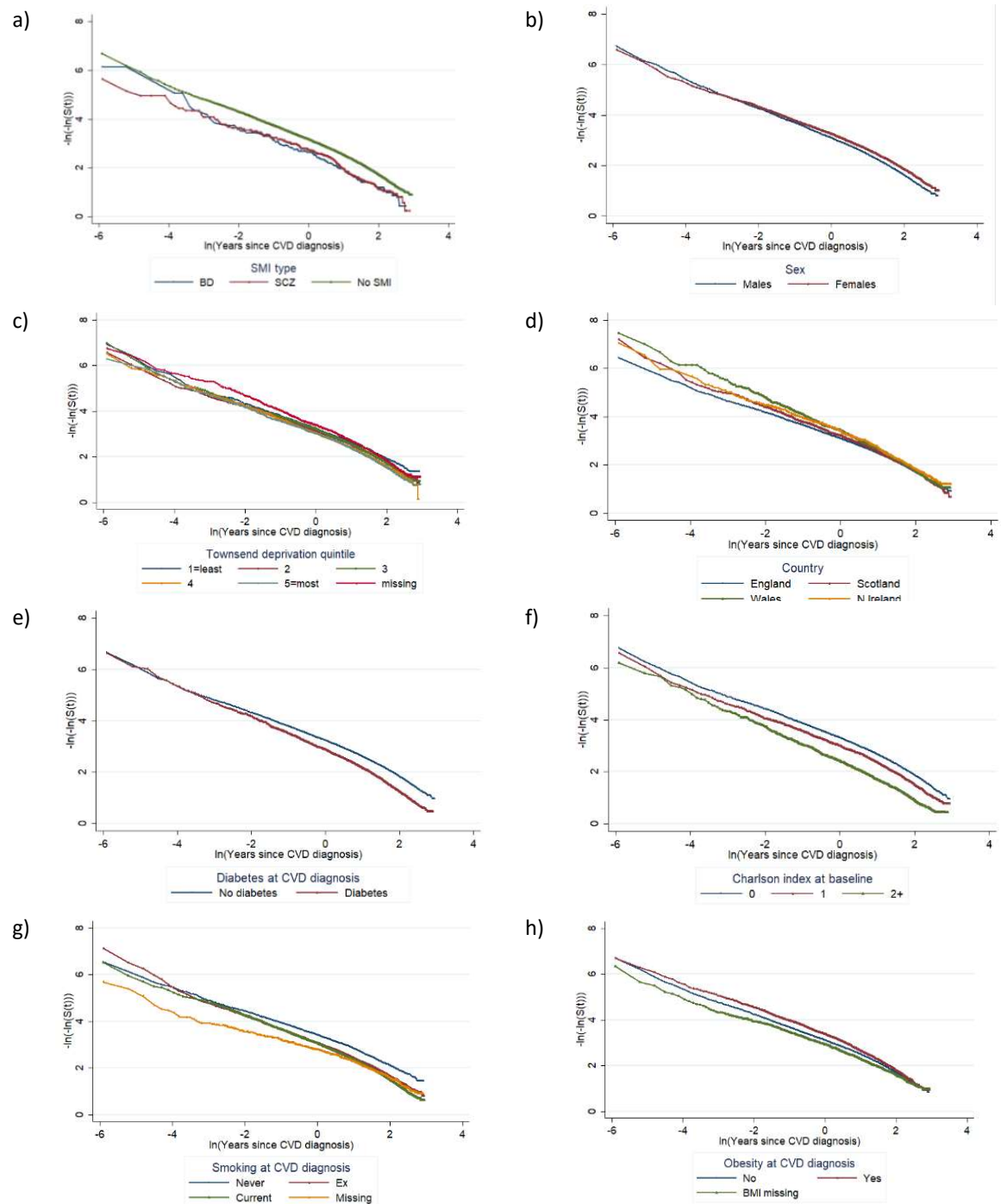
**Figure 4.29: Scaled Schoenfeld residuals for a) BD, b) schizophrenia, c) age d) sex, e) Charlson index=1, f) Charlson index=2+, g-k) Townsend quintiles 2-5,missing, l) Scotland, m) Wales, n) N. Ireland, o) diabetes mellitus, from multivariable Cox regression analysis of myocardial infarction case-fatality**

#### 4.4.6.3 Stroke

In analysis restricted to mortality after stroke diagnosis, 70,405 patients were included and there were 7,305 deaths. Analysis of fractional polynomials found that a second-degree polynomial with cubic terms for age was the best fit, however a linear term for year was adequate. According to log-log plots (Figure 4.30) and tests of the proportional hazards assumption (Table 4.29) there was evidence of non-proportional hazards for age, year,

Townsend quintile, country, diabetes mellitus, smoking and obesity. Interactions with time for these variables were included in minimally, partially, and fully adjusted models.

In univariable analysis (Table 4.29), the association between SMI and mortality after stroke was similar for BD and schizophrenia (BD: HR=1.77, 95% CI: 1.42-2.20; schizophrenia: HR=1.68, 95% CI: 1.41-1.99). HRs were also similar in the fully adjusted models, as seen in Table 4.30 (BD: HR=1.69, 95% CI: 1.35-2.11, schizophrenia: HR=1.63, 95% CI: 1.37-1.93). HRs also reduced over the study period (HR: 0.96, 95% CI: 0.95-0.97). This means that the hazard was reduced by 4% for each year after 2000. In contrast to MI, HRs were lower for females but were higher for patients with diabetes mellitus. There were some interactions showing increasing effects over time since stroke diagnosis, notably diabetes mellitus (HR: 1.03, 95% CI: 1.01-1.05), current smoking (HR: 1.07, 95% CI: 1.04-1.09) and missing Townsend score and smoking status. There was no evidence of an interaction between SMI and calendar year in the minimally, partially, or fully adjusted models (LR test:  $p=0.260$ ,  $0.251$ ,  $0.498$ , respectively).



SMI – severe mental illness, BD – bipolar disorder, SCZ – schizophrenia, CVD – cardiovascular disease

**Figure 4.30: Plots of survival function against time since stroke diagnosis (log scales) to assess proportional hazards assumption for a) SMI type, b) sex, c) deprivation quintile, d) country, e) diabetes mellitus, f) Charlson index, g) smoking, h) obesity**

**Table 4.29: Hazard ratios for all-cause mortality after stroke from univariable Cox regression analysis**

| Variable                                                                                | HR          | p      | lcl  | ucl  | PH test (zero slope of scaled Schoenfeld residuals), p-value |
|-----------------------------------------------------------------------------------------|-------------|--------|------|------|--------------------------------------------------------------|
| SMI: No SMI                                                                             | 1           |        |      |      |                                                              |
| BD                                                                                      | <b>1.77</b> | <0.001 | 1.42 | 2.20 | 0.445                                                        |
| SCZ                                                                                     | <b>1.68</b> | <0.001 | 1.41 | 1.99 | 0.596                                                        |
| <i>Global PH test for SMI</i>                                                           |             |        |      |      | <i>0.652</i>                                                 |
| Sex: Males                                                                              | 1           |        |      |      |                                                              |
| Females                                                                                 | <b>0.81</b> | <0.001 | 0.77 | 0.84 | 0.080                                                        |
| Age at CVD diagnosis (scaled and centred fractional polynomial terms): Age <sup>3</sup> | <b>1.05</b> | <0.001 | 1.04 | 1.06 | 0.007                                                        |
| Age <sup>3</sup> X log(age)                                                             | <b>0.98</b> | <0.001 | 0.97 | 0.98 | 0.010                                                        |
| <i>Global PH test for age</i>                                                           |             |        |      |      | <i>0.001</i>                                                 |
| Calendar year: (linear term)                                                            | <b>0.95</b> | <0.001 | 0.95 | 0.96 | 0.041                                                        |
| Townsend: 1 (least deprived)                                                            | 1           |        |      |      |                                                              |
| 2                                                                                       | <b>1.16</b> | <0.001 | 1.07 | 1.26 | 0.098                                                        |
| 3                                                                                       | <b>1.17</b> | <0.001 | 1.08 | 1.27 | 0.002                                                        |
| 4                                                                                       | <b>1.37</b> | <0.001 | 1.27 | 1.48 | 0.003                                                        |
| 5 (most deprived)                                                                       | <b>1.42</b> | <0.001 | 1.31 | 1.54 | <0.001                                                       |
| Missing                                                                                 | 1.04        | 0.369  | 0.95 | 1.14 | <0.001                                                       |
| <i>Global PH test for Townsend</i>                                                      |             |        |      |      | <i>&lt;0.001</i>                                             |
| Country: England                                                                        | 1           |        |      |      |                                                              |
| Scotland                                                                                | 0.96        | 0.261  | 0.91 | 1.03 | 0.038                                                        |
| Wales                                                                                   | <b>0.89</b> | 0.002  | 0.83 | 0.96 | 0.003                                                        |
| Northern Ireland                                                                        | <b>0.84</b> | 0.002  | 0.75 | 0.94 | 0.662                                                        |
| <i>Global PH test for country</i>                                                       |             |        |      |      | <i>0.010</i>                                                 |
| Diabetes mellitus <sup>1</sup> at CVD:                                                  | <b>1.67</b> | <0.001 | 1.59 | 1.77 | <0.001                                                       |
| Charlson index at baseline: 0                                                           | 1           |        |      |      |                                                              |
| 1                                                                                       | <b>1.41</b> | <0.001 | 1.33 | 1.49 | 0.492                                                        |
| 2+                                                                                      | <b>2.52</b> | <0.001 | 2.34 | 2.70 | 0.421                                                        |
| <i>Global PH test for Charlson</i>                                                      |             |        |      |      | <i>0.500</i>                                                 |
| Smoking at CVD:                                                                         |             |        |      |      |                                                              |
| Never smoked                                                                            | 1           |        |      |      |                                                              |
| Ex-smoker                                                                               | <b>1.54</b> | <0.001 | 1.44 | 1.64 | 0.003                                                        |
| Current smoker                                                                          | <b>1.75</b> | <0.001 | 1.65 | 1.86 | <0.001                                                       |
| Missing                                                                                 | <b>1.70</b> | <0.001 | 1.50 | 1.93 | 0.607                                                        |
| <i>Global PH test for smoking</i>                                                       |             |        |      |      | <i>&lt;0.001</i>                                             |
| Obesity at CVD:                                                                         |             |        |      |      |                                                              |
| No                                                                                      | 1           |        |      |      |                                                              |
| Yes                                                                                     | <b>0.88</b> | <0.001 | 0.83 | 0.93 | <0.001                                                       |
| Unrecorded                                                                              | <b>1.13</b> | 0.001  | 1.05 | 1.21 | 0.002                                                        |
| <i>Global PH test for obesity</i>                                                       |             |        |      |      | <i>&lt;0.001</i>                                             |

SMI – severe mental illness, BD – bipolar disorder, SCZ – schizophrenia, CVD – cardiovascular disease, PH- proportional hazards. <sup>1</sup> Includes type 1, non-type 1, and diabetes mellitus prescription (excluding patients prescribed metformin with a prior diagnosis of polycystic ovary syndrome). Values that exclude the null highlighted in **bold**

**Table 4.30: Hazard ratios for all-cause mortality after stroke from multivariable Cox regression analysis**

| Variable                                                               |                             | Minimally adjusted model <sup>1</sup> |        |      |      | Partially adjusted model <sup>2</sup> |        |      |      | Fully adjusted model <sup>3</sup> |        |      |      |
|------------------------------------------------------------------------|-----------------------------|---------------------------------------|--------|------|------|---------------------------------------|--------|------|------|-----------------------------------|--------|------|------|
|                                                                        |                             | HR                                    | p      | lcl  | ucl  | HR                                    | p      | lcl  | ucl  | HR                                | p      | lcl  | ucl  |
| <b>Main effects</b>                                                    |                             |                                       |        |      |      |                                       |        |      |      |                                   |        |      |      |
| SMI:                                                                   | No SMI                      | 1                                     |        |      |      | 1                                     |        |      |      | 1                                 |        |      |      |
|                                                                        | BD                          | <b>1.96</b>                           | <0.001 | 1.57 | 2.44 | <b>1.88</b>                           | <0.001 | 1.51 | 2.35 | <b>1.69</b>                       | <0.001 | 1.35 | 2.11 |
|                                                                        | SCZ                         | <b>1.82</b>                           | <0.001 | 1.53 | 2.16 | <b>1.75</b>                           | <0.001 | 1.47 | 2.08 | <b>1.63</b>                       | <0.001 | 1.37 | 1.93 |
| Sex:                                                                   | Females                     | <b>0.82</b>                           | <0.001 | 0.78 | 0.86 | <b>0.81</b>                           | <0.001 | 0.77 | 0.85 | <b>0.84</b>                       | <0.001 | 0.80 | 0.88 |
| Age at CVD diagnosis (scaled and centred fractional polynomial terms): |                             |                                       |        |      |      |                                       |        |      |      |                                   |        |      |      |
|                                                                        | Age <sup>3</sup>            | <b>1.04</b>                           | <0.001 | 1.02 | 1.05 | <b>1.04</b>                           | <0.001 | 1.02 | 1.05 | <b>1.04</b>                       | <0.001 | 1.02 | 1.05 |
|                                                                        | Age <sup>3</sup> X log(age) | <b>0.99</b>                           | <0.001 | 0.98 | 0.99 | <b>0.98</b>                           | <0.001 | 0.98 | 0.99 | <b>0.99</b>                       | <0.001 | 0.98 | 0.99 |
| Calendar year (linear term):                                           |                             | <b>0.95</b>                           | <0.001 | 0.95 | 0.96 | <b>0.96</b>                           | <0.001 | 0.95 | 0.96 | <b>0.96</b>                       | <0.001 | 0.95 | 0.97 |
| Townsend:                                                              | 1 (least deprived)          |                                       |        |      |      | 1                                     |        |      |      | 1                                 |        |      |      |
|                                                                        | 2                           |                                       |        |      |      | 1.10                                  | 0.080  | 0.99 | 1.23 | 1.07                              | 0.222  | 0.96 | 1.19 |
|                                                                        | 3                           |                                       |        |      |      | 1.09                                  | 0.125  | 0.98 | 1.21 | 1.02                              | 0.680  | 0.92 | 1.14 |
|                                                                        | 4                           |                                       |        |      |      | <b>1.33</b>                           | <0.001 | 1.19 | 1.48 | <b>1.20</b>                       | 0.001  | 1.07 | 1.33 |
|                                                                        | 5 (most deprived)           |                                       |        |      |      | <b>1.39</b>                           | <0.001 | 1.24 | 1.55 | <b>1.22</b>                       | 0.001  | 1.08 | 1.36 |
|                                                                        | Missing                     |                                       |        |      |      | 0.99                                  | 0.833  | 0.87 | 1.12 | 0.92                              | 0.214  | 0.82 | 1.05 |
| Country:                                                               | England                     |                                       |        |      |      | 1                                     |        |      |      | 1                                 |        |      |      |
|                                                                        | Scotland                    |                                       |        |      |      | 1.00                                  | 0.927  | 0.92 | 1.10 | 0.96                              | 0.402  | 0.88 | 1.05 |
|                                                                        | Wales                       |                                       |        |      |      | 0.94                                  | 0.229  | 0.85 | 1.04 | <b>0.89</b>                       | 0.034  | 0.80 | 0.99 |
|                                                                        | Northern Ireland            |                                       |        |      |      | 0.90                                  | 0.169  | 0.77 | 1.05 | 0.90                              | 0.172  | 0.77 | 1.05 |
| Diabetes mellitus at CVD:                                              |                             |                                       |        |      |      |                                       |        |      |      | <b>1.46</b>                       | <0.001 | 1.35 | 1.58 |
| Charlson index at baseline:                                            | 0                           |                                       |        |      |      |                                       |        |      |      | 1                                 |        |      |      |
|                                                                        | 1                           |                                       |        |      |      |                                       |        |      |      | <b>1.30</b>                       | <0.001 | 1.23 | 1.38 |
|                                                                        | 2+                          |                                       |        |      |      |                                       |        |      |      | <b>2.06</b>                       | <0.001 | 1.92 | 2.21 |
| Smoking at CVD:                                                        | Never smoked                |                                       |        |      |      |                                       |        |      |      | 1                                 |        |      |      |
|                                                                        | Ex-smoker                   |                                       |        |      |      |                                       |        |      |      | <b>1.23</b>                       | <0.001 | 1.13 | 1.34 |
|                                                                        | Current smoker              |                                       |        |      |      |                                       |        |      |      | <b>1.50</b>                       | <0.001 | 1.38 | 1.64 |
|                                                                        | Missing                     |                                       |        |      |      |                                       |        |      |      | 1.10                              | 0.295  | 0.91 | 1.35 |
| Obesity at CVD:                                                        | No                          |                                       |        |      |      |                                       |        |      |      | 1                                 |        |      |      |
|                                                                        | Yes                         |                                       |        |      |      |                                       |        |      |      | <b>0.82</b>                       | <0.001 | 0.76 | 0.88 |
|                                                                        | Unrecorded                  |                                       |        |      |      |                                       |        |      |      | <b>1.39</b>                       | <0.001 | 1.25 | 1.55 |
| <b>Time varying effects</b>                                            |                             |                                       |        |      |      |                                       |        |      |      |                                   |        |      |      |
| Age at CVD diagnosis (scaled and centred fractional polynomial terms): |                             |                                       |        |      |      |                                       |        |      |      |                                   |        |      |      |
|                                                                        | Age <sup>3</sup>            | 1.00                                  | 0.545  | 1.00 | 1.00 | 1.00                                  | 0.562  | 1.00 | 1.00 | 1.00                              | 0.837  | 1.00 | 1.00 |

| Variable        |                                        | Minimally adjusted model <sup>1</sup> |       |      |      | Partially adjusted model <sup>2</sup> |        |      |      | Fully adjusted model <sup>3</sup> |        |      |      |
|-----------------|----------------------------------------|---------------------------------------|-------|------|------|---------------------------------------|--------|------|------|-----------------------------------|--------|------|------|
|                 |                                        | HR                                    | p     | lcl  | ucl  | HR                                    | p      | lcl  | ucl  | HR                                | p      | lcl  | ucl  |
|                 | Age <sup>3</sup> X log(age)            | 1.00                                  | 0.755 | 1.00 | 1.00 | 1.00                                  | 0.784  | 1.00 | 1.00 | 1.00                              | 0.878  | 1.00 | 1.00 |
|                 | Calendar year (linear term):           | <b>1.00</b>                           | 0.007 | 1.00 | 1.01 | <b>1.00</b>                           | 0.046  | 1.00 | 1.01 | <b>1.00</b>                       | 0.043  | 1.00 | 1.01 |
| Townsend:       | 1 (least deprived)                     |                                       |       |      |      | 1                                     |        |      |      | 1                                 |        |      |      |
|                 | 2                                      |                                       |       |      |      | 1.02                                  | 0.132  | 0.99 | 1.05 | 1.02                              | 0.151  | 0.99 | 1.05 |
|                 | 3                                      |                                       |       |      |      | <b>1.05</b>                           | 0.001  | 1.02 | 1.08 | <b>1.04</b>                       | 0.005  | 1.01 | 1.07 |
|                 | 4                                      |                                       |       |      |      | <b>1.04</b>                           | 0.004  | 1.01 | 1.07 | 1.03                              | 0.072  | 1.00 | 1.05 |
|                 | 5 (most deprived)                      |                                       |       |      |      | <b>1.05</b>                           | 0.001  | 1.02 | 1.08 | <b>1.03</b>                       | 0.024  | 1.00 | 1.06 |
|                 | Missing                                |                                       |       |      |      | <b>1.06</b>                           | <0.001 | 1.03 | 1.09 | <b>1.05</b>                       | 0.001  | 1.02 | 1.08 |
| Country:        | England                                |                                       |       |      |      | 1                                     |        |      |      | 1                                 |        |      |      |
|                 | Scotland                               |                                       |       |      |      | 1.01                                  | 0.605  | 0.98 | 1.03 | 1.01                              | 0.637  | 0.98 | 1.03 |
|                 | Wales                                  |                                       |       |      |      | 1.02                                  | 0.120  | 1.00 | 1.04 | 1.02                              | 0.093  | 1.00 | 1.04 |
|                 | Northern Ireland                       |                                       |       |      |      | 1.00                                  | 0.915  | 0.97 | 1.04 | 1.00                              | 0.916  | 0.97 | 1.03 |
|                 | Diabetes mellitus <sup>4</sup> at CVD: |                                       |       |      |      |                                       |        |      |      | <b>1.03</b>                       | 0.001  | 1.01 | 1.05 |
| Smoking at CVD: | Never smoked                           |                                       |       |      |      |                                       |        |      |      | 1                                 |        |      |      |
|                 | Ex-smoker                              |                                       |       |      |      |                                       |        |      |      | <b>1.03</b>                       | 0.031  | 1.00 | 1.05 |
|                 | Current smoker                         |                                       |       |      |      |                                       |        |      |      | <b>1.07</b>                       | <0.001 | 1.04 | 1.09 |
|                 | Missing                                |                                       |       |      |      |                                       |        |      |      | <b>1.06</b>                       | 0.003  | 1.02 | 1.11 |
| Obesity at CVD: | No                                     |                                       |       |      |      |                                       |        |      |      | 1                                 |        |      |      |
|                 | Yes                                    |                                       |       |      |      |                                       |        |      |      | <b>1.03</b>                       | 0.008  | 1.01 | 1.04 |
|                 | Unrecorded                             |                                       |       |      |      |                                       |        |      |      | <b>0.97</b>                       | 0.009  | 0.94 | 0.99 |

<sup>1</sup> adjusted for SMI, age, sex, and calendar year, <sup>2</sup> adjusted for SMI, age, sex, calendar year, deprivation, and country, <sup>3</sup> adjusted for SMI, age, sex, calendar year, deprivation, country, diabetes mellitus, Charlson index, smoking, obesity, <sup>4</sup> Includes type 1, non-type 1, and diabetes mellitus prescription (excluding patients prescribed metformin with a prior diagnosis of polycystic ovary syndrome). SMI – severe mental illness, BD – bipolar disorder, SCZ – schizophrenia, CVD – cardiovascular disease. Values that exclude the null highlighted in **bold**

#### 4.4.7 Cardiovascular incidence

Of the original prevalent cohort, 8,967,993 patients were included in the analysis of CVD outcomes (Figure 4.31). Baseline characteristics for the study cohort are in Table 4.31. These were similar to the full prevalent cohort (Table 4.12), although the percentage with comorbidities (diabetes mellitus, obesity, BP over 140/90 mmHg) were lower than in the full cohort, due to the exclusion of patients with prior CVD and patients were, on average, younger.

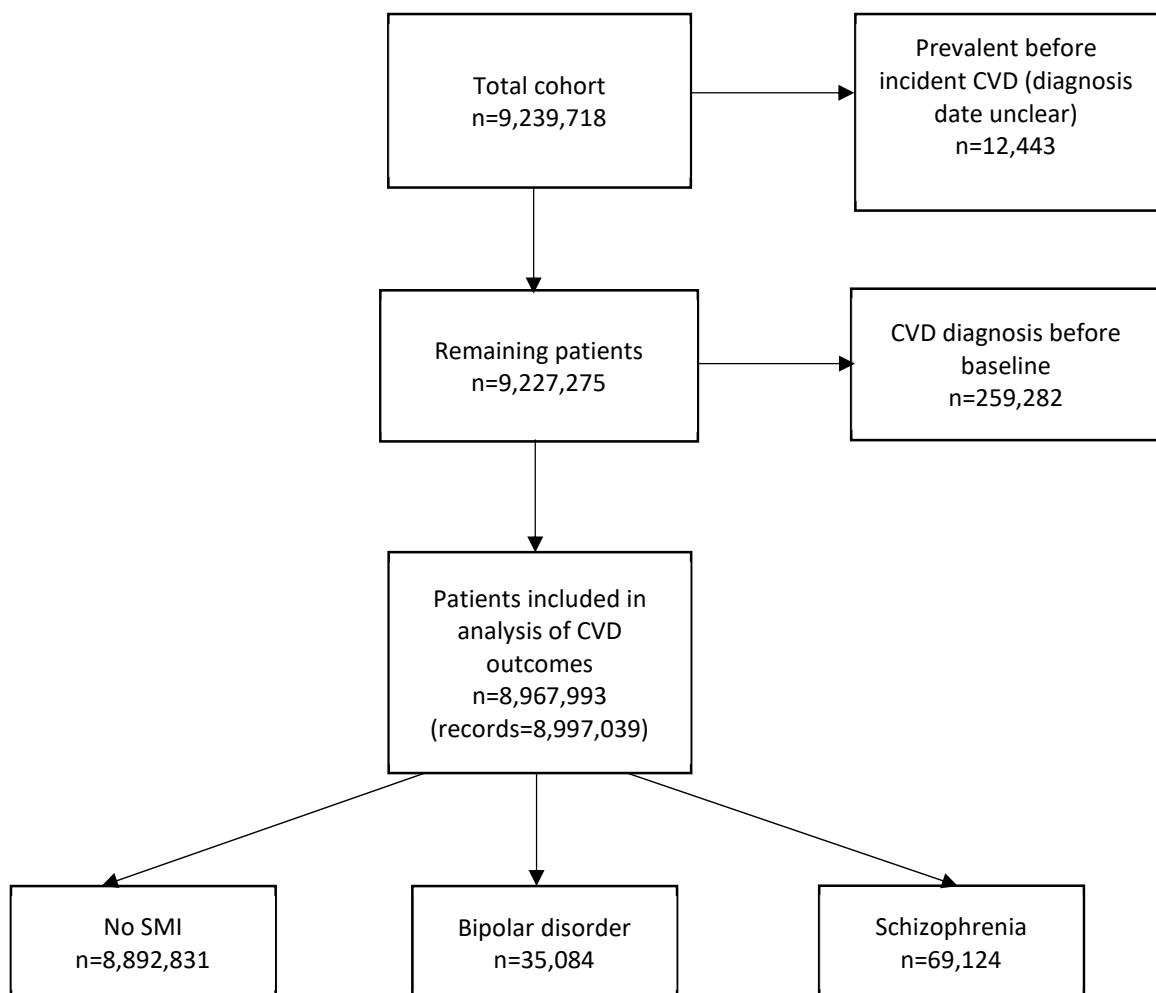


**Figure 4.31: Flow chart showing patients included in analysis of time to CVD incidence**



In total, 216,620 patients were diagnosed with CVD during the study period, including 1,163 with BD and 2,069 with schizophrenia. The overall crude CVD incidence rate per thousand PYAR was 3.92 (95% CI: 3.89-3.93). For those with SMI, rates were 6.21 (95% CI: 5.95-6.48) for those with schizophrenia and 6.93 (95% CI: 6.55-7.35) for those with BD. The rate for people without SMI was much lower, at 3.89 (95% CI: 3.88-3.91). Crude incidence rate ratios were 1.78 (95% CI: 1.68-1.89) for BD and 1.60 (95% CI: 1.53-1.67) for schizophrenia. These were reduced to 1.42 (95% CI: 1.34-1.51) and 1.36 (95% CI: 1.31-1.42), respectively, when adjusted by age and sex.

**Table 4.31: Baseline characteristics of patients included in CVD incidence analysis**

|                                                                      | <b>BD<sup>1</sup></b><br><b>(n=35,084)</b> | <b>SCZ<sup>1</sup></b><br><b>(n=69,124)</b> | <b>No SMI<sup>1</sup></b><br><b>(n=8,892,831)</b> |
|----------------------------------------------------------------------|--------------------------------------------|---------------------------------------------|---------------------------------------------------|
| Person years of follow-up:                                           | 167,598                                    | 333,043                                     | 54,827,414                                        |
| Median follow-up, years (IQR):                                       | 3.3 (1.2-7.2)                              | 3.3 (1.2-7.2)                               | 4.6 (1.8-9.7)                                     |
| Male, n (%):                                                         | 14,167 (40.4)                              | 41,515 (60.1)                               | 4,315,513 (48.5)                                  |
| Age at baseline, years: median (IQR):                                | 43.3 (33.0-54.5)                           | 40.7(30.8–52.6)                             | 34.2 (24.0–48.0)                                  |
| Townsend deprivation quintile (last recorded), n (%):                |                                            |                                             |                                                   |
| 1 (least deprived)                                                   | 4,620 (13.2)                               | 6,345 (9.2)                                 | 1,621,936 (18.2)                                  |
| 2                                                                    | 4,947 (14.1)                               | 7,540 (10.9)                                | 1,469,285 (16.5)                                  |
| 3                                                                    | 6,267 (17.9)                               | 10,942 (15.8)                               | 1,565,453 (17.6)                                  |
| 4                                                                    | 6,892 (19.6)                               | 14,797 (21.4)                               | 1,455,455 (16.4)                                  |
| 5 (most deprived)                                                    | 5,884 (16.8)                               | 16,505 (23.9)                               | 1,075,700 (12.1)                                  |
| Missing                                                              | 6,474 (18.5)                               | 12,995 (18.8)                               | 1,705,002 (19.2)                                  |
| Country, n (%):                                                      |                                            |                                             |                                                   |
| England                                                              | 23,822 (67.9)                              | 47,459 (68.7)                               | 6,301,220 (70.9)                                  |
| Scotland                                                             | 5,863 (16.7)                               | 10,050 (14.5)                               | 1,239,242 (13.9)                                  |
| Wales                                                                | 4,198 (12.0)                               | 8,610 (12.5)                                | 1,031,782 (11.6)                                  |
| Northern Ireland                                                     | 1,201 (3.4)                                | 3,005 (4.4)                                 | 320,587 (3.6)                                     |
| Diabetes mellitus at baseline, n (%):                                |                                            |                                             |                                                   |
| Diabetes mellitus (Type 1, non-type 1, or prescription) <sup>4</sup> | 2,244 (6.4)                                | 4,453 (6.4)                                 | 234,884 (2.6)                                     |
| Modified Charlson index <sup>2</sup> , n (%):                        |                                            |                                             |                                                   |
| 0                                                                    | 27,132 (77.3)                              | 55,615 (80.5)                               | 7,502,095 (84.4)                                  |
| 1                                                                    | 6,268 (17.9)                               | 11,113 (16.1)                               | 1,201,072 (13.5)                                  |
| 2 or more                                                            | 1,684 (4.8)                                | 2,396 (3.5)                                 | 189,664 (2.1)                                     |
| Smoking status at baseline, n (%):                                   |                                            |                                             |                                                   |
| Never smoked                                                         | 10,976 (31.3)                              | 17,634 (25.5)                               | 3,805,632 (42.8)                                  |
| Ex-smoker                                                            | 6,045 (17.2)                               | 8,585 (12.4)                                | 1,137,766 (12.8)                                  |
| Current smoker                                                       | 14,928 (42.6)                              | 34,041 (49.3)                               | 1,957,765 (22.0)                                  |
| Missing                                                              | 3,135 (8.9)                                | 8,864 (12.8)                                | 1,991,668 (22.4)                                  |
| Obesity at baseline, n (%) <sup>3</sup> :                            |                                            |                                             |                                                   |
| Defined by BMI (OR Read code if no BMI at baseline)                  | 8,218 (23.4)                               | 14,062 (20.3)                               | 1,068,984 (12.0)                                  |
| No obesity                                                           | 20,000 (57.0)                              | 37,462 (54.2)                               | 4,557,458 (51.3)                                  |
| Missing                                                              | 6,866 (19.6)                               | 17,600 (25.5)                               | 3,266,389 (36.7)                                  |
| Blood pressure at baseline, n (%):                                   |                                            |                                             |                                                   |
| ≥ 140/90 mmHg                                                        | 7,133 (20.3)                               | 13,027 (18.9)                               | 1,397,398 (15.7)                                  |
| <140/90 mmHg                                                         | 22,263 (63.5)                              | 41,166 (59.6)                               | 4,569,460 (51.4)                                  |
| BP missing                                                           | 5,688 (16.2)                               | 14,931 (21.6)                               | 2,925,973 (32.9)                                  |

<sup>1</sup> Patients may have periods of follow-up in more than one category. <sup>2</sup> Recorded at start date for each patient. <sup>3</sup> Disregarded if recorded at age<16 years. <sup>4</sup> Includes type 1, non-type 1, and diabetes mellitus prescription (excluding patients prescribed metformin with a prior diagnosis of polycystic ovary syndrome).

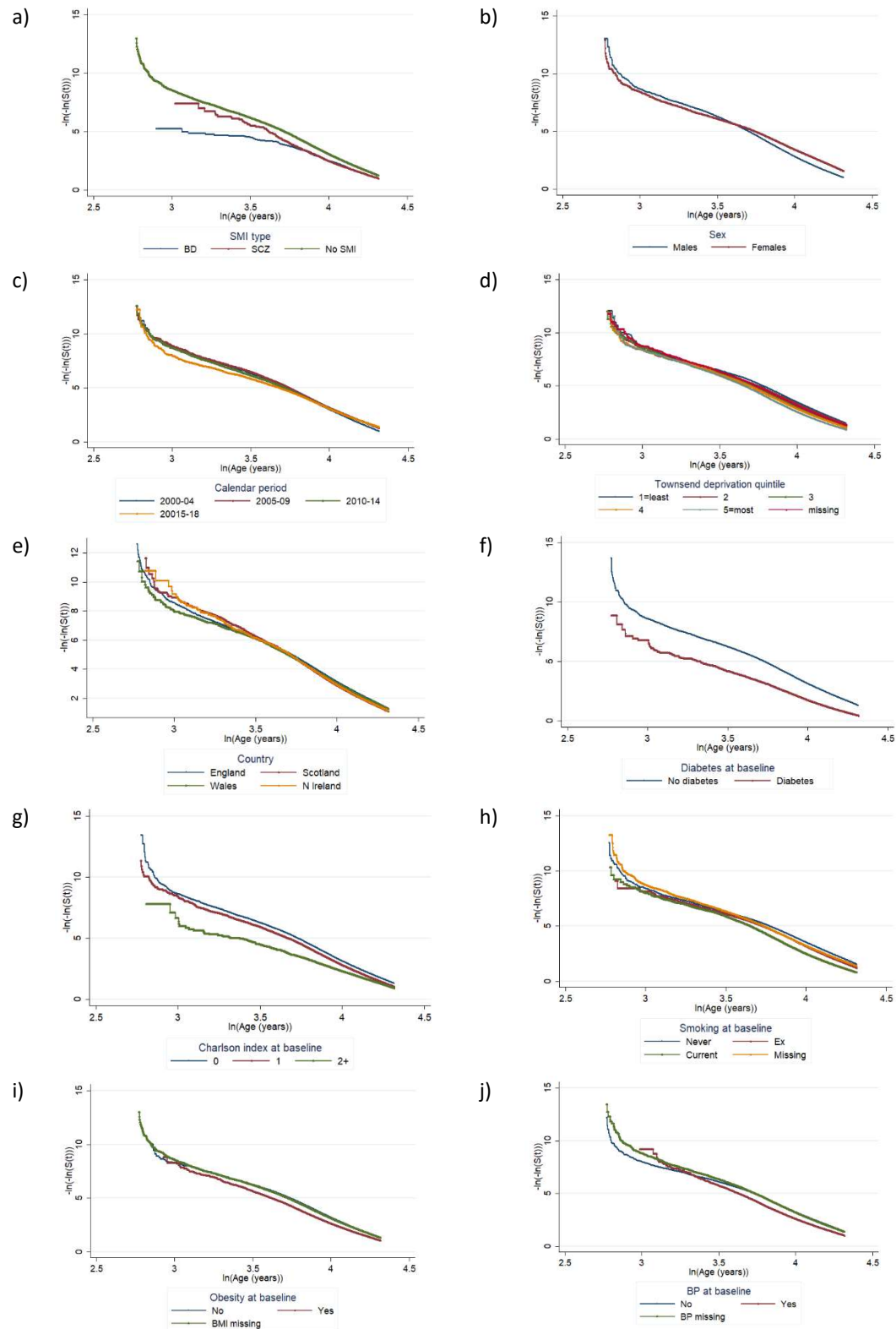
Figure 4.32 shows log-log plots of the included covariates to visually assess the assumption of proportional hazards and Table 4.32 shows p-values from statistical tests for non-zero slope of Schoenfeld residuals as formal tests for proportional hazards. There is evidence of

proportional hazards violations for each of the covariates, meaning that there is an association between different values of these variables and age at CVD diagnosis.

**Table 4.32: Statistical tests for proportional hazards from univariate Cox regression analyses of all-cause mortality, age as analysis time variable**

| Variable                           |                                    | PH test (zero slope of scaled Schoenfeld residuals), p-value |
|------------------------------------|------------------------------------|--------------------------------------------------------------|
| SMI:                               | No SMI                             |                                                              |
|                                    | Bipolar disorder                   | <0.001                                                       |
|                                    | Schizophrenia                      | <0.001                                                       |
|                                    | <i>Global PH test for SMI</i>      | <0.001                                                       |
| Sex:                               | Males                              |                                                              |
|                                    | Females                            | <0.001                                                       |
| Calendar period:                   | 2000-04                            |                                                              |
|                                    | 2005-09                            | <0.001                                                       |
|                                    | 2010-14                            | <0.001                                                       |
|                                    | 2015-19                            | <0.001                                                       |
|                                    | <i>Global PH test for period</i>   | <0.001                                                       |
| Townsend:                          | 1 (least deprived)                 |                                                              |
|                                    | 2                                  | <0.001                                                       |
|                                    | 3                                  | <0.001                                                       |
|                                    | 4                                  | <0.001                                                       |
|                                    | 5 (most deprived)                  | <0.001                                                       |
|                                    | Missing                            | <0.001                                                       |
|                                    | <i>Global PH test for Townsend</i> | <0.001                                                       |
| Country:                           | England                            |                                                              |
|                                    | Scotland                           | <0.001                                                       |
|                                    | Wales                              | <0.001                                                       |
|                                    | Northern Ireland                   | <0.001                                                       |
|                                    | <i>Global PH test for country</i>  | <0.001                                                       |
| Diabetes mellitus at baseline:     |                                    | <0.001                                                       |
| Charlson index:                    | 0                                  |                                                              |
|                                    | 1                                  | <0.001                                                       |
|                                    | 2+                                 | <0.001                                                       |
| <i>Global PH test for Charlson</i> |                                    | <0.001                                                       |
| Smoking at baseline:               | Never smoked                       |                                                              |
|                                    | Ex-smoker                          | <0.001                                                       |
|                                    | Current smoker                     | <0.001                                                       |
|                                    | Missing                            | <0.001                                                       |
| <i>Global PH test for smoking</i>  |                                    | <0.001                                                       |
| Obesity at baseline:               | No                                 |                                                              |
|                                    | Yes                                | <0.001                                                       |
|                                    | Unrecorded                         | <0.001                                                       |
| <i>Global PH test for obesity</i>  |                                    | <0.001                                                       |
| BP at baseline:                    | <140/90 mmHg                       |                                                              |
|                                    | ≥140/90 mmHg                       | <0.001                                                       |
|                                    | Missing                            | 0.695                                                        |
|                                    | <i>Global test for BP</i>          | <0.001                                                       |

PH – proportional hazards, SMI – severe mental illness, CVD – cardiovascular disease, BP – blood pressure



SMI – severe mental illness, BD – bipolar disorder, SCZ – schizophrenia, CVD – cardiovascular disease

**Figure 4.32: Plots of survival function against time to CVD incidence (log scales), with age as time variable, to assess proportional hazards assumption for a) SMI, b) sex, c) calendar period, d) deprivation quintile, e) country, f) diabetes mellitus, g) Charlson index, h) smoking, i) obesity, j) blood pressure**

Instead of using age as the time analysis variable, years since baseline was tried as an alternative. Although there were still significant proportional hazards violations (Table 4.33), visually the hazards appeared more proportional (Figure 4.33). Where there was lack of proportionality it occurred in the early part of follow-up. For example, in SMI (Figure 4.33a), the lines for BD and schizophrenia are separated up to around  $\ln(-2)$  years since baseline and then converge after that.  $\ln(-2)$  corresponds to 0.14 years or 49 days since baseline. The models fitted may thus be a better representation of the effect of SMI and the difference between BD and schizophrenia after about seven weeks since baseline.

**Table 4.33: Statistical tests for proportional hazards from univariate Cox regression analyses of all-cause mortality, years since baseline as time variable**

| Variable                       | PH test (zero slope of scaled Schoenfeld residuals), p-value |
|--------------------------------|--------------------------------------------------------------|
| SMI:                           |                                                              |
| No SMI                         |                                                              |
| Bipolar disorder               | 0.001                                                        |
| Schizophrenia                  | <0.001                                                       |
| Global PH test for SMI         | <0.001                                                       |
| Age group (years):             |                                                              |
| 16-24                          | 0.041                                                        |
| 25-34                          | <0.001                                                       |
| 35-44                          | <0.001                                                       |
| 45-54                          | <0.001                                                       |
| 55-64                          | <0.001                                                       |
| 65-74                          | <0.001                                                       |
| Global PH test for age group   |                                                              |
| Sex:                           |                                                              |
| Males                          |                                                              |
| Females                        | 0.001                                                        |
| Calendar period:               |                                                              |
| 2000-04                        |                                                              |
| 2005-09                        | <0.001                                                       |
| 2010-14                        | <0.001                                                       |
| 2015-19                        | 0.033                                                        |
| Global PH test for period      | <0.001                                                       |
| Townsend:                      |                                                              |
| 1 (least deprived)             |                                                              |
| 2                              | 0.155                                                        |
| 3                              | 0.085                                                        |
| 4                              | 0.023                                                        |
| 5 (most deprived)              | <0.001                                                       |
| Missing                        | <0.001                                                       |
| Global PH test for Townsend    | <0.001                                                       |
| Country:                       |                                                              |
| England                        |                                                              |
| Scotland                       | <0.001                                                       |
| Wales                          | 0.595                                                        |
| Northern Ireland               | 0.845                                                        |
| Global PH test for country     | <0.001                                                       |
| Diabetes mellitus at baseline: | <0.001                                                       |

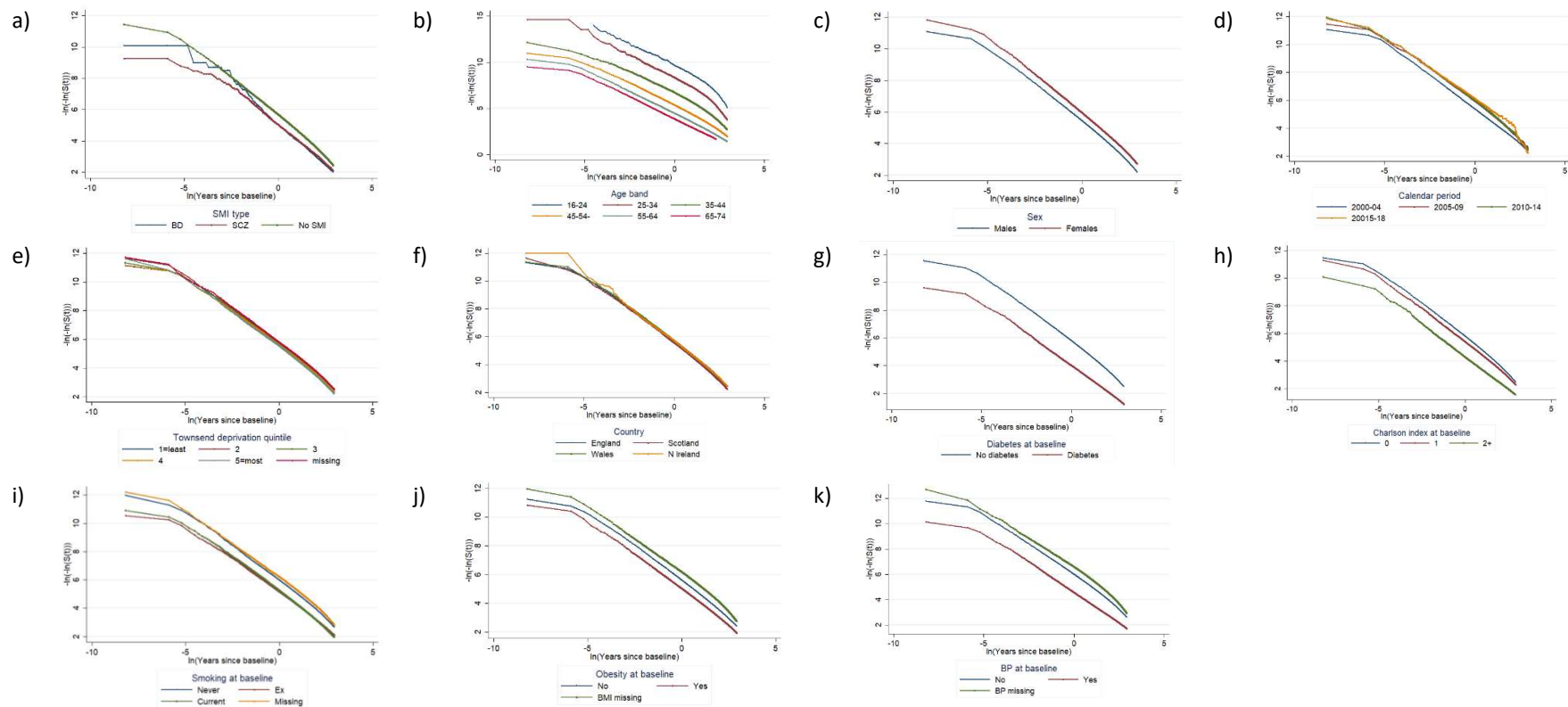
| Variable                           | PH test (zero slope of scaled Schoenfeld residuals), p-value |
|------------------------------------|--------------------------------------------------------------|
| Charlson index:                    | 0                                                            |
|                                    | 1                                                            |
|                                    | 2+                                                           |
| <i>Global PH test for Charlson</i> | <i>&lt;0.001</i>                                             |
| Smoking at baseline: Never smoked  |                                                              |
| Ex-smoker                          | <0.001                                                       |
| Current smoker                     | <0.001                                                       |
| Missing                            | <0.001                                                       |
| <i>Global PH test for smoking</i>  | <i>&lt;0.001</i>                                             |
| Obesity at baseline:               | No                                                           |
|                                    | Yes                                                          |
|                                    | Unrecorded                                                   |
| <i>Global PH test for obesity</i>  | <i>&lt;0.001</i>                                             |
| BP at baseline:                    | <140/90 mmHg                                                 |
|                                    | ≥140/90 mmHg                                                 |
|                                    | Missing                                                      |
| <i>Global test for BP</i>          | <i>&lt;0.001</i>                                             |

PH – proportional hazards, SMI – severe mental illness, CVD – cardiovascular disease, BP – blood pressure

Table 4.34 shows the results of Cox proportional hazards regression of CVD incidence for minimally, partially, and fully adjusted models. Unadjusted HRs for BD and schizophrenia were 1.75 (95% CI: 1.66-1.86) and 1.58 (95% CI: 1.51-1.65), respectively. HRs adjusted for age, sex and calendar period were substantial. After adjusting for deprivation and country in the partially adjusted model, HRs were substantially reduced for schizophrenia, less so for BD, suggesting that deprivation and country account for a large part of the excess risk of CVD incidence for patients with schizophrenia. Full adjustment further substantially reduced the risks, to HR=1.21 (95% CI: 1.15-1.29) for BD and 1.12 (95% CI: 1.07-1.17) for schizophrenia. This suggests that other risk factors of diabetes mellitus, smoking status, Charlson index, blood pressure account for another large part of the excess risks for SMI.

There was a steep gradient in HRs with increasing age and there was a large effect for sex, with females having a 40% lower risk of CVD diagnosis than males (unadjusted HR=0.61, 95% CI: 0.60-0.61). The risk of CVD halved over the study period (unadjusted HR=0.49, 95% CI:

0.47-0.51 for 2015-19 vs 2000-04). CVD incidence increased with deprivation and for the other three countries of the UK compared with England. There were large associations between comorbidities and CVD incidence (unadjusted figures for diabetes mellitus: HR=4.44, 95% CI: 4.37-4.50, Charlson index of 2+: HR=3.26, 95% CI: 3.20-3.32, high BP: 3.07, 95% CI: 3.04-3.09) which reduced as more covariates were added but remained important. Current smokers were twice as likely as those who had never smoked to have incidence of CVD. Obesity was associated with a 20% increase in CVD incidence once other covariates were adjusted for. In the univariable models, missing data for smoking status, BMI and BP were associated with reduced incidence of CVD diagnosis. The associations increased in the full model and in the full model missing data became positively associated with CVD incidence for smoking and obesity. Figure 4.34 shows scaled Schoenfeld residuals from the full model for all the included covariates. No anomalies or patterns were observed, indicating the model was an adequate fit to the data.



SMI – severe mental illness, BD – bipolar disorder, SCZ – schizophrenia, CVD – cardiovascular disease, BP – blood pressure

**Figure 4.33: Plots of survival function against time to CVD incidence (log scales), with years since baseline as time analysis variable, to assess proportional hazards assumption for a) SMI, b) age group, c) sex, d) calendar period, e) deprivation quintile, f) country, g) diabetes mellitus, h) Charlson index, i) smoking, j) obesity, k) blood pressure**

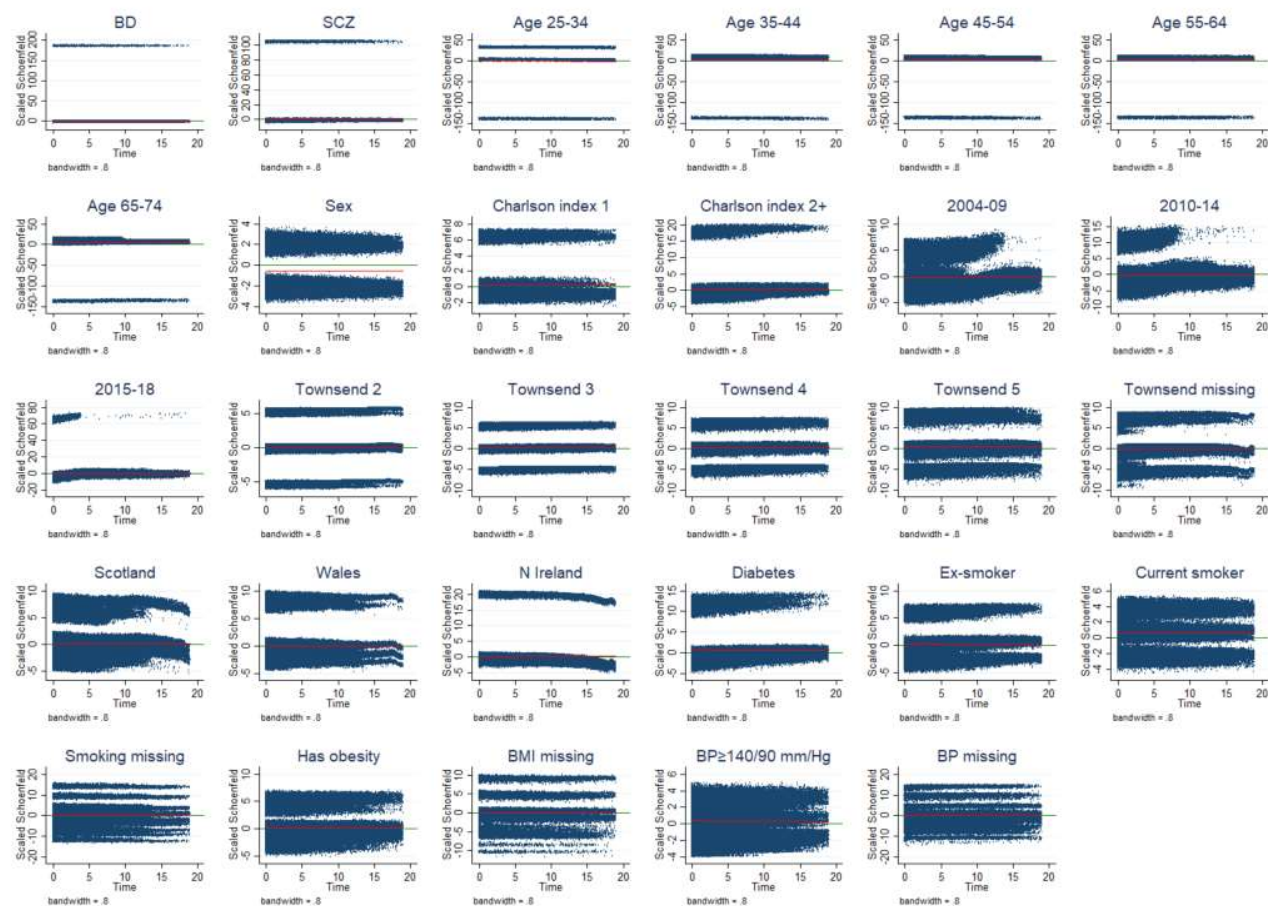


**Table 4.34: Hazard ratios for CVD incidence in univariable and multivariable Cox regression analyses**

|                                  |                    | Univariable (unadjusted) |        |       |       | Minimally adjusted <sup>1</sup> |        |       |       | Partially adjusted <sup>2</sup> |        |       |       | Fully adjusted <sup>3</sup> |        |       |       |
|----------------------------------|--------------------|--------------------------|--------|-------|-------|---------------------------------|--------|-------|-------|---------------------------------|--------|-------|-------|-----------------------------|--------|-------|-------|
| Variable                         |                    | HR                       | p      | lcl   | ucl   | HR                              | p      | lcl   | ucl   | HR                              | p      | lcl   | ucl   | HR                          | p      | lcl   | ucl   |
| SMI: No SMI (ref)                |                    | 1                        |        |       |       | 1                               |        |       |       | 1                               |        |       |       | 1                           |        |       |       |
|                                  | BD                 | <b>1.75</b>              | <0.001 | 1.66  | 1.86  | <b>1.45</b>                     | <0.001 | 1.37  | 1.54  | <b>1.38</b>                     | <0.001 | 1.31  | 1.46  | <b>1.21</b>                 | <0.001 | 1.15  | 1.29  |
|                                  | SCZ                | <b>1.58</b>              | <0.001 | 1.51  | 1.65  | <b>1.37</b>                     | <0.001 | 1.31  | 1.43  | <b>1.25</b>                     | <0.001 | 1.19  | 1.30  | <b>1.12</b>                 | <0.001 | 1.07  | 1.17  |
| Age group (years):               |                    |                          |        |       |       |                                 |        |       |       |                                 |        |       |       |                             |        |       |       |
|                                  | 16-24              | 1                        |        |       |       | 1                               |        |       |       | 1                               |        |       |       | 1                           |        |       |       |
|                                  | 25-34              | <b>4.54</b>              | <0.001 | 4.30  | 4.80  | <b>4.56</b>                     | <0.001 | 4.32  | 4.82  | <b>4.62</b>                     | <0.001 | 4.38  | 4.89  | <b>4.16</b>                 | <0.001 | 3.93  | 4.39  |
|                                  | 35-44              | <b>17.27</b>             | <0.001 | 16.40 | 18.18 | <b>17.06</b>                    | <0.001 | 16.20 | 17.96 | <b>17.63</b>                    | <0.001 | 16.75 | 18.56 | <b>15.28</b>                | <0.001 | 14.51 | 16.09 |
|                                  | 45-54              | <b>46.17</b>             | <0.001 | 43.89 | 48.57 | <b>45.78</b>                    | <0.001 | 43.52 | 48.16 | <b>47.73</b>                    | <0.001 | 45.37 | 50.21 | <b>38.68</b>                | <0.001 | 36.76 | 40.71 |
|                                  | 55-64              | <b>91.93</b>             | <0.001 | 87.40 | 96.69 | <b>92.77</b>                    | <0.001 | 88.19 | 97.57 | <b>97.37</b>                    | <0.001 | 92.57 | 102.4 | <b>73.72</b>                | <0.001 | 70.05 | 77.57 |
|                                  | 65-74              | <b>172.2</b>             | <0.001 | 163.6 | 181.2 | <b>177.1</b>                    | <0.001 | 168.3 | 186.4 | <b>185.2</b>                    | <0.001 | 176.0 | 194.9 | <b>134.3</b>                | <0.001 | 127.5 | 141.4 |
| Sex: Males (ref)                 |                    | 1                        |        |       |       | 1                               |        |       |       | 1                               |        |       |       | 1                           |        |       |       |
|                                  | Females            | <b>0.61</b>              | <0.001 | 0.60  | 0.61  | <b>0.55</b>                     | <0.001 | 0.55  | 0.56  | <b>0.55</b>                     | <0.001 | 0.55  | 0.56  | <b>0.57</b>                 | <0.001 | 0.57  | 0.58  |
| Calendar period:                 |                    |                          |        |       |       |                                 |        |       |       |                                 |        |       |       |                             |        |       |       |
|                                  | 2000-04 (ref)      | 1                        |        |       |       | 1                               |        |       |       | 1                               |        |       |       | 1                           |        |       |       |
|                                  | 2005-09            | <b>0.71</b>              | <0.001 | 0.71  | 0.72  | <b>0.89</b>                     | <0.001 | 0.89  | 0.90  | <b>0.85</b>                     | <0.001 | 0.84  | 0.86  | <b>0.83</b>                 | <0.001 | 0.82  | 0.84  |
|                                  | 2010-14            | <b>0.63</b>              | <0.001 | 0.62  | 0.64  | <b>0.88</b>                     | <0.001 | 0.87  | 0.90  | <b>0.80</b>                     | <0.001 | 0.79  | 0.81  | <b>0.77</b>                 | <0.001 | 0.76  | 0.79  |
|                                  | 2015-19            | <b>0.49</b>              | <0.001 | 0.47  | 0.51  | <b>0.83</b>                     | <0.001 | 0.80  | 0.86  | <b>0.78</b>                     | <0.001 | 0.75  | 0.81  | <b>0.77</b>                 | <0.001 | 0.75  | 0.80  |
| Townsend:                        |                    |                          |        |       |       |                                 |        |       |       |                                 |        |       |       |                             |        |       |       |
|                                  | 1 (least deprived) | 1                        |        |       |       |                                 |        |       |       | 1                               |        |       |       | 1                           |        |       |       |
|                                  | 2                  | <b>1.11</b>              | <0.001 | 1.09  | 1.12  |                                 |        |       |       | <b>1.10</b>                     | <0.001 | 1.09  | 1.12  | <b>1.07</b>                 | <0.001 | 1.05  | 1.08  |
|                                  | 3                  | <b>1.12</b>              | <0.001 | 1.11  | 1.14  |                                 |        |       |       | <b>1.27</b>                     | <0.001 | 1.25  | 1.29  | <b>1.17</b>                 | <0.001 | 1.16  | 1.19  |
|                                  | 4                  | <b>1.21</b>              | <0.001 | 1.19  | 1.22  |                                 |        |       |       | <b>1.50</b>                     | <0.001 | 1.48  | 1.52  | <b>1.31</b>                 | <0.001 | 1.29  | 1.33  |
|                                  | 5 (most deprived)  | <b>1.32</b>              | <0.001 | 1.30  | 1.34  |                                 |        |       |       | <b>1.78</b>                     | <0.001 | 1.75  | 1.81  | <b>1.47</b>                 | <0.001 | 1.45  | 1.49  |
|                                  | Missing            | <b>0.98</b>              | 0.005  | 0.96  | 0.99  |                                 |        |       |       | <b>1.19</b>                     | <0.001 | 1.17  | 1.21  | <b>1.12</b>                 | <0.001 | 1.10  | 1.14  |
| Country:                         |                    |                          |        |       |       |                                 |        |       |       |                                 |        |       |       |                             |        |       |       |
|                                  | England            | 1                        |        |       |       |                                 |        |       |       | 1                               |        |       |       | 1                           |        |       |       |
|                                  | Scotland           | <b>1.26</b>              | <0.001 | 1.25  | 1.28  |                                 |        |       |       | <b>1.22</b>                     | <0.001 | 1.21  | 1.24  | <b>1.21</b>                 | <0.001 | 1.20  | 1.23  |
|                                  | Wales              | <b>1.04</b>              | <0.001 | 1.03  | 1.06  |                                 |        |       |       | <b>1.08</b>                     | <0.001 | 1.06  | 1.09  | <b>1.04</b>                 | <0.001 | 1.02  | 1.05  |
|                                  | Northern Ireland   | <b>1.05</b>              | <0.001 | 1.03  | 1.07  |                                 |        |       |       | <b>1.17</b>                     | <0.001 | 1.15  | 1.20  | <b>1.20</b>                 | <0.001 | 1.18  | 1.23  |
| Diabetes mellitus <sup>4</sup> : |                    | <b>4.44</b>              | <0.001 | 4.37  | 4.50  |                                 |        |       |       |                                 |        |       |       | <b>1.97</b>                 | <0.001 | 1.94  | 2.00  |
| Charlson index:                  |                    |                          |        |       |       |                                 |        |       |       |                                 |        |       |       |                             |        |       |       |
|                                  | 0                  | 1                        |        |       |       |                                 |        |       |       |                                 |        |       |       | 1                           |        |       |       |
|                                  | 1                  | <b>1.31</b>              | <0.001 | 1.30  | 1.33  |                                 |        |       |       |                                 |        |       |       | <b>1.26</b>                 | <0.001 | 1.25  | 1.28  |
|                                  | 2+                 | <b>3.26</b>              | <0.001 | 3.20  | 3.32  |                                 |        |       |       |                                 |        |       |       | <b>1.36</b>                 | <0.001 | 1.33  | 1.38  |
| Smoking status:                  |                    |                          |        |       |       |                                 |        |       |       |                                 |        |       |       |                             |        |       |       |
|                                  | Never smoked       | 1                        |        |       |       |                                 |        |       |       |                                 |        |       |       | 1                           |        |       |       |
|                                  | Ex-smoker          | <b>1.99</b>              | <0.001 | 1.97  | 2.02  |                                 |        |       |       |                                 |        |       |       | <b>1.24</b>                 | <0.001 | 1.23  | 1.26  |
|                                  | Current smoker     | <b>2.05</b>              | <0.001 | 2.03  | 2.07  |                                 |        |       |       |                                 |        |       |       | <b>2.02</b>                 | <0.001 | 2.00  | 2.04  |

|                 | Univariable (unadjusted) |        |      |      | Minimally adjusted <sup>1</sup> |   |     |     | Partially adjusted <sup>2</sup> |   |     |     | Fully adjusted <sup>3</sup> |        |      |      |
|-----------------|--------------------------|--------|------|------|---------------------------------|---|-----|-----|---------------------------------|---|-----|-----|-----------------------------|--------|------|------|
| Variable        | HR                       | p      | lcl  | ucl  | HR                              | p | lcl | ucl | HR                              | p | lcl | ucl | HR                          | p      | lcl  | ucl  |
| Missing         | <b>0.82</b>              | <0.001 | 0.81 | 0.83 |                                 |   |     |     |                                 |   |     |     | <b>1.24</b>                 | <0.001 | 1.22 | 1.26 |
| Obesity:        |                          |        |      |      |                                 |   |     |     |                                 |   |     |     |                             |        |      |      |
| No              | 1                        |        |      |      |                                 |   |     |     |                                 |   |     |     | 1                           |        |      |      |
| Yes             | <b>1.65</b>              | <0.001 | 1.64 | 1.67 |                                 |   |     |     |                                 |   |     |     | <b>1.20</b>                 | <0.001 | 1.19 | 1.22 |
| Unrecorded      | <b>0.61</b>              | <0.001 | 0.60 | 0.61 |                                 |   |     |     |                                 |   |     |     | <b>1.04</b>                 | <0.001 | 1.03 | 1.05 |
| Blood pressure: |                          |        |      |      |                                 |   |     |     |                                 |   |     |     |                             |        |      |      |
| <140/90 mmHg    | 1                        |        |      |      |                                 |   |     |     |                                 |   |     |     | 1                           |        |      |      |
| ≥140/90 mmHg    | <b>3.07</b>              | <0.001 | 3.04 | 3.09 |                                 |   |     |     |                                 |   |     |     | <b>1.40</b>                 | <0.001 | 1.38 | 1.41 |
| Missing         | <b>0.62</b>              | <0.001 | 0.61 | 0.63 |                                 |   |     |     |                                 |   |     |     | <b>0.96</b>                 | <0.001 | 0.94 | 0.97 |

SMI – severe mental illness, BD – bipolar disorder, SCZ – schizophrenia, CVD – cardiovascular disease, ref – reference category, HR – hazard ratio, lcl – lower 95% confidence limit, ucl – upper 95% confidence limit. Variables measured at baseline.<sup>1</sup> adjusted for age, sex, calendar period. <sup>2</sup> adjusted for age, sex, calendar period, deprivation, country. <sup>3</sup> adjusted for age, sex, calendar period, deprivation, country, diabetes mellitus, CVD, Charlson index, smoking, obesity, blood pressure, <sup>4</sup> Includes type 1, non-type 1, and diabetes mellitus prescription (excluding patients prescribed metformin with a prior diagnosis of polycystic ovary syndrome). Values that exclude the null highlighted in **bold**

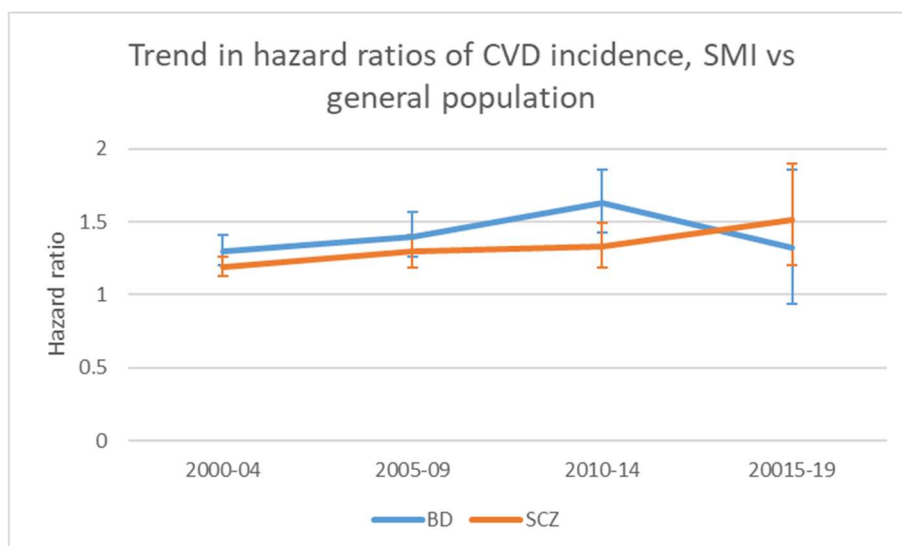


If hazards are proportional, smoothed line through residuals (shown in red) should have slope of zero. BD – bipolar disorder, SCZ – schizophrenia, BMI – body mass index, BP – blood pressure

**Figure 4.34: Scaled Schoenfeld residuals from Cox regression of CVD incidence for a) BD, b) schizophrenia, c) ages 25-34, d) ages 35-44, e) ages 45-54, f) ages 55-64, g) ages 65-74 years, h) sex, i) Charlson index=1, j) Charlson index=2+, k) period 2005-9, l) period 2010-14, m) period 2015-19, n-q) Townsend quintiles 2-5, r) missing Townsend score, s) Scotland, t) Wales, u) Northern Ireland, v) diabetes mellitus, w) ex-smoker, x) current smoker, y) smoking status missing, z) has obesity, aa) no obesity, ab) BMI missing, ac) BP $\geq$ 140/90 mmHg, ad) BP missing**

#### 4.4.7.1 Trend over time

There was some evidence that adding a SMI X calendar period interaction had an effect on the partially adjusted model, however, when comorbidities were added in the full model this effect disappeared. P-values from likelihood ratio tests for the addition of interaction terms in minimal, partial, and full models were 0.010, 0.022 and 0.340, respectively. Figure 4.35 shows the trend in CVD incidence over time by SMI from a Cox regression model, adjusted for age, sex, deprivation and country, with a SMI X calendar period interaction. For schizophrenia the risk of CVD incidence was greater than for the general population (confidence intervals excluded one) and appeared to increase over the study period. For BD, the risk of CVD incidence was also greater than the general population and showed a faster increase until 2010-14. After this time the HR decreased, and the confidence interval included one, suggesting no difference in CVD incidence between BD and the general population in 2015-19.



From Cox regression model adjusted for age, sex, deprivation, and country. BD – bipolar disorder, SCZ – schizophrenia, SMI – severe mental illness, CVD – cardiovascular disease

**Figure 4.35: Trend in hazard ratios for CVD incidence, SMI compared with general population, prevalent cohort**

## 4.5 Discussion

### 4.5.1 Summary

The main findings from the prevalent and incident cohort studies are shown by the diagrams in Figure 4.36 and Figure 4.37. The figures in the diagrams show the excess risks for schizophrenia and BD from Cox regression models adjusted for deprivation, country, smoking and comorbidities. They show substantial excess risks of all-cause mortality for both BD and schizophrenia, slightly lower, although still high, risks of mortality after diagnosis of CVD, but much smaller excess risk of CVD incidence. Excess risk of mortality is higher for schizophrenia, but this is not matched by a higher risk of CVD incidence.

#### Prevalent cohort

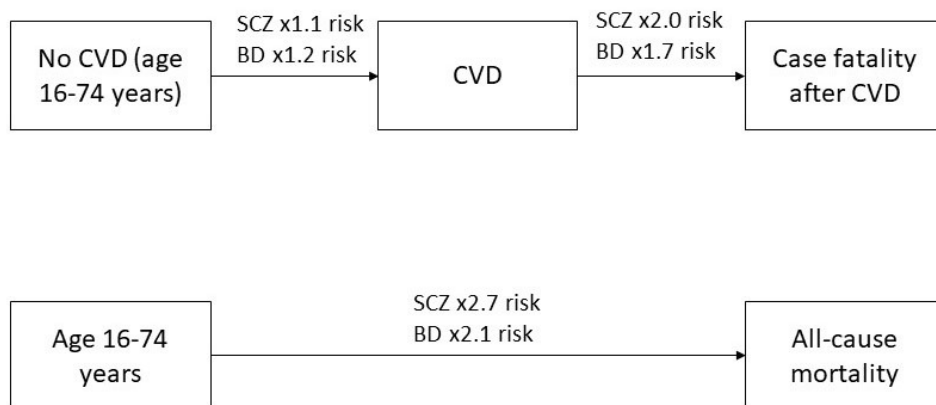


**Figure 4.36: Summary of findings for prevalent cohort**

### Incident cohort

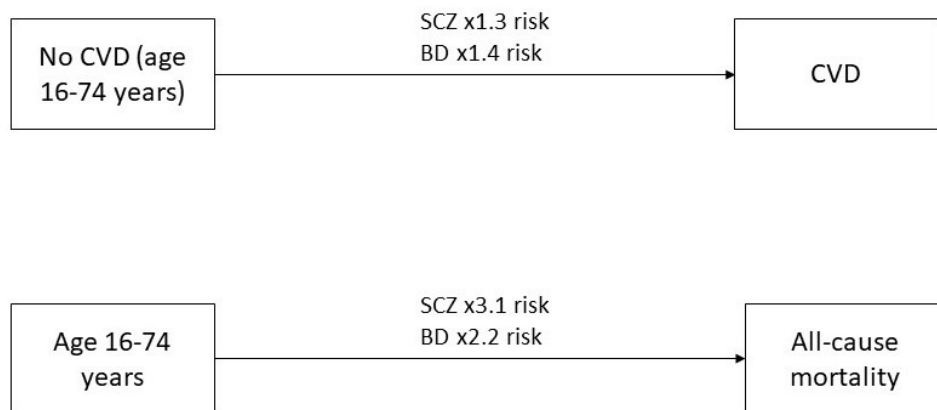


**Figure 4.37: Summary of findings for incident cohort**

The charts in Figure 4.38 and Figure 4.39 show the effect on BD and schizophrenia of adjustment for deprivation and country in the partially adjusted models and additional adjustment for smoking and comorbidities in the fully adjusted models.

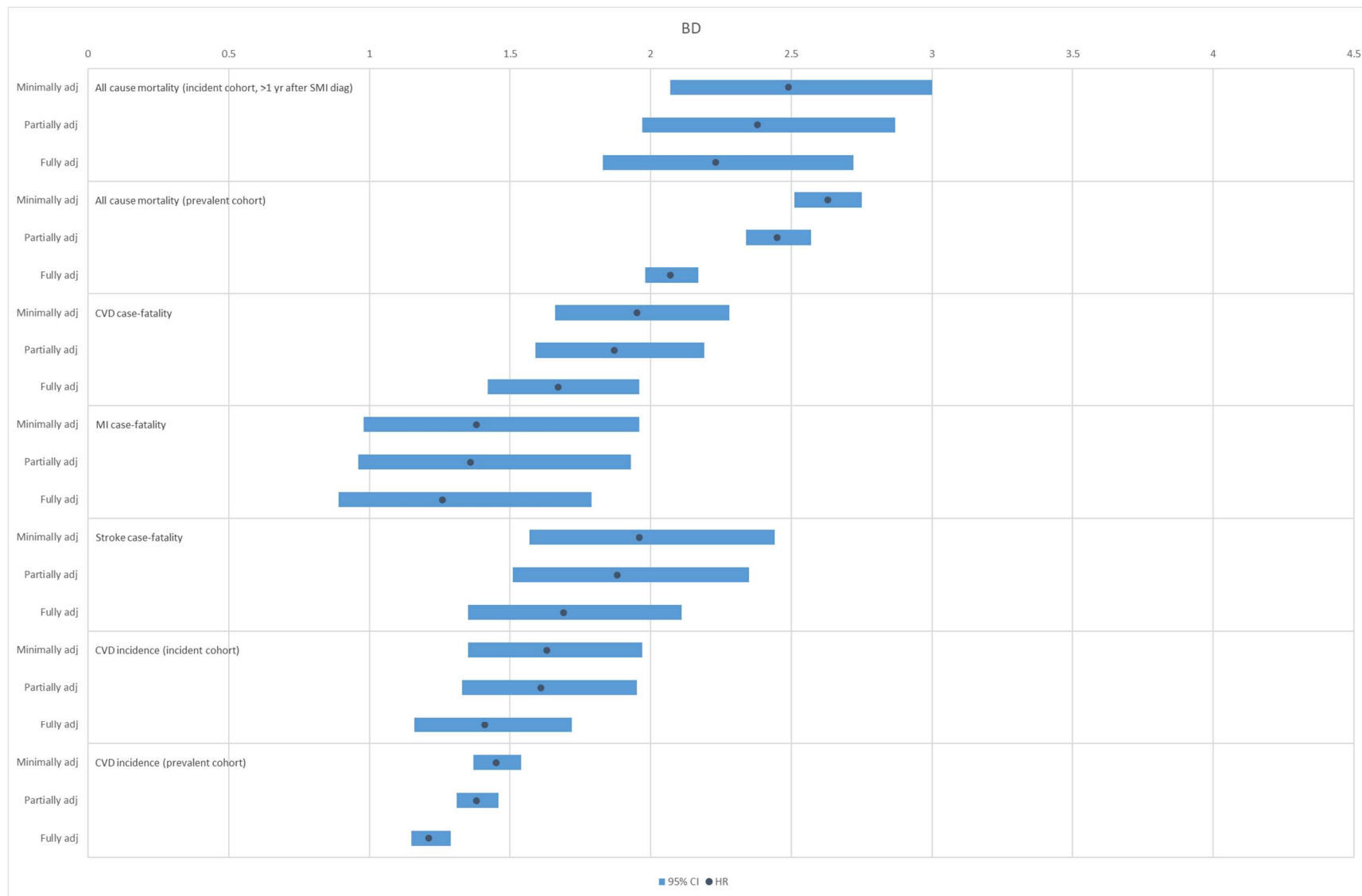


**Figure 4.38: Comparison of minimally, partially, and fully adjusted results for bipolar disorder**

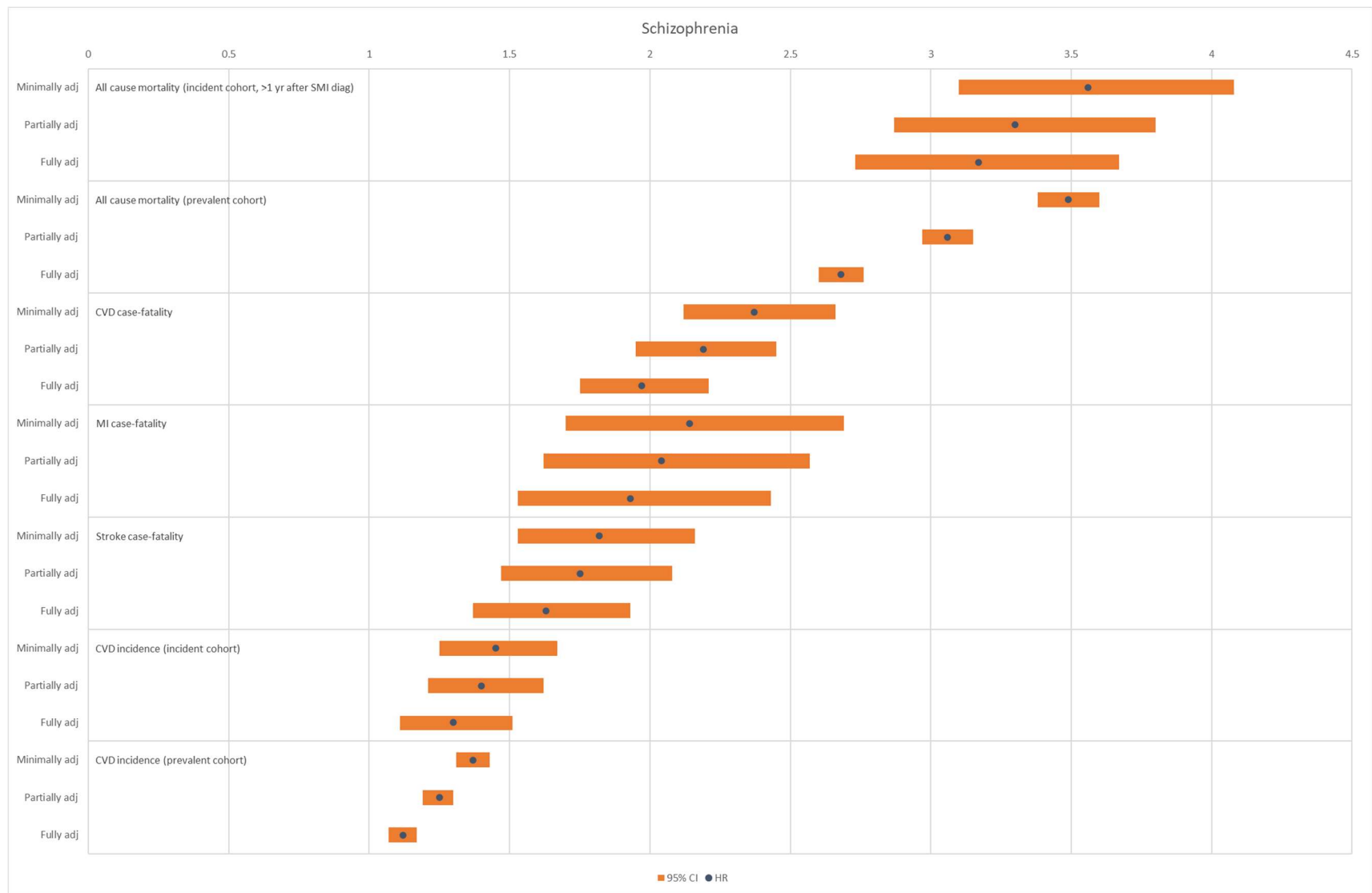


**Figure 4.39: Comparison of minimally, partially, and fully adjusted results for schizophrenia**



Adjustment for covariates reduced the HRs compared with minimally adjusted models but had a larger effect on all-cause mortality and CVD incidence HRs in the prevalent study compared with the incident study. In the prevalent study, adjustment for deprivation and country reduced the excess risks of all-cause mortality by 17.3% for schizophrenia and 11.0% for BD, whereas additional adjustment for smoking and comorbidities reduced the risks by a further 15.2% and 23.4% for schizophrenia and BD, respectively. For CVD incidence, in which the excess risk due to SMI was lower, the effect of covariates was proportionately greater. Deprivation and country reduced the excess risk by 32.4% for schizophrenia and 15.6% for BD, and smoking and comorbidities by a further 35.2% and 37.7% for schizophrenia and BD, respectively. In case-fatality analysis, adjustment for covariates resulted in relatively small reductions to HRs, particularly for case-fatality after MI and stroke.

#### 4.5.1.1 All-cause mortality

The matched incident cohort study found that SMI is strongly associated with premature all-cause mortality (before the age of 75 years). MRRs (adjusted by age and sex) were 3.45 for schizophrenia and 2.60 for BD. The effect was particularly striking in the year after SMI diagnosis, which could be partly explained by a high rate of suicides affecting patients newly diagnosed with SMI. (142, 202, 203) Both BD and schizophrenia were associated with mortality, but the effect was larger amongst patients with schizophrenia. Adjustment for deprivation, CVD, diabetes mellitus, other comorbidities, smoking, obesity, and blood pressure made modest differences to the HRs. This suggests that part of the relationship between SMI and mortality is due to those factors.

The prevalent cohort study also found substantial associations between SMI and mortality, particularly at younger ages. In this cohort, all-cause mortality was over two-fold higher than the general population for patients with BD and 2.7-fold higher for those with schizophrenia. Those with missing smoking status and unrecorded BMI had raised HRs compared with the reference categories (never smoked and no obesity, respectively), as did patients with missing ethnicity, although it should be noted that ethnicity recording improved over time. Unrecorded information could indicate a lack of engagement with primary care services which appears to be associated with a higher risk of mortality. In adjusted analyses, recorded obesity was associated with a lower mortality risk after age 45 years, compared with no obesity, whereas in univariable analysis obesity was associated with an increased mortality risk. In adjusted analysis, Scotland and Northern Ireland were associated with lower risks of mortality compared with England.

Adjustment for smoking, obesity, blood pressure, diabetes mellitus and comorbidities reduced the HRs for both BD and schizophrenia but had a larger effect for schizophrenia. This implies that a more of the relationship between schizophrenia and mortality is due to those risk factors than the relationship between BD and mortality.

Neither cohort study showed clear evidence of a change in association between SMI and mortality over time.

#### 4.5.1.2 Case-fatality

In this section it was shown that mortality after a diagnosis of CVD was increased by more than 70% for patients with BD and more than 90% for those with schizophrenia, compared with the general population after CVD diagnosis. Increasing age and having more

comorbidities increased the hazard of death compared to younger age and fewer comorbidities. It was also shown that CVD case-fatality for all patients reduced since the start of the 21<sup>st</sup> century, however it is unclear whether this also applies to patients with SMI. Countries of the UK outside England had smaller associations with CVD case-fatality than England.

After a diagnosis of MI, there was also a 90% increase in hazard of mortality for those with schizophrenia but for those with BD the hazard was similar to individuals without SMI. After a diagnosis of stroke, the hazard of mortality was over 70% higher than in the general population who also had a stroke for both BD and schizophrenia. This suggests that secondary prevention of CVD may be inferior in those with SMI, except for post-MI treatment for those with BD. It has been demonstrated that patients with SMI have reduced access to treatment after acute coronary syndrome. (208) A recent meta-analysis reported reduced likelihood of post-acute coronary syndrome revascularisation for those with SMI compared with those without SMI (schizophrenia; OR=0.46, 95% CI: 0.38-0.55; BD: OR=0.75, 95% CI: 0.63-0.89) and reduced likelihood of cardioprotective medication (relative risk: 0.89, 95% CI: 0.85-0.94). (208) Treatment after stroke has also shown to be sub-optimal in patients with SMI. (209)

#### 4.5.1.3 Cardiovascular incidence

The incident cohort study found a moderate association between SMI and CVD incidence, accounting for a 30-40% increase in CVD diagnosis, after adjusting for other known risk factors: diabetes mellitus, smoking, obesity, blood pressure and deprivation. However, the size of the association was smaller than that found for premature mortality. The association

with CVD incidence was stronger for BD than schizophrenia, whereas for mortality the effect was higher for schizophrenia.

This could be due to high rates of undiagnosed CVD amongst people with schizophrenia as have been reported in other studies. (52, 57, 160)

The prevalent cohort study also found 30-40% excess risk of CVD incidence for SMI when adjusted by age, sex, and calendar period. Adding adjustment for deprivation and country reduced the risk substantially for schizophrenia, but less for BD, suggesting that deprivation and country account for more of the difference between SMI and the general population for schizophrenia than BD. Adding other risk factors of smoking, obesity, diabetes mellitus and blood pressure further substantially reduced the risk, suggesting that those risk factors account for some more of the excess risk for SMI.

In univariable analysis, missing BMI, BP, and smoking status were associated with lower HRs for CVD incidence than reference categories (not having obesity, normotensive BP and never smoked, respectively). This may reflect lack of engagement with GP services: if patients do not attend the practice for BMI, BP, and smoking status to be recorded, then CVD may go undiagnosed. However, in multivariate analyses, missing BMI and smoking status were associated with higher HRs for CVD incidence than reference categories; BP moved closer to the null.

Countries of the UK outside England had larger HRs for CVD incidence than England.

#### 4.5.1.4 Change over time

The incident cohort was matched on index date, so it was not possible to add calendar year to the fully adjusted model. Instead, the cohort was split into four calendar periods and

separate Cox regression models were applied to each period. This analysis showed no evidence of a change in mortality over time; however, the confidence intervals were wide, and the calendar periods were not granular enough to detect changes from year to year. In the prevalent cohort study, calendar period was categorised into five-year bands and there was no evidence of differential temporal changes in mortality by SMI at this level of granularity. It is possible that within the five-year bands SMI had different effects on mortality, but it was not possible to detect these.

The incident cohort showed a widening of the gap in CVD incidence for schizophrenia in 2005-09 and BD in 2010-14, compared with matched non-SMI comparators, although this disappeared by 2015-19. In the prevalent cohort a partially adjusted model showed a widening gap in CVD incidence between SMI and the general population; the only evidence of the gap narrowing was for BD in 2015-19.

#### **4.5.2 Comparison with other literature:**

##### **4.5.2.1 SMI incidence and prevalence**

Crude SMI incidence rates of 47.2 per 100,000 PYAR, (95% CI: 46.7-47.8) and 20.4 (95% CI: 20.1-20.8) and 32.4 (95% CI: 31.9-32.8) PYAR for BD and schizophrenia, respectively, were found in the prevalent cohort study. These are higher than those found in a systematic review of psychoses in England between 1950 and 2009 for BD (3.7 per 100,000 PYAR, 95% CI: 3.0-4.5) and schizophrenia (15.2, 95% CI: 11.9-19.5). (210) However, in that review, the incidence rate for all psychoses (31.7 per 10,000 PYAR, 95% CI: 24.6-40.9) was more like the current study. A study of SMI incidence using data from THIN (211) found incidence rates of

15.0 per 100,000 PYAR (95% CI: 14.4-15.5) for BD and 9.2 per 100,000 PYAR (95% CI: 8.8-9.6) for schizophrenia, again rather lower than the prevalent cohort study reported here. In that study, the authors acknowledge that their recorded incidence of schizophrenia is lower than in population incidence studies and speculate that GPs may have been wary of recording patients with an initial schizophrenia diagnosis. The incidence rate for BD in the prevalent cohort study is broadly similar to that of European studies reported by the same authors. (211) The current study may have also used different Read codes to define SMI than the other THIN study. (211) It was not possible to record true incidence of SMI in the cohort study as patients may have been previously diagnosed with SMI in another practice. Attempts were made to exclude previously diagnosed patients by excluding patients with Read codes suggestive of previous disease as incident cases.

Prevalence rates in the prevalent cohort study were BD: 0.40% and schizophrenia: 0.78%. These were a little higher than the most recent figure of 0.95% for prevalence of SMI recorded by GPs in England in 2021/22, (212) and prevalence increased during the cohort study. A 2014 psychiatric survey in Great Britain found 2% prevalence in the adult sample screened for BD and a prevalence of 0.7% for schizophrenia. (8) However, worldwide the World Health Organisation puts the worldwide adult prevalence of schizophrenia at 0.45%. (213) Globally, the prevalence of BD is estimated at 0.51%. (214)

#### 4.5.2.2 Age at SMI diagnosis

The distribution of age at SMI incidence was slightly older than expected (Appendix XXVII ), however broadly similar to other authors. (210, 215-218)

#### 4.5.2.3 Multiple SMI diagnoses

In this cohort, 3.2% of those with schizophrenia changed to a diagnosis of BD during their follow-up period and 4.8% of those with BD changed to schizophrenia. These were similar for schizophrenia, but lower for BD than the 3.0% and 8.3%, respectively, found in a Taiwanese study. (219) The latter study, however, had a longer follow-up of seven years, compared with the median of 3.4 years for BD, 3.3 years for schizophrenia and 4.7 years for those without SMI in the current study. The available data did not allow for more than one change of SMI diagnosis during follow-up. However, the numbers who did switch from BD to schizophrenia or vice versa during their study period were relatively small (only 3.5% of those diagnosed with SMI), so the number with multiple switches is likely to be even smaller. Some patients changed diagnoses before the start of their follow-up. It may be that they also changed diagnosis during the follow-up period. This information was not available, however, as only the earliest dates of BD and schizophrenia diagnoses were available. Numbers affected are again likely to be small as only 6.4% of those with SMI had both diagnoses recorded before the start of follow-up.

#### 4.5.2.4 All-cause mortality

The age/sex adjusted mortality rate ratios (MRRs) of 3.45 for schizophrenia and 2.60 for BD found in this study are similar to the SMRs of 3.65 and 3.27 for schizophrenia, 2.65 and 2.39 for BD reported for two cohorts in a large Taiwanese study. (71) However, the fully adjusted HR of 2.68 for schizophrenia corresponds with the relative risk of 2.5 for schizophrenia which was reported by two recent systematic reviews and meta-analyses. (37, 54) Another, larger

systematic review reported a risk ratio of 2.94, 95% CI: 2.75-3.14, based on 57 studies. (40) The HR for BD of 2.07 was also very similar to the relative risks of 2.0 and 2.02 from recent meta-analyses, based on 19 and 39 studies, respectively. (37, 39) A large cohort study in the UK covering the period 2000-2014 reported adjusted HRs of 1.79 and 2.08 for BD and schizophrenia, respectively. (72) However, these studies did not restrict to an upper age limit. As the prevalent cohort study has found, HRs are reduced in older populations, so it could be expected that rates in our study of patients aged 16-74 years would be higher.

Recently reported figures from NHS data in England showed that in 2016-18 adults aged 18-74 years with SMI had mortality rates 4.5 times that of the general population, which were closer to those found in the incident study which had very high risk of mortality in the first year after SMI diagnosis. (183) Although covering a similar age population to our study, mortality rates in this study were higher than those found by the prevalent study. One reason for the disparity may have been that in the latter study, SMI was defined by referrals to secondary mental health services, whereas our study also included patients managed in primary care.

The prevalent study showed no consistent evidence of changes in mortality rates over time for SMI patients compared with the general population. However, another UK study showed more definite increases between 2004 and 2014 for schizophrenia, and between 2006 and 2014 for BD. (72) There was also evidence that the disparity between SMI and the general population in England increased between 2015 to 2019. (183)



#### 4.5.2.5 CVD case-fatality

The adjusted case-fatality ratios after MI in the prevalent cohort study were 1.93, 95% CI: 1.53-2.43 and 1.26, 95% CI: 0.89-1.79 for schizophrenia and BD, respectively. These are broadly similar to the relative risks of mortality after acute coronary syndrome found by a recent meta-analysis, which were 1.60, 95% CI: 1.31-1.96 and 1.09, 95% CI: 0.84-1.40 for schizophrenia and BD, respectively. (208)

Additionally, the case-fatality ratios after stroke diagnosis found in the current study for schizophrenia: 1.63, 95% CI: 1.37-1.93 were within the confidence limits of those found in a recent systematic review of post-stroke mortality (HR=1.37, 95% CI: 1.30-1.44). (220)

#### 4.5.2.6 CVD incidence

The excess risk of CVD diagnosis for BD and schizophrenia found by the incident cohort study (BD: HR=1.41, 95% CI: 1.16-1.72; schizophrenia: HR=1.30, 95% CI: 1.11-1.51) was broadly within the range of the findings of the systematic review for total CVD events. However, the HRs were smaller than those found by two recent reviews. (54, 83) The adjusted HRs found by the prevalent cohort study were smaller still (BD: HR=1.21, 95% CI: 1.15-1.29; schizophrenia: HR=1.12, 95% CI: 1.07-1.17). Other authors have found reduced relative risks of CVD incidence compared with CVD mortality for those with SMI vs the general population. (52, 169, 221) At an individual level, women with BD and both sexes with schizophrenia have been found to die from cardiovascular causes but no prior diagnosis of CVD. (57)

Low relative risks of CVD incidence may also relate to problems in ascertainment of CVD in those with SMI. This may be due to lack of recognition of symptoms, either by the individual, resulting in delays in seeking healthcare or by health professionals misattributing physical

symptoms reported by those with SMI to problems associated with their mental illness, so-called diagnostic overshadowing. (55, 222)

In the prevalent study, the smaller HRs compared with the incident study could be the result of a healthy survivor effect. The prevalent cohort contains both new cases of SMI, diagnosed during follow-up, and historic cases, diagnosed some time before follow-up. For each of the historic cases included in the study, there will be others, diagnosed with SMI at the same time, who will have died before the study period, some of whom would have had CVD. The historic SMI cases included in the study will be healthier than those who died before the study (healthy survivors). The HR of CVD incidence in the prevalent study is thus diluted by these healthy historic cases. Also, those who had CVD before the start of follow-up were excluded, making the group of included historic cases healthier still.

As well as the healthy survivor effect, differences in CVD incidence between the prevalent and incident cohorts could be accounted for by incident SMI patients coming into the study more recently and thus being subject to better healthcare provision (*i.e.* CVD more likely to be diagnosed). 39% of the historic SMI patients started their follow-up in 2010 or later, compared with 52% of the incident patients.

#### 4.5.2.7 CVD mortality compared with incidence

The greater excess risks of all-cause mortality and CVD case-fatality compared with CVD incidence for those with SMI found in these studies have also been noted by other authors. In one large cohort study only 26.3% of schizophrenia patients who died from CHD had been previously diagnosed with the condition, whereas 43.7% of patients without schizophrenia who died from CHD had been previously diagnosed. (52) Similarly, another large register-

based cohort study found an incidence rate ratio of 1.11 (95% CI: 1.08-1.14) for CHD in those with SMI compared with the general population, whereas excess mortality from CHD was much higher (MRR=2.90, 95% CI: 2.71-3.10). (221)

#### **4.5.3 Strengths and limitations:**

##### **4.5.3.1 Strengths**

One strength of the two cohort studies lies in the fact that they are large studies, representative of the UK population. The incident SMI cohort was well matched to the non-SMI comparison group in terms of age, sex, and general practices, whereas the prevalent cohort included the whole population without SMI as a comparator group. As the number of participants were so large, it was possible to adjust for multiple covariates with a high degree of precision. There was a high degree of consistency in results, with schizophrenia having a greater association with the outcomes considered than BD.

##### **4.5.3.2 Limitations**

There were also some limitations. The data were collected for routine patient care. Some data fields may not be completed for some patients *e.g.* blood pressure because they may not be relevant to the current care of the patient. That results in missing data, which, in the case of blood pressure may be more likely to be missing in healthy patients.

The analysis was adjusted for several important confounders, such as deprivation and smoking status, however it was not possible to adjust for the confounding effect of ethnicity due to too much missing data (52.4%), particularly in the early years of the study.

There may be inaccuracies in the recording of exposures and outcomes. Different general practices may use different Read codes to define SMI, and both schizophrenia and BD can be hard to differentiate from other, more transient psychoses at first presentation. However, attempts were made to make Read code lists as complete as possible by reference to published lists used by other studies. The use of SMI-specific medications to define SMI was explored, although including medications appeared to reduce the ability to correctly identify patients with SMI. The nature of the dataset meant that some patients may have been identified as incident cases, when in fact they were prevalent cases that had previously been registered at another practice. Attempts to minimise this were made by creating separate lists of incident and prevalent Read codes for SMI.

Patients who did not have an SMI Read code but who were prescribed some SMI-specific medications or who had Read codes indicating they had been added to an SMI register were only included in the non-SMI comparison group in the prevalent study. As a result, some people with quite severe psychosis could have been included in the non-SMI group, rather than the SMI group. The effect of this would be to make the groups more similar than they would have otherwise been, making the reported effect sizes for SMI more conservative.

One limitation of removing those with “other SMI” from the definition of SMI used in the incident cohort relates to the selection of the non-SMI comparison group. Patients with “other SMI” were no longer eligible to be part of the SMI group. However, because the original selection process for non-SMI comparators excluded those with “other SMI”, these patients were not able to be included in the matched non-SMI comparison group either. This is unlikely to have had much effect.

Outcomes may not always have been accurately recorded. The fact of death is likely to be captured in THIN data, however the actual date of death could be inaccurate as it is not needed for ongoing patient care. Some dates of death were found to be well beyond the end of the patient record. Dates of death occurring more than one day after the end of the patient record were excluded to try and eliminate bias.

Cause of death was not available in the dataset, so it was not possible to directly compare with the results of the systematic review of SMI and CVD mortality. Instead, all-cause mortality and CVD case-fatality were proxy outcomes for CVD-related mortality.

CVD incidence was an important outcome, and it relies on complete recording in patient records for correct ascertainment. It is possible there was differential ascertainment or recording in those with SMI and without SMI. Indeed, the systematic review found low CHD incidence amongst those with schizophrenia compared with controls but the reverse for other combinations of SMI and CVD. In both the cohort studies the risk of CVD incidence was elevated for both BD and schizophrenia. If the cohort was subject to under-ascertainment for individuals with SMI, the true HRs would be likely to be even larger than those found in the study.

The status of diabetes mellitus, CVD, smoking, obesity, and blood pressure were the most recently recorded for each patient at the start of each age band. The covariates were also updated if values changed at the start of a new calendar period. In a sensitivity analysis the HRs were compared with HRs obtained using the covariate values at baseline instead. Using baseline values resulted in larger HRs for obesity, high BP, missing smoking status and missing BP compared with HRs for covariates updated during the study period. The HRs for

ex-smoking and missing BMI were smaller when using baseline values than HRs for covariates updated at the start of age bands/calendar periods. The difference was particularly noticeable in obesity, in which the effect of obesity at ages over 45 years became protective when using updated values for obesity, whereas in analyses using baseline BMI values, obesity was associated with increased mortality. The so-called “obesity paradox” where obesity has an apparent protective effect on mortality has been reported in other studies of older adults. (223) It has been demonstrated elsewhere (224) that the obesity paradox could be due to “collider stratification bias”, whereby stratification by CVD led to confounding by unmeasured factors affecting both CVD and mortality. In the fully adjusted model, both CVD and diabetes mellitus have been adjusted for, as well as obesity. In a sensitivity analysis of ages 55-64 years, CVD and diabetes mellitus were removed as covariates from the fully adjusted model. The HRs for other covariates remained broadly similar, but the effect of obesity was reversed and no longer had a protective effect on mortality (HR=1.05, 95% CI: 1.02-1.07). Diabetes mellitus and CVD may thus act as colliders in the relationship between obesity and mortality in this dataset.

Violations of the proportional hazards assumption were found in some of the models used. Attempts were made to improve model fit by stratification, splitting up follow-up time and including variables interacted with time. However, using a model with non-proportional hazards does not necessarily imply that the results are invalid. Proportional hazards assumes that the effect of the covariate does not vary with time. A simpler model allowing some variation over time may be adequate for the purposes of demonstrating an association between SMI and CVD incidence. (225)

#### **4.5.4 Implications for clinical practice/policy/further research**

The cohort studies have shown that SMI is consistently associated with more than a two-fold increase in mortality compared with the general population. The studies have considered both prevalent and incident diagnoses of SMI and both BD and schizophrenia. The lack of a consistent trend in since 2000 indicates that relative all-cause mortality for people with SMI has not changed much over the last two decades. Mortality rates have not worsened compared with the general population, however, neither have they much improved from the high levels that existed at the turn of the century.

Adjusted models found that the case-fatality rate for all CVD, including angina, TIA, and PAD, as well as more severe CVD outcomes such as MI and stroke was at least 50% higher for people with SMI compared with the general population. There could be some lead-time bias in when CVD is diagnosed for patients with SMI compared to those without. If less severe CVD diagnoses are diagnosed earlier in those without SMI, the prevalent study CVD case-fatality rate ratio could under-estimate the true scale of the difference between SMI and non-SMI. If lead time bias in CVD diagnosis were an issue, then it might be expected that case-fatality rate ratios would be smaller for MI and stroke, which are more likely to be diagnosed and recorded at the time of occurrence. This is borne out for MI in BD, in particular, but MI and stroke case-fatality rate ratios for schizophrenia are also slightly reduced compared with those for all CVD. Further research of case-fatality could focus on sex differences as women are more likely to have silent MI.

SMI was only moderately associated with incidence of overall CVD diagnosis. It was beyond the scope of this PhD, but future work could explore the effect of SMI on incidence of MI and stroke separately as these conditions are less likely to go undiagnosed or unrecorded.

Analysis of the prevalent cohort showed that missing data for smoking status, BMI and BP were associated with reduced incidence of CVD diagnosis in univariable models. However, this was reversed in multivariate models. The associations increased in the full model and in the full model missing data became positively associated with CVD incidence for smoking and obesity. Unrecorded BMI and smoking status may be indicators of lack of engagement with healthcare services more generally. Lack of engagement may result in CVD and other conditions going undiagnosed and unrecorded, but additionally, lack of treatment for CVD risk factors. Patients with missing clinical data are likely to be a heterogeneous group. They are either well and therefore do not frequently attend the general practice or they are unwell and are not receiving adequate care. HRs have reversed after adjusting for covariates (*e.g.* deprivation, DM, BP, smoking) which are associated with ill health. If a patient has DM, lives in a deprived area, has a high Charlson index and yet smoking is not recorded, it could indicate poor patient care, whereas if a patient with no DM and a low Charlson index, who lives in an affluent area has unrecorded smoking status it does not necessarily indicate poor care. There is a need for more work to explore the associations between missing data, CVD incidence and treatment of CVD risk factors.

England had higher risks of all-cause mortality and CVD case-fatality, yet lower risk of CVD incidence than other countries of the UK for those with SMI relative to the general population. This may reflect the differing healthcare systems operating within the devolved nations. The QOF, introduced in 2004 for general practices in England, is a system of



renumeration for GPs, based on them developing registers of patients with long-term conditions and receiving payment for their care. (190) Thus, in England there are incentives to recording a diagnosis of CVD. However, apart from the QOF, there are differences between the nations in waiting list sizes, availability of interventions and access to those interventions, particularly in rural areas. Populations in Wales and Northern Ireland, for example, are less concentrated in cities.

#### **4.5.5 Summary of chapter**

The purpose of the cohort studies described in this chapter was to answer three main questions:

1. Are people with SMI at increased mortality risk compared with the general population?
2. Are people with SMI at increased risk of cardiovascular incidence compared with the general population?
3. Have the risks changed over time, and do they vary by type of SMI, country, or deprivation quintile?

This chapter has established that there is an excess risk of all-cause mortality, CVD and stroke case-fatality and CVD incidence for patients with BD and schizophrenia in two primary care cohorts. The risks differ for BD and schizophrenia and there is a gradient by deprivation quintile, with higher risks in the more deprived areas. Countries of the UK outside England generally had lower risks of mortality but higher risks of CVD incidence. There was no clear and consistent evidence of changes over time. The next chapter will consider CVD incidence in the prevalent cohort and utilise mediation analysis to explore the role of CVD risk factors – obesity, diabetes mellitus, high blood pressure and smoking.

## CHAPTER 5 MEDIATION ANALYSIS

### 5.1 Introduction

Previously, in the systematic review (Chapter 3 ) and the cohort study (Chapter 4 ) it was shown that for people with SMI (both BD and schizophrenia) there is a higher incidence of CVD. This chapter goes beyond association to explore causal pathways between SMI and CVD using mediation analysis to investigate the role of CVD risk factors.

The cohort analysis in Chapter 4 showed that SMI and risk factors, including smoking, diabetes mellitus, obesity and blood pressure all had an association with CVD. Figure 5.1 shows a diagrammatic representation of this. This chapter will attempt to answer the question of *how* SMI is related to the higher risk of CVD. The hypothesis being tested is that people with SMI have more risk factors (*e.g.* smoking, high BP, diabetes mellitus, obesity) which in turn lead to a higher risk of CVD. If this is not the case, it suggests there is another mechanism. This could be deprivation status (SMI is associated with higher deprivation, which is associated with higher rates of CVD), less treatment of risk factors in those with SMI, leading to higher incidence of CVD, or some other mechanism leading to higher incidence of CVD. Mediation analysis will be used to explore the hypothesis of more risk factors in those with SMI causing the higher incidence of CVD.

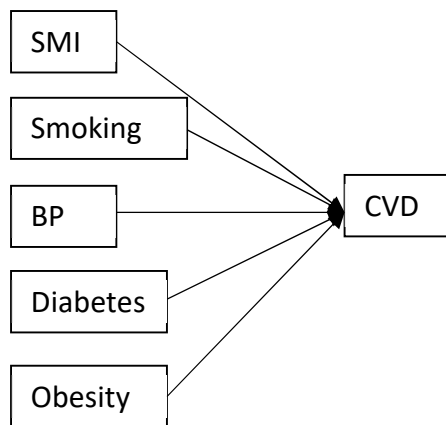
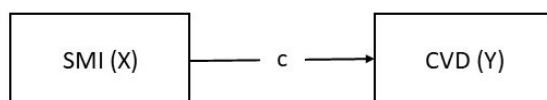


**Figure 5.1: Representation of the relationship between SMI and risk factors in Cox regression analysis**

Early work, particularly by David Kenny, (226-228) represented causal relationships between an exposure, X, and an outcome, Y as path diagrams. These path diagrams, applied to SMI and CVD are described below. In Figure 5.2(i), the total effect of SMI on CVD is accounted for by path c. However, in Figure 5.2(ii), the relationship between SMI and CVD is mediated by an intervening variable, M, *e.g.* smoking. SMI is causally associated with smoking, which in turn causes CVD. Here the direct effect of X on Y is shown by path c' and the indirect (or mediated) effect by path ab. In the mediated model, the total effect of X on Y is the sum of the direct and indirect effect.

i)



ii)

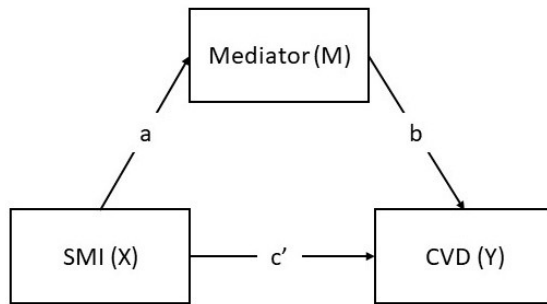


**Figure 5.2: Path diagrams representing causal relationship between exposure, X (SMI) and outcome, Y (CVD) showing i) total effect of X on Y, ii) effect of X on Y, mediated by mediator (M)**

The paths a, b, c, and c' are estimated by the coefficients from multiple regression analyses.

Using these coefficients, the proportion of the X-Y relationship that is mediated can be

calculated. In the case of ordinary least squares regression, with continuous values for X, Y

and M, the total effect  $c = c' + ab$ . The proportion mediated is estimated by  $1-c/c'$  or

equivalently by  $ab/c$ . However, this equivalence does not hold for different types of data,

*e.g.* where the outcome is binary, or where there is time to event data, such as in the

current study. Where data are not continuous, coefficients require standardisation to enable

them to be estimated on the same scale of measurement. (229)

In the Baron and Kenny approach, four steps establish the presence of mediation:

Step 1: Show that X is associated with Y

Step 2: Show that X is associated with M

Step 3: Show that M is associated with Y

Step 4: Establish whether the mediator completely or partially mediates the

relationship between X and Y. (226, 228, 230)

These steps can be performed by fitting three regression models: Y on X without the mediator, M on X, and Y on X adjusted for the mediator. However, there are also several important assumptions to be made in interpreting the results of the direct and indirect effects (231):

- Exposure-outcome confounding should be controlled
- Mediator-outcome confounding should be controlled
- Exposure-mediator confounding should be controlled
- The exposure should not affect any mediator-outcome confounder

Sensitivity analysis can test the robustness of these assumptions in the cohort study data. (231)

Recent work has built on the early work by Kenny and others and has considered the interaction between the exposure and mediator and using a counterfactual or potential outcomes approach allowed for a four-way decomposition of the total effect. (232) The four components are: (i) the effect due to neither interaction nor mediation (the controlled direct effect or CDE), (ii) the effect of interaction alone (reference interaction:  $INT_{ref}$ ), (iii) the effect due to both mediation and interaction (mediated interaction:  $INT_{med}$ ), and (iv) the effect of mediation alone (the pure indirect effect: PIE). (232) A Stata command, `med4way` (233) can be used to run causal mediation analysis, producing the four components of the total effect and can accommodate both time to event and binary outcome data. This methodology is appropriate for rare events. In this study only 216,620 out of 8,967,993 participants (2.4%) experienced a CVD incident event.

## 5.2 Methodology

### 5.2.1 Mediation analysis of CVD incidence

Med4way was used to explore the effects of smoking, high blood pressure, diabetes mellitus and obesity as potential mediators of the relationship between SMI and CVD incidence. It was not possible to assess the effect of cholesterol as a mediator because the proportion of missing measurements was too high. To simplify the analyses, the included mediators were converted to binary variables, indicating whether the mediator was recorded as present at baseline. These are shown in Table 5.1.

**Table 5.1: Binary values for potential mediators**

| Potential mediator  | Mediator present at baseline if:                                                                               | Mediator not present at baseline if:                                                            |
|---------------------|----------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------|
| Smoking             | Current smoker                                                                                                 | Never smoked OR ex-smoker OR smoking status unrecorded                                          |
| High blood pressure | BP $\geq$ 140 mmHg systolic OR $\geq$ 90 mmHg diastolic                                                        | BP < 140 mmHg systolic AND < 90 mmHg diastolic OR BP unrecorded                                 |
| Diabetes mellitus   | Type 1 OR non-type 1 DM at baseline OR DM prescription in the absence of prior PCOS if metformin               | No diabetes mellitus recorded                                                                   |
| Obesity             | BMI $\geq$ 30 kg/m <sup>2</sup> (or $\geq$ 27.5 kg/m <sup>2</sup> if non-White ethnicity) OR obesity Read code | BMI <30 kg/m <sup>2</sup> (or <27.5 kg/m <sup>2</sup> if non-White ethnicity) OR BMI unrecorded |

BP – blood pressure, DM – diabetes mellitus, PCOS – polycystic ovary syndrome, BMI – body mass index

BD and schizophrenia were considered separately and half the cohort with no SMI was used as the reference population for each SMI. The data were set as time to event data with the time since baseline used as the time analysis variable. In the first set of analyses, minimally adjusted models that included only ten-year age band and sex as covariates were used. In a further set of partially adjusted analyses, country, and Townsend deprivation quintile (with missing as a separate category) were added. In a final set of fully adjusted models, indicator variables for calendar period (2005-09, 2010-14, 2015-19 vs 2000-04) and Charlson index (1,

2+ vs 0) were added. Additionally, in the fully adjusted analysis, indicator variables for the three covariates not being tested as a potential mediator were included *i.e.* ex-smoker, current-smoker, smoking status unknown vs never smoked; BP $\geq$ 140/90 mmHg, BP unknown vs BP<140/90 mmHg; diabetes mellitus (as above); recorded obesity, BMI unknown vs BMI<30/27.5 kg/m<sup>2</sup>.

Cox proportional hazards regression was performed to obtain the effects on the outcome, which was time to first diagnosis of any CVD. The effect on the binary mediators was obtained by logistic regression.

HRs and ORs from Cox regression and logistic regression, respectively were tabulated. For each mediator, the total effect of SMI on CVD was decomposed into the four components discussed above (CDE, INT<sub>ref</sub>, INT<sub>med</sub>, PIE) and the proportion mediated reported. (232)

Decomposition of the total effect is dependent on the values chosen for the covariates (232) and values must be selected to produce the results of the decomposition. Values were chosen which could be applied across the different models to compare the proportion of the effect mediated by smoking, high blood pressure, diabetes mellitus and obesity. Where possible median values were chosen for the covariates, otherwise base values were used (*e.g.* no diabetes mellitus, no obesity), except for calendar period, where the latest time point was selected. Values chosen were as follows:

- In minimally adjusted models (adjusted by age and sex only): males aged 55-64 years
- In partially adjusted models (adjusted by age, sex, deprivation, and country): males aged 55-64 years, median deprivation quintile, England
- In fully adjusted models (adjusted by age, sex, deprivation, country, calendar period, Charlson index plus smoking, BP, diabetes mellitus and obesity, where not acting as

the mediator): males aged 55-64 years, median deprivation quintile, England, 2015-19, Charlson index 1, ex-smoker, BP<140/90 mmHg, no diabetes mellitus, no obesity.

Figure 5.3 summarises the main steps in the mediation analysis of the association between SMI and CVD incidence.

| Mediation analysis | <ul style="list-style-type: none"> <li>• Four potential mediators: smoking, blood pressure, obesity and diabetes mellitus coded as binary variables and assessed in separate analyses</li> <li>• Logistic regression used for effects of SMI on mediators (ORs)</li> <li>• Cox regression used for effects of mediator on time to CVD incidence (HRs)</li> <li>• Cox regression used for effects of SMI on time to CVD incidence, controlled for mediators (HRs)</li> <li>• Minimally, partially, and fully adjusted models</li> <li>• Covariates not being assessed as the mediator controlled for in the fully adjusted models</li> <li>• Total excess risk of SMI on CVD incidence decomposed into controlled direct effect, reference interaction, mediated interaction, and pure indirect effect</li> <li>• Proportion of the effect mediated by each of the potential mediators calculated</li> <li>• Sensitivity analyses conducted</li> </ul> |
|--------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|--------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

SMI – severe mental illness, CVD – cardiovascular disease, ORs – odds ratios, HRs – hazard ratios

**Figure 5.3: Summary of mediation analysis of SMI and CVD incidence**

#### 5.2.1.1 Sensitivity analysis

Several sensitivity analyses were conducted.

The value for each of the potential mediators was the latest status recorded at baseline. This could have been a long time before the start of follow-up. For example, around 21% of patients with a record of smoking status at baseline had the status recorded >3 years before baseline. A status of “current” smoker may thus be outdated. Sensitivity analyses were therefore carried out recoding the mediators of smoking, high BP, and obesity to known measurements within (i) three years, (ii) one year, of baseline. It was not possible to conduct



a similar sensitivity analysis for diabetes mellitus without excluding large numbers of patients, *i.e.* those diagnosed three years or one year before baseline.

A separate sensitivity analysis checked the effect of smoking as a mediator with baseline status of current plus ex-smoker vs never smoked and smoking status unknown.

The mediating effect of deprivation was explored by including Townsend quintile five (yes/no) as a binary mediator in fully adjusted models that included all the other four potential mediators (smoking, BP, diabetes mellitus and obesity).

In a further set of sensitivity analyses, the last values of the mediators before the endpoint for each patient were used, instead of the baseline values. This was an attempt to better comply with the assumption for the temporal order of exposure-mediator-outcome which is needed to imply causation.

Final sensitivity analyses explored the effect of changing the values of the covariates, since decomposition of the total effect is dependent on covariate values. (232) Three example sets of covariate values: (i) high risk, (ii) low risk, and (iii) median risk were chosen and the proportion mediated by the baseline values of the four potential mediators (current smoking, BP  $\geq$  140/90 mmHg, diabetes mellitus and obesity) was calculated.

The three sets of covariate values were as follows:

(i) high risk: male, age 65-74 years, most deprived quintile, England, Charlson index 1, calendar period 2015-19, current smoker at baseline, with diabetes mellitus at baseline, with obesity at baseline, BP  $\geq$  140/90 mmHg at baseline

(ii) low risk: female, age 45-54 years, least deprived quintile, Wales, Charlson index 0, calendar period 2010-14, non-smoker at baseline, no diabetes mellitus at baseline, no obesity at baseline, BP < 140/90 mmHg at baseline

(iii) median risk: male, age 55-64 years, median deprivation quintile, Scotland, Charlson index 2+, calendar period 2005-09, ex-smoker at baseline, no diabetes mellitus at baseline, no obesity at baseline, BP $\geq$ 140/90 mmHg at baseline.

These potential values for covariates were included in minimally adjusted, partially adjusted, and fully adjusted models. Not all covariates were included in all models. For example, the minimally adjusted model included age and sex only, so the values of the other covariates were not needed for those models. Two partially adjusted models were run: the first included age, sex, deprivation, and country; the second included the same covariates, with the addition of calendar period and Charlson index. The fully adjusted models included the additional variables of smoking, blood pressure, diabetes mellitus and obesity, where not acting as the mediator.

#### 5.2.1.1.1 Mediation E-values

To test the strong assumption required for mediation analysis that there be no unmeasured confounders acting on the exposure and outcome, (231) the method of Smith and VanderWeele (234) was used to calculate mediational E-values as described by VanderWeele and Ding. (235) The formula used was based on that given by (234):

$$\text{Mediational E-value} = \text{HR}^{\text{obs}} + \sqrt{\text{HR}^{\text{obs}}} \times (\text{HR}^{\text{obs}} - 1)$$

where  $\text{HR}^{\text{obs}}$  replaces the observed risk ratio used by Smith, as the magnitude of the observed HR for the direct or indirect effect. The HR approximates the risk ratio for rare outcomes (<15%). (235) The E-value is the minimum strength of association that would be needed for an unmeasured confounder to have with both the exposure and the outcome to explain away the observed effect. (235) A large value indicates that substantial unmeasured

confounding would be needed to explain away the observed association between exposure and outcome. The formula was also used with the lower limit of the 95% CI for the HR for the observed indirect effect to calculate a lower bound for the strength of association needed to explain away the observed effect.

### **5.2.2 Mediation analysis of all-cause mortality**

Further mediation analyses considered the four potential mediators of current smoking, BP $\geq$ 140/90 mmHg, diabetes mellitus and obesity recorded at baseline and endpoint on the outcome of all-cause mortality. Logistic regression analyses of the effect of SMI on the mediators (path a) and Cox regression analyses of the effect of the mediators (path b), and SMI controlled for the mediators (path c'), on all-cause mortality were performed. In Cox regression the time from start of follow-up to the earliest of date of death, attaining age 75 years, transferring out of the practice or end of patient follow-up was used as the analysis time. Analyses were adjusted by ten-year age group, sex, country, Townsend deprivation quintile, five-year calendar period, Charlson index. Also, by smoking status, blood pressure, diabetes mellitus and obesity, where not included as the mediator.

## **5.3 Results**

### **5.3.1 Cardiovascular incidence**

Table 5.2 shows the results of logistic regression and Cox proportional hazards regression to obtain ORs and HRs for coefficients a, b, and c' in Figure 5.2(i). As previously found in Chapter 4, there is evidence of a direct effect of SMI on CVD incidence (path c'), when adjusted for each of the mediators – smoking, blood pressure  $\geq$ 140/90 mmHg, diabetes mellitus and obesity. There is also evidence of an association between SMI and mediator for smoking, diabetes mellitus and obesity. There is some association between BD and high blood pressure in the minimally and partially adjusted models, but this disappears in the

fully adjusted model (path a). Schizophrenia and high blood pressure appear to be negatively associated. All mediators were associated with CVD incidence (path b).

Table 5.3 to Table 5.6 show the proportions of the association between SMI and CVD incidence that is mediated by smoking, high BP, diabetes mellitus and obesity, respectively, after adjustment for age and sex, fixing the covariates to males aged 55-64 years. For smoking,

Table 5.3 shows the total excess relative risk of BD on CVD was 0.45, 95% CI: 0.37-0.54. This can be decomposed into 63% due to a controlled direct effect and 34% due to a pure indirect effect, mediated through current smoking at baseline. The overall proportion mediated was 32.8% (95% CI: 24.8%-40.7%). The effects due to interaction between BD and smoking were negligible.

For schizophrenia, the total excess risk on CVD was 0.41 (95% CI: 0.35-0.47). The controlled direct effect accounted for 47% and the pure indirect effect accounted for 48% of the total effect. The overall proportion mediated by smoking was 45.5% (95% CI: 37.5%-53.4%).

Regarding blood pressure, the excess risk of CVD incidence was 0.41 (95% CI: 0.33-0.50) due to BD and 0.26 (95% CI: 0.17-0.35) due to schizophrenia (Table 5.4). However, the controlled direct effect accounted for most of the excess risk at 85% and 92% for BD and schizophrenia, respectively. The mediating effects of high blood pressure at baseline were thus trivial: 0.8% (95% CI: 0.1%-1.4%) for BD and -0.4% (95% CI: -0.9%-0.1%) for schizophrenia.

The mediating effect of diabetes mellitus at baseline was moderate, at 10.9% (95% CI: 5.9%-15.8) and 18.4% (95% CI: 13.7%-23.0%) for BD and schizophrenia, respectively (Table 5.5).

However, the mediating effect of obesity was smaller, accounting for 8.1% (95% CI: 3.2%-12.9%) of the total excess risk of BD on CVD incidence and 6.8% (95% CI: 3.3%-10.3%) of the excess risk of schizophrenia on CVD (Table 5.6).

When deprivation and country were added as covariates, the mediating effects due to smoking, blood pressure, diabetes mellitus and obesity at baseline were similar to the models adjusted for age and sex only (

Table 5.7 to Table 5.10). Mediation due to smoking accounted for 31.7% (95% CI: 22.9%-40.5%) of the effect of BD on CVD and 50.3% (95% CI: 39.1%-61.4%) of the effect of schizophrenia on CVD.

In the fully adjusted models, (Table 5.11 to Table 5.14) the mediating effects of smoking and diabetes mellitus became somewhat stronger. The effect of smoking increased to 34.5% (95% CI: 25.8%-43.2%) for BD and 53.5% (95% CI: 43.2%-63.9%) for schizophrenia (

Table 5.11) and for diabetes mellitus increased to 13.8% (95% CI: 7.0%-20.5%) for BD and 35.1% (95% CI: 25.0%-45.2%) for schizophrenia (Table 5.13). However, the mediating effects of blood pressure and obesity were non-significant or negligible (Table 5.12, Table 5.14).



**Table 5.2: Mediation analysis of SMI on CVD incidence, mediated by smoking, high blood pressure, diabetes mellitus, obesity**

| Potential mediator (binary variable) | SMI | Effect of SMI on mediator (path a) <sup>1</sup> |        |      |      | Effect of mediator on CVD (path b) <sup>2</sup> |        |      |      | Effect of SMI on CVD, controlled for mediator (path c') <sup>2</sup> |        |      |      |
|--------------------------------------|-----|-------------------------------------------------|--------|------|------|-------------------------------------------------|--------|------|------|----------------------------------------------------------------------|--------|------|------|
|                                      |     | OR                                              | p      | lcl  | ucl  | HR                                              | p      | lcl  | ucl  | HR                                                                   | p      | lcl  | ucl  |
| Minimally adjusted <sup>3</sup>      |     |                                                 |        |      |      |                                                 |        |      |      |                                                                      |        |      |      |
| Smoking                              | BD  | 2.51                                            | <0.001 | 2.46 | 2.56 | 1.94                                            | <0.001 | 1.91 | 1.96 | 1.38                                                                 | <0.001 | 1.27 | 1.49 |
|                                      | SCZ | 3.24                                            | <0.001 | 3.19 | 3.29 | 1.91                                            | <0.001 | 1.89 | 1.93 | 1.28                                                                 | <0.001 | 1.20 | 1.36 |
| BP                                   | BD  | 1.04                                            | 0.003  | 1.01 | 1.07 | 1.49                                            | <0.001 | 1.47 | 1.51 | 1.55                                                                 | <0.001 | 1.44 | 1.67 |
|                                      | SCZ | 0.98                                            | 0.120  | 0.96 | 1.00 | 1.49                                            | <0.001 | 1.47 | 1.51 | 1.45                                                                 | <0.001 | 1.38 | 1.53 |
| Diabetes mellitus                    | BD  | 2.06                                            | <0.001 | 1.98 | 2.16 | 2.17                                            | <0.001 | 2.12 | 2.21 | 1.43                                                                 | <0.001 | 1.35 | 1.52 |
|                                      | SCZ | 2.20                                            | <0.001 | 2.13 | 2.27 | 2.16                                            | <0.001 | 2.12 | 2.21 | 1.34                                                                 | <0.001 | 1.27 | 1.40 |
| Obesity                              | BD  | 1.82                                            | <0.001 | 1.78 | 1.87 | 1.39                                            | <0.001 | 1.37 | 1.41 | 1.43                                                                 | <0.001 | 1.34 | 1.53 |
|                                      | SCZ | 1.66                                            | <0.001 | 1.63 | 1.70 | 1.37                                            | <0.001 | 1.35 | 1.40 | 1.37                                                                 | <0.001 | 1.31 | 1.44 |
| Partially adjusted <sup>4</sup>      |     |                                                 |        |      |      |                                                 |        |      |      |                                                                      |        |      |      |
| Smoking                              | BD  | 2.36                                            | <0.001 | 2.31 | 2.41 | 1.84                                            | <0.001 | 1.82 | 1.87 | 1.33                                                                 | <0.001 | 1.23 | 1.44 |
|                                      | SCZ | 2.87                                            | <0.001 | 2.83 | 2.92 | 1.81                                            | <0.001 | 1.79 | 1.84 | 1.19                                                                 | <0.001 | 1.12 | 1.27 |
| BP                                   | BD  | 1.04                                            | 0.003  | 1.01 | 1.07 | 1.49                                            | <0.001 | 1.47 | 1.51 | 1.46                                                                 | <0.001 | 1.36 | 1.57 |
|                                      | SCZ | 0.98                                            | 0.059  | 0.96 | 1.00 | 1.49                                            | <0.001 | 1.47 | 1.51 | 1.31                                                                 | <0.001 | 1.24 | 1.38 |
| Diabetes mellitus                    | BD  | 1.99                                            | <0.001 | 1.90 | 2.08 | 2.10                                            | <0.001 | 2.05 | 2.14 | 1.36                                                                 | <0.001 | 1.28 | 1.45 |
|                                      | SCZ | 2.05                                            | <0.001 | 1.98 | 2.11 | 2.10                                            | <0.001 | 2.05 | 2.14 | 1.21                                                                 | <0.001 | 1.15 | 1.26 |
| Obesity                              | BD  | 1.75                                            | <0.001 | 1.71 | 1.79 | 1.35                                            | <0.001 | 1.33 | 1.37 | 1.36                                                                 | <0.001 | 1.27 | 1.45 |
|                                      | SCZ | 1.55                                            | <0.001 | 1.53 | 1.59 | 1.33                                            | <0.001 | 1.31 | 1.35 | 1.24                                                                 | <0.001 | 1.18 | 1.30 |
| Fully adjusted                       |     |                                                 |        |      |      |                                                 |        |      |      |                                                                      |        |      |      |
| Smoking <sup>5</sup>                 | BD  | 2.22                                            | <0.001 | 2.17 | 2.27 | 1.86                                            | <0.001 | 1.83 | 1.88 | 1.31                                                                 | <0.001 | 1.20 | 1.41 |
|                                      | SCZ | 2.80                                            | <0.001 | 2.75 | 2.84 | 1.83                                            | <0.001 | 1.80 | 1.85 | 1.18                                                                 | <0.001 | 1.11 | 1.26 |
| BP <sup>6</sup>                      | BD  | 1.00                                            | 0.77   | 0.97 | 1.02 | 1.41                                            | <0.001 | 1.39 | 1.43 | 1.30                                                                 | <0.001 | 1.20 | 1.40 |
|                                      | SCZ | 0.95                                            | <0.001 | 0.93 | 0.97 | 1.41                                            | <0.001 | 1.39 | 1.43 | 1.16                                                                 | <0.001 | 1.10 | 1.23 |
| Diabetes mellitus <sup>7</sup>       | BD  | 1.59                                            | <0.001 | 1.52 | 1.67 | 1.97                                            | <0.001 | 1.93 | 2.02 | 1.26                                                                 | <0.001 | 1.18 | 1.34 |
|                                      | SCZ | 1.79                                            | <0.001 | 1.73 | 1.85 | 1.98                                            | <0.001 | 1.94 | 2.02 | 1.13                                                                 | <0.001 | 1.08 | 1.19 |
| Obesity <sup>8</sup>                 | BD  | 1.48                                            | <0.001 | 1.44 | 1.52 | 1.21                                            | <0.001 | 1.19 | 1.22 | 1.24                                                                 | <0.001 | 1.16 | 1.33 |
|                                      | SCZ | 1.40                                            | <0.001 | 1.37 | 1.43 | 1.19                                            | <0.001 | 1.17 | 1.21 | 1.15                                                                 | <0.001 | 1.09 | 1.21 |

SMI – severe mental illness, CVD – cardiovascular disease, BD – bipolar disorder, SCZ – schizophrenia, OR – odds ratio, HR – hazard ratio, lcl – lower 95% confidence limit, ucl – upper 95% confidence limit, BP – blood pressure  $\geq 140/90$  mmHg. <sup>1</sup> Logistic regression, <sup>2</sup> Cox proportional hazards regression, <sup>3</sup> adjusted for age and sex, <sup>4</sup> adjusted for age, sex, deprivation, country, <sup>5</sup> adjusted for age, sex, deprivation, country, BP, diabetes mellitus, obesity, <sup>6</sup> adjusted for age, sex, deprivation, country, smoking, diabetes mellitus, obesity, <sup>7</sup> adjusted for age, sex, deprivation, country, smoking, BP, obesity, <sup>8</sup> adjusted for age, sex, deprivation, country, smoking, BP, diabetes mellitus. Diabetes mellitus includes type 1, non-type 1, and diabetes mellitus prescription (excluding patients prescribed metformin with a prior diagnosis of polycystic ovary syndrome).

**Table 5.3: Decomposition of the total effect of SMI on CVD incidence due to mediation and interaction with smoking, minimally adjusted models, males, ages 55-64 years**

| Component                   | Bipolar disorder     |        |       |      |                         |        |       |       | Schizophrenia        |        |       |      |                         |        |       |       |
|-----------------------------|----------------------|--------|-------|------|-------------------------|--------|-------|-------|----------------------|--------|-------|------|-------------------------|--------|-------|-------|
|                             | Excess relative risk | p      | lcl   | ucl  | Proportion attributable | p      | lcl   | ucl   | Excess relative risk | p      | lcl   | ucl  | Proportion attributable | p      | lcl   | ucl   |
| CDE                         | 0.29                 | <0.001 | 0.13  | 0.44 | 63%                     | <0.001 | 37%   | 90%   | 0.19                 | <0.001 | 0.09  | 0.30 | 47%                     | <0.001 | 36%   | 68%   |
| INT <sub>ref</sub>          | 0.02                 | 0.801  | -0.12 | 0.16 | 4%                      | 0.803  | -27%  | 35%   | 0.03                 | 0.540  | -0.07 | 0.13 | 7%                      | 0.548  | -17%  | 32%   |
| INT <sub>med</sub>          | -0.005               | 0.801  | -0.04 | 0.03 | -1%                     | 0.803  | -9%   | 7%    | -0.01                | 0.540  | -0.02 | 0.02 | -3%                     | 0.548  | -11%  | 6%    |
| PIE                         | 0.15                 | <0.001 | 0.15  | 0.16 | 34%                     | <0.001 | 27%   | 40%   | 0.20                 | <0.001 | 0.19  | 0.20 | 48%                     | <0.001 | 41%   | 55%   |
| Total                       | 0.45                 | <0.001 | 0.37  | 0.54 | 100%                    |        |       |       | 0.41                 | <0.001 | 0.35  | 0.47 | 100%                    |        |       |       |
| Overall proportion mediated |                      |        |       |      | 32.8%                   | <0.001 | 24.8% | 40.7% |                      |        |       |      | 45.5%                   | <0.001 | 37.5% | 53.4% |

Adjusted by age and sex only. lcl – lower 95% confidence limit, ucl – upper 95% confidence limit, CDE – controlled direct effect, INT<sub>ref</sub> - reference interaction, INT<sub>med</sub> - mediated interaction, PIE - pure indirect effect

**Table 5.4: Decomposition of the total effect of SMI on CVD incidence due to mediation and interaction with blood pressure  $\geq 140/90$  mmHg, minimally adjusted models, males, ages 55-64 years**

| Component                   | Bipolar disorder     |        |        |        |                         |        |      |      | Schizophrenia        |        |         |        |                         |        |       |      |
|-----------------------------|----------------------|--------|--------|--------|-------------------------|--------|------|------|----------------------|--------|---------|--------|-------------------------|--------|-------|------|
|                             | Excess relative risk | p      | lcl    | ucl    | Proportion attributable | p      | lcl  | ucl  | Excess relative risk | p      | lcl     | ucl    | Proportion attributable | p      | lcl   | ucl  |
| CDE                         | 0.35                 | <0.001 | 0.20   | 0.50   | 85%                     | <0.001 | 60%  | 110% | 0.32                 | <0.001 | 0.21    | 0.43   | 92%                     | <0.001 | 70%   | 113% |
| INT <sub>ref</sub>          | 0.06                 | 0.248  | -0.04  | 0.16   | 14%                     | 0.270  | -11% | 40%  | 0.03                 | 0.416  | -0.04   | 0.10   | 9%                      | 0.429  | -13%  | 31%  |
| INT <sub>med</sub>          | -0.001               | 0.282  | -0.003 | 0.0009 | -0.2%                   | 0.301  | -1%  | 0.2% | 0.0002               | 0.471  | -0.0004 | 0.0008 | 0.1%                    | 0.481  | -0.1% | 0.2% |
| PIE                         | 0.002                | 0.003  | 0.001  | 0.007  | 1%                      | 0.004  | 0.3% | 1.7% | -0.002               | 0.120  | -0.004  | 0.0004 | -0.5%                   | 0.125  | -1%   | 1%   |
| Total                       | 0.41                 | <0.001 | 0.33   | 0.50   | 100%                    |        |      |      | 0.26                 | <0.001 | 0.17    | 0.35   | 100%                    |        |       |      |
| Overall proportion mediated |                      |        |        |        | 0.8%                    | 0.022  | 0.1% | 1.4% |                      |        |         |        | -0.4%                   | 0.135  | -0.9% | 0.1% |

Adjusted by age and sex only. lcl – lower 95% confidence limit, ucl – upper 95% confidence limit, CDE – controlled direct effect, INT<sub>ref</sub> - reference interaction, INT<sub>med</sub> - mediated interaction, PIE - pure indirect effect

**Table 5.5: Decomposition of the total effect of SMI on CVD incidence due to mediation and interaction with diabetes mellitus, minimally adjusted models, males, ages 55-64 years**

| Component                   | Bipolar disorder     |        |       |       |                         |        |      |       | Schizophrenia        |        |       |      |                         |        |       |       |
|-----------------------------|----------------------|--------|-------|-------|-------------------------|--------|------|-------|----------------------|--------|-------|------|-------------------------|--------|-------|-------|
|                             | Excess relative risk | p      | lcl   | ucl   | Proportion attributable | p      | lcl  | ucl   | Excess relative risk | p      | lcl   | ucl  | Proportion attributable | p      | lcl   | ucl   |
| CDE                         | 0.07                 | 0.685  | -0.28 | 0.42  | 17%                     | 0.679  | -63% | 97%   | 0.25                 | 0.066  | -0.02 | 0.51 | 66%                     | 0.046  | 1%    | 130%  |
| INT <sub>ref</sub>          | 0.31                 | 0.071  | -0.03 | 0.64  | 72%                     | 0.092  | -12% | 156%  | 0.06                 | 0.637  | -0.19 | 0.31 | 16%                     | 0.642  | -52%  | 84%   |
| INT <sub>med</sub>          | -0.02                | 0.072  | -0.04 | 0.002 | -5%                     | 0.093  | -10% | 1%    | -0.004               | 0.637  | -0.02 | 0.01 | -1%                     | 0.642  | -6%   | 4%    |
| PIE                         | 0.07                 | <0.001 | 0.06  | 0.07  | 16%                     | <0.001 | 12%  | 19%   | 0.07                 | <0.001 | 0.07  | 0.08 | 20%                     | <0.001 | 16%   | 23%   |
| Total                       | 0.43                 | <0.001 | 0.34  | 0.51  | 100%                    |        |      |       | 0.38                 | <0.001 | 0.32  | 0.44 | 100%                    |        |       |       |
| Overall proportion mediated |                      |        |       |       | 10.9%                   | <0.001 | 5.9% | 15.8% |                      |        |       |      | 18.4%                   | <0.001 | 13.7% | 23.0% |

Adjusted by age and sex only. lcl – lower 95% confidence limit, ucl – upper 95% confidence limit, CDE – controlled direct effect, INT<sub>ref</sub> - reference interaction, INT<sub>med</sub> - mediated interaction, PIE - pure indirect effect. Diabetes mellitus includes type 1, non-type 1, and diabetes mellitus prescription (excluding patients prescribed metformin with a prior diagnosis of polycystic ovary syndrome).

**Table 5.6: Decomposition of the total effect of SMI on CVD incidence due to mediation and interaction with obesity, minimally adjusted models, males, ages 55-64 years**

| Component                   | Bipolar disorder     |        |       |      |                         |        |      |       | Schizophrenia        |        |       |       |                         |        |      |       |
|-----------------------------|----------------------|--------|-------|------|-------------------------|--------|------|-------|----------------------|--------|-------|-------|-------------------------|--------|------|-------|
|                             | Excess relative risk | p      | lcl   | ucl  | Proportion attributable | p      | lcl  | ucl   | Excess relative risk | p      | lcl   | ucl   | Proportion attributable | p      | lcl  | ucl   |
| CDE                         | 0.37                 | <0.001 | 0.19  | 0.56 | 86%                     | <0.001 | 52%  | 121%  | 0.29                 | <0.001 | 0.15  | 0.42  | 79%                     | <0.001 | 47%  | 111%  |
| INT <sub>ref</sub>          | 0.02                 | 0.779  | -0.14 | 0.19 | 6%                      | 0.780  | -33% | 45%   | 0.05                 | 0.410  | -0.07 | 0.18  | 15%                     | 0.418  | -21% | 50%   |
| INT <sub>med</sub>          | -0.003               | 0.779  | -0.02 | 0.02 | -0.7%                   | 0.780  | 6%   | 4%    | -0.005               | 0.410  | -0.02 | 0.008 | 2%                      | 0.418  | -5%  | 2%    |
| PIE                         | 0.04                 | <0.001 | 0.04  | 0.04 | 9%                      | <0.001 | 7%   | 11%   | 0.03                 | <0.001 | 0.03  | 0.03  | 8%                      | <0.001 | 7%   | 10%   |
| Total                       | 0.43                 | <0.001 | 0.35  | 0.52 | 100%                    |        |      |       | 0.36                 | <0.001 | 0.30  | 0.42  | 100%                    |        |      |       |
| Overall proportion mediated |                      |        |       |      | 8.1%                    | <0.001 | 3.2% | 12.9% |                      |        |       |       | 6.8%                    | <0.001 | 3.3% | 10.3% |

Adjusted by age and sex only. lcl – lower 95% confidence limit, ucl – upper 95% confidence limit, CDE – controlled direct effect, INT<sub>ref</sub> - reference interaction, INT<sub>med</sub> - mediated interaction, PIE - pure indirect effect

**Table 5.7: Decomposition of the total effect of SMI on CVD incidence due to mediation and interaction with smoking, partially adjusted models, males, ages 55-64 years, median deprivation, England**

| Component                   | Bipolar disorder     |        |       |      |                         |        |       |       | Schizophrenia        |        |       |       |                         |        |       |       |
|-----------------------------|----------------------|--------|-------|------|-------------------------|--------|-------|-------|----------------------|--------|-------|-------|-------------------------|--------|-------|-------|
|                             | Excess relative risk | p      | lcl   | ucl  | Proportion attributable | p      | lcl   | ucl   | Excess relative risk | p      | lcl   | ucl   | Proportion attributable | p      | lcl   | ucl   |
| CDE                         | 0.21                 | 0.005  | 0.06  | 0.35 | 55%                     | <0.001 | 25%   | 86%   | 0.07                 | 0.154  | -0.03 | 0.17  | 25%                     | 0.106  | -5%   | 56%   |
| INT <sub>ref</sub>          | 0.05                 | 0.457  | -0.08 | 0.18 | 13%                     | 0.471  | -22%  | 48%   | 0.07                 | 0.128  | -0.02 | 0.15  | 24%                     | 0.155  | -9%   | 58%   |
| INT <sub>med</sub>          | -0.01                | 0.457  | -0.04 | 0.02 | -3%                     | 0.471  | -12%  | 6%    | -0.02                | 0.128  | -0.05 | 0.006 | -8%                     | 0.155  | -18%  | 3%    |
| PIE                         | 0.13                 | <0.001 | 0.13  | 0.14 | 35%                     | <0.001 | 27%   | 42%   | 0.16                 | <0.001 | 0.16  | 0.17  | 58%                     | <0.001 | 46%   | 70%   |
| Total                       | 0.38                 | <0.001 | 0.30  | 0.46 | 100%                    |        |       |       | 0.28                 | <0.001 | 0.22  | 0.33  | 100%                    |        |       |       |
| Overall proportion mediated |                      |        |       |      | 31.7%                   | <0.001 | 22.9% | 40.5% |                      |        |       |       | 50.3%                   | <0.001 | 39.1% | 61.4% |

Adjusted by age and sex only. lcl – lower 95% confidence limit, ucl – upper 95% confidence limit, CDE – controlled direct effect, INT<sub>ref</sub> - reference interaction, INT<sub>med</sub> - mediated interaction, PIE - pure indirect effect

**Table 5.8: Decomposition of the total effect of SMI on CVD incidence due to mediation and interaction with blood pressure ≥140/90 mmHg, partially adjusted models, males, ages 55-64 years, median deprivation, England**

| Component                   | Bipolar disorder     |        |        |        |                         |        |       |      | Schizophrenia        |        |         |        |                         |        |       |       |
|-----------------------------|----------------------|--------|--------|--------|-------------------------|--------|-------|------|----------------------|--------|---------|--------|-------------------------|--------|-------|-------|
|                             | Excess relative risk | p      | lcl    | ucl    | Proportion attributable | p      | lcl   | ucl  | Excess relative risk | p      | lcl     | ucl    | Proportion attributable | p      | lcl   | ucl   |
| CDE                         | 0.27                 | <0.001 | 0.13   | 0.41   | 81%                     | <0.001 | 52%   | 110% | 0.18                 | 0.001  | 0.07    | 0.28   | 81%                     | <0.001 | 49%   | 114%  |
| INT <sub>ref</sub>          | 0.06                 | 0.198  | -0.03  | 0.15   | 18%                     | 0.227  | -11%  | 48%  | 0.04                 | 0.210  | -0.02   | 0.11   | 19%                     | 0.245  | -13%  | 52%   |
| INT <sub>med</sub>          | -0.001               | 0.238  | -0.003 | 0.0008 | -0.3%                   | 0.263  | -0.9% | 0.2% | 0.0004               | 0.296  | -0.0003 | 0.001  | 0.1%                    | 0.323  | -0.2% | 0.5%  |
| PIE                         | 0.004                | 0.003  | 0.001  | 0.007  | 1%                      | 0.005  | 0.4%  | 2%   | -0.002               | 0.059  | -0.004  | 0.0001 | -0.9%                   | 0.069  | -1.9% | 0.07% |
| Total                       | 0.33                 | <0.001 | 0.25   | 0.41   | 100%                    |        |       |      | 0.22                 | <0.001 | 0.16    | 0.27   | 100%                    |        |       |       |
| Overall proportion mediated |                      |        |        |        | 0.9%                    | 0.020  | 0.1%  | 1.7% |                      |        |         |        | -0.7%                   | 0.075  | -1.6% | 0.07% |

Adjusted by age and sex only. lcl – lower 95% confidence limit, ucl – upper 95% confidence limit, CDE – controlled direct effect, INT<sub>ref</sub> - reference interaction, INT<sub>med</sub> - mediated interaction, PIE - pure indirect effect

**Table 5.9: Decomposition of the total effect of SMI on CVD incidence due to mediation and interaction with diabetes mellitus, partially adjusted models, males, ages 55-64 years, median deprivation, England**

| Component                   | Bipolar disorder     |        |       |        |                         |        |       |       | Schizophrenia        |        |       |       |                         |        |       |       |
|-----------------------------|----------------------|--------|-------|--------|-------------------------|--------|-------|-------|----------------------|--------|-------|-------|-------------------------|--------|-------|-------|
|                             | Excess relative risk | p      | lcl   | ucl    | Proportion attributable | p      | lcl   | ucl   | Excess relative risk | p      | lcl   | ucl   | Proportion attributable | p      | lcl   | ucl   |
| CDE                         | -0.03                | 0.861  | -0.35 | 0.29   | -8%                     | 0.863  | -102% | 85%   | 0.09                 | 0.442  | -0.15 | 0.33  | 39%                     | 0.421  | -56%  | 134%  |
| INT <sub>ref</sub>          | 0.34                 | 0.032  | 0.03  | 0.65   | 98%                     | 0.050  | -0.1% | 195%  | 0.09                 | 0.431  | -0.14 | 0.32  | 38%                     | 0.447  | -60%  | 137%  |
| INT <sub>med</sub>          | -0.02                | 0.033  | -0.04 | -0.002 | -6%                     | 0.051  | -12%  | 0.02% | -0.006               | 0.431  | -0.02 | 0.009 | -2%                     | 0.447  | -9%   | 4%    |
| PIE                         | 0.06                 | <0.001 | 0.05  | 0.06   | -17%                    | <0.001 | 13%   | 21%   | 0.06                 | <0.001 | 0.06  | 0.06  | 25%                     | <0.001 | 19%   | 31%   |
| Total                       | 0.35                 | <0.001 | 0.27  | 0.43   | 100%                    |        |       |       | 0.24                 | <0.001 | 0.19  | 0.30  | 100%                    |        |       |       |
| Overall proportion mediated |                      |        |       |        | 10.7%                   | <0.001 | 5.5%  | 16.1% |                      |        |       |       | 22.7%                   | <0.001 | 16.2% | 29.2% |

Adjusted by age and sex only. lcl – lower 95% confidence limit, ucl – upper 95% confidence limit, CDE – controlled direct effect, INT<sub>ref</sub> - reference interaction, INT<sub>med</sub> - mediated interaction, PIE - pure indirect effect. Diabetes mellitus includes type 1, non-type 1, and diabetes mellitus prescription (excluding patients prescribed metformin with a prior diagnosis of polycystic ovary syndrome).

**Table 5.10: Decomposition of the total effect of SMI on CVD incidence due to mediation and interaction with obesity, partially adjusted models, males, ages 55-64 years, median deprivation, England**

| Component                   | Bipolar disorder     |        |       |      |                         |        |      |       | Schizophrenia        |        |       |       |                         |        |      |       |
|-----------------------------|----------------------|--------|-------|------|-------------------------|--------|------|-------|----------------------|--------|-------|-------|-------------------------|--------|------|-------|
|                             | Excess relative risk | p      | lcl   | ucl  | Proportion attributable | p      | lcl  | ucl   | Excess relative risk | p      | lcl   | ucl   | Proportion attributable | p      | lcl  | ucl   |
| CDE                         | 0.30                 | 0.001  | 0.13  | 0.47 | 84%                     | <0.001 | 44%  | 124%  | 0.15                 | 0.019  | 0.02  | 0.27  | 65%                     | 0.007  | 18%  | 111%  |
| INT <sub>ref</sub>          | 0.03                 | 0.716  | -0.13 | 0.19 | 8%                      | 0.718  | -37% | 53%   | 0.06                 | 0.265  | -0.05 | 0.18  | 28%                     | 0.279  | -23% | 78%   |
| INT <sub>med</sub>          | -0.003               | 0.716  | -0.02 | 0.01 | -0.9%                   | 0.718  | -6%  | 4%    | -0.006               | 0.265  | -0.02 | 0.004 | -2%                     | 0.279  | -7%  | 2%    |
| PIE                         | 0.03                 | <0.001 | 0.03  | 0.03 | 9%                      | <0.001 | 7%   | 11%   | 0.02                 | <0.001 | 0.02  | 0.02  | 10%                     | <0.001 | 7%   | 12%   |
| Total                       | 0.36                 | <0.001 | 0.28  | 0.44 | 100%                    |        |      |       | 0.23                 | <0.001 | 0.18  | 0.28  | 100%                    |        |      |       |
| Overall proportion mediated |                      |        |       |      | 7.7%                    | 0.003  | 2.6% | 12.9% |                      |        |       |       | 7.5%                    | 0.001  | 3.1% | 11.8% |

Adjusted by age and sex only. lcl – lower 95% confidence limit, ucl – upper 95% confidence limit, CDE – controlled direct effect, INT<sub>ref</sub> - reference interaction, INT<sub>med</sub> - mediated interaction, PIE - pure indirect effect

**Table 5.11: Decomposition of the total effect of SMI on CVD incidence due to mediation and interaction with smoking, fully adjusted models, males, ages 55-64 years, median deprivation, England, Charlson index 1, 2015-19, no diabetes mellitus, BP<140/90 mmHg, no obesity**

| Component                   | Bipolar disorder     |        |       |      |                         |        |       |       | Schizophrenia        |        |        |      |                         |        |       |       |
|-----------------------------|----------------------|--------|-------|------|-------------------------|--------|-------|-------|----------------------|--------|--------|------|-------------------------|--------|-------|-------|
|                             | Excess relative risk | p      | lcl   | ucl  | Proportion attributable | p      | lcl   | ucl   | Excess relative risk | p      | lcl    | ucl  | Proportion attributable | p      | lcl   | ucl   |
| CDE                         | 0.19                 | 0.007  | 0.05  | 0.33 | 55%                     | <0.001 | 25%   | 85%   | 0.09                 | 0.055  | -0.002 | 0.19 | 33%                     | 0.019  | 5%    | 61%   |
| INT <sub>ref</sub>          | 0.03                 | 0.538  | -0.08 | 0.15 | 10%                     | 0.553  | -23%  | 44%   | 0.04                 | 0.350  | -0.04  | 0.11 | 13%                     | 0.376  | -16%  | 42%   |
| INT <sub>med</sub>          | -0.01                | 0.538  | -0.04 | 0.02 | -3%                     | 0.553  | -12%  | 6%    | -0.01                | 0.350  | -0.04  | 0.01 | -5%                     | 0.376  | -15%  | 6%    |
| PIE                         | 0.13                 | <0.001 | 0.12  | 0.13 | 37%                     | <0.001 | 28%   | 46%   | 0.16                 | <0.001 | 0.16   | 0.17 | 58%                     | <0.001 | 46%   | 71%   |
| Total                       | 0.34                 | <0.001 | 0.26  | 0.42 | 100%                    |        |       |       | 0.28                 | <0.001 | 0.22   | 0.34 | 100%                    |        |       |       |
| Overall proportion mediated |                      |        |       |      | 34.5%                   | <0.001 | 25.8% | 43.2% |                      |        |        |      | 53.5%                   | <0.001 | 43.2% | 63.9% |

Adjusted by age, sex, country, deprivation, calendar period, Charlson index, blood pressure, diabetes mellitus, obesity. lcl – lower 95% confidence limit, ucl – upper 95% confidence limit, CDE – controlled direct effect, INT<sub>ref</sub> - reference interaction, INT<sub>med</sub> - mediated interaction, PIE - pure indirect effect. Diabetes mellitus includes type 1, non-type 1, and diabetes mellitus prescription (excluding patients prescribed metformin with a prior diagnosis of polycystic ovary syndrome).

**Table 5.12: Decomposition of the total effect of SMI on CVD incidence due to mediation and interaction with blood pressure ≥140/90 mmHg, fully adjusted models, males, ages 55-64 years, median deprivation, England, Charlson index 1, 2015-19, ex-smoker, no diabetes mellitus, no obesity**

| Component                   | Bipolar disorder     |        |         |       |                         |       |       |      | Schizophrenia        |        |         |        |                         |       |       |       |
|-----------------------------|----------------------|--------|---------|-------|-------------------------|-------|-------|------|----------------------|--------|---------|--------|-------------------------|-------|-------|-------|
|                             | Excess relative risk | p      | lcl     | ucl   | Proportion attributable | p     | lcl   | ucl  | Excess relative risk | p      | lcl     | ucl    | Proportion attributable | p     | lcl   | ucl   |
| CDE                         | 0.12                 | 0.067  | -0.01   | 0.25  | 55%                     | 0.033 | 5%    | 106% | 0.06                 | 0.229  | -0.04   | 0.15   | 51%                     | 0.164 | -21%  | 124%  |
| INT <sub>ref</sub>          | 0.10                 | 0.069  | -0.007  | 0.20  | 44%                     | 0.085 | -6%   | 95%  | 0.06                 | 0.128  | -0.02   | 0.13   | 51%                     | 0.165 | -21%  | 123%  |
| INT <sub>med</sub>          | 0.0001               | 0.773  | -0.0008 | 0.001 | 0.06%                   | 0.774 | -0.4% | 0.5% | 0.0009               | 0.151  | -0.0003 | 0.002  | 0.8%                    | 0.187 | -0.4% | 2%    |
| PIE                         | -0.0003              | 0.770  | -0.003  | 0.002 | -0.2%                   | 0.771 | -1.2% | 0.9% | -0.004               | <0.001 | -0.005  | -0.002 | -3%                     | 0.002 | -5%   | -1%   |
| Total                       | 0.22                 | <0.001 | 0.15    | 0.29  | 100%                    |       |       |      | 0.11                 | <0.001 | 0.06    | 0.16   | 100%                    |       |       |       |
| Overall proportion mediated |                      |        |         |       | -0.1%                   | 0.772 | -0.7% | 0.5% |                      |        |         |        | -2.5%                   | 0.006 | -4.2% | -0.7% |

Adjusted by age, sex, country, deprivation, calendar period, Charlson index, smoking, diabetes mellitus, obesity. lcl – lower 95% confidence limit, ucl – upper 95% confidence limit, CDE – controlled direct effect, INT<sub>ref</sub> - reference interaction, INT<sub>med</sub> - mediated interaction, PIE - pure indirect effect. Diabetes mellitus includes type 1, non-type 1, and diabetes mellitus prescription (excluding patients prescribed metformin with a prior diagnosis of polycystic ovary syndrome).

**Table 5.13: Decomposition of the total effect of SMI on CVD incidence due to mediation and interaction with diabetes mellitus, fully adjusted models, males, ages 55-64 years, median deprivation, England, Charlson index 1, 2015-19, ex-smoker, BP<140/90 mmHg, no obesity**

| Component                   | Bipolar disorder     |        |       |        |                         |        |       |       | Schizophrenia        |        |       |      |                         |        |       |       |
|-----------------------------|----------------------|--------|-------|--------|-------------------------|--------|-------|-------|----------------------|--------|-------|------|-------------------------|--------|-------|-------|
|                             | Excess relative risk | p      | lcl   | ucl    | Proportion attributable | p      | lcl   | ucl   | Excess relative risk | p      | lcl   | ucl  | Proportion attributable | p      | lcl   | ucl   |
| CDE                         | -0.09                | 0.554  | -0.37 | 0.20   | -38%                    | 0.579  | -171% | 95%   | 0.06                 | 0.579  | -0.15 | 0.28 | 35%                     | 0.553  | -81%  | 151%  |
| INT <sub>ref</sub>          | 0.28                 | 0.033  | 0.02  | 0.54   | 124%                    | 0.076  | -13%  | 261%  | 0.05                 | 0.605  | -0.14 | 0.25 | 30%                     | 0.622  | -88%  | 148%  |
| INT <sub>med</sub>          | -0.02                | 0.034  | -0.03 | -0.001 | -8%                     | 0.077  | -17%  | 0.8%  | -0.004               | 0.605  | -0.02 | 0.01 | -2%                     | 0.622  | -12%  | 7%    |
| PIE                         | 0.05                 | <0.001 | 0.04  | 0.06   | 22%                     | <0.001 | 14%   | 29%   | 0.07                 | <0.001 | 0.06  | 0.07 | 38%                     | <0.001 | 25%   | 50%   |
| Total                       | 0.23                 | <0.001 | 0.15  | 0.30   | 100%                    |        |       |       | 0.17                 | <0.001 | 0.12  | 0.23 | 100%                    |        |       |       |
| Overall proportion mediated |                      |        |       |        | 13.8%                   | <0.001 | 7.0%  | 20.5% |                      |        |       |      | 35.1%                   | <0.001 | 25.0% | 45.2% |

Adjusted by age, sex, country, deprivation, calendar period, Charlson index, smoking, blood pressure, obesity. lcl – lower 95% confidence limit, ucl – upper 95% confidence limit, CDE – controlled direct effect, INT<sub>ref</sub> - reference interaction, INT<sub>med</sub> - mediated interaction, PIE - pure indirect effect. Diabetes mellitus includes type 1, non-type 1, and diabetes mellitus prescription (excluding patients prescribed metformin with a prior diagnosis of polycystic ovary syndrome)

**Table 5.14: Decomposition of the total effect of SMI on CVD incidence due to mediation and interaction with obesity, fully adjusted models, males, ages 55-64 years, median deprivation, England, Charlson index 1, 2015-19, ex-smoker, no diabetes mellitus, BP<140/90 mmHg**

| Component                   | Bipolar disorder     |        |       |       |                         |        |       |       | Schizophrenia        |        |        |       |                         |        |       |       |
|-----------------------------|----------------------|--------|-------|-------|-------------------------|--------|-------|-------|----------------------|--------|--------|-------|-------------------------|--------|-------|-------|
|                             | Excess relative risk | p      | lcl   | ucl   | Proportion attributable | p      | lcl   | ucl   | Excess relative risk | p      | lcl    | ucl   | Proportion attributable | p      | lcl   | ucl   |
| CDE                         | 0.16                 | 0.027  | 0.02  | 0.30  | 73%                     | 0.005  | 22%   | 124%  | 0.04                 | 0.476  | -0.07  | 0.14  | 31%                     | 0.430  | -47%  | 109%  |
| INT <sub>ref</sub>          | 0.05                 | 0.411  | -0.07 | 0.17  | 23%                     | 0.431  | -34%  | 79%   | 0.08                 | 0.081  | -0.009 | 0.16  | 64%                     | 0.132  | -19%  | 147%  |
| INT <sub>med</sub>          | -0.006               | 0.412  | -0.02 | 0.008 | -3%                     | 0.431  | -9%   | 4%    | -0.007               | 0.081  | -0.02  | 0.001 | -6%                     | 0.132  | -14%  | 2%    |
| PIE                         | 0.02                 | <0.001 | 0.01  | 0.02  | 7%                      | <0.001 | 5%    | 10%   | 0.01                 | <0.001 | 0.01   | 0.01  | 11%                     | <0.001 | 6%    | 15%   |
| Total                       | 0.22                 | <0.001 | 0.15  | 0.29  | 100%                    |        |       |       | 0.12                 | <0.001 | 0.07   | 0.17  | 100%                    |        |       |       |
| Overall proportion mediated |                      |        |       |       | 4.7%                    | 0.117  | -1.2% | 10.6% |                      |        |        |       | 4.6%                    | 0.170  | -2.0% | 11.1% |

Adjusted by age, sex, country, deprivation, calendar period, Charlson index, smoking, blood pressure, diabetes mellitus. lcl – lower 95% confidence limit, ucl – upper 95% confidence limit, CDE – controlled direct effect, INT<sub>ref</sub> - reference interaction, INT<sub>med</sub> - mediated interaction, PIE - pure indirect effect. Diabetes mellitus includes type 1, non-type 1, and diabetes mellitus prescription (excluding patients prescribed metformin with a prior diagnosis of polycystic ovary syndrome)

### 5.3.1.1 Results of sensitivity analyses

#### 5.3.1.1.1 Mediators restricted to within three years/one year of baseline

Restricting positive values of mediators to status recorded within three years of baseline made only small differences to the results. Restricting to measurements within one year reduced the percentage mediated by smoking to 28.6% (95% CI: 20.9%-36.3%) for BD and for schizophrenia to 40.7% (95% CI: 31.1%-50.3%). Results for the other mediators of blood pressure and obesity were largely unchanged.

#### 5.3.1.1.2 Smoker defined as current or ex-smoker

However, in the sensitivity analysis in which the definition of smoker as a mediator was changed to current and ex-smoker vs never smoked and unknown smoking status, the proportion mediated was reduced compared with results where smoker was defined as current smoker only (Table 5.15). The mediating effect of current or ex-smoker reduced to 19.2% of the total effect (95% CI 14.2%-24.2%) for BD and 29.7% (95% CI: 23.9%-35.6%) for schizophrenia. Thus, a record of current smoking is a more important mediator of CVD diagnosis than being an ex-smoker.

#### 5.3.1.1.3 Effect of deprivation as a mediator

In a fully adjusted mediation analysis with covariate values set to the values previously described (section 5.2.1), the most deprived Townsend quintile was found to mediate 0.8% (95% CI: -0.5% to 2.0%) and 1.3% (95% CI: -1.4% to 3.9%) of the effect of BD and schizophrenia, respectively, on CVD incidence.



#### 5.3.1.1.1.4 Use of last recorded values for mediators

In the sensitivity analysis that used the last recorded values for the four mediators, instead of the baseline values, the percentages mediated by current smoking at endpoint were higher than the percentages mediated by current smoking at baseline for both BD and schizophrenia. Table 5.16 shows a comparison of the status of the mediators at baseline and at endpoint. The endpoint was the earliest of date of CVD diagnosis, date of first or subsequent SMI or end of follow-up. The percentage of records with missing smoking status, BMI and BP decreased substantially between baseline and endpoint. The percentage of current smokers was broadly similar between the two time points and the percentage with  $BP \geq 140/90$  mmHg increased slightly, whereas the percentage with diabetes mellitus doubled and the percentage with obesity increased by around 40% for those with SMI and by around 50% for those without SMI.

Table 5.17 shows the results of mediation analysis on CVD incidence with the last recorded values for the four potential mediators. Compared with the analysis that used baseline values, the effect of SMI on CVD, controlled for each of the mediators (path  $c'$ ) was broadly similar. There were some differences in the effects of SMI on the mediators (path  $a$ ). The odds of having SMI were higher for patients recorded as current smokers at endpoint compared with baseline (BD: OR=2.34, 95% CI: 2.29-2.39 vs OR=2.22, 95% CI: 2.17-2.27); schizophrenia: OR=3.03, 95% CI: 2.98-3.07 vs OR=2.80, 95% CI: 2.75-2.84). Also, there were slightly lower odds of having schizophrenia for people with diabetes mellitus at endpoint compared with baseline (OR=1.67, 95% CI: 1.63-1.71 vs 1.79, 95% CI: 1.73-1.85) but slightly higher odds of schizophrenia for obesity recorded at endpoint compared with baseline (OR=1.49, 95% CI: 1.47-1.52 vs 1.40, 95% CI: 1.37-1.43).

There were also some differences in the effect of mediators recorded at endpoint and baseline on CVD incidence (path b). The HR for current smoking and BP $\geq$ 140/90 mmHg was higher when measured at endpoint than at baseline, whereas the HR for diabetes mellitus at endpoint was lower than at baseline. The effect of obesity on CVD incidence was similar whether recorded at endpoint or baseline.

Using the same values for covariates of males, ages 55-64 years, median deprivation, England, Charlson index 1 and 2015-19, with no diabetes mellitus, BP<140-90mmHg and no obesity recorded at end point, there were some differences in the percentage of the effect of SMI on CVD that was mediated when comparing mediator status recorded at endpoint with status recorded at baseline. A record of current smoking at endpoint mediated 41.1% (95% CI: 32.6%-49.5%) for BD and 59.4% (95% CI: 48.6%-70.4%) for schizophrenia (Table 5.18), whereas the corresponding percentages for current smoking at baseline (Table 5.11) were 34.5% (95% CI: 25.8%-43.2%) and 53.5% (95% CI: 43.2%-63.9%), respectively. The mediating effects of BP recorded at endpoint were negative (Table 5.19). Prevalent diabetes mellitus at endpoint had a mediating effect for schizophrenia, but not BD (Table 5.20): BD: 2% (95% CI: -2% to 7%), schizophrenia: 16.1% (95% CI: 4.8%-27.5%), whereas the mediating effect of obesity at end point, was non-significant for both BD and schizophrenia (Table 5.21).

#### 5.3.1.1.1.5 Selecting different covariate values

The next set of sensitivity analyses explored the effect of fixing the values of the covariates to different levels: “higher risk”, “lower risk” and “median risk”. Table 5.22 to Table 5.25 show the proportion of the total effect mediated by smoking, blood pressure, diabetes

mellitus and obesity, respectively. Smoking mediated 30-35% of the effect of BD on CVD across all the models and for each of the sets of covariates. However, around 50% of the effect of schizophrenia on CVD was mediated by smoking in the fully adjusted model, although the percentage was slightly less in the minimally adjusted model (Table 5.22). Blood pressure did not have a significant mediating effect for BD, once other factors were adjusted for in the fully adjusted model, whereas for schizophrenia  $BP \geq 140/90$  mmHg mediated a slightly negative amount (Table 5.23).

The mediating effect of diabetes mellitus was different depending on the values chosen for the covariates (Table 5.24). Where covariate values were chosen so that the level of CVD risk was relatively high (example (i): males, aged 65-74 years, deprived, current smoker, obesity,  $BP \geq 140/90$  mmHg) the mediating effects of diabetes mellitus were similar to those for smoking for both BD and schizophrenia (percentage mediated: BD: 36.0% (95% CI: 20.3%-51.7%); schizophrenia: 54.9% (95% CI: 37.6%-72.1%)). However, where values of covariates chosen so that CVD risk was relatively lower (example (ii): females, aged 45-54 years, least deprived, no comorbidity, no obesity, non-smoker,  $BP < 140/90$  mmHg) the mediating effect of diabetes mellitus was much lower (percentage mediated: BD: 4.3% (95% CI: 1.7%-6.9%); schizophrenia: 14.3% (95% CI: 8.2%-20.4%)).

The mediating effect of obesity was small (Table 5.25), with wide confidence intervals, once other factors had been adjusted for and only just excluded the null for covariates with high levels of other risk factors (Table 5.25, column (i): “higher risk” covariate values). In the fully adjusted model, the percentages mediated were BD: 5.4% (95% CI: 0.2%-10.6%); schizophrenia: 7.1% (95% CI: 0.06%-14.1%).

Interpretation:

In terms of the excess relative risk mediated by smoking compared with diabetes mellitus, in the higher risk group the excess relative risk for schizophrenia on CVD was 0.28 (*i.e.* HR=1.28) and smoking mediated 51.2% of the effect. Smoking thus mediated 51.2% of  $0.28 = 0.14$ . Diabetes mellitus, however, mediated a smaller amount of the excess relative risk: 54.9% of  $0.17 = 0.09$ . In the lower risk group the excess relative risk mediated by smoking was similar (49.8% of  $0.28 = 0.14$ ), but the excess relative risk mediated by diabetes mellitus was smaller (14.3% of  $0.15 = 0.02$ ).

#### 5.3.1.1.1.6 E-values

The coefficients for the pure indirect effects of BD and schizophrenia on CVD incidence mediated by baseline and endpoint current smoking were baseline: 0.13 and 0.16 (Table 5.11); endpoint: 0.17 and 0.22 (Table 5.18) for BD and schizophrenia, respectively. When converted to HRs the mediational E-values (234) can be calculated as 1.51 and 1.59 for baseline and 1.62 and 1.74 for endpoint values for BD and schizophrenia, respectively. The mediational E-values for the corresponding lower 95% CIs were 1.49, 1.59, 1.59 and 1.74. Thus, an unmeasured confounder associated with both BD and CVD, with HRs > 1.49, would be enough to explain away the observed mediational effect of baseline smoking on BD. Similarly, an unmeasured confounder associated with both schizophrenia and CVD, with HR>1.59, would be enough to explain away the baseline smoking mediational effect on schizophrenia. Unmeasured confounders with HRs of 1.59 and 1.74 would explain away the mediational effect of smoking at endpoint on BD and schizophrenia, respectively.

**Table 5.15: Decomposition of the total effect of SMI on CVD incidence due to mediation and interaction with smoking, fully adjusted models, sensitivity analysis: smoker defined as current/ex-smoker vs never smoked/smoking status unknown, males, ages 55-64 years, median deprivation, England, Charlson index 1, 2015-19, no diabetes mellitus, BP<140/90 mmHg, no obesity**

| Component                   | Bipolar disorder     |        |       |      |                         |        |       |       | Schizophrenia        |        |        |      |                         |        |       |       |
|-----------------------------|----------------------|--------|-------|------|-------------------------|--------|-------|-------|----------------------|--------|--------|------|-------------------------|--------|-------|-------|
|                             | Excess relative risk | p      | lcl   | ucl  | Proportion attributable | p      | lcl   | ucl   | Excess relative risk | p      | lcl    | ucl  | Proportion attributable | p      | lcl   | ucl   |
| CDE                         | 0.25                 | <0.001 | 0.15  | 0.35 | 82%                     | <0.001 | 70%   | 94%   | 0.19                 | <0.001 | 0.12   | 0.26 | 78%                     | <0.001 | 66%   | 89%   |
| INT <sub>ref</sub>          | -0.003               | 0.879  | -0.05 | 0.04 | -1%                     | 0.877  | -15%  | 13%   | -0.02                | 0.261  | -0.05  | 0.01 | -7%                     | 0.220  | -19%  | 4%    |
| INT <sub>med</sub>          | 0.001                | 0.879  | -0.02 | 0.02 | 0.4%                    | 0.877  | -5%   | 6%    | 0.008                | 0.261  | -0.006 | 0.02 | 3%                      | 0.220  | -2%   | 9%    |
| PIE                         | 0.06                 | <0.001 | 0.06  | 0.06 | 19%                     | <0.001 | 14%   | 24%   | 0.07                 | <0.001 | 0.06   | 0.07 | 26%                     | <0.001 | 20%   | 33%   |
| Total                       | 0.31                 | <0.001 | 0.23  | 0.39 | 100%                    |        |       |       | 0.25                 | <0.001 | 0.19   | 0.31 | 100%                    |        |       |       |
| Overall proportion mediated |                      |        |       |      | 19.2%                   | <0.001 | 14.2% | 24.2% |                      |        |        |      | 29.7%                   | <0.001 | 23.9% | 35.6% |

Adjusted by age, sex, country, deprivation, calendar period, Charlson index, blood pressure, diabetes mellitus, obesity. lcl – lower 95% confidence limit, ucl – upper 95% confidence limit, CDE – controlled direct effect, INT<sub>ref</sub> - reference interaction, INT<sub>med</sub> - mediated interaction, PIE - pure indirect effect. Diabetes mellitus includes type 1, non-type 1, and diabetes mellitus prescription (excluding patients prescribed metformin with a prior diagnosis of polycystic ovary syndrome).

**Table 5.16: Baseline and endpoint status of diabetes mellitus, smoking, obesity and blood pressure, patients included in analysis of CVD outcomes**

| Potential mediator                                  | Baseline                      |                                |                                      | Endpoint                      |                                |                                      |
|-----------------------------------------------------|-------------------------------|--------------------------------|--------------------------------------|-------------------------------|--------------------------------|--------------------------------------|
|                                                     | BD <sup>1</sup><br>(n=35,084) | SCZ <sup>1</sup><br>(n=69,124) | No SMI <sup>1</sup><br>(n=8,892,831) | BD <sup>1</sup><br>(n=35,084) | SCZ <sup>1</sup><br>(n=69,124) | No SMI <sup>1</sup><br>(n=8,892,831) |
| Diabetes mellitus, n (%):                           |                               |                                |                                      |                               |                                |                                      |
| Type 1, non-type 1, or DM prescription <sup>2</sup> | 2,244 (6.4)                   | 4,453 (6.4)                    | 234,884 (2.6)                        | 4,403 (12.6)                  | 8,841 (12.8)                   | 540,498 (6.1)                        |
| Smoking status, n (%):                              |                               |                                |                                      |                               |                                |                                      |
| Non-smoker                                          | 10,976 (31.3)                 | 17,634 (25.5)                  | 3,805,632 (42.8)                     | 10,119 (28.8)                 | 16,355 (23.7)                  | 4,058,949 (45.6)                     |
| Ex-smoker                                           | 6,045 (17.2)                  | 8,585 (12.4)                   | 1,137,766 (12.8)                     | 9,365 (26.7)                  | 14,413 (20.9)                  | 2,010,808 (22.6)                     |
| Current smoker                                      | 14,928 (42.6)                 | 34,041 (49.3)                  | 1,957,765 (22.0)                     | 14,737 (42.1)                 | 35,533 (51.4)                  | 2,078,021 (23.4)                     |
| Missing                                             | 3,135 (8.9)                   | 8,864 (12.8)                   | 1,991,668 (22.4)                     | 833 (2.4)                     | 2,823 (4.1)                    | 745,053 (8.4)                        |
| Obesity <sup>3</sup> , n (%):                       |                               |                                |                                      |                               |                                |                                      |
| Has obesity <sup>4</sup>                            | 8,218 (23.4)                  | 14,062 (20.3)                  | 1,068,984 (12.0)                     | 11,016 (31.4)                 | 19,959 (28.9)                  | 1,617,639 (18.2)                     |
| No obesity                                          | 20,000 (57.0)                 | 37,462 (54.2)                  | 4,557,458 (51.3)                     | 20,835 (59.4)                 | 40,089 (58.0)                  | 5,190,023 (58.4)                     |
| Missing                                             | 6,866 (19.6)                  | 17,600 (25.5)                  | 3,266,389 (36.7)                     | 3,233 (9.2)                   | 9,076 (13.1)                   | 2,085,169 (23.5)                     |
| Blood pressure, n (%):                              |                               |                                |                                      |                               |                                |                                      |
| ≥ 140/90 mmHg                                       | 7,133 (20.3)                  | 13,027 (18.9)                  | 1,397,398 (15.7)                     | 7,924 (22.6)                  | 14,949 (21.6)                  | 1,699,957 (19.1)                     |
| <140/90 mmHg                                        | 22,263 (63.5)                 | 41,166 (59.6)                  | 4,569,460 (51.4)                     | 25,277 (72.1)                 | 48,342 (69.9)                  | 5,635,284 (63.4)                     |
| BP missing                                          | 5,688 (16.2)                  | 14,931 (21.6)                  | 2,925,973 (32.9)                     | 1,883 (5.4)                   | 5,833 (8.4)                    | 1,557,590 (17.5)                     |

<sup>1</sup> Patients may have periods of follow-up in more than one category, <sup>2</sup> Diabetes mellitus includes type 1, non-type 1, and diabetes mellitus prescription (excluding patients prescribed metformin with a prior diagnosis of polycystic ovary syndrome), <sup>3</sup> Disregarded if recorded at age<16 years, <sup>4</sup> Defined by BMI or Read code if no BMI at baseline. BD – bipolar disorder, SCZ – schizophrenia, SMI – severe mental illness, DM – diabetes mellitus, BP – blood pressure, mmHg – millimetres of mercury

**Table 5.17: Mediation analysis of SMI on CVD incidence, mediated by last recorded status of smoking, high blood pressure, diabetes mellitus, obesity, fully adjusted models**

| Potential mediator (binary variable) | SMI | Effect of SMI on mediator (path a) <sup>1</sup> |        |      |      | Effect of mediator on CVD (path b) <sup>2</sup> |        |      |      | Effect of SMI on CVD, controlled for mediator (path c') <sup>2</sup> |        |      |      |
|--------------------------------------|-----|-------------------------------------------------|--------|------|------|-------------------------------------------------|--------|------|------|----------------------------------------------------------------------|--------|------|------|
|                                      |     | OR                                              | p      | lcl  | ucl  | HR                                              | p      | lcl  | ucl  | HR                                                                   | p      | lcl  | ucl  |
| Smoking <sup>3</sup>                 | BD  | 2.34                                            | <0.001 | 2.29 | 2.39 | 2.15                                            | <0.001 | 2.12 | 2.18 | 1.30                                                                 | <0.001 | 1.20 | 1.41 |
|                                      | SCZ | 3.03                                            | <0.001 | 2.98 | 3.07 | 2.16                                            | <0.001 | 2.13 | 2.19 | 1.21                                                                 | <0.001 | 1.13 | 1.29 |
| BP <sup>4</sup>                      | BD  | 0.96                                            | 0.001  | 0.93 | 0.98 | 1.74                                            | <0.001 | 1.72 | 1.76 | 1.28                                                                 | <0.001 | 1.19 | 1.38 |
|                                      | SCZ | 0.92                                            | <0.001 | 0.90 | 0.93 | 1.72                                            | <0.001 | 1.70 | 1.74 | 1.17                                                                 | <0.001 | 1.11 | 1.24 |
| Diabetes mellitus <sup>5</sup>       | BD  | 1.51                                            | <0.001 | 1.46 | 1.56 | 1.25                                            | <0.001 | 1.23 | 1.27 | 1.26                                                                 | <0.001 | 1.18 | 1.34 |
|                                      | SCZ | 1.67                                            | <0.001 | 1.63 | 1.71 | 1.26                                            | <0.001 | 1.24 | 1.28 | 1.09                                                                 | <0.001 | 1.04 | 1.15 |
| Obesity <sup>6</sup>                 | BD  | 1.53                                            | <0.001 | 1.50 | 1.57 | 1.16                                            | <0.001 | 1.14 | 1.18 | 1.25                                                                 | <0.001 | 1.17 | 1.35 |
|                                      | SCZ | 1.49                                            | <0.001 | 1.47 | 1.52 | 1.16                                            | <0.001 | 1.14 | 1.17 | 1.10                                                                 | <0.001 | 1.04 | 1.16 |

SMI – severe mental illness, CVD – cardiovascular disease, BD – bipolar disorder, SCZ – schizophrenia, OR – odds ratio, HR – hazard ratio, lcl – lower 95% confidence limit, ucl – upper 95% confidence limit, BP – blood pressure ≥140/90 mmHg. <sup>1</sup> Logistic regression, <sup>2</sup> Cox proportional hazards regression, <sup>3</sup> adjusted for age, sex, deprivation, country, BP, diabetes mellitus, obesity, <sup>4</sup> adjusted for age, sex, deprivation, country, smoking, diabetes mellitus, obesity, <sup>5</sup> adjusted for age, sex, deprivation, country, smoking, BP, obesity, <sup>6</sup> adjusted for age, sex, deprivation, country, smoking, BP, diabetes mellitus. Diabetes mellitus includes type 1, non-type 1, and diabetes mellitus prescription (excluding patients prescribed metformin with a prior diagnosis of polycystic ovary syndrome)

**Table 5.18: Decomposition of the total effect of SMI on CVD incidence due to mediation and interaction with last recorded smoking status, fully adjusted models, males, ages 55-64 years, median deprivation, England, Charlson index 1, 2015-19, no diabetes mellitus, BP<140/90 mmHg, no obesity**

| Component                   | Bipolar disorder     |        |       |      |                         |        |       |       | Schizophrenia        |        |       |       |                         |        |       |       |
|-----------------------------|----------------------|--------|-------|------|-------------------------|--------|-------|-------|----------------------|--------|-------|-------|-------------------------|--------|-------|-------|
|                             | Excess relative risk | p      | lcl   | ucl  | Proportion attributable | p      | lcl   | ucl   | Excess relative risk | p      | lcl   | ucl   | Proportion attributable | p      | lcl   | ucl   |
| CDE                         | 0.25                 | 0.003  | 0.08  | 0.41 | 60%                     | <0.001 | 30%   | 91%   | 0.002                | 0.974  | -0.10 | 0.10  | 0.5%                    | 0.974  | -32%  | 33%   |
| INT <sub>ref</sub>          | -0.005               | 0.938  | -0.14 | 0.13 | -1%                     | 0.938  | -35%  | 32%   | 0.12                 | 0.007  | 0.03  | 0.21  | 40%                     | 0.019  | 7%    | 73%   |
| INT <sub>med</sub>          | 0.001                | 0.938  | -0.03 | 0.03 | 0.3%                    | 0.938  | -8%   | 8%    | -0.04                | 0.007  | -0.07 | -0.01 | -13%                    | 0.019  | -23%  | -2%   |
| PIE                         | 0.17                 | <0.001 | 0.16  | 0.17 | 41%                     | <0.001 | 32%   | 49%   | 0.22                 | <0.001 | 0.22  | 0.23  | 72%                     | <0.001 | 59%   | 86%   |
| Total                       | 0.41                 | <0.001 | 0.33  | 0.49 | 100%                    |        |       |       | 0.31                 | <0.001 | 0.25  | 0.37  | 100%                    |        |       |       |
| Overall proportion mediated |                      |        |       |      | 41.1%                   | <0.001 | 32.6% | 49.5% |                      |        |       |       | 59.5%                   | <0.001 | 48.6% | 70.4% |

Adjusted by age, sex, country, deprivation, calendar period, Charlson index, blood pressure, diabetes mellitus, obesity. lcl – lower 95% confidence limit, ucl – upper 95% confidence limit, CDE – controlled direct effect, INT<sub>ref</sub> - reference interaction, INT<sub>med</sub> - mediated interaction, PIE - pure indirect effect.

**Table 5.19: Decomposition of the total effect of SMI on CVD incidence due to mediation and interaction with last recorded blood pressure  $\geq 140/90$  mmHg, fully adjusted models, males, ages 55-64 years, median deprivation, England, Charlson index 1, 2015-19, ex-smoker, no diabetes mellitus, no obesity**

| Component                   | Bipolar disorder     |        |        |        |                         |        |       |       | Schizophrenia        |        |        |        |                         |       |       |       |
|-----------------------------|----------------------|--------|--------|--------|-------------------------|--------|-------|-------|----------------------|--------|--------|--------|-------------------------|-------|-------|-------|
|                             | Excess relative risk | p      | lcl    | ucl    | Proportion attributable | p      | lcl   | ucl   | Excess relative risk | p      | lcl    | ucl    | Proportion attributable | p     | lcl   | ucl   |
| CDE                         | 0.22                 | 0.003  | 0.08   | 0.37   | 100%                    | <0.001 | 45%   | 154%  | -0.02                | 0.753  | -0.11  | 0.08   | -17%                    | 0.764 | -130% | 96%   |
| INT <sub>ref</sub>          | 0.006                | 0.920  | -0.12  | 0.13   | 3%                      | 0.920  | -51%  | 57%   | 0.11                 | 0.006  | 0.03   | 0.19   | 126%                    | 0.031 | 12%   | 240%  |
| INT <sub>med</sub>          | 0.00007              | 0.920  | -0.001 | 0.002  | 0.03%                   | 0.920  | -0.6% | 0.7%  | 0.003                | 0.008  | 0.0007 | 0.005  | 3%                      | 0.036 | 0.2%  | 5%    |
| PIE                         | -0.005               | 0.001  | -0.009 | -0.002 | -2%                     | 0.005  | -4%   | -0.7% | -0.01                | <0.001 | -0.01  | -0.008 | -12%                    | 0.001 | -18%  | -5%   |
| Total                       | 0.23                 | <0.001 | 0.15   | 0.30   | 100%                    |        |       |       | 0.09                 | <0.001 | 0.04   | 0.14   | 100%                    |       |       |       |
| Overall proportion mediated |                      |        |        |        | -2.3%                   | 0.008  | -4.1% | -0.5% |                      |        |        |        | -8.6%                   | 0.002 | -14%  | -3.2% |

Adjusted by age, sex, country, deprivation, calendar period, Charlson index, smoking, diabetes mellitus, obesity. lcl – lower 95% confidence limit, ucl – upper 95% confidence limit, CDE – controlled direct effect, INT<sub>ref</sub> - reference interaction, INT<sub>med</sub> - mediated interaction, PIE - pure indirect effect

**Table 5.20: Decomposition of the total effect of SMI on CVD incidence due to mediation and interaction with last recorded diabetes mellitus status, fully adjusted models, males, ages 55-64 years, median deprivation, England, Charlson index 1, 2015-19, ex-smoker, BP<140/90 mmHg, no obesity**

| Component                   | Bipolar disorder     |        |       |       |                         |        |      |      | Schizophrenia        |        |       |       |                         |        |      |       |
|-----------------------------|----------------------|--------|-------|-------|-------------------------|--------|------|------|----------------------|--------|-------|-------|-------------------------|--------|------|-------|
|                             | Excess relative risk | p      | lcl   | ucl   | Proportion attributable | p      | lcl  | ucl  | Excess relative risk | p      | lcl   | ucl   | Proportion attributable | p      | lcl  | ucl   |
| CDE                         | 0.10                 | 0.202  | -0.06 | 0.26  | 45%                     | 0.167  | -19% | 108% | 0.06                 | 0.319  | -0.06 | 0.17  | 56%                     | 0.267  | -43% | 155%  |
| INT <sub>ref</sub>          | 0.12                 | 0.112  | -0.03 | 0.28  | 53%                     | 0.124  | -15% | 120% | 0.03                 | 0.598  | -0.08 | 0.13  | 28%                     | 0.606  | -78% | 134%  |
| INT <sub>med</sub>          | -0.009               | 0.113  | -0.02 | 0.002 | -4%                     | 0.125  | -8%  | 1%   | -0.003               | 0.598  | -0.01 | 0.007 | -3%                     | 0.606  | -12% | 7%    |
| PIE                         | 0.01                 | <0.001 | 0.01  | 0.02  | 6%                      | <0.001 | 4%   | 8%   | 0.02                 | <0.001 | 0.02  | 0.02  | 19%                     | <0.001 | 10%  | 28%   |
| Total                       | 0.23                 | <0.001 | 0.16  | 0.30  | 100%                    |        |      |      | 0.10                 | <0.001 | 0.05  | 0.15  | 100%                    |        |      |       |
| Overall proportion mediated |                      |        |       |       | 2%                      | 0.295  | -2%  | 7%   |                      |        |       |       | 16.1%                   | 0.005  | 4.8% | 27.5% |

Adjusted by age, sex, country, deprivation, calendar period, Charlson index, smoking, blood pressure, obesity. lcl – lower 95% confidence limit, ucl – upper 95% confidence limit, CDE – controlled direct effect, INT<sub>ref</sub> - reference interaction, INT<sub>med</sub> - mediated interaction, PIE - pure indirect effect



**Table 5.21: Decomposition of the total effect of SMI on CVD incidence due to mediation and interaction with last recorded obesity status, fully adjusted models, males, ages 55-64 years, median deprivation, England, Charlson index 1, 2015-19, ex-smoker, no diabetes mellitus, BP<140/90 mmHg**

| Component                   | Bipolar disorder     |        |       |       |                         |        |       |      | Schizophrenia        |        |       |       |                         |        |       |       |
|-----------------------------|----------------------|--------|-------|-------|-------------------------|--------|-------|------|----------------------|--------|-------|-------|-------------------------|--------|-------|-------|
|                             | Excess relative risk | p      | lcl   | ucl   | Proportion attributable | p      | lcl   | ucl  | Excess relative risk | p      | lcl   | ucl   | Proportion attributable | p      | lcl   | ucl   |
| CDE                         | 0.15                 | 0.019  | 0.02  | 0.27  | 66%                     | 0.004  | 20%   | 111% | 0.04                 | 0.380  | -0.05 | 0.13  | 44%                     | 0.310  | -41%  | 130%  |
| INT <sub>ref</sub>          | 0.07                 | 0.203  | -0.04 | 0.18  | 32%                     | 0.217  | -19%  | 83%  | 0.04                 | 0.288  | -0.03 | 0.12  | 47%                     | 0.323  | -46%  | 139%  |
| INT <sub>med</sub>          | -0.009               | 0.203  | -0.02 | 0.004 | -4%                     | 0.217  | -10%  | 2%   | -0.005               | 0.289  | -0.01 | 0.004 | -5%                     | 0.323  | -16%  | 5%    |
| PIE                         | 0.01                 | <0.001 | 0.01  | 0.02  | 6%                      | <0.001 | 4%    | 8%   | 0.01                 | <0.001 | 0.01  | 0.01  | 15%                     | <0.001 | 7%    | 23%   |
| Total                       | 0.22                 | <0.001 | 0.15  | 0.29  | 100%                    |        |       |      | 0.09                 | <0.001 | 0.04  | 0.14  | 100%                    |        |       |       |
| Overall proportion mediated |                      |        |       |       | 2.3%                    | 0.467  | -3.8% | 8.3% |                      |        |       |       | 9.2%                    | 0.086  | -1.3% | 19.7% |

Adjusted by age, sex, country, deprivation, calendar period, Charlson index, smoking, blood pressure, diabetes mellitus. lcl – lower 95% confidence limit, ucl – upper 95% confidence limit, CDE – controlled direct effect, INT<sub>ref</sub> - reference interaction, INT<sub>med</sub> - mediated interaction, PIE - pure indirect effect

**Table 5.22 Overall proportion of total effect mediated by current smoking at baseline for minimally, partially and fully adjusted models, for three example sets of covariate values: (i) “higher risk”, (ii) “lower risk”(iii) “median risk”**

| Adjusted by:                                                                                                                 | Covariate values (i) <sup>1</sup> |        |       |       | Covariate values (ii) <sup>2</sup> |        |       |       | Covariate values (iii) <sup>3</sup> |        |       |       |
|------------------------------------------------------------------------------------------------------------------------------|-----------------------------------|--------|-------|-------|------------------------------------|--------|-------|-------|-------------------------------------|--------|-------|-------|
|                                                                                                                              | Overall proportion mediated       | p      | lcl   | ucl   | Overall proportion mediated        | p      | lcl   | ucl   | Overall proportion mediated         | p      | lcl   | ucl   |
| <b>Bipolar disorder</b>                                                                                                      |                                   |        |       |       |                                    |        |       |       |                                     |        |       |       |
| Age and sex (minimally adjusted)                                                                                             | 29.5%                             | <0.001 | 21.5% | 37.5% | 33.2%                              | <0.001 | 25.3% | 41.1% | 32.8%                               | <0.001 | 24.7% | 40.7% |
| Age, sex, deprivation, country (partially adjusted)                                                                          | 32.8%                             | <0.001 | 24.0% | 41.5% | 27.9%                              | <0.001 | 19.1% | 36.6% | 31.8%                               | <0.001 | 22.9% | 40.6% |
| Age, sex, deprivation, country, calendar period, Charlson index (partially adjusted)                                         | 31.0%                             | <0.001 | 22.6% | 39.3% | 26.9%                              | <0.001 | 18.6% | 35.2% | 31.2%                               | <0.001 | 22.8% | 39.5% |
| Age, sex, deprivation, country, calendar period, Charlson index, diabetes mellitus, obesity, blood pressure (fully adjusted) | 32.4%                             | <0.001 | 23.4% | 41.3% | 30.9%                              | <0.001 | 21.9% | 39.9% | 35.0%                               | <0.001 | 26.4% | 43.6% |
| <b>Schizophrenia</b>                                                                                                         |                                   |        |       |       |                                    |        |       |       |                                     |        |       |       |
| Age and sex (minimally adjusted)                                                                                             | 41.9%                             | <0.001 | 33.6% | 50.2% | 45.8%                              | <0.001 | 37.9% | 53.7% | 45.5%                               | <0.001 | 37.5% | 53.5% |
| Age, sex, deprivation, country (partially adjusted)                                                                          | 51.5%                             | <0.001 | 40.5% | 62.5% | 45.6%                              | <0.001 | 34.1% | 57.0% | 50.4%                               | <0.001 | 39.3% | 61.5% |
| Age, sex, deprivation, country, calendar period, Charlson index (partially adjusted)                                         | 47.4%                             | <0.001 | 37.6% | 57.3% | 42.8%                              | <0.001 | 32.6% | 53.1% | 48.0%                               | <0.001 | 38.3% | 57.8% |
| Age, sex, deprivation, country, calendar period, Charlson index, diabetes mellitus, obesity, blood pressure (fully adjusted) | 51.2%                             | <0.001 | 40.4% | 62.0% | 49.8%                              | <0.001 | 38.8% | 60.7% | 54.2%                               | <0.001 | 44.0% | 64.5% |

lcl – lower 95% confidence limit, ucl – upper 95% confidence limit, <sup>1</sup> male, age 65-74 years, most deprived, England, Charlson 1, 2015-19, diabetes mellitus, obese, BP≥140/90 mmHg, <sup>2</sup> female, age 45-54 years, least deprived, Wales, Charlson 0, 2010-14, no diabetes mellitus, no obesity, BP<140/90 mmHg, <sup>3</sup> male, age 55-64 years, median deprivation, Scotland, Charlson 2+, 2005-09, no diabetes mellitus, no obesity, BP≥140/90 mmHg

**Table 5.23 Overall proportion of total effect mediated by blood pressure  $\geq 140/90$  mmHg at baseline for minimally, partially and fully adjusted models, for three example sets of covariate values: (i) “higher risk”, (ii) “lower risk”(iii) “median risk”**

| Adjusted by:                                                                                                          | Covariate values (i) <sup>1</sup> |       |       |       | Covariate values (ii) <sup>2</sup> |       |       |       | Covariate values (iii) <sup>3</sup> |       |       |       |
|-----------------------------------------------------------------------------------------------------------------------|-----------------------------------|-------|-------|-------|------------------------------------|-------|-------|-------|-------------------------------------|-------|-------|-------|
|                                                                                                                       | Overall proportion mediated       | p     | lcl   | ucl   | Overall proportion mediated        | p     | lcl   | ucl   | Overall proportion mediated         | p     | lcl   | ucl   |
| <b>Bipolar disorder</b>                                                                                               |                                   |       |       |       |                                    |       |       |       |                                     |       |       |       |
| Age and sex (minimally adjusted)                                                                                      | 0.8%                              | 0.018 | 0.1%  | 1.4%  | 0.5%                               | 0.032 | 0.05% | 1.0%  | 0.8%                                | 0.022 | 0.1%  | 1.4%  |
| Age, sex, deprivation, country (partially adjusted)                                                                   | 1.0%                              | 0.015 | 0.2%  | 1.7%  | 0.6%                               | 0.030 | 0.06% | 1.2%  | 0.9%                                | 0.021 | 0.1%  | 1.7%  |
| Age, sex, deprivation, country, calendar period, Charlson index (partially adjusted)                                  | 2.1%                              | 0.001 | 0.8%  | 3.3%  | 1.2%                               | 0.006 | 0.4%  | 2.1%  | 2.1%                                | 0.001 | 0.8%  | 3.3%  |
| Age, sex, deprivation, country, calendar period, Charlson index, diabetes mellitus, obesity, smoking (fully adjusted) | -0.1%                             | 0.772 | -1.0% | 0.7%  | -0.05%                             | 0.772 | -0.4% | 0.3%  | -0.1%                               | 0.772 | -0.9% | 0.7%  |
| <b>Schizophrenia</b>                                                                                                  |                                   |       |       |       |                                    |       |       |       |                                     |       |       |       |
| Age and sex (minimally adjusted)                                                                                      | -0.4%                             | 0.133 | -0.9% | 0.1%  | -0.3%                              | 0.139 | -0.6% | 0.09% | -0.4%                               | 0.135 | -0.9% | 0.1%  |
| Age, sex, deprivation, country (partially adjusted)                                                                   | -0.8%                             | 0.072 | -1.6% | 0.07% | -0.5%                              | 0.080 | -1.1% | 0.06% | -0.7%                               | 0.076 | -1.5% | 0.07% |
| Age, sex, deprivation, country, calendar period, Charlson index (partially adjusted)                                  | 0.9%                              | 0.019 | 0.1%  | 1.6%  | 0.5%                               | 0.028 | 0.06% | 1.0%  | 0.9%                                | 0.019 | 0.1%  | 1.6%  |
| Age, sex, deprivation, country, calendar period, Charlson index, diabetes mellitus, obesity, smoking (fully adjusted) | -3.4%                             | 0.010 | -6.0% | -0.8% | -1.4%                              | 0.010 | -2.4% | -0.3% | -3.1%                               | 0.005 | -5.2% | -0.9% |

lcl – lower 95% confidence limit, ucl – upper 95% confidence limit, <sup>1</sup> male, age 65-74 years, most deprived, England, Charlson 1, 2015-19, diabetes mellitus, obese, current smoker, <sup>2</sup> female, age 45-54 years, least deprived, Wales, Charlson 0, 2010-14, no diabetes mellitus, no obesity, non-smoker, <sup>3</sup> male, age 55-64 years, median deprivation, Scotland, Charlson 2+, 2005-09, no diabetes mellitus, no obesity, ex-smoker

**Table 5.24 Overall proportion of total effect mediated by diabetes mellitus at baseline for minimally, partially and fully adjusted models, for three example sets of covariate values: (i) “higher risk”, (ii) “lower risk”(iii) “median risk”**

| Adjusted by:                                                                                                       | Covariate values (i) <sup>1</sup> |        |       |       | Covariate values (ii) <sup>2</sup> |        |      |       | Covariate values (iii) <sup>3</sup> |        |       |       |
|--------------------------------------------------------------------------------------------------------------------|-----------------------------------|--------|-------|-------|------------------------------------|--------|------|-------|-------------------------------------|--------|-------|-------|
|                                                                                                                    | Overall proportion mediated       | p      | lcl   | ucl   | Overall proportion mediated        | p      | lcl  | ucl   | Overall proportion mediated         | p      | lcl   | ucl   |
| <b>Bipolar disorder</b>                                                                                            |                                   |        |       |       |                                    |        |      |       |                                     |        |       |       |
| Age and sex (minimally adjusted)                                                                                   | 15.0%                             | <0.001 | 8.8%  | 21.1% | 6.3%                               | <0.001 | 3.1% | 9.4%  | 10.9%                               | <0.001 | 5.9%  | 15.8% |
| Age, sex, deprivation, country (partially adjusted)                                                                | 17.7%                             | <0.001 | 10.3% | 25.0% | 5.9%                               | <0.001 | 2.7% | 9.2%  | 10.5%                               | <0.001 | 5.3%  | 15.8% |
| Age, sex, deprivation, country, calendar period, Charlson index (partially adjusted)                               | 21.8%                             | <0.001 | 15.0% | 28.7% | 5.8%                               | <0.001 | 2.8% | 8.8%  | 11.9%                               | <0.001 | 6.6%  | 17.2% |
| Age, sex, deprivation, country, calendar period, Charlson index, smoking, obesity, blood pressure (fully adjusted) | 36.0%                             | <0.001 | 20.3% | 51.7% | 4.3%                               | 0.001  | 1.7% | 6.9%  | 11.2%                               | <0.001 | 5.4%  | 17.1% |
| <b>Schizophrenia</b>                                                                                               |                                   |        |       |       |                                    |        |      |       |                                     |        |       |       |
| Age and sex (minimally adjusted)                                                                                   | 24.1%                             | <0.001 | 18.8% | 29.4% | 11.5%                              | <0.001 | 8.1% | 14.9% | 18.4%                               | <0.001 | 13.7% | 23.0% |
| Age, sex, deprivation, country (partially adjusted)                                                                | 33.7%                             | <0.001 | 26.2% | 41.1% | 13.8%                              | <0.001 | 9.1% | 18.5% | 22.4%                               | <0.001 | 16.0% | 28.9% |
| Age, sex, deprivation, country, calendar period, Charlson index (partially adjusted)                               | 37.9%                             | <0.001 | 31.7% | 44.2% | 13.7%                              | <0.001 | 9.5% | 18.0% | 24.5%                               | <0.001 | 18.5% | 30.4% |
| Age, sex, deprivation, country, calendar period, Charlson index, smoking, obesity, blood pressure (fully adjusted) | 54.9%                             | <0.001 | 37.6% | 72.1% | 14.3%                              | <0.001 | 8.2% | 20.4% | 29.9%                               | <0.001 | 20.3% | 39.5% |

lcl – lower 95% confidence limit, ucl – upper 95% confidence limit, <sup>1</sup> male, age 65-74 years, most deprived, England, Charlson 1, 2015-19, obese, smoker, BP≥140/90 mmHg, <sup>2</sup> female, age 45-54 years, least deprived, Wales, Charlson 0, 2010-14, no obesity, non-smoker, BP<140/90 mmHg, <sup>3</sup> male, age 55-64 years, median deprivation, Scotland, Charlson 2+, 2005-09, no obesity, ex-smoker, BP≥140/90 mmHg

**Table 5.25 Overall proportion of total effect mediated by obesity at baseline for minimally, partially and fully adjusted models, for three example sets of covariate values: (i) “higher risk”, (ii) “lower risk”(iii) “median risk”**

| Adjusted by:                                                                                                                 | Covariate values (i) <sup>1</sup> |        |       |       | Covariate values (ii) <sup>2</sup> |        |       |       | Covariate values (iii) <sup>3</sup> |        |       |       |
|------------------------------------------------------------------------------------------------------------------------------|-----------------------------------|--------|-------|-------|------------------------------------|--------|-------|-------|-------------------------------------|--------|-------|-------|
|                                                                                                                              | Overall proportion mediated       | p      | lcl   | ucl   | Overall proportion mediated        | p      | lcl   | ucl   | Overall proportion mediated         | p      | lcl   | ucl   |
| <b>Bipolar disorder</b>                                                                                                      |                                   |        |       |       |                                    |        |       |       |                                     |        |       |       |
| Age and sex (minimally adjusted)                                                                                             | 7.8%                              | 0.001  | 3.1%  | 12.6% | 8.8%                               | 0.001  | 3.7%  | 13.9% | 8.1%                                | 0.001  | 3.3%  | 12.9% |
| Age, sex, deprivation, country (partially adjusted)                                                                          | 8.3%                              | 0.002  | 2.9%  | 13.7% | 8.0%                               | 0.003  | 2.8%  | 13.3% | 8.4%                                | 0.002  | 3.0%  | 13.8% |
| Age, sex, deprivation, country, calendar period, Charlson index (partially adjusted)                                         | 8.5%                              | 0.001  | 3.6%  | 13.3% | 7.1%                               | 0.002  | 3.6%  | 2.6%  | 7.3%                                | 0.002  | 2.8%  | 11.9% |
| Age, sex, deprivation, country, calendar period, Charlson index, diabetes mellitus, smoking, blood pressure (fully adjusted) | 5.4%                              | 0.041  | 0.2%  | 10.6% | 3.9%                               | 0.135  | -1.2% | 9.0%  | 5.5%                                | 0.096  | -1.0% | 11.9% |
| <b>Schizophrenia</b>                                                                                                         |                                   |        |       |       |                                    |        |       |       |                                     |        |       |       |
| Age and sex (minimally adjusted)                                                                                             | 6.5%                              | <0.001 | 3.1%  | 10.0% | 7.5%                               | <0.001 | 3.7%  | 11.2% | 6.8%                                | <0.001 | 3.3%  | 10.3% |
| Age, sex, deprivation, country (partially adjusted)                                                                          | 8.0%                              | 0.001  | 3.4%  | 12.6% | 7.8%                               | 0.001  | 3.3%  | 12.3% | 8.2%                                | 0.001  | 3.5%  | 12.8% |
| Age, sex, deprivation, country, calendar period, Charlson index (partially adjusted)                                         | 8.7%                              | <0.001 | 4.6%  | 12.8% | 7.2%                               | <0.001 | 3.5%  | 11.0% | 7.5%                                | <0.001 | 3.6%  | 12.8% |
| Age, sex, deprivation, country, calendar period, Charlson index, diabetes mellitus, smoking, blood pressure (fully adjusted) | 7.1%                              | 0.048  | 0.06% | 14.1% | 3.7%                               | 0.190  | -1.8% | 9.1%  | 5.7%                                | 0.139  | -1.8% | 13.2% |

lcl – lower 95% confidence limit, ucl – upper 95% confidence limit, <sup>1</sup> male, age 65-74 years, most deprived, England, Charlson 1, 2015-19, diabetes mellitus, smoker, BP≥140/90 mmHg, <sup>2</sup> female, age 45-54 years, least deprived, Wales, Charlson 0, 2010-14, no diabetes mellitus, non-smoker, BP<140/90 mmHg, <sup>3</sup> male, age 55-64 years, median deprivation, Scotland, Charlson 2+, 2005-09, no diabetes mellitus, ex-smoker, BP≥140/90 mmHg

### 5.3.2 All-cause mortality

The effects of SMI on mortality, controlled for the mediators (path c') were broadly similar whether the mediator status was recorded at baseline or endpoint (Table 5.26, Table 5.31). For each of the four mediators, the association between SMI and all-cause mortality was greater for schizophrenia than BD.

Current smoking at baseline mediated around one fifth of the effect of SMI on mortality for both BD and schizophrenia (BD: 18.8% (95% CI: 16.1%-21.5%), schizophrenia: 20.0% (95% CI: 18.2%-21.8%)) (Table 5.27). The results were slightly stronger for current smoking at endpoint (Table 5.32): percentage mediated was 20.4% (95% CI: 18.2%-22.6%) for BD and 22.3% (95% CI: 20.8%-23.8%) for schizophrenia. The percentages mediated by BP both at baseline and endpoint were non-significant or very small (<1%) (Table 5.28, Table 5.33).

Diabetes mellitus recorded at baseline mediated around 4% of the effect of SMI on mortality (BD: 4.9% (95% CI: 3.0%-5.8%); schizophrenia: 4.2% (95% CI: 2.9%-5.5%)). However, when measured at endpoint, the mediation effect was negligible.

The effect of obesity recorded at endpoint for both BD and schizophrenia (Table 5.35), and at baseline for schizophrenia (Table 5.30), was negative (endpoint: BD: -4.7% (95% CI: -6.7% to -2.7%), schizophrenia: -4.0%, (95% CI: -5.1% to -3.0%)), suggesting a protective effect for obesity. Similar results were found when unadjusted by the other potential mediators of smoking, BP and diabetes mellitus. The apparent protective effect whereby reduced obesity was associated with increased risk of mortality could be due to weight loss in those approaching end of life.

**Table 5.26: Mediation analysis of SMI on all-cause mortality, mediated by baseline status of smoking, high blood pressure, diabetes mellitus, obesity, fully adjusted models**

| Potential mediator (binary variable) | SMI | Effect of SMI on mediator (path a) <sup>1</sup> |        |      |      | Effect of mediator on mortality (path b) <sup>2</sup> |        |      |      | Effect of SMI on mortality, controlled for mediator (path c') <sup>2</sup> |        |      |      |
|--------------------------------------|-----|-------------------------------------------------|--------|------|------|-------------------------------------------------------|--------|------|------|----------------------------------------------------------------------------|--------|------|------|
|                                      |     | OR                                              | p      | lcl  | ucl  | HR                                                    | OR     | p    | lcl  | HR                                                                         | p      | OR   | p    |
| Smoking <sup>3</sup>                 | BD  | 2.19                                            | <0.001 | 2.15 | 2.24 | 2.06                                                  | <0.001 | 2.03 | 2.09 | 2.22                                                                       | <0.001 | 2.08 | 2.37 |
|                                      | SCZ | 2.76                                            | <0.001 | 2.72 | 2.81 | 2.10                                                  | <0.001 | 2.07 | 2.13 | 2.89                                                                       | <0.001 | 2.77 | 3.02 |
| BP <sup>4</sup>                      | BD  | 0.99                                            | 0.554  | 0.96 | 1.02 | 1.17                                                  | <0.001 | 1.15 | 1.18 | 2.20                                                                       | <0.001 | 2.07 | 2.33 |
|                                      | SCZ | 0.95                                            | <0.001 | 0.93 | 0.97 | 1.18                                                  | <0.001 | 1.16 | 1.20 | 2.86                                                                       | <0.001 | 2.75 | 2.97 |
| Diabetes mellitus <sup>5</sup>       | BD  | 1.57                                            | <0.001 | 1.51 | 1.64 | 1.99                                                  | <0.001 | 1.95 | 2.04 | 2.18                                                                       | <0.001 | 2.07 | 2.29 |
|                                      | SCZ | 1.74                                            | <0.001 | 1.69 | 1.79 | 2.01                                                  | <0.001 | 1.96 | 2.05 | 2.83                                                                       | <0.001 | 2.74 | 2.93 |
| Obesity <sup>6</sup>                 | BD  | 1.46                                            | <0.001 | 1.43 | 1.50 | 1.00                                                  | 0.662  | 0.98 | 1.01 | 2.13                                                                       | <0.001 | 2.02 | 2.25 |
|                                      | SCZ | 1.37                                            | <0.001 | 1.34 | 1.40 | 0.99                                                  | 0.103  | 0.97 | 1.00 | 2.79                                                                       | <0.001 | 2.70 | 2.89 |

SMI – severe mental illness, CVD – cardiovascular disease, BD – bipolar disorder, SCZ – schizophrenia, OR – odds ratio, HR – hazard ratio, lcl – lower 95% confidence limit, ucl – upper 95% confidence limit, BP – blood pressure ≥140/90 mmHg. <sup>1</sup> Logistic regression, <sup>2</sup> Cox proportional hazards regression, <sup>3</sup> adjusted for age, sex, deprivation, country, BP, diabetes mellitus, obesity, <sup>4</sup> adjusted for age, sex, deprivation, country, smoking, diabetes mellitus, obesity, <sup>5</sup> adjusted for age, sex, deprivation, country, smoking, BP, obesity, <sup>6</sup> adjusted for age, sex, deprivation, country, smoking, BP, diabetes mellitus

**Table 5.27: Decomposition of the total effect of SMI on all-cause mortality due to mediation and interaction with baseline smoking status, fully adjusted models, males, ages 55-64 years, median deprivation, England, Charlson index 1, 2015-19, no diabetes mellitus, BP<140/90 mmHg, no obesity**

| Component                   | Bipolar disorder     |        |       |       |                         |        |       |       | Schizophrenia        |        |       |       |                         |        |       |       |
|-----------------------------|----------------------|--------|-------|-------|-------------------------|--------|-------|-------|----------------------|--------|-------|-------|-------------------------|--------|-------|-------|
|                             | Excess relative risk | p      | lcl   | ucl   | Proportion attributable | p      | lcl   | ucl   | Excess relative risk | p      | lcl   | ucl   | Proportion attributable | p      | lcl   | ucl   |
| CDE                         | 1.46                 | <0.001 | 1.26  | 1.66  | 109%                    | <0.001 | 101%  | 117%  | 2.33                 | <0.001 | 2.16  | 2.49  | 110%                    | <0.001 | 106%  | 113%  |
| INT <sub>ref</sub>          | -0.38                | <0.001 | -0.53 | -0.22 | -28%                    | <0.001 | -39%  | -18%  | -0.63                | <0.001 | -0.76 | -0.50 | -30%                    | <0.001 | -35%  | -24%  |
| INT <sub>med</sub>          | 0.10                 | <0.001 | 0.06  | 0.15  | 8%                      | <0.001 | 5%    | 11%   | 0.23                 | <0.001 | 0.18  | 0.27  | 11%                     | <0.001 | 9%    | 13%   |
| PIE                         | 0.15                 | <0.001 | 0.14  | 0.15  | 811                     | <0.001 | 10%   | 12%   | 0.20                 | <0.001 | 0.19  | 0.21  | 9%                      | <0.001 | 9%    | 10%   |
| Total                       | 1.34                 | <0.001 | 1.22  | 1.45  | 100%                    |        |       |       | 2.12                 | <0.001 | 2.02  | 2.22  | 100%                    |        |       |       |
| Overall proportion mediated |                      |        |       |       | 18.8%                   | <0.001 | 16.1% | 21.5% |                      |        |       |       | 20.0%                   | <0.001 | 18.2% | 21.8% |

Adjusted by age, sex, country, deprivation, calendar period, Charlson index, blood pressure, diabetes mellitus, obesity. lcl – lower 95% confidence limit, ucl – upper 95% confidence limit, CDE – controlled direct effect INT<sub>ref</sub> - reference interaction, INT<sub>med</sub> - mediated interaction, PIE - pure indirect effect

**Table 5.28: Decomposition of the total effect of SMI on all-cause mortality due to mediation and interaction with baseline blood pressure  $\geq 140/90$  mmHg, fully adjusted models, males, ages 55-64 years, median deprivation, England, Charlson index 1, 2015-19, ex-smoker, no diabetes mellitus, no obesity**

| Component                   | Bipolar disorder     |        |         |        |                         |        |        |       | Schizophrenia        |        |        |        |                         |        |        |        |
|-----------------------------|----------------------|--------|---------|--------|-------------------------|--------|--------|-------|----------------------|--------|--------|--------|-------------------------|--------|--------|--------|
|                             | Excess relative risk | p      | lcl     | ucl    | Proportion attributable | p      | lcl    | ucl   | Excess relative risk | p      | lcl    | ucl    | Proportion attributable | p      | lcl    | ucl    |
| CDE                         | 0.96                 | <0.001 | 0.79    | 1.12   | 88.7%                   | <0.001 | 75.9%  | 101%  | 1.48                 | <0.001 | 1.33   | 1.62   | 88.4%                   | <0.001 | 81.2%  | 95.6%  |
| INT <sub>ref</sub>          | 0.12                 | 0.084  | -0.02   | 0.26   | 11.3%                   | 0.083  | -1.5%  | 24%   | 0.19                 | 0.001  | 0.07   | 0.31   | 11.5%                   | 0.001  | 4.5%   | 18.6%  |
| INT <sub>med</sub>          | 0.0003               | 0.575  | -0.0008 | 0.001  | 0.03%                   | 0.575  | -0.07% | 0.1   | 0.003                | 0.008  | 0.0008 | 0.005  | 0.2%                    | 0.008  | 0.05%  | 0.3%   |
| PIE                         | -0.0003              | 0.553  | -0.001  | 0.0007 | -0.03%                  | 0.553  | -0.1%  | 0.06  | -0.002               | <0.001 | -0.003 | -0.001 | -0.1%                   | <0.001 | -0.2%  | -0.06% |
| Total                       | 1.08                 | <0.001 | 0.98    | 1.18   | 100%                    |        |        |       | 1.67                 | <0.001 | 1.59   | 1.75   | 100%                    |        |        |        |
| Overall proportion mediated |                      |        |         |        | 0.003%                  | 0.851  | -0.03% | 0.04% |                      |        |        |        | 0.07%                   | 0.225  | -0.04% | 0.2%   |

Adjusted by age, sex, country, deprivation, calendar period, Charlson index, smoking, diabetes mellitus, obesity. lcl – lower 95% confidence limit, ucl – upper 95% confidence limit, CDE – controlled direct effect, INT<sub>ref</sub> - reference interaction, INT<sub>med</sub> - mediated interaction, PIE - pure indirect effect

**Table 5.29: Decomposition of the total effect of SMI on all-cause mortality due to mediation and interaction with baseline diabetes mellitus status, fully adjusted models, males, ages 55-64 years, median deprivation, England, Charlson index 1, 2015-19, ex-smoker, BP<140/90 mmHg, no obesity**

| Component                   | Bipolar disorder     |        |       |      |                         |        |       |        | Schizophrenia        |        |       |      |                         |        |       |        |
|-----------------------------|----------------------|--------|-------|------|-------------------------|--------|-------|--------|----------------------|--------|-------|------|-------------------------|--------|-------|--------|
|                             | Excess relative risk | p      | lcl   | ucl  | Proportion attributable | p      | lcl   | ucl    | Excess relative risk | p      | lcl   | ucl  | Proportion attributable | p      | lcl   | ucl    |
| CDE                         | 1.03                 | <0.001 | 0.68  | 1.37 | 94.0%                   | <0.001 | 67.6% | 120.4% | 1.62                 | <0.001 | 1.34  | 1.91 | 96.2%                   | <0.001 | 82.3% | 110.1% |
| INT <sub>ref</sub>          | 0.01                 | 0.939  | -0.30 | 0.32 | 1.1%                    | 0.939  | -27%  | 29.3%  | -0.007               | 0.959  | -0.26 | 0.25 | -0.4%                   | 0.959  | -16%  | 14.8%  |
| INT <sub>med</sub>          | -0.0009              | 0.939  | -0.02 | 0.02 | -0.08%                  | 0.939  | -2.1% | 1.9%   | 0.0006               | 0.959  | -0.02 | 0.02 | 0.04%                   | 0.959  | -1.3% | 1.4%   |
| PIE                         | 0.05                 | <0.001 | 0.05  | 0.06 | 5.0%                    | <0.001 | 4.3%  | 5.7%   | 0.07                 | <0.001 | 0.06  | 0.07 | 4.1%                    | <0.001 | 3.7%  | 4.5%   |
| Total                       | 1.09                 | <0.001 | 0.99  | 1.20 | 100%                    |        |       |        | 1.69                 | <0.001 | 1.60  | 1.78 | 100%                    |        |       |        |
| Overall proportion mediated |                      |        |       |      | 4.9%                    | <0.001 | 3.0%  | 6.8%   |                      |        |       |      | 4.2%                    | <0.001 | 2.9%  | 5.5%   |

Adjusted by age, sex, country, deprivation, calendar period, Charlson index, smoking, blood pressure, obesity. lcl – lower 95% confidence limit, ucl – upper 95% confidence limit, CDE – controlled direct effect, INT<sub>ref</sub> - reference interaction, INT<sub>med</sub> - mediated interaction, PIE - pure indirect effect



**Table 5.30: Decomposition of the total effect of SMI on all-cause mortality due to mediation and interaction with baseline obesity status, fully adjusted models, males, ages 55-64 years, median deprivation, England, Charlson index 1, 2015-19, ex-smoker, no diabetes mellitus, BP<140/90 mmHg**

| Component                   | Bipolar disorder     |        |        |        |                         |        |       |       | Schizophrenia        |        |        |        |                         |        |       |       |
|-----------------------------|----------------------|--------|--------|--------|-------------------------|--------|-------|-------|----------------------|--------|--------|--------|-------------------------|--------|-------|-------|
|                             | Excess relative risk | p      | lcl    | ucl    | Proportion attributable | p      | lcl   | ucl   | Excess relative risk | p      | lcl    | ucl    | Proportion attributable | p      | lcl   | ucl   |
| CDE                         | 0.89                 | <0.001 | 0.72   | 1.07   | 85.2%                   | <0.001 | 72.3% | 98.2% | 1.26                 | <0.001 | 1.11   | 1.41   | 78.1%                   | <0.001 | 70.6% | 85.6% |
| INT <sub>ref</sub>          | 0.18                 | 0.023  | 0.02   | 0.33   | 16.7%                   | 0.025  | 2.1%  | 31.3% | 0.39                 | <0.001 | 0.26   | 0.52   | 24.2%                   | <0.001 | 16.0% | 32.5% |
| INT <sub>med</sub>          | -0.02                | 0.023  | -0.04  | -0.003 | -1.9%                   | 0.026  | -3.6% | -0.2% | -0.04                | <0.001 | -0.05  | -0.02  | -2.3%                   | <0.001 | -3.0% | -1.5% |
| PIE                         | -0.0003              | 0.662  | -0.002 | 0.001  | -0.03%                  | 0.662  | -0.2% | 0.1%  | -0.001               | 0.103  | -0.002 | 0.0002 | -0.06%                  | 0.103  | -0.1% | 0.01% |
| Total                       | 1.05                 | <0.001 | 0.95   | 1.15   | 100%                    |        |       |       | 1.61                 | <0.001 | 1.53   | 1.70   | 100%                    |        |       |       |
| Overall proportion mediated |                      |        |        |        | -1.9%                   | 0.023  | -3.6% | 0.3%  |                      |        |        |        | -2.3%                   | <0.001 | -3.1% | -1.5% |

Adjusted by age, sex, country, deprivation, calendar period, Charlson index, smoking, blood pressure, diabetes mellitus, lcl – lower 95% confidence limit, ucl – upper 95% confidence limit, CDE – controlled direct effect, INT<sub>ref</sub> - reference interaction, INT<sub>med</sub> - mediated interaction, PIE - pure indirect effect

**Table 5.31: Mediation analysis of SMI on all-cause mortality, mediated by last recorded status of smoking, high blood pressure, diabetes mellitus, obesity, fully adjusted models**

| Potential mediator (binary variable) | SMI | Effect of SMI on mediator (path a) <sup>1</sup> |        |      |      | Effect of mediator on mortality (path b) <sup>2</sup> |        |      |      | Effect of SMI on mortality, controlled for mediator (path c') <sup>2</sup> |        |      |      |
|--------------------------------------|-----|-------------------------------------------------|--------|------|------|-------------------------------------------------------|--------|------|------|----------------------------------------------------------------------------|--------|------|------|
|                                      |     | OR                                              | p      | lcl  | ucl  | HR                                                    | p      | lcl  | ucl  | HR                                                                         | p      | lcl  | ucl  |
| Smoking <sup>3</sup>                 | BD  | 2.33                                            | <0.001 | 2.28 | 2.38 | 2.13                                                  | <0.001 | 2.10 | 2.16 | 2.22                                                                       | <0.001 | 2.08 | 2.36 |
|                                      | SCZ | 3.00                                            | <0.001 | 2.96 | 3.05 | 2.17                                                  | <0.001 | 2.14 | 2.20 | 2.78                                                                       | <0.001 | 2.65 | 2.91 |
| BP <sup>4</sup>                      | BD  | 0.96                                            | 0.007  | 0.94 | 0.99 | 0.96                                                  | <0.001 | 0.95 | 0.98 | 2.08                                                                       | <0.001 | 1.97 | 2.20 |
|                                      | SCZ | 0.94                                            | <0.001 | 0.92 | 0.96 | 0.97                                                  | <0.001 | 0.96 | 0.99 | 2.71                                                                       | <0.001 | 2.61 | 2.81 |
| Diabetes mellitus <sup>5</sup>       | BD  | 1.47                                            | <0.001 | 1.42 | 1.51 | 1.41                                                  | <0.001 | 1.38 | 1.43 | 2.34                                                                       | <0.001 | 2.22 | 2.47 |
|                                      | SCZ | 1.61                                            | <0.001 | 1.57 | 1.65 | 1.43                                                  | <0.001 | 1.41 | 1.46 | 2.94                                                                       | <0.001 | 2.84 | 3.04 |
| Obesity <sup>6</sup>                 | BD  | 1.50                                            | <0.001 | 1.46 | 1.53 | 0.78                                                  | <0.001 | 0.76 | 0.79 | 2.08                                                                       | <0.001 | 1.97 | 2.20 |
|                                      | SCZ | 1.45                                            | <0.001 | 1.43 | 1.48 | 0.77                                                  | <0.001 | 0.76 | 0.78 | 2.65                                                                       | <0.001 | 2.55 | 2.74 |

SMI – severe mental illness, CVD – cardiovascular disease, BD – bipolar disorder, SCZ – schizophrenia, OR – odds ratio, HR – hazard ratio, lcl – lower 95% confidence limit, ucl – upper 95% confidence limit, BP – blood pressure ≥140/90 mmHg. <sup>1</sup> Logistic regression, <sup>2</sup> Cox proportional hazards regression, <sup>3</sup> adjusted for age, sex, deprivation, country, BP, diabetes mellitus, obesity, <sup>4</sup> adjusted for age, sex, deprivation, country, smoking, diabetes mellitus, obesity, <sup>5</sup> adjusted for age, sex, deprivation, country, smoking, BP, obesity, <sup>6</sup> adjusted for age, sex, deprivation, country, smoking, BP, diabetes mellitus

**Table 5.32: Decomposition of the total effect of SMI on all-cause mortality due to mediation and interaction with last recorded smoking status, fully adjusted models, males, ages 55-64 years, median deprivation, England, Charlson index 1, 2015-19, no diabetes mellitus, BP<140-90mmHg, no obesity**

| Component                   | Bipolar disorder     |        |       |       |                         |        |       |       | Schizophrenia        |        |       |       |                         |        |       |       |
|-----------------------------|----------------------|--------|-------|-------|-------------------------|--------|-------|-------|----------------------|--------|-------|-------|-------------------------|--------|-------|-------|
|                             | Excess relative risk | p      | lcl   | ucl   | Proportion attributable | p      | lcl   | ucl   | Excess relative risk | p      | lcl   | ucl   | Proportion attributable | p      | lcl   | ucl   |
| CDE                         | 1.39                 | <0.001 | 1.20  | 1.58  | 104%                    | <0.001 | 98%   | 109%  | 2.18                 | <0.001 | 2.02  | 2.33  | 104%                    | <0.001 | 102%  | 107%  |
| INT <sub>ref</sub>          | -0.32                | <0.001 | -0.44 | -0.21 | -24%                    | <0.001 | -31%  | -17%  | -0.56                | <0.001 | -0.65 | -0.46 | -27%                    | <0.001 | -30%  | -23%  |
| INT <sub>med</sub>          | 0.12                 | <0.001 | 0.08  | 0.16  | 9%                      | <0.001 | 6%    | 12%   | 0.26                 | <0.001 | 0.22  | 0.31  | 13%                     | <0.001 | 11%   | 14%   |
| PIE                         | 0.15                 | <0.001 | 0.15  | 0.16  | 11%                     | <0.001 | 10%   | 13%   | 0.20                 | <0.001 | 0.19  | 0.21  | 10%                     | <0.001 | 9%    | 10%   |
| Total                       | 1.35                 | <0.001 | 1.22  | 1.47  | 100%                    |        |       |       | 2.08                 | <0.001 | 1.97  | 2.19  | 100%                    |        |       |       |
| Overall proportion mediated |                      |        |       |       | 20.4%                   | <0.001 | 18.2% | 22.6% |                      |        |       |       | 22.3%                   | <0.001 | 20.8% | 23.8% |

Adjusted by age, sex, country, deprivation, calendar period, Charlson index, blood pressure, diabetes mellitus, obesity. lcl – lower 95% confidence limit, ucl – upper 95% confidence limit, CDE – controlled direct effect, INT<sub>ref</sub> - reference interaction, INT<sub>med</sub> - mediated interaction, PIE - pure indirect effect

**Table 5.33: Decomposition of the total effect of SMI on all-cause mortality due to mediation and interaction with last recorded blood pressure ≥140/90 mmHg, fully adjusted models, males, ages 55-64 years, median deprivation, England, Charlson index 1, 2015-19, ex-smoker, no diabetes mellitus, no obesity**

| Component                   | Bipolar disorder     |        |         |        |                         |        |         |        | Schizophrenia        |        |         |        |                         |        |        |        |
|-----------------------------|----------------------|--------|---------|--------|-------------------------|--------|---------|--------|----------------------|--------|---------|--------|-------------------------|--------|--------|--------|
|                             | Excess relative risk | p      | lcl     | ucl    | Proportion attributable | p      | lcl     | ucl    | Excess relative risk | p      | lcl     | ucl    | Proportion attributable | p      | lcl    | ucl    |
| CDE                         | 1.13                 | <0.001 | 0.95    | 1.31   | 100%                    | <0.001 | 99.2%   | 101%   | 1.48                 | <0.001 | 1.34    | 1.62   | 99.2%                   | <0.001 | 98.6%  | 99.8%  |
| INT <sub>ref</sub>          | -0.0004              | 0.930  | -0.009  | 0.008  | -0.03%                  | 0.930  | -0.8%   | 0.7%   | 0.01                 | 0.002  | 0.004   | 0.02   | 0.8%                    | 0.005  | 0.3%   | 1.3%   |
| INT <sub>med</sub>          | -0.00001             | 0.930  | -0.0003 | 0.0003 | -0.001%                 | 0.930  | -0.03%  | 0.03%  | 0.0007               | 0.005  | 0.0002  | 0.001  | 0.05%                   | 0.010  | 0.02%  | 0.08%  |
| PIE                         | 0.00005              | 0.019  | 0.00001 | 0.0001 | 0.005%                  | 0.020  | 0.0007% | 0.009% | 0.00007              | 0.002  | 0.00003 | 0.0001 | 0.005%                  | 0.001  | 0.002% | 0.007% |
| Total                       | 1.13                 | <0.001 | 0.96    | 1.30   | 100%                    |        |         |        | 1.49                 | <0.001 | 1.36    | 1.63   | 100%                    |        |        |        |
| Overall proportion mediated |                      |        |         |        | 0.003%                  | 0.805  | -0.02%  | 0.03%  |                      |        |         |        | 0.05%                   | 0.006  | 0.01%  | 0.09%  |

Adjusted by age, sex, country, deprivation, calendar period, Charlson index, smoking, diabetes mellitus, obesity. lcl – lower 95% confidence limit, ucl – upper 95% confidence limit, CDE – controlled direct effect, INT<sub>ref</sub> - reference interaction, INT<sub>med</sub> - mediated interaction, PIE - pure indirect effect

**Table 5.34: Decomposition of the total effect of SMI on all-cause mortality due to mediation and interaction with last recorded diabetes mellitus status, fully adjusted models, males, ages 55-64 years, median deprivation, England, Charlson index 1, 2015-19, ex-smoker, BP<140-90mmHg, no obesity**

| Component                   | Bipolar disorder     |        |        |        |                         |        |       |       | Schizophrenia        |        |        |        |                         |        |       |        |
|-----------------------------|----------------------|--------|--------|--------|-------------------------|--------|-------|-------|----------------------|--------|--------|--------|-------------------------|--------|-------|--------|
|                             | Excess relative risk | p      | lcl    | ucl    | Proportion attributable | p      | lcl   | ucl   | Excess relative risk | p      | lcl    | ucl    | Proportion attributable | p      | lcl   | ucl    |
| CDE                         | 0.52                 | <0.001 | 0.37   | 0.67   | 96.8%                   | <0.001 | 95.0% | 98.6% | 0.88                 | <0.001 | 0.75   | 1.00   | 98.1%                   | <0.001 | 97.5% | 98.8%  |
| INT <sub>ref</sub>          | 0.02                 | <0.001 | 0.01   | 0.03   | 3.6%                    | 0.002  | 1.3%  | 5.9%  | 0.02                 | <0.001 | 0.01   | 0.03   | 2.2%                    | <0.001 | 1.3%  | 3.1%   |
| INT <sub>med</sub>          | -0.006               | <0.001 | -0.008 | -0.004 | -1.1%                   | 0.003  | -1.8% | -0.4% | -0.007               | <0.001 | -0.009 | -0.005 | -0.8%                   | <0.001 | -1.1% | -0.5%  |
| PIE                         | 0.004                | <0.001 | 0.003  | 0.004  | 0.7%                    | <0.001 | 0.5%  | 0.9%  | 0.004                | <0.001 | 0.004  | 0.005  | 0.5%                    | <0.001 | 0.4%  | 0.6%   |
| Total                       | 0.53                 | <0.001 | 0.39   | 0.68   | 100%                    |        |       |       | 0.89                 | <0.001 | 0.77   | 1.02   | 100%                    |        |       |        |
| Overall proportion mediated |                      |        |        |        | -0.4%                   | 0.155  | -0.9% | 0.1%  |                      |        |        |        | -0.3%                   | 0.029  | -0.6% | -0.03% |

Adjusted by age, sex, country, deprivation, calendar period, Charlson index, smoking, blood pressure, obesity. lcl – lower 95% confidence limit, ucl – upper 95% confidence limit, CDE – controlled direct effect, INT<sub>ref</sub> - reference interaction, INT<sub>med</sub> - mediated interaction, PIE - pure indirect effect

**Table 5.35: Decomposition of the total effect of SMI on all-cause mortality due to mediation and interaction with last recorded obesity status, fully adjusted models, males, ages 55-64 years, median deprivation, England, Charlson index 1, 2015-19, ex-smoker, no diabetes mellitus, BP<140-90mmHg**

| Component                   | Bipolar disorder     |        |       |       |                         |        |       |       | Schizophrenia        |        |       |       |                         |        |       |       |
|-----------------------------|----------------------|--------|-------|-------|-------------------------|--------|-------|-------|----------------------|--------|-------|-------|-------------------------|--------|-------|-------|
|                             | Excess relative risk | p      | lcl   | ucl   | Proportion attributable | p      | lcl   | ucl   | Excess relative risk | p      | lcl   | ucl   | Proportion attributable | p      | lcl   | ucl   |
| CDE                         | 0.93                 | <0.001 | 0.76  | 1.09  | 94.4%                   | <0.001 | 90.0% | 99.3% | 1.36                 | <0.001 | 1.21  | 1.50  | 92.8%                   | <0.001 | 89.9% | 95.6% |
| INT <sub>ref</sub>          | 0.10                 | 0.001  | 0.04  | 0.16  | 10.3%                   | 0.003  | 3.4%  | 17.1% | 0.17                 | <0.001 | 0.12  | 0.21  | 11.3%                   | <0.001 | 7.4%  | 15.2% |
| INT <sub>med</sub>          | -0.03                | 0.001  | -0.04 | -0.01 | -2.7%                   | 0.003  | -4.6% | -0.9% | -0.04                | <0.001 | -0.05 | -0.03 | -2.8%                   | <0.001 | -3.8% | -1.8% |
| PIE                         | -0.02                | <0.001 | -0.02 | -0.02 | -2.0%                   | <0.001 | -2.3% | -1.7% | -0.02                | <0.001 | -0.02 | -0.02 | -1.2%                   | <0.001 | -1.4% | -1.1% |
| Total                       | 0.98                 | <0.001 | 0.85  | 1.11  | 100%                    |        |       |       | 1.46                 | <0.001 | 1.35  | 1.58  | 100%                    |        |       |       |
| Overall proportion mediated |                      |        |       |       | -4.7%                   | <0.001 | -6.7% | -2.7% |                      |        |       |       | -4.0%                   | <0.001 | -5.1% | -3.0% |

Adjusted by age, sex, country, deprivation, calendar period, Charlson index, smoking, blood pressure, diabetes mellitus. lcl – lower 95% confidence limit, ucl – upper 95% confidence limit, CDE – controlled direct effect INT<sub>ref</sub> - reference interaction, INT<sub>med</sub> - mediated interaction, PIE - pure indirect effect

## 5.4 Discussion

### 5.4.1 Summary

The cohort analysis in Chapter 4 found that incidence of CVD diagnosis was over 30% higher for people with BD and schizophrenia compared with the general population, when adjusted for age, sex, and calendar period. When deprivation and country were also adjusted for, the HRs were reduced substantially (BD: 1.45 vs 1.38, Schizophrenia: 1.37 vs 1.25). Deprivation and country together thus reduced the excess risk by about 16% and 32% for BD and schizophrenia, respectively. When other baseline risk factors, diabetes mellitus, Charlson index, smoking, obesity, and blood pressure were added the HRs were reduced further (BD: 1.21, schizophrenia: 1.12). Thus, these baseline clinical risk factors together reduced the excess risk by 45% and 52%, for BD and schizophrenia, respectively, after deprivation was accounted for.

In this chapter, mediation analysis has shown that 35% of the excess risk for BD and 54% of that for schizophrenia was mediated through known smoking at baseline, after adjusting for other possible risk factors. Results were similar, but less strong when adjusted for fewer risk factors and for both higher and lower risk individuals in the sensitivity analyses. Current smoking at endpoint increased the percentage mediated to 41% and 60% for BD and schizophrenia, respectively.

Diabetes mellitus at baseline also had a substantial effect, although the effect at endpoint was much smaller for schizophrenia and non-significant for BD. Thus, the effect of DM on risk of CVD appears mainly attributable to longstanding DM. If DM develops after SMI diagnosis it seems to have less effect on the risk of CVD. In the whole cohort the HR for the

association between DM at baseline and CVD incidence was 1.98, compared with 1.26 for the association of DM at endpoint and CVD.

At baseline, for individuals with a median level of risk, diabetes mellitus mediated 14% of the excess risk for BD and 35% for schizophrenia. However, the percentage mediated was higher for individuals at higher risk (males, older, smokers) than those at lower risk (females, younger, non-smokers); BD: 36% vs 4%, schizophrenia: 55% vs 14%. This finding may appear counter intuitive. However, Appendix XXVIII shows in more detail how that is the case. The interpretation is that diabetes mellitus is more strongly associated with SMI in low-risk compared with high-risk patients because the high-risk patients have other factors associated with diabetes mellitus risk than just SMI. Also, diabetes mellitus is more likely to lead to CVD in low-risk than high-risk patients because the high-risk have other factors associated with CVD incidence than diabetes mellitus alone. As diabetes mellitus mediates only 14% of the excess risk for schizophrenia and 4% for BD, other factors must be more important in accounting for the excess risk of CVD in low-risk populations with SMI. One such factor could be antipsychotic medication leading to weight gain and diabetes mellitus during the study period.

The other risk factors of obesity and high blood pressure had no mediating effect, recorded either at baseline or at endpoint. Indeed, the effect of having  $BP \geq 140/90$  mmHg was negative when the last recorded BP status was used. The effect of obesity could be diminished by the inclusion of diabetes mellitus and blood pressure in the model.

Deprivation, when added as a mediator, did not account for a significant amount of the excess risk.

Of the alternative hypotheses for the association between SMI and CVD that were discussed in the introduction to this chapter, the fact that patients with SMI were more than twice as likely as the general population to be smokers at baseline accounted for around half of their excess risk of CVD incidence. The odds of still being a current smoker at endpoint was even higher for those with SMI compared with those without SMI, particularly for schizophrenia, and the mediating effect of smoking was correspondingly higher than at baseline. A similar proportion of the excess CVD risk was mediated by diabetes mellitus, but only for those at high risk of CVD, for example those who were already smokers, male and over age 65 years. Although this analysis has shown that a large proportion of the excess risk of CVD incidence for patients with SMI is mediated by smoking, and diabetes mellitus in some population groups, a substantial proportion remains unexplained. Factors that may account for the residual excess risk include risk factors that were not able to be included, *e.g.* high cholesterol, antipsychotic medication, lack of engagement with healthcare, or poorer care received, or some other mechanism. Missing information on smoking status, BP, and BMI could be considered proxies for lack of engagement with primary care. In Chapter 4, fully adjusted analysis found that missing baseline information for smoking status and BMI were associated with higher CVD incidence whereas missing BP was associated with lower CVD incidence. It was not possible to assess “missingness” as a mediator of the relationship between SMI and CVD and still adjust for known smoking, BMI, and BP due to collinearity. Smoking and diabetes mellitus were also significant mediators for all-cause mortality, although the associations were not as strong as for CVD incidence, probably due to the association of other causes of death with SMI, such as suicide, accidents, and neglect. (41,

236) Around 20% of the excess risk of all-cause mortality for those with SMI was mediated by smoking and around 4% by diabetes mellitus.

An apparent protective effect was found for obesity in all-cause mortality. This may be due to weight loss experienced by frail and elderly patients reaching end of life. (237)

#### **5.4.2 Comparison with other literature**

To my knowledge there have been no studies assessing the mediating effect of modifiable risk factors on the association between SMI and CVD incidence or all-cause mortality. Other authors have used a similar approach to investigate potential mediators of the association between SMI and outcomes related to CVD, or to investigate CVD risk factors on the association between exposures other than SMI (*e.g.* SES or educational level) and CVD mortality or incidence.

A recent Italian cohort study, including around 1,500 with SMI, found that poor adherence to post-MI healthcare mediated 4.1% and 11.3% of the association between SMI and further cardiovascular hospital admission and all-cause mortality, respectively. (238)

However, in an Italian cross-sectional study of 119 SMI patients and 119 without SMI, the potential mediators of family history of CVD or antipsychotic dose did not mediate the association between SMI and metabolic syndrome. (239) In this study, smoking status was found to mediate 10% of the effect and while this was non-significant, the authors acknowledge that the relatively low prevalence of metabolic syndrome in the study sample may have limited the power of the study. (239)

In the current analysis, smoking at endpoint mediated around 60% and 41% of the association between CVD incidence and schizophrenia and BD, respectively. There are some

studies that have considered smoking as a mediator of the effect of SES or education on CVD. These studies found that smoking mediated smaller proportions than that found in this thesis. A Spanish study found that smoking mediated around 35% of the association between SES and subclinical atherosclerosis. (240) In an observational analysis of a cohort of over 200,000 participants from the UK Biobank study, 19% of the association between educational level and CVD was mediated by smoking, 17% by BMI and 8% by BP, together totalling 41%. (241) A Danish cohort study of nearly 70,000 participants found that smoking mediated 8% and 6% of the excess risk of educational level on CHD for men and women, respectively, whereas BMI mediated 21% and 14%. (242) However, this last study considered both current and ex-smokers together.

A US cohort study involving 7,000 participants investigated the mediating effects of CVD risk factors on the association between degree-level education and CVD incidence. (243) This study found that the total effect mediated by a combination of BMI, BP, cholesterol, smoking, and DM was 38.5%; smoking alone accounted for 18.8%. (243) An Austrian cohort study of 117,000 individuals aged under 50 years and 55,000 participants older than this investigated the effect of sex on CHD mortality. (244) The study found that the largest proportion of the association in people aged under 50 years was mediated by systolic BP (21.7%). (244) Smoking only mediated 4.2% of the association in this age group, but an increasing amount at older ages (13.1% in ages 65-74 years). (244)

Another US study of 15,000 participants found that smoking, physical inactivity, and poor diet together mediated only 19% of the association between social isolation and CVD-related mortality (22% for all-cause mortality). (245) However, a study of 467,000 individuals from the UK Biobank cohort that investigated the effect of social isolation on CVD-related



mortality found that behavioural risk factors (smoking, alcohol consumption and physical inactivity) mediated a similar proportion to socioeconomic factors (Townsend deprivation index, education, and household income) (35% and 34% for behavioural and socioeconomic, respectively). (246) In the same study, biological risk factors (BMI, BP and handgrip strength mediated only 17%. (246) Mediated proportions were similar for all-cause mortality. (246) Mediation analysis examining the association between SES and CVD incidence conducted in a UK cohort of nearly 400,000 individuals found that CVD risk factors of smoking, alcohol consumption, physical inactivity and poor diet together mediated only 3.7% of the difference between the lowest and highest socioeconomic category. (247) For CVD-related mortality and all-cause mortality the percentages mediated were 3.0% and 4.0%, respectively. (247) However, analysis of a US cohort of 44,500 participants found that the same risk factors mediated 12.3% of the association between SES and all-cause mortality. (247)

In this thesis, it was found that smoking at baseline mediated 34.5% and 53.5% of the excess risk of CVD incidence for BD and schizophrenia, respectively. The mediating effect of smoking on the relationship between SMI and CVD incidence in this thesis is substantially greater than the effect of smoking on either the relationship between SES and CVD incidence or the relationship between education and CVD incidence reported above. (241-243, 247) This could be due to the high prevalence of smoking amongst patients with SMI in the current study (42.4% and 49.1% of those with BD and schizophrenia, respectively were current smokers at baseline vs 22.2% without SMI).

Mediation analysis of the prevalent cohort found 18.8% and 20.0% of the excess risk of all-cause mortality for BD and schizophrenia, respectively were mediated by smoking. This is within the range of values found by other studies of the mediating effect of smoking on the

association between social isolation, SES, or sex on all-cause or CVD-related mortality. (244-247)

### **5.4.3 Strengths and limitations**

A strength of this analysis is that no other studies appear to have analysed the mediation effects of smoking, BP, diabetes mellitus and obesity on the association between SMI and CVD incidence. The large cohort size of nearly nine million patients, over 75,000 with SMI, enables a high precision in the estimates and multiple covariates to be included. The cohort is representative of the UK population. Smoking was found to mediate a substantial proportion of the excess risk, and the results were consistent, whether measured at baseline or at end of follow-up.

There are also some limitations. To study the effect of SMI on the mediators, the variables were reduced to binary values with a consequent loss of information. Patients were recorded as smokers only if their last smoking status either at baseline, or at endpoint, was recorded as a current smoker. Similarly, those with high blood pressure or obesity were only recorded as such if their last recorded BP measurement before baseline or endpoint was  $\geq 140/90$  mmHg or their last recorded BMI was over  $30 \text{ kg/m}^2$  ( $27.5$  if they were recorded as having non-White ethnicity).

To study the proportion of the excess risk mediated, the values of the covariates had to be fixed. The effect was explored by setting to example values corresponding to high, low, and median levels of the risk factors, but that led to inconsistencies in the effect of diabetes mellitus. However, this was explained by the different background levels of diabetes mellitus and CVD risk affecting the high and low risk populations.

The temporal ordering of exposure – mediator – outcome may not have been followed correctly for some patients. However, in sensitivity analysis to include only recently recorded values for mediators current smoking still mediated half of the effect of schizophrenia on and 27% of the effect of BD on CVD incidence. When the last recorded values of smoking, BP and BMI were used, the mediation effects of current smoking became much larger. There was missing data on smoking status, BP, or BMI for many patients. Thus, numbers known to have the mediators present is an underestimate of the true number. It is unclear whether this would bias the results.

Mediation analysis depends on no uncontrolled confounding between exposure and outcome, mediator and outcome, and exposure and mediator to imply causation. Sensitivity analysis found that moderate levels of an unmeasured confounder could be enough to explain away the observed mediation effects of smoking. One important risk factor for CVD that was not included was lipid measurement. However, people with SMI have not been found to have higher total cholesterol levels, (248) so lipids are unlikely to confound the results. Other risk factors known to be associated with both SMI and CVD are alcohol and other substance abuse, lack of physical activity and poor diet, (56, 249, 250) but it was not possible to account for these in the analysis. Neither was adjustment for the confounding effects of ethnicity possible due to too much missing data.

#### **5.4.4 Implications**

This mediation analysis has resulted in some significant findings, particularly that recorded current smoking status accounts for more than half of the excess risk of CVD incidence for people with schizophrenia. It mediates a larger proportion of the excess risk than the other

significant risk factor, diabetes mellitus. The rate of smoking amongst people with SMI is high. The age/sex adjusted odds of current smoking at baseline for people with schizophrenia in this study was 3.24 (95% CI: 3.19-3.29); for BD it was 2.51 (95% CI: 2.46-2.56). In the prevalent cohort study the prevalence of current smoking was 42.4% and 49.1% for BD and schizophrenia, respectively, vs 22.2% for those without SMI. In England, the prevalence of smoking reported from primary care amongst people with SMI in 2014/15 was 40.5%, compared with 16.4% for all adults. (251) An earlier source (252) reported even higher smoking rates for people taking antipsychotic medication from two national surveys: the Health Survey for England 2010 (44.7% (95% CI: 26.7-64.2)) and the Adult Psychiatric Morbidity Survey 2007 (59.2% (95% CI: 41.3-75.0)). US smoking prevalence in schizophrenia was found to be as high as 59.1% in 2007. (253) There is a perception amongst mental health professionals that people with SMI don't want to quit smoking or it may be too difficult for them to achieve. (254, 255) However smoking cessation can be achieved by those with SMI, (256) it has positive effects on common mental health conditions, such as depression and anxiety (257) and has an association with antipsychotic medication, so that dosages may be reduced for patients who quit smoking. (258)

#### **5.4.5 Recommendations for further research**

Further work is needed to identify the factors accounting for the residual excess CVD risk. One approach could be the use of directed acyclic graphs (DAGs) to tease out factors confounding the relationship between SMI and CVD. (259) Future work could identify the mechanisms affecting causation between variables on the causal pathway. More insight could also be gained by stratification into subgroups to take the analysis further.

#### **5.4.6 Conclusions**

The mediation analysis described in the chapter has explored the causal relationship between SMI and CVD incidence by focussing on four potential mediators: smoking, diabetes mellitus, blood pressure, and obesity. Smoking has been found to account for up to 60% of the excess risk of CVD incidence for schizophrenia and around 40% for BD. Diabetes mellitus accounts for some of the remaining excess, particularly long-standing DM, and it has a greater effect in those with other CVD risk factors.

## CHAPTER 6 DISCUSSION

### 6.1 Introduction to chapter

This chapter summarises the main findings of the thesis, together with its strengths and limitations, discusses implications of the findings and makes recommendations for future research.

### 6.2 Summary of findings

This thesis has used three different methodologies to investigate the association between SMI and CVD. The systematic review (Chapter 2) found that CVD-related mortality for people with SMI is up to twice that of the general population. Relative risks of mortality from CVD, CHD and CVA were all higher for schizophrenia than BD (CVD: HR/Rate Ratio: 1.91 vs 1.52; CHD: SMR: 1.94 vs 1.67; CVA: SMR: 1.93 vs 1.55). The systematic review also found that SMRs showed a stronger association between CVD-related mortality and SMI during the 1990s and 2000s compared with earlier decades, suggesting that the gap between those with SMI and the general population appears to be widening. However, this trend did not appear to continue into the 2010s. The systematic review of the association between SMI and CVD incidence described in Chapter 3 found rates for those with SMI, which were up to two thirds higher than those for the general population for CHD in BD and CVA and total CVD for both BD and schizophrenia. However, most of the pooled estimates showed no difference in CHD incidence between those with schizophrenia and the general population. There was no clear trend in CVD incidence over time, although the highest rates appeared to be in the five-year period from 2000 to 2004.

In Chapter 4 two large cohort studies found the risk of all-cause mortality (also adjusted for a wide range of risk factors) was over twice as high as the general population for BD and 2.7 times that of the general population for schizophrenia. Excess mortality was particularly high in the first year after SMI diagnosis. Risk of mortality after CVD diagnosis was also substantial, at 1.7 and 2.0 times that of the general population for BD and schizophrenia, respectively. There was also elevated risk of CVD incidence for those with SMI compared with the general population. However, whereas mortality risks for schizophrenia were higher than those for BD, the difference was reversed for CVD incidence. In Chapter 4 the effect of adjusting for the confounding factors of deprivation, country, comorbidities, including diabetes mellitus and obesity, smoking status and high blood pressure was explored. It was found that adjusting for deprivation and country accounted for part of the excess risks in mortality and CVD incidence, more so for schizophrenia than BD. Smoking status and comorbidities accounted for a further part of the excess risks.

In Chapter 5, mediation analysis explored the association between SMI and CVD incidence by considering CVD risk factors on the causal pathway between SMI and CVD. Of four risk factors considered (smoking, diabetes mellitus, blood pressure and obesity), smoking was the most important, mediating 34.5% and 53.5% of the excess risk for BD and schizophrenia, respectively, after adjustment for other risk factors. Diabetes mellitus also had a substantial effect, mediating 13.8% and 35.1% for BD and schizophrenia, respectively. However, obesity and hypertension had no significant extra mediating effect, after accounting for smoking and diabetes mellitus. Sensitivity analysis showed that the effect of smoking remained strong, whether recorded at baseline or endpoint, but the mediating effect of diabetes mellitus was

greater when recorded at baseline, rather than endpoint, and greater in individuals with other CVD risk factors, such as males, older people, and smokers.

There was less of a mediating effect for smoking in all-cause mortality, but it was still substantial (18.8% and 20.0% for BD and schizophrenia, respectively). Higher rates of mortality for those with SMI due to unnatural causes, particularly suicide, but also accidents and homicide, and natural causes including endocrine and metabolic diseases (including diabetes mellitus), digestive diseases (which includes alcoholic liver disease), and infectious diseases (including human immunodeficiency virus (HIV), tuberculosis and hepatitis) could explain some of the rest of the difference. (41, 236)

### **6.2.1 Comparison between the cohort studies and the systematic review**

The outcomes investigated by the systematic review were CVD-related mortality and CVD incidence, with different types of CVD and different SMI diagnoses included in separate meta-analyses. The cohort studies investigated all-cause mortality, case-fatality after CVD diagnosis, and CVD incidence, comparing those exposed to schizophrenia and BD with the general population without SMI.

CVD case-fatality HRs for BD and schizophrenia from the prevalent cohort study were similar to pooled estimates of relative risks for CVD-related mortality from the systematic review (Figure 6.1). Figure 6.1 shows more variance in the cohort study stroke and MI case-fatality HRs when compared with systematic review results for CVA and CHD mortality, although confidence intervals overlap the ranges of the pooled estimates. The HR for stroke case-fatality in schizophrenia is particularly low, when compared with the systematic review



pooled HR/rate ratio. This latter pooled estimate was strongly influenced by a very large Swedish register study. In this study ascertainment of CVA was very good due to the high level of data linkage in national registers, however the study did not include patients with schizophrenia that were only seen in outpatients, so may represent a more severely ill cohort of SMI patients. (170) Thus, the systematic review result may overestimate the excess risk of CVA mortality in patients with schizophrenia. The HR for stroke case-fatality from the prevalent cohort study was 1.63, which is close to the relative risks found by other recent systematic reviews. (40, 82)

Relative risks of CVD incidence for both BD and schizophrenia obtained from the incident cohort study were very similar to the pooled estimates from the systematic review (Figure 6.2). HRs from the prevalent cohort study were smaller, but in the case of schizophrenia were within the confidence limits of the pooled HR/rate ratios. The HR of CVD incidence for BD from the prevalent cohort seems small in comparison to the systematic review pooled estimates. This may be due to a healthy survivor effect as described in Chapter 4 or diagnostic overshadowing leading to reduced ascertainment of CVD in those with SMI by primary care.

The systematic review found wider disparities in relative CVD-related mortality in the 1990s and 2000s compared to earlier decades. The prevalent cohort study covered the period 2000-2019, so the findings of the systematic review could not be compared directly with the cohort studies. However, there was no evidence from the prevalent cohort study of changes in CVD, MI, or stroke case-fatality for patients with SMI relative to the general population over the period of the study (2000-19).

Regarding CVD incidence, there was some evidence of a reduction between 2010-14 and 2015-19 for those with BD compared with the general population, in the partially adjusted model. However, this could be accounted for by changes in levels of smoking and comorbidities because the interaction with time disappeared after adjustment for these factors.

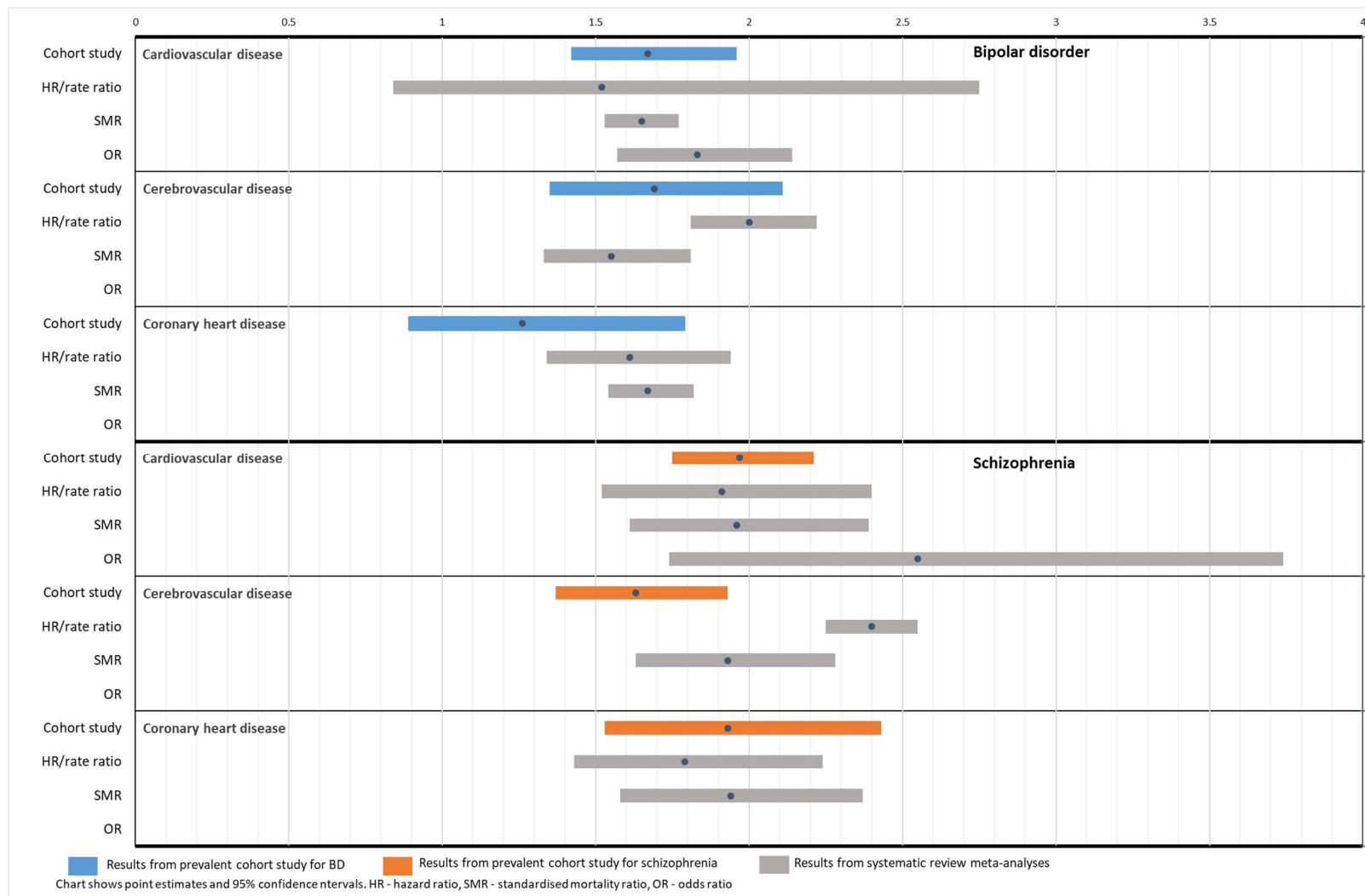


**Figure 6.1: Comparison of CVD, stroke, and MI case-fatality HRs from prevalent cohort study with CVD-related, CVA and CHD mortality from systematic review pooled estimates**

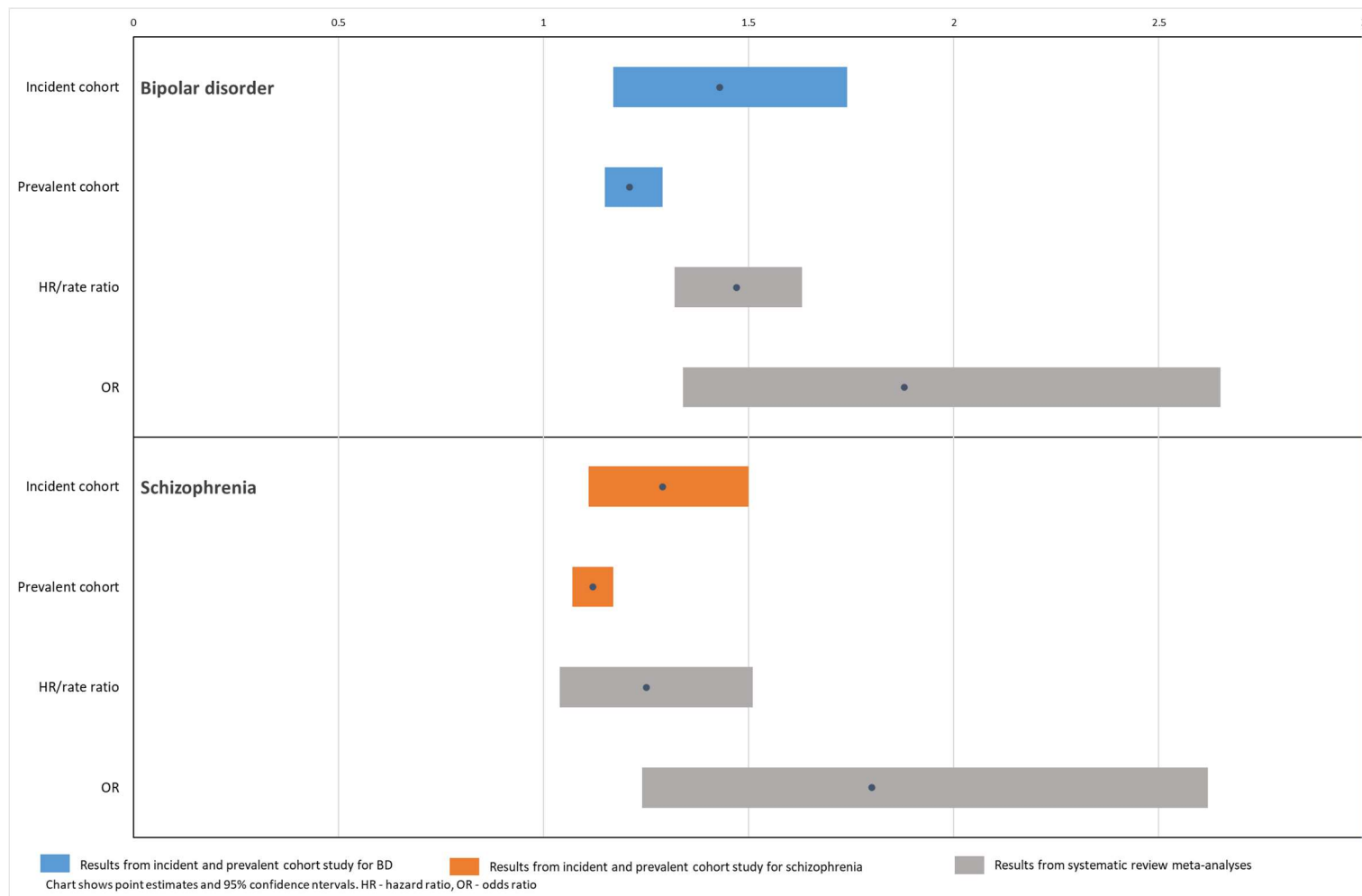


**Figure 6.2: Comparison of HRs for CVD incidence from prevalent and incident cohort study with CVD incidence from systematic review pooled estimates**

## 6.3 Strengths and limitations

### 6.3.1 Strengths

This thesis has used three methodologies to explore the effect of SMI on CVD-related mortality and incidence. All have been large-scale studies, enabling multiple explanatory factors to be considered and estimates with a high degree of precision to be made. The systematic review included 108 studies in the narrative review, with 59 mortality studies (involving  $\geq 1,841,356$  cases, 29,321,409 controls) and 28 incidence studies ( $\geq 401,909$  cases, 14,372,146 controls) included in quantitative synthesis. The prevalent cohort included 9,243,001 participants, of which 109,570 had a diagnosis of SMI, the incident cohort comprised 24,988 patients with SMI and 74,964 matched non-SMI comparators. The mediation analysis included 8,967,993 patients, 75,162 with an SMI diagnosis.

The systematic review established the excess risk of CVD-related mortality and incidence for SMI, which was confirmed in a UK primary care population by the findings of the cohort studies. The relative effects of potential mediators of the excess risk were then explored by mediation analysis.

The THIN database used for analysis is large and representative of the UK population, moreover, it has been shown to be suitable for the study of patients with SMI. (174, 211)

### 6.3.2 Limitations

Although several potential confounding factors were adjusted for in the analysis of the cohort studies and the mediation analysis, it was not possible to adjust for ethnicity as over half of participants had missing data (see Chapter 4, Figure 4.3). A study using the CPRD

database showed that completeness of ethnicity recording in primary care improved dramatically after recording was incentivised by the QOF in 2006/7 to 2011/12. (260) In this study, completeness of ethnicity recording in CPRD was further improved (from 78.7% to 97.1%) for patients newly registered after 1 April 2006 by linking with ethnicity records from HES inpatient data, which is available in CPRD. (260) Unfortunately, it was not possible to link the THIN data used in the analysis for this thesis with HES, which would have improved the completeness of ethnicity recording, allowing the analysis to control for the potentially confounding effect of ethnicity.

Health behaviours, comorbidities and other health data such as smoking, diabetes mellitus, obesity and blood pressure were considered as confounders in the systematic reviews detailed in chapters 2 and 3, and the cohort studies described in chapter 4. This was because the purpose of these analyses was to quantify the risks of mortality and CVD incidence associated with SMI. However, in the mediation analysis of chapter 5 these covariates were considered as mediators as the purpose was to determine causal pathways of the association between SMI and CVD. It can be difficult to distinguish between mediators and confounders of a relationship between an exposure and an outcome, the difference being that a mediator is presumed to be caused by the exposure, but a confounder is not. (261) In the mediation analysis models were used to test the hypotheses that SMI causes smoking, obesity, diabetes mellitus and high blood pressure, which in turn cause a diagnosis of CVD. These hypotheses may not be correct or may be over-simplified or there may be other unmeasured confounders acting on the relationships. The use of a DAG to describe the network of causal assumptions underlying the relationships between the study variables

could be helpful in understand which covariates to treat as confounders and which are possible mediators. (262)

Baseline values were used for the variables investigated as mediators in the mediation analysis. However, these variables (BMI, blood pressure, smoking status, and presence of diabetes mellitus) are likely to change for individuals over time. To explore the effect of changes in the mediators during the study period, the effect of using the mediators recorded at endpoint was tested in sensitivity analyses. The mediating effect of smoking on the association of SMI and CVD incidence was similar whether recorded at the start or end of follow-up, but the proportions of the total effect attributed to DM, BP and obesity were negligible or reduced at the endpoint compared with baseline. Smoking rates are slow to change, so smoking status at the endpoint was the same as at baseline for most patients. People are less likely to start smoking as adults, so changes in status tend to be from smoker to ex-smoker. (263) Over the period of the cohort studies, the percentage of British smokers who had quit smoking increased from 46.5% in 2000 to 61.3% in 2018, an annual rate of change of 0.8%. (264)

More complicated models could include time-varying confounders and mediators, but that was beyond the time and computing resources available for this thesis.

#### 6.3.2.1 Missingness

As well as missing data on ethnicity, the lack of complete data on cholesterol meant that the effects of this important CVD risk data could not be evaluated. Other covariates in the prevalent cohort had high levels of missing data at baseline (BMI: 36.1%, smoking status: 21.9%, systolic BP: 32.0%). These are not missing completely at random as patients with

schizophrenia had lower rates of missing values; those with BD lower still. Methods of dealing with missingness include complete-case analysis, where only participants with no missing data are included; multiple imputation, where missing values are imputed based on the distribution of other variables; or the missing indicator method, where missing values are grouped into a “missing” category. (265) For simplicity, and to use the available information in the dataset the last of these was used for confounders in this research. However, this may have introduced bias to the HRs by residual confounding. (265) For example, one third of participants in the prevalent cohort had missing BMI. BMI is more likely to be recorded for those with SMI than the general population but those with more severe SMI may be less likely to attend the practice and have measurements recorded, thus there may be a difference between those with recorded BMI and those without. An alternative method would have been to use multiple imputation which would produce unbiased estimates. (265)

## 6.4 Comparison with other literature

### 6.4.1 Systematic review

#### 6.4.1.1 CVD mortality

There was generally good agreement between the elevated risks of CVD, CHD and CVA mortality for schizophrenia and BD found by the systematic review and the results reported in other recent large systematic reviews. (39, 40, 54) Findings for BD were similar to those of other meta-analyses, but other authors reported slightly larger relative risks than the current study for CVD and CHD, but slightly smaller than the current study for CVA. (39, 40, 54)



#### 6.4.1.2 CVD incidence

The findings from the systematic review regarding the increased risk of CVD incidence for those with SMI compared to the general population were broadly in line with other authors for CVA diagnosis and total CVD events in both schizophrenia and BD. (54, 81, 83) Regarding incidence of CHD diagnosis, the positive association with BD shown by HRs was not found by other systematic reviews that did not include recent primary studies. (54, 81) Evidence of an association between CHD diagnosis and schizophrenia, however, was unclear, both in terms of the results of the current systematic review and other systematic reviews, with pooled results in both directions being found.

#### 6.4.2 Cohort studies

SMI incidence rates in the incident cohort study were higher than other studies. (210, 211) This may have been due to the inclusion of different Read codes to define SMI compared with other studies or the inclusion of previously diagnosed patients who had changed general practice. SMI prevalence rates were a little higher than the most recent rate recorded for all GPs in England, (212) although this may be due to the inclusion of a broader set of Read codes. Age at SMI diagnosis was slightly older than expected compared with other studies, possibly because of the inclusion of prevalent SMI patients who had changed practice.

Fully adjusted HRs of 2.68 and 2.07 for schizophrenia and BD, respectively, were broadly similar to those reported by other systematic reviews for all-cause mortality. (37, 39, 54) Case-fatality rates after MI and stroke were also broadly similar to those found by recent reviews. (208, 220) In contrast, the risks of CVD diagnosis for both BD and schizophrenia

found by the incident and prevalent cohort studies were smaller than the relative risks reported by recent reviews. (54, 83) This may relate to a healthy survivor effect or under-ascertainment of CVD amongst those with SMI as has been reported by other studies. (52),(57) Opportunities for diagnosis, recording and treatment of CVD may be routinely missed by primary care. A recent study found that people with schizophrenia and women with BD were more likely than those without SMI to die from undiagnosed CVD, but 98% of those with SMI had previous primary or specialised physical health care contact, compared with 88% of others who died from CVD. (57)

#### **6.4.3 Mediation analysis**

To my knowledge, this thesis is the first research to use mediation analysis to explore the relative effects of CVD risk factors on the association between SMI and CVD incidence. Other studies have investigated mediating factors in the relationship between SMI and other cardiovascular outcomes or have researched the extent to which CVD risk factors mediate the relationship between education or SES and CVD-related mortality or incidence. (238-247) In the current study smoking mediated 60% and 41% of the association between CVD incidence and schizophrenia and BD, respectively. This was greater than the proportion mediated by smoking in any of the other studies referred to above.

#### **6.5 Implications**

The findings of this thesis highlight some significant health disparities for those with SMI compared with the general population and some evidence that they are not improving over time, suggesting that current interventions are not effective for people with SMI. The research confirms the importance of smoking cessation and physical health monitoring in

this population, which may be lacking. Therefore, there is a need to develop new effective evidence-based interventions and policies to support these elements of the care of people with SMI to improve their health outcomes. As well as health benefits to individuals with SMI there will likely be health economic benefits too.

Of the four risk factors for CVD investigated in this research, smoking was found to explain a large part of the difference in CVD incidence between those with SMI and the general population. Smoking rates for people with SMI are higher than the general population. (251) The trend over recent years has been for smoking rates to reduce for both the general population and those with mental health conditions, however, there remains a wide disparity. (251) Quit rates are lower for those with SMI, and they are less likely to use smoking cessation services which give the best chance of success in quitting. (252, 255, 256, 263) There is also a common misconception that people with SMI don't want to quit. (255) However, quitting smoking has important benefits for those with SMI in addition to the potential reduction in CVD risk. There are interactions between smoking and use of antipsychotic medications. Antipsychotic dose can be reduced in non-smokers compared with smokers for the same level of benefit. (258) Smoking cessation may also elicit behavioural improvements. A recent study in a psychiatric hospital in London, UK found a reduction in violent assaults after the introduction of a smoking ban. (266) If patients are unable to smoke in hospital it may lead to an increase in quit rates. However, despite the English government's commitment in their 2017 Tobacco Control Plan to making all mental health services smoke free by 2018, 18% of mental health trusts did not, in 2019, have a comprehensive smokefree policy. (251, 263) Thus, policies are needed to help support

smoking cessation - for example national smoke free policies for mental health trusts that are enforceable.

In addition to smoking, the prevalence of diabetes mellitus, particularly long-standing DM, accounted for a further substantial part of the excess risk of CVD in those with schizophrenia, and to a lesser extent those with BD. Diabetes had a greater effect on relative risk of CVD incidence in those with other CVD risk factors (older age, being male, having higher levels of deprivation, smoking, blood pressure or obesity). Thus, the importance of physical health monitoring in patients with SMI and diabetes comorbidity is emphasised, focussing on those with known CVD risk factors.

## 6.6 Recommendations for future research

The findings of this thesis highlight the need to develop and implement interventions for smoking cessation in people with SMI. A recent review of behavioural interventions to reduce CVD risk in those with SMI summarised several recommendations. (267) These included early intervention from the start of mental health treatment for smoking and other CVD risk behaviours, educating those with SMI about how reducing CVD risk behaviours can improve mental health, personalised and tailored interventions, in person or telehealth options for delivery, multidisciplinary teams, sufficient intensity and duration of interventions. Regarding smoking cessation, combined pharmacological and behavioural interventions are most effective in those with SMI. (267) There is evidence that digital smoking cessation interventions can be successful in this population, although further research in this area is needed. (268) Recent research has shown that a SMI-specific smoking cessation intervention can achieve higher incidence of successful quitting at 6 months than usual care, although more resources may be needed to sustain this to 12 months. (256) There is also a need for regular physical health monitoring, in particular cardiovascular risk assessments. In England, patients with SMI are entitled to an annual physical health check provided by their GP. (269) It is recommended the health check includes estimating the risk of developing CVD using a risk prediction tool such as QRISK. (270) The latest NICE guidance recommends the use of QRISK3 which includes SMI and use of atypical antipsychotic medicine as predictors. (271-273) Risk prediction tools that do not account for SMI could underestimate CVD risk in this patient group. (274, 275) Although the health check is monitored as part of QOF, physical health monitoring may not be effective for those with SMI in terms of engagement or behaviour change. (276) There is currently no systematic

review evidence of the effectiveness of physical health monitoring for those with SMI. (277)

Development of effective interventions again tailored to this population are needed to ensure engagement with physical health reviews and risk assessments with the aim of primary prevention and reduction of CVD risk. Diabetes prevention is an important part of this. There is good evidence that diet and physical activity together can reduce the incidence of type 2 diabetes in the general population. (278) The Diabetes Prevention Programme in the US is one lifestyle intervention that has achieved success through multidisciplinary approaches delivered by specialist health professionals. (279) It is argued that the principles of this programme, focussing on individualised support, frequent contact, structured education, exercise supervision and motivational strategies could and should be offered and provided specifically to those with SMI. (279)

These recommendations would have the greatest impact on patients.

It was beyond the scope of this thesis and the electronic health record data available to look at the impact of physical activity or poor diet, but both these factors are important for cardiovascular health. The prevalence of physical inactivity and poor diet are high in those with SMI and warrant further investigation. (249)

The cohort studies highlighted that although all-cause mortality for individuals with SMI is two to three times higher than the general population, and CVD case-fatality is up to twice as high for those with SMI compared with others, the relative risks are more modest for CVD incidence. Under-ascertainment of CVD in those with SMI could account for some of this variance. This could be investigated by examining the relative risks of MI and stroke incidence for those with SMI compared with the general population, as these severe conditions are more likely to be diagnosed and recorded than more subtle CVD diagnoses,

such as angina. Less severe symptoms could be overlooked, ignored, or misunderstood.

Excess post-stroke case-fatality remains for both BD and schizophrenia, and post-MI case-fatality for schizophrenia compared with others. This suggests that differential access to secondary prevention is a problem and warrants further investigation.

The mediation analysis has investigated possible mediators of the relationships between SMI and two outcomes: CVD incidence and all-cause mortality. Although a substantial amount of the excess risk in CVD incidence was explained by mediation analysis, a large amount remains unexplained. Extensions to the work could explore variations by sex, CVD diagnoses, access to treatments or antipsychotic use to gain more insight.

In this research, the study period ended in 2019. There was not much consistent evidence of a time trend, but there appeared to be a narrowing of the gap between those with SMI and the general population in the later years of the study period. More recent data would allow further examination of these temporal effects.

The models used in this thesis have simplified a complicated primary care dataset which has variables that change over time by fixing covariates to values recorded at baseline. Some sensitivity analysis was conducted to investigate the effect of replacing with endpoint values, but more complex modelling could explore time-varying covariates in more detail. In particular the effect of weight trajectories on cardiovascular outcomes, which may be influenced by prescription of antipsychotic medication.

The mediation analysis has also been simplified by analysing potential mediators individually. This could be extended using directed acyclic graphs to represent the complex relationships between exposure, outcome, and potential mediators. (259)

As discussed in the limitations section there were issues with ethnicity recording which could have been improved using HES linked data in CPRD. An aim of future research should be to explore the effect of ethnicity on these outcomes in people with SMI.

SMI was defined using Read codes. Another definition considered included patients prescribed SMI-specific antipsychotic medication as well as Read codes. However, there were many patients prescribed antipsychotic medications who concerningly had no Read code indicating the presence of SMI. The age distribution of these patients did not fit the expected profile of patients with BD and schizophrenia; thus, they were not included in the definition of SMI used in the studies. However, more investigation of these patients and whether they do have SMI would be of value.

## 6.7 Conclusions

The aim of this thesis was to summarise evidence of the association between SMI and CVD mortality and incidence, explore factors associated with risk of poor outcomes and examine causal factors in the relationship between SMI and CVD incidence. It has found that for those with SMI, rates of all-cause mortality, CVD case-fatality and CVD are significantly higher than the general population. This has been shown in multiple studies, using robust methods and with large datasets. There is some evidence of worsening outcomes over time. However, although still raised compared with the general population, the risk of CVD diagnosis in those with SMI was not as great as the risk of all-cause and CVD-related mortality, suggesting that CVD may be under-diagnosed in the SMI population. Post-stroke case-fatality rates were high in those with SMI compared with the general population, as were post-MI rates for those with schizophrenia, suggesting differential access to secondary prevention.



Smoking appears to be a key risk factor and there is evidence that smoking cessation is possible for those with SMI. However, although smoking, and to a lesser extent diabetes mellitus account for a large proportion of the excess risk for those with SMI, a substantial part remains unexplained by the risk factors considered. Differential access to primary and secondary care treatments could account for some of the excess risk and warrants further investigation. Overall, the thesis highlights the need to improve the care of physical health, and particularly cardiovascular health, of those with SMI through new policies and interventions.

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## APPENDIX I DEVIATIONS FROM SYSTEMATIC REVIEW PROTOCOL

| Protocol                                 | Deviation                                                | Rationale                                                                                                                                                                                                                                                                                                                |
|------------------------------------------|----------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Ages 16 years+                           | Ages 16-65 years                                         | The upper age limit was chosen because onset of psychotic disorder is uncommon at older ages, but transient psychosis can be associated with dementia making it difficult to distinguish between this and SMI                                                                                                            |
| Include RCTs                             | Exclude RCTs                                             | Not appropriate for research question                                                                                                                                                                                                                                                                                    |
| Subgroup analysis by length of follow-up | Subgroup analysis by length of follow-up not carried out | Most studies did not report the mean duration of follow-up. Also, it may not be a reliable source of heterogeneity. For prevalent cases it may be biased because people included are those who haven't already died. For incident cases then outcomes may not occur in a short follow-up. Will also depend on age group. |

## APPENDIX II SEARCH STRATEGIES FOR THE ASSOCIATION BETWEEN SEVERE MENTAL ILLNESS AND CARDIOVASCULAR DISEASE BY DATABASE

### MEDLINE, via Ovid platform, 1946 to November Week 3 2021

Search dates: 19 September 2017 (including MEDLINE in-Process), updated 8 March 2019 (including MEDLINE in-Process), and 30 November 2021

- 1 ((serious or severe or chronic or persistent) adj ("mental illness\*" or "mental disorder\$1" or "mental disease\$1")).ti,ab.
- 2 exp Schizophrenia/ or Schizophrenia.mp.
- 3 exp Schizotypal Personality Disorder/ or Schizotypal Personality Disorder\$1.mp.
- 4 ("dementia pr?ecox" or "schizo affective" or schizoaffective or schizophreniform or hebephrenia or paraphrenia or oneirophrenia).mp.
- 5 affective disorders, psychotic/ or capgras syndrome/ or delusional parasitosis/ or morgellons disease/ or paranoid disorders/ or psychotic disorders/
- 6 ("psychotic affective disorder\$1" or capgras or "delusional misidentification syndrome" or morgellons or "cotard\$2 syndrome" or "delusional parasitosis" or "delusional disorder\$1" or "psychotic disorder\$1" or psychos#s).mp.
- 7 Paranoid Disorders/ or ("paranoid disorder\$1" or "paranoid ideation" or paranoia).mp.
- 8 ("sander\$2 disease" or "folie a deux" or "boufee delirante" or "sensitiver beziehungswahn").mp.
- 9 exp "bipolar and related disorders"/ or bipolar disorder\$1.mp.
- 10 ((manic or bipolar) adj depression\$1).ti,ab.
- 11 mania.mp.
- 12 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11
- 13 Cardiovascular Diseases/ or Cardiovascular disease\$1.mp.
- 14 ((coronary or isch?emic) adj2 (disease or occlusion or stenosis or thrombosis)).ti,ab.
- 15 exp Myocardial Ischemia/
- 16 (myocardial adj (isch?emia or infarct\$)).ti,ab.
- 17 exp Angina Pectoris/ or angina.mp.
- 18 exp Myocardial Revascularization/
- 19 ((coronary or myocardial or heart or cardiac) adj2 (revasculari?ation or angioplasty or atherectomy or bypass)).ti,ab.
- 20 exp Heart Failure/
- 21 ((heart or cardiac or ventricular) adj failure).ti,ab.
- 22 exp Ventricular Dysfunction/
- 23 ((ventricular or systolic or diastolic) adj (dysfunction or impairment)).ti,ab.
- 24 exp brain ischemia/ or exp intracranial arterial diseases/ or exp "intracranial embolism and thrombosis"/ or exp stroke/
- 25 (stroke or "cerebrovascular accident").mp.
- 26 ((brain or cerebral or intracranial) adj2 (infarct\$ or thrombosis or embolism)).ti,ab.
- 27 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26
- 28 12 and 27
- 29 limit 28 to humans
- 30 limit 29 to "qualitative (best balance of sensitivity and specificity)"
- 31 29 not 30
- 32 limit 31 to "reviews (best balance of sensitivity and specificity)"
- 33 31 not 32
- 34 limit 33 to systematic reviews
- 35 33 not 34
- 36 limit 35 to yr="2019 -Current"

**Embase, via Ovid platform, 1974 to 2021 November 29**

Search dates: 19 September 2017, updated 8 March 2019 and 30 November 2021

- 1 ((serious or severe or chronic or persistent) adj ("mental illness\*" or "mental disorder\$1" or "mental disease")).ti,ab.
- 2 schizophrenia/ or schizophrenia.mp.
- 3 schizotypal personality disorder/ or schizotypal personality disorder\$1.ti,ab.
- 4 ("dementia pr?ecox" or "dementia precox" or schizoaffective or "schizo affective" or schizophreniform or hebephrenia or paraphrenia or oneirophrenia).ti,ab.
- 5 affective psychosis/ or schizoaffective psychosis/ or Capgras syndrome/ or delusional parasitosis/ or Morgellons disease/ or delusional misidentification/ or delusional disorder/
- 6 ("psychotic affective disorder\$1" or capgras or "delusional misidentification" or morgellons or "cotard\$2 syndrome" or "delusional parasitosis" or "delusional disorder\$1" or "psychotic disorder\$1" or psychos#s).ti,ab.
- 7 psychosis/
- 8 paranoid psychosis/ or ("paranoid psychos#s" or "paranoid disorder\$1" or "paranoid ideation" or paranoia).ti,ab.
- 9 ("sander\$2 disease" or "folie a deux" or "boufee delirante" or "sensitiver beziehungswahn").ti,ab.
- 10 exp bipolar disorder/ or bipolar disorder\$1.mp.
- 11 ((manic or bipolar) adj depression\$1).ti,ab.
- 12 mania.ti,ab.
- 13 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12
- 14 cardiovascular disease/ or cardiovascular disease\$1.ti,ab.
- 15 ((coronary or isch?emic) adj2 (disease or occlusion or stenosis or thrombos#s)).ti,ab.
- 16 ischemic heart disease/ or exp acute coronary syndrome/ or exp angina pectoris/ or coronary artery atherosclerosis/ or coronary artery obstruction/ or coronary artery thrombosis/ or exp heart infarction/ or heart muscle ischemia/ or ischemic cardiomyopathy/
- 17 (myocardial adj (isch?emia or infarct\$)).ti,ab.
- 18 angina pectoris/ or angina.ti,ab.
- 19 heart muscle revascularization/
- 20 ((coronary or myocardial or heart or cardiac) adj2 (revasculari?ation or angioplasty or atherectomy or bypass)).ti,ab.
- 21 heart failure/
- 22 ((heart or cardiac or ventricular) adj failure).ti,ab.
- 23 heart ventricle function/
- 24 ((ventricular or systolic or diastolic) adj (dysfunction or impairment)).ti,ab.
- 25 cerebrovascular disease/ or exp brain infarction/ or exp brain ischemia/ or exp cerebrovascular accident/
- 26 (stroke or "cerebrovascular accident" or tia or "transient isc?emic attack").ti,ab.
- 27 ((brain or cerebral or intracranial) adj2 (infarct\$ or thrombos?s or embolism)).ti,ab.
- 28 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27
- 29 13 and 28
- 30 limit 29 to human
- 31 limit 30 to "qualitative (best balance of sensitivity and specificity)"
- 32 30 not 31
- 33 limit 32 to "reviews (best balance of sensitivity and specificity)"
- 34 32 not 33



## PsycInfo via Ovid platform, 1967 to November Week 4 2021

Search dates: 19 September 2017, updated 8 March 2019 and 30 November 2021

- 1 ((serious or severe or chronic or persistent) adj ("mental illness\*" or "mental disorder\$1" or "mental disease")).ti,ab.
- 2 exp schizophrenia/ or schizophrenia.mp.
- 3 exp schizotypal personality disorder/ or Schizotypal Personality Disorder\$1.mp.
- 4 ("dementia praecox" or "dementia precox" or schizoaffective or "schizo affective" or schizophreniform or hebephrenia or paraphrenia or oneirophrenia).mp.
- 5 affective psychosis/ or exp schizoaffective disorder/ or capgras syndrome/
- 6 ("psychotic affective disorder\$1" or capgras or "delusional misidentification syndrome" or morgellons or "cotard\$2 syndrome" or "delusional parasitosis" or "delusional disorder\$1" or "psychotic disorder\$1").mp.
- 7 exp psychosis/ or psychos#s.mp.
- 8 paranoid schizophrenia/ or paranoid personality disorder/ or exp "paranoia (psychosis)"/ or ("paranoid disorder\$1" or "paranoid ideation" or paranoia).mp.
- 9 ("sander\$2 disease" or "folie a deux" or "boufee delirante" or "sensitiver beziehungswahn").mp.
- 10 exp bipolar disorder/ or bipolar disorder\$1.mp.
- 11 ((manic or bipolar) adj depression\$1).ti,ab.
- 12 mania.mp.
- 13 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12
- 14 cardiovascular disorders/ or exp heart disorders/ or exp arteriosclerosis/ or exp ischemia/
- 15 ((coronary or isch?emic) adj2 (disease or occlusion or stenosis or thrombos#s)).ti,ab.
- 16 (myocardial adj (isch?emia or infarct\$)).ti,ab.
- 17 ((coronary or myocardial or heart or cardiac) adj2 (revasculari?ation or angioplasty or atherectomy or bypass)).ti,ab.
- 18 ((heart or cardiac or ventricular) adj failure).ti,ab.
- 19 ((ventricular or systolic or diastolic) adj (dysfunction or impairment)).ti,ab.
- 20 cerebrovascular disorders/ or cerebral arteriosclerosis/ or exp cerebral ischemia/ or cerebrovascular accidents/
- 21 (stroke or "cerebrovascular accident").mp.
- 22 ((brain or cerebral or intracranial) adj2 (infarct\$ or thrombos?s or embolism)).ti,ab.
- 23 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22
- 24 13 and 23
- 25 limit 24 to human

## Cinahl via EBSCO platform

Search dates: 19 September 2017, updated 8 March 2019 and 30 November 2021

| #   | Query                                                                                                                                                                    |
|-----|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| S29 | S27 AND S28                                                                                                                                                              |
| S28 | S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26                                                                           |
| S27 | S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12<br>TI ("brain" OR "cerebral" OR "intracranial") W2 ("infarct*" OR "thrombos?s" OR                |
| S26 | "embolism") OR AB ("brain" OR "cerebral" OR "intracranial") W2 ("infarct*" OR "thrombos?s" OR "embolism")                                                                |
| S25 | ""stroke" OR "cerebrovascular accident""                                                                                                                                 |
| S24 | (MH "Cerebral Ischemia+") OR (MH "Intracranial Arterial Diseases+") OR (MH "Intracranial Embolism and Thrombosis+") OR (MH "Stroke+")                                    |
| S23 | TI ("ventricular" OR "systolic" OR "diastolic") W1 ("dysfunction" OR "impairment") OR AB ("ventricular" OR "systolic" OR "diastolic") W1 ("dysfunction" OR "impairment") |

S22 (MH "Ventricular Dysfunction+")  
 S21 TI ("heart" OR "cardiac" OR "ventricular") W1 "failure" OR AB ("heart" OR "cardiac" OR  
 "ventricular") W1 "failure"  
 S20 (MH "Heart Failure+")  
 S19 TI ("coronary" OR "myocardial" OR "heart" OR "cardiac") W2 ("revasculari#ation" OR  
 "angioplasty" OR "atherectomy" OR "bypass") OR AB ("coronary" OR "myocardial" OR  
 "heart" OR "cardiac") W2 ("revasculari#ation" OR "angioplasty" OR "atherectomy" OR  
 "bypass")  
 S18 (MH "Myocardial Revascularization+")  
 S17 ""angina""  
 S16 TI "myocardial" W1 ("isch#emia" OR "infarct\*") OR AB "myocardial" W1 ("isch#emia" OR  
 "infarct\*")  
 S15 (MH "Myocardial Ischemia+")  
 S14 TI ("coronary" OR "isch#emic") W2 ("disease\*" OR "occlusion" OR "stenos?s" OR  
 "thrombos?s") OR AB ("coronary" OR "isch#emic") W2 ("disease\*" OR "occlusion" OR  
 "stenos?s" OR "thrombos?s")  
 S13 (MH "Cardiovascular Diseases") OR "cardiovascular disease\*"  
 S12 ""mania""  
 S11 TI ("manic" OR "bipolar") W1 "depression\*" OR AB ("manic" OR "bipolar") W1  
 "depression\*"  
 S10 ""bipolar disorder\*""  
 S9 ""folie a deux" OR "boufee delirante" OR "sensitiver beziehungswahn""  
 S8 ""paranoid disorder\*" OR "paranoid ideation" OR "paranoia""  
 S7 ""paranoid disorder\*" OR "paranoid ideation" OR "paranoia""  
 S6 ""psychotic affective disorder\*" OR "capgras" OR "delusional misidentification" OR  
 "morgellons" OR "cotard\*" OR "delusional parasitosis" OR "delusional disorder\*" OR  
 "psychotic disorder\*" OR "psychos?s""  
 S5 ""psychotic affective disorder\*" OR "capgras" OR "delusional misidentification" OR  
 "morgellons" OR "cotard\*" OR "delusional parasitosis" OR "delusional disorder\*" OR  
 "psychotic disorder\*" OR "psychos?s""  
 S4 (MH "Morgellons disease")  
 S3 ""schizophrenia" OR "schizotypal personality disorder\*" OR "dementia pr#ecox" OR  
 "schizo affective " OR "schizo affective" OR "schizophreniform" OR "hebephrenia" OR  
 "paraphrenia" OR "oneirophrenia"" OR (MH "Bipolar Disorder") OR (MH "Schizo affective  
 Disorder")  
 S2 (MH "Psychotic Disorders") OR (MH "Affective Disorders, Psychotic+") OR (MH  
 "Delusions+") OR (MH "Psychoses, Substance-Induced+") OR (MH "Schizophrenia+")  
 S1 TI ("serious" OR "severe" OR "chronic" OR "persistent") W1 ("mental illness\*" OR "mental  
 disorder\*" OR "mental disease\*") OR AB ("serious" OR "severe" OR "chronic" OR  
 "persistent") W1 ("mental illness\*" OR "mental disorder\*" OR "mental disease\*")

## Web of Science conference proceedings abstracts

Search dates: 19 September 2017, updated 8 March 2019 and 30 November 2021

|    |                                                                                                                                                                                                                                |
|----|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 1  | TI=((severe OR serious OR chronic OR persistent) NEAR/1 ("mental illness*" OR "mental disorder*" OR "mental disease*"))                                                                                                        |
| 2  | TI=(schizophrenia OR "schizotypal personality disorder*" OR schizoaffective OR "schizo affective" OR "dementia pr\$ecox" OR schizophreniform OR hebephrenia OR paraphrenia OR oneirophrenia)                                   |
| 3  | TI=("psychotic affective disorder*" OR capgras OR "delusional parasitosis" OR "delusional misidentification syndrome" OR morgellons OR "cotard\$2 syndrome" OR "delusional disorder*" OR "psychotic disorder*" OR "psychos?s") |
| 4  | TI=("paranoid disorder" OR "paranoid ideation" OR paranoia)                                                                                                                                                                    |
| 5  | TI=("sander\$2 disease" OR "folie a deux" OR "boufee delirante" OR "sensitiver beziehungswahn")                                                                                                                                |
| 6  | TS=(bipolar NEAR/2 disorder* OR schizophrenia)                                                                                                                                                                                 |
| 7  | TI=(mania OR (manic NEAR/1 depression))                                                                                                                                                                                        |
| 8  | #7 OR #6 OR #5 OR #4 OR #3 OR #2 OR #1                                                                                                                                                                                         |
| 9  | TS=("cardiovascular disease")                                                                                                                                                                                                  |
| 10 | TI=(coronary NEAR/2 (disease OR occlusion OR stenosis OR thrombosis) OR ischemic NEAR/2 (disease OR occlusion OR stenosis OR thrombosis))                                                                                      |
| 11 | TI=("acute coronary syndrome" OR angina OR "coronary artery atherosclerosis" OR "coronary artery obstruction" OR (heart OR myocardial infarct*))                                                                               |
| 12 | TI=("myocardial ischemia")                                                                                                                                                                                                     |
| 13 | TI=((coronary OR myocardial OR heart OR cardiac) NEAR/2 (revascularization OR angioplasty OR atherectomy OR bypass))                                                                                                           |
| 14 | TI=((heart OR cardiac OR ventricular) NEAR/1 failure)                                                                                                                                                                          |
| 15 | TI=((ventricular OR systolic OR diastolic) NEAR/1 (dysfunction OR impairment))                                                                                                                                                 |
| 16 | TI=("cerebrovascular disease" OR "brain infarction" OR "brain ischemia" OR "cerebrovascular accident" OR stroke OR tia OR "transient ischemic attack")                                                                         |
| 17 | TI=((brain OR cerebral OR intracranial) NEAR/2 (infarct* OR thrombosis or embolism))                                                                                                                                           |
| 18 | #17 OR #16 OR #15 OR #14 OR #13 OR #12 OR #11 OR #10 OR #9                                                                                                                                                                     |
| 19 | #18 AND #8                                                                                                                                                                                                                     |

## Zetoc conference proceedings abstracts

Search dates: 19 September 2017, updated 8 March 2019 and 30 November 2021

|                                  |
|----------------------------------|
| mental cardio*                   |
| mental coronary                  |
| mental myocardial                |
| Mental angina                    |
| Mental heart                     |
| mental cardiac                   |
| Mental ventric*                  |
| schizo* cardio*                  |
| schizo* coronary                 |
| schizo* myocardial               |
| Schizo* angina                   |
| schizo* heart                    |
| schizo* cardiac                  |
| schizo* ventric*                 |
| bipolar disorder cardio*         |
| bipolar disorder coronary        |
| bipolar disorder myocardial      |
| bipolar disorder angina          |
| bipolar disorder heart           |
| bipolar disorder cardiac         |
| bipolar disorder ventric*        |
| bipolar disorder stroke          |
| schizophrenia stroke             |
| mental ischaemi*                 |
| schizo* ischaemi*                |
| bipolar disorder ischemi*        |
| bipolar disorder ischaemi*       |
| schizo* ischemi*                 |
| mental ischemi*                  |
| bipolar disorder cerebrovascular |
| schizo* cerebrovascular          |
| psychosis cardio*                |
| Psychosis coronary               |
| Psychosis myocardial             |
| Psychosis angina                 |
| Psychosis heart                  |
| psychosis cardiac                |
| psychosis ventric*               |
| psychosis stroke                 |
| psychosis cerebrovascular        |

## Cochrane database

Search dates: 19 September 2017, updated 9 March 2019 (Cochrane reviews and systematic reviews), 10 September 2019 (CENTRAL trials register, trials added up to 8 March 2019 only) and 1 December 2021

| ID  | Search term                                                                                                                     |
|-----|---------------------------------------------------------------------------------------------------------------------------------|
| #1  | ((serious or severe or chronic or persistent) next ("mental illness*" or "mental disorder*" or "mental disease"))               |
| #2  | schizophrenia or schizoaffective or schizotypal or schizophreniform                                                             |
| #3  | bipolar near/2 disorder                                                                                                         |
| #4  | "psychotic disorder" or psychosis or psychotic                                                                                  |
| #5  | delusional (disorder or parasitosis or misidentification)                                                                       |
| #6  | paranoid (disorder or ideation) or paranoia                                                                                     |
| #7  | "manic depression" or mania                                                                                                     |
| #8  | MeSH descriptor: [Bipolar and Related Disorders] explode all trees                                                              |
| #9  | MeSH descriptor: [Psychoses, Substance-Induced] explode all trees                                                               |
| #10 | MeSH descriptor: [Schizophrenia Spectrum and Other Psychotic Disorders] explode all trees                                       |
| #11 | {or #1-#10}                                                                                                                     |
| #12 | cardiovascular disease*                                                                                                         |
| #13 | (coronary or ischaemic or ischemic) near/2 (disease or occlusion or stenosis or thrombosis)                                     |
| #14 | ("coronary" or "myocardial" or "heart" or "cardiac") near/2 ("revascularization" or "angioplasty" or "atherectomy" or "bypass") |
| #15 | (heart or cardiac or ventricular) next (failure or dysfunction or impairment)                                                   |
| #16 | stroke or "cerebrovascular accident"                                                                                            |
| #17 | transient ischemic attack                                                                                                       |
| #18 | MeSH descriptor: [Cardiovascular Diseases] explode all trees                                                                    |
| #19 | MeSH descriptor: [Stroke] explode all trees                                                                                     |
| #20 | MeSH descriptor: [Heart Failure] explode all trees                                                                              |
| #21 | MeSH descriptor: [Myocardial Revascularization] explode all trees                                                               |
| #22 | {or #12-#21}                                                                                                                    |
| #23 | #11 and #22                                                                                                                     |

## APPENDIX III SYSTEMATIC REVIEW DATA EXTRACTION FORM

**Appendix table III.1: List of variables extracted from eligible studies**

| Variable list                                                                             |         |                    |
|-------------------------------------------------------------------------------------------|---------|--------------------|
| Date of extraction                                                                        |         |                    |
| Record number (Endnote)                                                                   |         |                    |
| Author/year                                                                               |         |                    |
| If same study, why is this record different?                                              |         |                    |
| Country                                                                                   |         |                    |
| Source of Data                                                                            |         |                    |
| Setting                                                                                   |         |                    |
| Period of Data Collecting                                                                 |         |                    |
| Period of results                                                                         |         |                    |
| SMI definition                                                                            |         |                    |
| CVD definition                                                                            |         |                    |
| Diagnosis type (schizophrenia, bipolar disorder, mixed SMI)                               |         |                    |
| Control group (general population, no SMI)                                                |         |                    |
| Inclusion criteria Case                                                                   |         |                    |
| Inclusion Criteria Control                                                                |         |                    |
| Design (cohort, case-control)                                                             |         |                    |
| N Case                                                                                    |         |                    |
| N Controls                                                                                |         |                    |
| Number of extra covariates used in the analysis (excluding age and sex)                   |         |                    |
| Type of covariates used in the analysis (if SMR assume have matched by age, sex and year) |         |                    |
| Follow-up (years mean)                                                                    |         |                    |
| N Cerebrovascular                                                                         | P, M, F | Exposed, unexposed |
| N CHD                                                                                     | P, M, F | Exposed, unexposed |
| N HEART FAILURE                                                                           | P, M, F | Exposed, unexposed |
| N CVD                                                                                     | P, M, F | Exposed, unexposed |
| N Cerebrovascular DEATH                                                                   | P, M, F | Exposed, unexposed |
| N CHD DEATH                                                                               | P, M, F | Exposed, unexposed |
| N CVD DEATH                                                                               | P, M, F | Exposed, unexposed |
| Risk ratio Cerebrovascular                                                                | P, M, F | Adj, unadj         |
| Risk ratio 95% confidence limits                                                          | P, M, F | Adj, unadj         |
| Risk ratio CHD                                                                            | P, M, F | Adj, unadj         |
| Risk ratio 95% confidence limits                                                          | P, M, F | Adj, unadj         |
| Risk ratio HF                                                                             | P, M, F | Adj, unadj         |
| Risk ratio 95% confidence limits                                                          | P, M, F | Adj, unadj         |
| Risk ratio CVD                                                                            | P, M, F | Adj, unadj         |
| Risk ratio 95% confidence limits                                                          | P, M, F | Adj, unadj         |
| Risk ratio DEATH Cerebrovascular                                                          | P, M, F | Adj, unadj         |
| Risk ratio 95% confidence limits                                                          | P, M, F | Adj, unadj         |

| Variable list                    |         |            |
|----------------------------------|---------|------------|
| Risk ratio DEATH CHD             | P, M, F | Adj, unadj |
| Risk ratio 95% confidence limits | P, M, F | Adj, unadj |
| Risk ratio DEATH CVD             | P, M, F | Adj, unadj |
| Risk ratio 95% confidence limits | P, M, F | Adj, unadj |
| Rate Ratio Cerebrovascular       | P, M, F | Adj, unadj |
| Rate ratio 95% confidence limits | P, M, F | Adj, unadj |
| Rate Ratio CHD                   | P, M, F | Adj, unadj |
| Rate ratio 95% confidence limits | P, M, F | Adj, unadj |
| Rate Ratio HF                    | P, M, F | Adj, unadj |
| Rate ratio 95% confidence limits | P, M, F | Adj, unadj |
| Rate Ratio CVD                   | P, M, F | Adj, unadj |
| Rate ratio 95% confidence limits | P, M, F | Adj, unadj |
| Rate Ratio DEATH Cerebrovascular | P, M, F | Adj, unadj |
| Rate ratio 95% confidence limits | P, M, F | Adj, unadj |
| Rate Ratio DEATH CHD             | P, M, F | Adj, unadj |
| Rate ratio 95% confidence limits | P, M, F | Adj, unadj |
| Rate Ratio DEATH CVD             | P, M, F | Adj, unadj |
| Rate ratio 95% confidence limits | P, M, F | Adj, unadj |
| HR CEREBROVASCULAR               | P, M, F | Adj, unadj |
| HR 95% confidence limits         | P, M, F | Adj, unadj |
| HR CHD                           | P, M, F | Adj, unadj |
| HR 95% confidence limits         | P, M, F | Adj, unadj |
| HR HEART FAILURE                 | P, M, F | Adj, unadj |
| HR 95% confidence limits         | P, M, F | Adj, unadj |
| HR CVD                           | P, M, F | Adj, unadj |
| HR 95% confidence limits         | P, M, F | Adj, unadj |
| HR DEATH Cerebrovascular         | P, M, F | Adj, unadj |
| HR 95% confidence limits         | P, M, F | Adj, unadj |
| HR DEATH CHD                     | P, M, F | Adj, unadj |
| HR 95% confidence limits         | P, M, F | Adj, unadj |
| HR DEATH CVD                     | P, M, F | Adj, unadj |
| HR 95% confidence limits         | P, M, F | Adj, unadj |
| OR Cerebrovascular               | P, M, F | Adj, unadj |
| OR 95% confidence limits         | P, M, F | Adj, unadj |
| OR CHD                           | P, M, F | Adj, unadj |
| OR 95% confidence limits         | P, M, F | Adj, unadj |
| OR HEART FAILURE                 | P, M, F | Adj, unadj |
| OR 95% confidence limits         | P, M, F | Adj, unadj |
| OR CVD                           | P, M, F | Adj, unadj |
| OR 95% confidence limits         | P, M, F | Adj, unadj |
| SMR Cerebrovascular              | P, M, F | Unadj      |
| SMR 95% confidence limits        | P, M, F | Unadj      |
| SMR CHD                          | P, M, F | Unadj      |
| SMR CHD 95% confidence limits    | P, M, F | Unadj      |
| SMR HEART FAILURE                | P, M, F | Unadj      |

| Variable list                                                                                                                                                                                                                                                                                                                                                                         |                    |       |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------|-------|
| SMR HF 95% confidence limits                                                                                                                                                                                                                                                                                                                                                          | P, M, F            | Unadj |
| SMR CVD                                                                                                                                                                                                                                                                                                                                                                               | P, M, F            | Unadj |
| SMR CVD 95% confidence limits                                                                                                                                                                                                                                                                                                                                                         | P, M, F            | Unadj |
| Mean age baseline                                                                                                                                                                                                                                                                                                                                                                     | Exposed, unexposed |       |
| SD age baseline                                                                                                                                                                                                                                                                                                                                                                       | Exposed, unexposed |       |
| Male (%)                                                                                                                                                                                                                                                                                                                                                                              | Exposed, unexposed |       |
| Basal BMI                                                                                                                                                                                                                                                                                                                                                                             | Exposed, unexposed |       |
| SD BMI                                                                                                                                                                                                                                                                                                                                                                                | Exposed, unexposed |       |
| White ethnicity %                                                                                                                                                                                                                                                                                                                                                                     | Exposed, unexposed |       |
| Alcohol comorbidity %                                                                                                                                                                                                                                                                                                                                                                 | Exposed, unexposed |       |
| Substance abuse %                                                                                                                                                                                                                                                                                                                                                                     | Exposed, unexposed |       |
| Obesity %                                                                                                                                                                                                                                                                                                                                                                             | Exposed, unexposed |       |
| Diabetes %                                                                                                                                                                                                                                                                                                                                                                            | Exposed, unexposed |       |
| Congestive Heart Failure %                                                                                                                                                                                                                                                                                                                                                            | Exposed, unexposed |       |
| Coronary Artery Disease %                                                                                                                                                                                                                                                                                                                                                             | Exposed, unexposed |       |
| Stroke %                                                                                                                                                                                                                                                                                                                                                                              | Exposed, unexposed |       |
| Any Baseline CVD                                                                                                                                                                                                                                                                                                                                                                      | Exposed, unexposed |       |
| Hypertension %                                                                                                                                                                                                                                                                                                                                                                        | Exposed, unexposed |       |
| Hyperlipidemia %                                                                                                                                                                                                                                                                                                                                                                      | Exposed, unexposed |       |
| Smoking %                                                                                                                                                                                                                                                                                                                                                                             | Exposed, unexposed |       |
| CKD/Renal %                                                                                                                                                                                                                                                                                                                                                                           | Exposed, unexposed |       |
| Respiratory %                                                                                                                                                                                                                                                                                                                                                                         | Exposed, unexposed |       |
| Married %                                                                                                                                                                                                                                                                                                                                                                             | Exposed, unexposed |       |
| Employed %                                                                                                                                                                                                                                                                                                                                                                            | Exposed, unexposed |       |
| Poor income %                                                                                                                                                                                                                                                                                                                                                                         | Exposed, unexposed |       |
| Least Urbanized %                                                                                                                                                                                                                                                                                                                                                                     | Exposed, unexposed |       |
| Is age at diagnosis between 16 and 65?                                                                                                                                                                                                                                                                                                                                                |                    |       |
| Limitations                                                                                                                                                                                                                                                                                                                                                                           |                    |       |
| Medication                                                                                                                                                                                                                                                                                                                                                                            |                    |       |
| Notes                                                                                                                                                                                                                                                                                                                                                                                 |                    |       |
| SMI – severe mental illness, CHD – coronary heart disease, CVD – cardiovascular disease, N – number, HR – hazard ratio, OR – odds ratio, SMR – standardised mortality ratio, P – persons, M – males, F – females, Unad – results from models adjusted for age and sex only, Adj – fully adjusted models, SD – standard deviation, BMI – body mass index, CKD – chronic kidney disease |                    |       |

Adapted from data extraction form kindly supplied by first and second authors of previous review <sup>1</sup>

<sup>1</sup> Correll CU, Solmi M, Veronese N, Bortolato B, Rosson S, Santonastaso P, et al. Prevalence, incidence and mortality from cardiovascular disease in patients with pooled and specific severe mental illness: A large-scale meta-analysis of 3,211,768 patients and 113,383,368 controls. *World Psychiatry* 2017;16(2):163-80.



## APPENDIX IV EXAMPLE CALCULATIONS FOR ESTIMATING NUMBERS OF EXPOSED AND CONTROLS WHERE NOT REPORTED BY PRIMARY STUDIES

The number of people with SMI and number of controls for age groups 18-49 years and 50-75 years were unreported in a 2007 UK study of primary care records.<sup>1</sup> To estimate these numbers, the following methodology was used.

- The total number of SMI exposed and controls for ages 18+ years were reported as 461,36 and 300,246, respectively
- The median and interquartile age ranges for exposed and controls were extracted from the study, which were median: 46.4, IQR: 32.2-63.7 and median: 38.0, IQR: 26.3-55.8, respectively
- The distribution of the 2001 UK population aged 18 years and over by single year of age was calculated by summing the results from all local authorities.<sup>2</sup>
- The percentages of the UK population for each year of age were calculated
- For UK as a whole, the median age was 45 years and the IQR 32-60.5
- The UK population was thus slightly younger than the exposed population in the study but older than the control population
- Two sets of weighting factors were applied to the UK population percentages to adjust the age distribution so that the median and IQR roughly matched a) the exposed and b) the control study populations
- The weighted percentages were applied to the number of exposed and controls from the study (*i.e* 46,136 and 300,246) to give an estimated number exposed and controls for each year of age
- The estimated numbers of exposed and controls were summed for ages 18-49 and 50-75 years to calculate the estimated numbers for these age groups
- The estimated exposed population numbers were further broken down into schizophrenia and bipolar disorder using the percentages reported in the paper (40.2% schizophrenia and 23.3% bipolar disorder)

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<sup>1</sup> Osborn D, Levy G, Nazareth I, Petersen I, Islam A, King M. Relative risk of cardiovascular and cancer mortality in people with severe mental illness from the United Kingdom's general practice research database. *Arch Gen Psychiatry*. 2007;64(2):242 - 9.

<sup>2</sup> Office for National Statistics. Estimates of the population for the UK, England and Wales, Scotland and Northern Ireland 2020 [accessed June 15, 2020]. Available from: <https://www.ons.gov.uk/peoplepopulationandcommunity/populationandmigration/populationestimates/datasets/populationestimatesforukenglandandwalesscotlandandnorthernireland>.

## APPENDIX V RISK OF BIAS FORMS FOR MORTALITY AND INCIDENCE STUDIES

**Appendix table V.1: Risk of bias form for cohort studies**

|                                   |                                                                                                 | Assessment                                                                                                                        |                                                                                                                                                                                |                                                                                                                                      |
|-----------------------------------|-------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------|
| Risk of bias assessment criteria: |                                                                                                 | Yes                                                                                                                               | Unclear                                                                                                                                                                        | No                                                                                                                                   |
| Selection                         | Truly or somewhat representative of the average person with SMI in the community                | Community setting                                                                                                                 | People from insurance claims databases, inpatients (but not long stay) - likely to be more severe cases, but in some countries most people with SMI are admitted at some stage | Long stay inpatients, specific ethnic, sex, occupation groups. People on specific medication <i>e.g.</i> lithium, clozapine          |
|                                   | Non-exposed drawn from the same community as the exposed cohort                                 | Matched or unmatched controls from same database source as cases                                                                  | General population for same geographic area as cases. Whole population register studies with cohort follow-up.                                                                 | General population from larger or different geographic area. Any study using population mortality rates to calculate expected rates. |
|                                   | Ascertainment of exposure from secure record <i>e.g.</i> medical record or structured interview | Clinical records in administrative databases. Medical insurance claims databases with high population coverage <i>e.g.</i> Taiwan | Records from most insurance claims databases                                                                                                                                   | Self-reported diagnosis or based on sickness or disability records without validation.                                               |
|                                   | Demonstration that CVD was not present at start of study                                        | Good methodology for excluding people with prior CVD                                                                              | Some description of methods for excluding people with CVD, but unclear whether effective. May exclude people with some but not all CVD diagnoses <i>e.g.</i> stroke but not MI | Any outcome of CVD mortality if previous CVD not accounted for                                                                       |
| Comparability                     | Study controls for age and sex                                                                  | All papers should control for age and sex, either by matching or in analysis                                                      | Could be CT if very broad age groups (age bands >10 years)                                                                                                                     | Shouldn't be any in this category                                                                                                    |
|                                   | Study controls for any additional sociodemographic factor (Deprivation, ethnicity,              | More than one factor sociodemographic factor (Deprivation, ethnicity,                                                             | Only one sociodemographic factor                                                                                                                                               | No sociodemographic factors                                                                                                          |

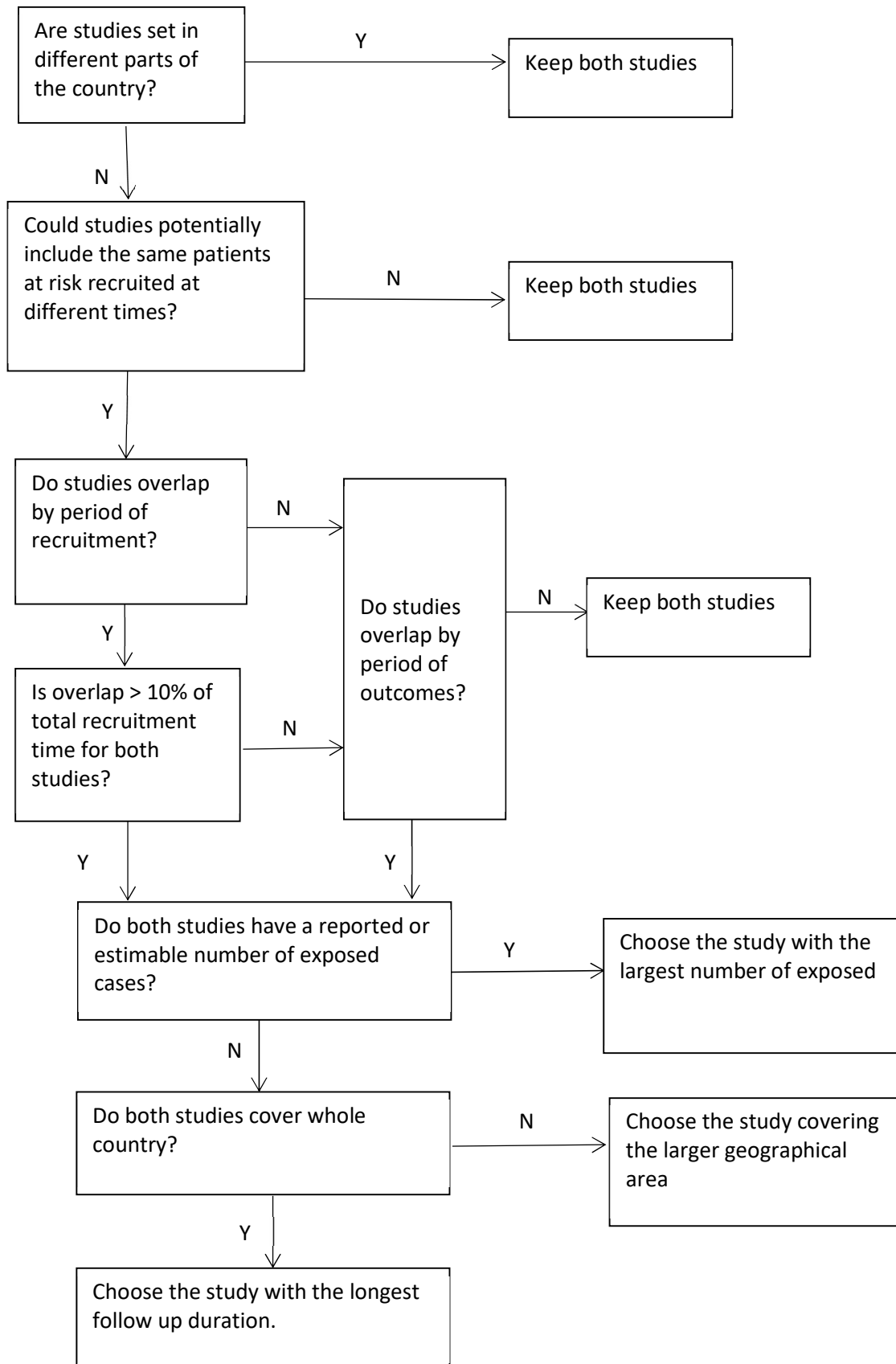
|                                   |                                                                                                                                                                                                                                                                                                                                                                                                 | Assessment                                                                                                                                                                                    |                                                                                                                                                           |                                                                       |
|-----------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------|
| Risk of bias assessment criteria: |                                                                                                                                                                                                                                                                                                                                                                                                 | Yes                                                                                                                                                                                           | Unclear                                                                                                                                                   | No                                                                    |
|                                   | ethnicity, other sociodemographic)                                                                                                                                                                                                                                                                                                                                                              | sociodemographic, income, employment, urban/rural, education, etc)                                                                                                                            |                                                                                                                                                           |                                                                       |
|                                   | Have the authors taken account of any additional lifestyle confounding factors (in design or analysis)?                                                                                                                                                                                                                                                                                         | Several of: Smoking, BMI, BP, comorbidity, alcohol, medication. (Diabetes plus another relevant comorbidity would fall into this category.)                                                   | One of: Smoking, BMI, BP, comorbidity, alcohol, medication (if two medications <i>e.g.</i> cholesterol lowering + BP lowering, then put in this category) | None                                                                  |
| Outcome                           | Assessment of CVD by independent blind assessment or record linkage. Was the outcome accurately measured to minimise bias?<br>• do the measurements truly reflect what you want them to (have they been validated)<br>• has a reliable system been established for detecting all the cases (for measuring disease occurrence)<br>• were the measurement methods similar in the different groups | For deaths or CVD events with no indication of prior CVD diagnosis we can't be sure of ascertaining all cases. Studies only fall in this category if they capture all CHD or stroke diagnoses | Linked records. Best mortality studies have autopsy-confirmed CVD deaths                                                                                  | Patient reported outcome                                              |
|                                   | Was follow-up long enough for outcomes to occur (min of 5 years)                                                                                                                                                                                                                                                                                                                                | All follow-up at least 5 years or if likely that the majority (>90%) are over 5 years.                                                                                                        | Mean at least 5 years                                                                                                                                     | Mean less than 5 years                                                |
|                                   | Adequacy of follow-up of SMI and non-SMI cohorts: complete follow-up - all subjects accounted for or subjects lost to follow-up unlikely to introduce bias or statement that loss to follow-up in both groups was similar                                                                                                                                                                       | Small rate of loss to follow-up or statement accounting for all subjects. Scandinavian (and Taiwanese) studies could fall into this category                                                  | Studies where it is unclear if people leaving the area would have affected results or if follow-up is specifically mentioned                              | High levels of loss to follow-up or no mention of numbers followed up |

**Appendix table V.2: Risk of bias form for case-control studies**

|                                   |                                                                                                            | Assessment                                                                                                                               |                                                                                                                                                                                |                                                                              |
|-----------------------------------|------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------|
| Risk of bias assessment criteria: |                                                                                                            | Yes                                                                                                                                      | Unclear                                                                                                                                                                        | No                                                                           |
| Selection                         | Adequate definition of cases with CVD                                                                      | All cases of CVD captured and validated. If deaths, then are we sure that cases include all people with previous CVD diagnosis.          | Some description of methods for excluding people with CVD, but unclear whether effective. May exclude people with some but not all CVD diagnoses <i>e.g.</i> stroke but not MI | No info on case definition                                                   |
|                                   | Cases with CVD are representative of defined population and reliable system used for selecting cases       | Cases are representative and selection bias unlikely                                                                                     | Unclear if selection bias                                                                                                                                                      | Could be selection bias                                                      |
|                                   | Selection of controls without CVD                                                                          | Controls selected from community and representative of defined population                                                                | Hospital controls                                                                                                                                                              | No info on selection of controls                                             |
|                                   | Definition of controls - demonstration of no history of CVD                                                | Good methodology for selecting controls with no history of CVD                                                                           | Some description of methods for excluding people with CVD, but unclear whether effective. May exclude people with some but not all CVD diagnoses <i>e.g.</i> stroke but not MI | Any outcome of CVD mortality or CVD events if previous CVD not accounted for |
| Comparability                     | Study controls for age and sex                                                                             | All papers should control for age and sex, either by matching or in analysis                                                             | Could be CT if very broad age groups (age bands >10 years)                                                                                                                     | Shouldn't be any in this category                                            |
|                                   | Study controls for any additional sociodemographic factor (Deprivation, ethnicity, other sociodemographic) | More than one factor sociodemographic factor (Deprivation, ethnicity, sociodemographic, income, employment, urban/rural, education, etc) | Only one sociodemographic factor                                                                                                                                               | No sociodemographic factors                                                  |

|                                   |                                                                                                                                                                                                                                                                                                          | Assessment                                                                                                                                             |                                                                                                                                                           |                                                                                        |
|-----------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------|
| Risk of bias assessment criteria: |                                                                                                                                                                                                                                                                                                          | Yes                                                                                                                                                    | Unclear                                                                                                                                                   | No                                                                                     |
|                                   | Study controls for additional lifestyle factor                                                                                                                                                                                                                                                           | Several of: Smoking, BMI, BP, comorbidity, alcohol, medication. (Diabetes plus another relevant comorbidity would fall into this category.)            | One of: Smoking, BMI, BP, comorbidity, alcohol, medication (if two medications <i>e.g.</i> cholesterol lowering + BP lowering, then put in this category) | None                                                                                   |
| Exposure                          | Ascertainment of exposure from secure record <i>e.g.</i> medical record or structured interview <ul style="list-style-type: none"> <li>do the measurements truly reflect what you want them to (have they been validated)</li> <li>were the measurement methods similar in cases and controls</li> </ul> | Do we assume that clinical records in admin databases are good quality? Some studies have done more to confirm diagnoses. Are those of better quality? | Records from insurance claims databases - or are they good quality?                                                                                       | Self-reported diagnosis or based on sickness or disability records without validation. |
|                                   | Does SMI exposure precede CVD outcome?                                                                                                                                                                                                                                                                   | Yes                                                                                                                                                    | Unclear                                                                                                                                                   | No                                                                                     |
|                                   | Same method of ascertainment for cases and controls                                                                                                                                                                                                                                                      | Same method used                                                                                                                                       | Unclear if different methods are used                                                                                                                     | No info on method of ascertainment                                                     |
|                                   | Non-response rate                                                                                                                                                                                                                                                                                        | Same rate for both groups                                                                                                                              | Unclear if cases have a different response rate from controls                                                                                             | No info on non-response rate                                                           |

## APPENDIX VI DECISION RULES FOR OVERLAPPING STUDIES



## APPENDIX VII LIST OF INCLUDED MORTALITY STUDIES

| Study ID          | Article                                                                                                                                                                                                                                                             |
|-------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Ahrens, 1995      | Ahrens, B., Müller-Oerlinghausen, B., Schou, M., Wolf, T., Alda, M., Grof, E., et al. (1995). Excess cardiovascular and suicide mortality of affective disorders may be reduced by lithium prophylaxis. <i>Journal of Affective Disorders</i> , 33(2), 67-75.       |
| Ajetunmobi, 2013  | Ajetunmobi, O., Taylor, M., Stockton, D., & Wood, R. (2013). Early death in those previously hospitalised for mental healthcare in Scotland: A nationwide cohort study, 1986-2010. <i>BMJ Open</i> , 3(7), e002768.                                                 |
| Allebeck, 1986    | Allebeck, P., & Wistedt, B. (1986). Mortality in Schizophrenia: A Ten-Year Follow-up Based on the Stockholm County Inpatient Register. <i>Archives of General Psychiatry</i> , 43(7), 650-653.                                                                      |
| Anderson, 1991    | Anderson, C., Connelly, J., Johnstone, E. C., & Owens, D. G. C. (1991). Disabilities and circumstances of schizophrenic patients - A follow-up study: V. Cause of death. <i>British Journal of Psychiatry</i> , 159(OCT. SUPPL. 13), 30-33.                         |
| Angst, 2002       | Angst, F., Stassen, H. H., Clayton, P. J., & Angst, J. (2002). Mortality of patients with mood disorders: follow-up over 34-38 years. <i>Journal of Affective Disorders</i> , 68(2-3), 167-181.                                                                     |
| Bjorkenstam, 2012 | Björkenstam, E., Ljung, R., Burström, B., Mittendorfer-Rutz, E., Hallqvist, J., & Weitoft, G. R. (2012). Quality of medical care and excess mortality in psychiatric patients—a nationwide register-based study in Sweden. <i>BMJ Open</i> , 2(1).                  |
| Brink, 2018       | Brink, M., Green, A., Bojesen, A. B., Lamberti, J. S., Conwell, Y., & Andersen, K. (2018). Excess medical comorbidity and mortality across the lifespan in schizophrenia.: A nationwide Danish register study. <i>Schizophrenia Research</i> .                      |
| Brodersen, 2000   | Brodersen, A., Licht, R. W., Vestergaard, P., Olesen, A. V., & Mortensen, P. B. (2000). Sixteen-year mortality in patients with affective disorder commenced on lithium. <i>British Journal of Psychiatry</i> , 176, 429-433.                                       |
| Brook, 1984       | Brook, O. H. (1985). Mortality in the long-stay population of Dutch mental hospitals. <i>Acta Psychiatr Scand</i> , 71(6), 626-635.                                                                                                                                 |
| Brown, 2010       | Brown, S., Kim, M., Mitchell, C., & Inskip, H. (2010). Twenty-five year mortality of a community cohort with schizophrenia. <i>Br J Psychiatr</i> , 196(2), 116 - 121.                                                                                              |
| Buda, 1988        | Buda, M., Tsuang, M. T., & Fleming, J. A. (1988). Causes of Death in DSM-III Schizophrenics and Other Psychotics (Atypical Group): A Comparison With the General Population. <i>Archives of General Psychiatry</i> , 45(3), 283-285.                                |
| Callaghan, 2014   | Callaghan, R. C., Veldhuizen, S., Jeysingh, T., Orlan, C., Graham, C., Kakouris, G., et al. (2014). Patterns of tobacco-related mortality among individuals diagnosed with schizophrenia, bipolar disorder, or depression. <i>J Psychiatr Res</i> , 48(1), 102-110. |
| Casadebaig, 1999  | Casadebaig, F., & Philippe, A. (1999). Mortality among schizophrenic patients. <i>Encephale-Revue De Psychiatrie Clinique Biologique Et Therapeutique</i> , 25(4), 329-337.                                                                                         |
| Castagnini, 2013  | Castagnini, A., Foldager, L., & Bertelsen, A. (2013). Excess mortality of acute and transient psychotic disorders: comparison with bipolar affective disorder and schizophrenia. <i>Acta Psychiatr Scand</i> , 128(5), 370-375.                                     |
| Chan, 2021        | Chan, J. K. N., Wong, C. S. M., Yung, N. C. L., Chen, E. Y. H., & Chang, W. C. (2021). Excess mortality and life-years lost in people with bipolar disorder: an 11-year population-based cohort study. <i>Epidemiology and psychiatric sciences</i> , 30, e39.      |
| Crump, 2013a      | Crump, C., Sundquist, K., & Sundquist, J. (2013). Comorbidities and mortality in persons with schizophrenia: a Swedish national cohort study. <i>Am J Psychiatr</i> , 170, 324 - 333.                                                                               |
| Crump, 2013b      | Crump, C., Sundquist, K., Winkleby, M. A., & Sundquist, J. (2013). Comorbidities and mortality in bipolar disorder: A swedish national cohort study. <i>JAMA Psychiatry</i> , 70(9), 931-939.                                                                       |

| Study ID          | Article                                                                                                                                                                                                                                                                                        |
|-------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Cunningham, 2014* | Cunningham, R., Peterson, D., Sarfati, D., Stanley, J., & Collings, S. (2014). Premature mortality in adults using New Zealand psychiatric services. <i>New Zealand Medical Journal</i> , 127(1394), 31-41.                                                                                    |
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| Das-Munshi, 2017  | Das-Munshi, J., Chang, C. K., Dutta, R., Morgan, C., Nazroo, J., Stewart, R., & Prince, M. J. (2017). Ethnicity and excess mortality in severe mental illness: a cohort study. <i>The Lancet Psychiatry</i> , 4(5), 389-399.                                                                   |
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| Hayes, 2017       | Hayes, J. F., Marston, L., Walters, K., King, M. B., Osborn, D. P., & Osborn, D. P. J. (2017). Mortality gap for people with bipolar disorder and schizophrenia: UK-based cohort study 2000-2014. <i>British Journal of Psychiatry</i> , 211(3), 175-181.                                      |
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| Hoang, 2011       | Hoang, U., Stewart, R., & Goldacre, M. J. (2011). Mortality after hospital discharge for people with schizophrenia or bipolar disorder: retrospective study of linked English hospital episode statistics, 1999-2006. <i>BMJ</i> , 343, d5422.                                                 |
| Høye, 2011        | Høye, A., Jacobsen, B. K., & Hansen, V. (2011). Increasing mortality in schizophrenia: are women at particular risk? A follow-up of 1111 patients admitted during 1980-2006 in Northern Norway. <i>Schizophrenia Research</i> , 132(2-3), 228-232.                                             |



| Study ID          | Article                                                                                                                                                                                                                                                                                                                                                               |
|-------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| John, 2018        | John, A., McGregor, J., Jones, I., Lee, S. C., Walters, J. T. R., Owen, M. J., . . . Lloyd, K. (2018). Premature mortality among people with severe mental illness - New evidence from linked primary care data. <i>SCHIZOPHRENIA RESEARCH</i> , 199, 154-162.                                                                                                        |
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| Kiviniemi, 2010   | Kiviniemi, M., Suvisaari, J., Pirkola, S., Hakkinen, U., Isohanni, M., & Hakko, H. (2010). Regional differences in five-year mortality after a first episode of schizophrenia in Finland. <i>Psychiatr Serv</i> , 61(3), 272-279.                                                                                                                                     |
| Kredentser, 2014* | Kredentser, M. S., Martens, P. J., Chochinov, H. M., & Prior, H. J. (2014). Cause and rate of death in people with schizophrenia across the lifespan: A population-based study in Manitoba, Canada. <i>Journal of Clinical Psychiatry</i> , 75(2), 154-160.                                                                                                           |
| Lahti, 2012       | Lahti, M., Tiihonen, J., Wildgust, H., Beary, M., Hodgson, R., Kajantie, E., et al. (2012). Cardiovascular morbidity, mortality and pharmacotherapy in patients with schizophrenia. <i>Psychological medicine</i> , 42(11), 2275-2285.                                                                                                                                |
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| Laursen, 2013     | Laursen, T. M., Wahlbeck, K., Hallgren, J., Westman, J., Ösby, U., Alinaghizadeh, H., et al. (2013). Life expectancy and death by diseases of the circulatory system in patients with bipolar disorder or schizophrenia in the Nordic countries. <i>PLOs ONE</i> , 8(6), e67133.                                                                                      |
| Laursen, 2014     | Laursen, T. M., Mortensen, P. B., MacCabe, J. H., Cohen, D., & Gasse, C. (2014). Cardiovascular drug use and mortality in patients with schizophrenia or bipolar disorder: a Danish population-based study. <i>Psychological Medicine</i> , 44(8), 1625-1637.                                                                                                         |
| Laursen, 2019     | Laursen, T. M., Plana-Ripoll, O., Andersen, P. K., McGrath, J. J., Toender, A., Nordentoft, M., . . . Erlangsen, A. (2019). Cause-specific life years lost among persons diagnosed with schizophrenia: Is it getting better or worse? <i>Schizophrenia research</i> , 206, 284-290.                                                                                   |
| Lawrence, 2003    | Lawrence, D. M., Holman, C. D. a. J., Jablensky, A. V., & Hobbs, M. S. T. (2003). Death rate from ischaemic heart disease in Western Australian psychiatric patients 1980-1998. <i>Br J Psychiatry</i> , 182, 31-36.                                                                                                                                                  |
| Lawrence, 2013*   | Lawrence, D., Hancock, K., & Kisely, S. (2013). The gap in life expectancy from preventable physical illness in psychiatric patients in Western Australia: retrospective analysis of population based registers. <i>BMI</i> , 346, f2539.                                                                                                                             |
| Lemogne, 2013     | Lemogne, C., Nabi, H., Melchior, M., Goldberg, M., Limosin, F., Consoli, S. M., & Zins, M. (2013). Mortality associated with depression as compared with other severe mental disorders: a 20-year follow-up study of the GAZEL cohort. <i>Journal of Psychiatric Research</i> , 47(7), 851-857.                                                                       |
| Lesage, 2015**    | Lesage A, Rochette L, Émond V, Pelletier É, St-Laurent D, Diallo FB, et al. (2015). A Surveillance System to Monitor Excess Mortality of People With Mental Illness in Canada. <i>Canadian Journal of Psychiatry</i> , 60(12), 571-579.                                                                                                                               |

| Study ID            | Article                                                                                                                                                                                                                                                                                                                                                                  |
|---------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Lumme, 2016*        | Lumme, S., Pirkola, S., Manderbacka, K., & Keskimäki, I. (2016). Excess Mortality in Patients with Severe Mental Disorders in 1996-2010 in Finland. <i>PLoS ONE</i> , 11(3), e0152223.                                                                                                                                                                                   |
| Manderbacka, 2012   | Manderbacka K, Arffman M, Sund R, Haukka J, Keskimäki I, Wahlbeck K. (2012). How does a history of psychiatric hospital care influence access to coronary care: a cohort study. <i>BMJ Open</i> , 2(2), e000831.                                                                                                                                                         |
| Morden, 2012        | Morden, N. E., Lai, Z., Goodrich, D. E., MacKenzie, T., McCarthy, J. F., Austin, K., et al. M. (2012). Eight-year trends of cardiometabolic morbidity and mortality in patients with schizophrenia. <i>Gen Hosp Psychiatry</i> , 34(4), 368-379.                                                                                                                         |
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| Mortensen, 1993     | Mortensen, P. B., & Juel, K. (1993). Mortality and causes of death in first admitted schizophrenic patients. <i>British Journal of Psychiatry</i> , 163(AUG.), 183-189.                                                                                                                                                                                                  |
| Murray-Thomas, 2013 | Murray-Thomas, T., Jones, M. E., Patel, D., Brunner, E., Shatapathy, C. C., Motsko, S., & Van Staa, T. P. (2013). Risk of mortality (including sudden cardiac death) and major cardiovascular events in atypical and typical antipsychotic users: a study with the general practice research database. <i>Cardiovascular Psychiatry &amp; Neurology</i> , 247486-247486. |
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| Nordentoft, 2013    | Nordentoft, M., Wahlbeck, K., Hallgren, J., Westman, J., Ösby, U., Alinaghizadeh, H., et al. (2013). Excess mortality, causes of death and life expectancy in 270,770 patients with recent onset of mental disorders in Denmark, Finland and Sweden. <i>PLoS ONE</i> , 8(1), e55176.                                                                                     |
| Odegard, 1967       | Odegard, O. (1967). Mortality in Norwegian psychiatric hospitals 1950-1962. <i>Acta genetica et statistica medica</i> , 17(1), 137-153.                                                                                                                                                                                                                                  |
| Olfson, 2015        | Olfson, M., Gerhard, T., Huang, C., Crystal, S., & Stroup, T. S. (2015). Premature Mortality Among Adults With Schizophrenia in the United States. <i>JAMA Psychiatry</i> , 72(12), 1172-1181.                                                                                                                                                                           |
| Osborn, 2007        | Osborn, D., Levy, G., Nazareth, I., Petersen, I., Islam, A., & King, M. (2007). Relative risk of cardiovascular and cancer mortality in people with severe mental illness from the United Kingdom's general practice research database. <i>Arch Gen Psychiatr</i> , 64(2), 242 - 249.                                                                                    |
| Ösby, 2000a         | Ösby, U., Correia, N., Brandt, L., Ekblom, A., & Sparen, P. (2000). Mortality and causes of death in schizophrenia in Stockholm county, Sweden. <i>Schizophrenia Research</i> , 45(1-2), 21-28.                                                                                                                                                                          |
| Ösby, 2000b         | Ösby, U., Correia, N., Brandt, L., Ekblom, A., & Sparen, P. (2000). Time trends in schizophrenia mortality in Stockholm County, Sweden: Cohort study. <i>British Medical Journal</i> , 321(7259), 483-484.                                                                                                                                                               |
| Ösby, 2001          | Ösby, U., Brandt, L., Correia, N., Ekblom, A., & Sparen, P. (2001). Excess mortality in bipolar and unipolar disorder in Sweden. <i>Archives of General Psychiatry</i> , 58(9), 844-850.                                                                                                                                                                                 |
| Ösby, 2016          | Ösby, U., Westman, J., Hallgren, J., & Gissler, M. (2016). Mortality trends in cardiovascular causes in schizophrenia, bipolar and unipolar mood disorder in Sweden 1987-2010. <i>Eur J Public Health</i> .                                                                                                                                                              |
| Pan, 2020           | Pan, Y.-J., Yeh, L.-L., Chan, H.-Y., & Chang, C.-K. (2020). Excess mortality and shortened life expectancy in people with major mental illnesses in Taiwan. <i>Epidemiology and psychiatric sciences</i> , 29, e156.                                                                                                                                                     |

| Study ID             | Article                                                                                                                                                                                                                                                                               |
|----------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Park, 2015           | Park, S., Kim, S. Y., & Hong, J. P. (2015). Cause-specific mortality of psychiatric inpatients and outpatients in a general hospital in Korea. <i>Asia Pac J Public Health</i> , 27(2), 164-175.                                                                                      |
| Prior, 1996          | Prior, P., Hassall, C., & Cross, K. W. (1996). Causes of death associated with psychiatric illness. <i>Journal of Public Health Medicine</i> , 18(4), 381-389.                                                                                                                        |
| Saku, 1995           | Saku, M., Tokudome, S., Ikeda, M., Kono, S., Makimoto, K., Uchimura, H., et al. (1995). Mortality in psychiatric patients, with a specific focus on cancer mortality associated with schizophrenia. <i>International Journal of Epidemiology</i> , 24(2), 366-372.                    |
| Salazar-Fraile, 1998 | Salazar-Fraile, J., Gomez-Beneyto, M., Perez-Hovos, S., & Hurtado-Navarro, I. (1998). Mortality among psychiatric patients referred to the mental health services in Valencia. <i>Soc Psychiatry Psychiatr Epidemiol</i> , 33(5), 224-229.                                            |
| Sanchez, 2021        | Sanchez, M. C., Escuriola, M. F., Sanmartin, M. I. F., Solntseva, I., Baquero, D. B., & Arno, A. G. (2021). Cardiovascular disease and mortality in people with schizophrenia or antipsychotic treatment: A cohort study in primary care. <i>Psychiatry Research</i> , 306, 114233    |
| Tanskanen, 2018      | Tanskanen, A., Tiihonen, J., & Taipale, H. (2018). Mortality in schizophrenia: 30-year nationwide follow-up study. <i>Acta Psychiatr Scand</i> , 138(6), 492-499.                                                                                                                     |
| Termorshuizen, 2013  | Termorshuizen, F., Wierdsma, A. I., Smeets, H. M., Visser, E., Drukker, M., Nijman, H., & Sytema, S. (2013). Cause-Specific Mortality Among Patients With Psychosis: Disentangling the Effects of Age and Illness Duration. <i>Psychosomatics</i> , 54(6), 536-545.                   |
| Torniaainen, 2015    | Torniaainen, M., Mittendorfer-Rutz, E., Tanskanen, A., Bjorkenstam, C., Suvisaari, J., Alexanderson, K., & Tiihonen, J. (2015). Antipsychotic treatment and mortality in schizophrenia. <i>Schizophr Bull</i> , 41(3), 656-663.                                                       |
| Tsuang, 1980         | Tsuang, M. T., Woolson, R. F., & Fleming, J. A. (1980). Causes of death in schizophrenia and manic-depression. <i>British Journal of Psychiatry</i> , 136, 239-242.                                                                                                                   |
| Vance, 2019          | Vance, M. C., Wiitala, W. L., Sussman, J. B., Pfeiffer, P., & Hayward, R. A. (2019). Increased Cardiovascular Disease Risk in Veterans With Mental Illness. <i>Circulation</i> , 12(10), e005563                                                                                      |
| Weeke, 1986          | Weeke, A., & Vaeth, M. (1986). EXCESS MORTALITY OF BIPOLAR AND UNIPOLAR MANIC-DEPRESSIVE PATIENTS. <i>Journal of Affective Disorders</i> , 11(3), 227-234.                                                                                                                            |
| Weeke, 1987          | Weeke, A., Juel, K., & Vaeth, M. (1987). Cardiovascular death and manic-depressive psychosis. <i>Journal of Affective Disorders</i> , 13(3), 287-292.                                                                                                                                 |
| Westman, 2013        | Westman, J., Hällgren, J., Wahlbeck, K., Erlinge, D., Alfredsson, L., & Ösby, U. (2013). Cardiovascular mortality in bipolar disorder: a population-based cohort study in Sweden. <i>BMJ Open</i> , 3(4).                                                                             |
| Westman, 2017        | Westman, J., Eriksson, S. V., Gissler, M., Hallgren, J., Prieto, M. L., Bobo, W. V., et al. (2018). Increased cardiovascular mortality in people with schizophrenia: a 24-year national register study. <i>Epidemiology and psychiatric sciences</i> , 27(5), 519-527.                |
| Yung, 2021           | Yung, N. C. L., Wong, C. S. M., Chan, J. K. N., Chen, E. Y. H., & Chang, W. C. (2021). Excess Mortality and Life-Years Lost in People with Schizophrenia and Other Non-affective Psychoses: An 11-Year Population-Based Cohort Study. <i>Schizophrenia Bulletin</i> , 47(2), 474-484. |
| Zilber, 1989         | Zilber, N., Schufman, N., & Lerner, Y. (1989). Mortality among psychiatric patients-the groups at risk. <i>Acta Psychiatr Scand</i> , 79(3), 248-256.                                                                                                                                 |

\* extra data kindly supplied by paper's corresponding author

\*\* extra data kindly supplied by paper's second author

## APPENDIX VIII LIST OF INCLUDED INCIDENCE STUDIES

| Study ID            | Article                                                                                                                                                                                                                                                                                                            |
|---------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Bent-Ennakhil, 2018 | Bent-Ennakhil, N., Cecile Perier, M., Sobocki, P., Gothefors, D., Johansson, G., Milea, D., & Empana, J. P. (2018). Incidence of cardiovascular diseases and type-2-diabetes mellitus in patients with psychiatric disorders. <i>Nordic Journal of Psychiatry</i> , 72(7), 455-461.                                |
| Brink, 2018         | Brink, M., Green, A., Bojesen, A. B., Lamberti, J. S., Conwell, Y., & Andersen, K. (2018). Excess medical comorbidity and mortality across the lifespan in schizophrenia: A nationwide Danish register study. <i>Schizophrenia Research (in press)</i> .                                                           |
| Carney, 2006        | Carney, C. P., Jones, L., & Woolson, R. F. (2006). Medical comorbidity in women and men with schizophrenia: a population-based controlled study. <i>Journal of general internal medicine</i> , 21(11), 1133-1137.                                                                                                  |
| Chen, 2015          | Mu-Hong, C., Cheng-Ta, L., Ju-Wei, H., Kai-Lin, H., Wei-Chen, L., Wen-Han, C., et al. (2015). Atopic Diseases and Subsequent Ischemic Stroke Among Patients With Schizophrenia: A Nationwide Longitudinal Study. <i>Psychosomatic Medicine</i> , 77(9), 1031-1038.                                                 |
| Crump, 2013a        | Crump, C., Sundquist, K., & Sundquist, J. (2013). Comorbidities and mortality in persons with schizophrenia: a Swedish national cohort study. <i>Am J Psychiatr</i> , 170, 324 - 333.                                                                                                                              |
| Crump, 2013b        | Crump, C., Sundquist, K., Winkleby, M. A., & Sundquist, J. (2013). Comorbidities and mortality in bipolar disorder: A swedish national cohort study. <i>JAMA Psychiatry</i> , 70(9), 931-939.                                                                                                                      |
| Curkendall, 2004    | Curkendall, S. M., Mo, J., Glasser, D. B., Rose Stang, M., & Jones, J. K. (2004). Cardiovascular disease in patients with schizophrenia in Saskatchewan, Canada. <i>The Journal of clinical psychiatry</i> , 65(5), 715-720.                                                                                       |
| Foroughi, 2018      | Foroughi, M., Medina-Inojosa, J. R., Lopez-Jimenez, F., Saeidifard, F., Viniciguerra, M., Frye, M. A., & Morgan, R. J. (2018). Risk of Atherosclerotic Cardiovascular Disease in Patients With Bipolar Disorder and Accuracy of a Cardiovascular Risk Calculator. <i>Biological Psychiatry</i> , 83(9), S283-S283. |
| Foroughi, 2021      | Foroughi, M., Medina Inojosa, J. R., Lopez-Jimenez, F., Saeidifard, F., Suarez, L., Stokin, G. B., et al. (2022). Association of Bipolar Disorder With Major Adverse Cardiovascular Events: A Population-Based Historical Cohort Study. <i>Psychosomatic Medicine</i> , 84(1).                                     |
| Gale, 2013          | Gale, C. R., Batty, G. D., Osborn, D. P. J., Tynelius, P., & Rasmussen, F. (2014). Mental disorders across the adult life course and future coronary heart disease: evidence for general susceptibility. <i>Circulation</i> , 129(2), 186-193.                                                                     |
| Goldstein, 2014     | Goldstein, B. I., Schaffer, A., Wang, S., & Blanco, C. (2015). Excessive and premature new-onset cardiovascular disease among adults with bipolar disorder in the US NESARC cohort. <i>The Journal of clinical psychiatry</i> , 76(2), 163-169.                                                                    |
| Gur, 2017           | Gur, S., Weizman, S., Stubbs, B., Matalon, A., Meyerovitch, J., Hermesh, H., & Krivoy, A. (2018). Mortality, morbidity and medical resources utilization of patients with schizophrenia: A case-control community-based study. <i>Psychiatry research</i> , 260, 177-181.                                          |
| Hayes, 2017         | Hayes, J. F., Marston, L., Walters, K., King, M. B., Osborn, D. P., & Osborn, D. P. J. (2017). Mortality gap for people with bipolar disorder and schizophrenia: UK-based cohort study 2000-2014. <i>British Journal of Psychiatry</i> , 211(3), 175-181.                                                          |
| Hsu, 2021           | Hsu, J.-H., Chien, I. C., & Lin, C.-H. (2021). Increased risk of ischemic heart disease in patients with bipolar disorder: A population-based study. <i>Journal of affective disorders</i> , 281, 721-726.                                                                                                         |
| Jackson, 2020       | Jackson, C. A., Kerssens, J., Fleetwood, K., Smith, D. J., Mercer, S. W., & Wild, S. H. (2020). Incidence of ischaemic heart disease and stroke among people with psychiatric disorders: retrospective cohort study. <i>British journal of psychiatry</i> , 217(2), 442-449.                                       |
| Jakobsen, 2008      | Jakobsen, A. H., Foldager, L., Parker, G., & Munk-Jorgensen, P. (2008). Quantifying links between acute myocardial infarction and depression, anxiety and schizophrenia using case register databases. <i>Journal of Affective Disorders</i> , 109(1/2), 177-181.                                                  |

| Study ID             | Article                                                                                                                                                                                                                                                                                                                          |
|----------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Kessing, 2021        | Kessing, L. V., Ziersen, S. C., Andersen, P. K., & Vinberg, M. (2021). A nation-wide population-based longitudinal study mapping physical diseases in patients with bipolar disorder and their siblings. <i>Journal of affective disorders</i> , 282, 18-25.                                                                     |
| Kugathasan, 2018     | Kugathasan P., Laursen T.M., Grontved S., Jensen S.E., Aagaard J., Nielsen R.E. (2018). Increased long-term mortality after myocardial infarction in patients with schizophrenia. <i>Schizophrenia Research</i> . 2018;199:103-8.                                                                                                |
| Lahti, 2012          | Lahti, M., Tiihonen, J., Wildgust, H., Beary, M., Hodgson, R., Kajantie, E., et al. (2012). Cardiovascular morbidity, mortality and pharmacotherapy in patients with schizophrenia. <i>Psychological Medicine</i> , 42(11), 2275-2285.                                                                                           |
| Laursen, 2010        | Laursen, T. M., Munk-Olsen, T., & Gasse, C. (2011). Chronic somatic comorbidity and excess mortality due to natural causes in persons with schizophrenia or bipolar affective disorder. <i>PLoS ONE</i> , 6 (9) (no pagination)(e24597).                                                                                         |
| Laursen, 2011        | Laursen, T. M., & Nordentoft, M. (2011). Heart disease treatment and mortality in schizophrenia and bipolar disorder-Changes in the Danish population between 1994 and 2006. <i>Journal of Psychiatric Research</i> , 45(1), 29-35.                                                                                              |
| Lawrence, 2003       | Lawrence, D. M., Holman, C. D. a. J., Jablensky, A. V., & Hobbs, M. S. T. (2003). Death rate from ischaemic heart disease in Western Australian psychiatric patients 1980-1998. <i>The British journal of psychiatry : the journal of mental science</i> , 182, 31-36.                                                           |
| Lin, 2010            | Lin, H. C., Chen, Y. H., & Lee, H. C. (2010). Increased risk of acute myocardial infarction after acute episode of schizophrenia: 6 year follow-up study. <i>Australian and New Zealand Journal of Psychiatry</i> , 44(3), 273-279.                                                                                              |
| Manderbacka, 2012    | Manderbacka, K., Arffman, M., Sund, R., Haukka, J., Keskimäki, I., Wahlbeck, K. (2012). How does a history of psychiatric hospital care influence access to coronary care: a cohort study. <i>BMJ Open</i> , 2(2), e000831.                                                                                                      |
| McDermott, 2005      | McDermott, S., Moran, R., Platt, T., Isaac, T., Wood, H., & Dasari, S. (2005). Heart disease, schizophrenia, and affective psychoses: epidemiology of risk in primary care. <i>Community Mental Health Journal</i> , 41(6), 747-755.                                                                                             |
| Momen, 2020*         | Momen, N. C., Plana-Ripoll, O., Agerbo, E., Benros, M. E., Borglum, A. D., Christensen, M. K., . . . McGrath, J. J. (2020). Association between Mental Disorders and Subsequent Medical Conditions. <i>The New England journal of medicine</i> , 382(18), 1721-1731.                                                             |
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| Study ID            | Article                                                                                                                                                                                                                                                                |
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\* extra data kindly supplied by paper's corresponding author

## APPENDIX IX LIST OF EXCLUDED STUDIES

| Article                                                                                                                                                                                                                                                                                                                                            | Reason* |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------|
| Ahrens, B., Grof, P., Moller, H. J., Muller-Oerlinghausen, B., & Wolf, T. (1995). Extended survival of patients on long-term lithium treatment. <i>Canadian Journal of Psychiatry - Revue Canadienne de Psychiatrie</i> , 40(5), 241-246.                                                                                                          | 5       |
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| Article                                                                                                                                                                                                                                                                                                                            | Reason* |
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| Westaby, J., Pankajakshan, C. N., & Sheppard, M. N. (2017). Incidence of psychiatric illnesses in sudden cardiac deaths. <i>Laboratory Investigation</i> , 97, 85A.                                                                                                           | 1       |
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| Wood, J. B., Evenson, R. C., Cho, D. W., & Hagan, B. J. (1985). MORTALITY VARIATIONS AMONG PUBLIC MENTAL-HEALTH PATIENTS. <i>Acta Psychiatrica Scandinavica</i> , 72(3), 218-229.                                                                                             | 1       |
| Wu, C. S., Lai, M. S., & Gau, S. S. F. (2015). Complications and mortality in patients with schizophrenia and diabetes: Population based cohort study. <i>Br. J. Psychiatry</i> , 207(5).                                                                                     | 2       |

\* Reason for exclusion: 1 - Unsuitable study design or methodology unclear, 2 - Unsuitable population, 3 - Unsuitable or inadequately defined outcome, 4 - Unsuitable or inadequately defined exposure, 5 - Duplicate study, 6 - Full text not available, 7 - Not able to translate, 8 - Not a primary study, 9 - No suitable comparator, 10 - No CVD x SMI results, 11 - No useable measure

## APPENDIX X RISK OF BIAS ASSESSMENT FOR INCLUDED MORTALITY STUDIES

**Appendix table X.1: Risk of bias assessment of studies reporting cardiovascular mortality outcomes, cohort studies**

| Study ID          | Selection                                                                        |                                                                 |                                                                                          | Comparability                                            |                                |                                             | Outcome                                                  |                                                                                                                                    |                                                              |                                                  |
|-------------------|----------------------------------------------------------------------------------|-----------------------------------------------------------------|------------------------------------------------------------------------------------------|----------------------------------------------------------|--------------------------------|---------------------------------------------|----------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------|--------------------------------------------------|
|                   | Truly or somewhat representative of the average person with SMI in the community | Non-exposed drawn from the same community as the exposed cohort | Ascertainment of exposure from secure record e.g. medical record or structured interview | Demonstration that CVD was not present at start of study | Study controls for age and sex | Study controls for socio-demographic factor | Study controls for additional cardiovascular risk factor | Outcome accurately measured & validated, similar methods used for cases and controls, reliable system for measuring CVD occurrence | Follow-up long enough for outcomes to occur (min of 5 years) | Adequacy of follow-up of SMI and non-SMI cohorts |
| Ahrens, 1995      | N                                                                                | N                                                               | Y                                                                                        | N                                                        | Y                              | N                                           | N                                                        | CT                                                                                                                                 | CT                                                           | N                                                |
| Ajetunmobi, 2013  | CT                                                                               | N                                                               | Y                                                                                        | N                                                        | Y                              | Y                                           | N                                                        | CT                                                                                                                                 | CT                                                           | CT                                               |
| Allebeck, 1986    | CT                                                                               | N                                                               | Y                                                                                        | N                                                        | Y                              | N                                           | N                                                        | CT                                                                                                                                 | Y                                                            | Y                                                |
| Anderson, 1991    | Y                                                                                | CT                                                              | Y                                                                                        | N                                                        | Y                              | N                                           | N                                                        | CT                                                                                                                                 | CT                                                           | N                                                |
| Angst, 2002       | N                                                                                | N                                                               | CT                                                                                       | N                                                        | Y                              | N                                           | CT                                                       | CT                                                                                                                                 | Y                                                            | Y                                                |
| Bjorkenstam, 2012 | CT                                                                               | CT                                                              | Y                                                                                        | N                                                        | Y                              | N                                           | CT                                                       | CT                                                                                                                                 | N                                                            | Y                                                |
| Brink, 2018       | CT                                                                               | Y                                                               | Y                                                                                        | Y                                                        | Y                              | Y                                           | CT                                                       | Y                                                                                                                                  | Y                                                            | CT                                               |
| Brodersen, 2000   | N                                                                                | N                                                               | Y                                                                                        | N                                                        | Y                              | N                                           | N                                                        | CT                                                                                                                                 | Y                                                            | Y                                                |
| Brook, 1984       | N                                                                                | N                                                               | Y                                                                                        | N                                                        | CT                             | N                                           | N                                                        | N                                                                                                                                  | N                                                            | N                                                |
| Brown, 2010       | Y                                                                                | N                                                               | Y                                                                                        | N                                                        | Y                              | N                                           | N                                                        | CT                                                                                                                                 | Y                                                            | Y                                                |
| Buda, 1988        | CT                                                                               | N                                                               | Y                                                                                        | N                                                        | Y                              | N                                           | N                                                        | CT                                                                                                                                 | Y                                                            | Y                                                |
| Callaghan, 2014   | CT                                                                               | N                                                               | Y                                                                                        | N                                                        | Y                              | CT                                          | N                                                        | CT                                                                                                                                 | CT                                                           | CT                                               |
| Casadebaig, 1999  | CT                                                                               | N                                                               | Y                                                                                        | N                                                        | Y                              | N                                           | N                                                        | CT                                                                                                                                 | N                                                            | N                                                |
| Castagnini, 2013  | Y                                                                                | N                                                               | Y                                                                                        | N                                                        | Y                              | N                                           | N                                                        | CT                                                                                                                                 | CT                                                           | Y                                                |
| Chan, 2021        | Y                                                                                | N                                                               | Y                                                                                        | N                                                        | Y                              | N                                           | N                                                        | CT                                                                                                                                 | CT                                                           | CT                                               |
| Crump, 2013a      | Y                                                                                | CT                                                              | Y                                                                                        | CT                                                       | Y                              | Y                                           | Y                                                        | CT                                                                                                                                 | Y                                                            | Y                                                |
| Crump, 2013b      | Y                                                                                | CT                                                              | Y                                                                                        | CT                                                       | Y                              | Y                                           | Y                                                        | CT                                                                                                                                 | Y                                                            | Y                                                |
| Cunningham, 2014  | Y                                                                                | N                                                               | Y                                                                                        | N                                                        | Y                              | N                                           | N                                                        | CT                                                                                                                                 | N                                                            | CT                                               |
| Curkendall, 2004  | CT                                                                               | Y                                                               | CT                                                                                       | CT                                                       | Y                              | N                                           | Y                                                        | CT                                                                                                                                 | N                                                            | N                                                |
| Dalgard, 1966     | CT                                                                               | CT                                                              | CT                                                                                       | N                                                        | Y                              | Y                                           | N                                                        | CT                                                                                                                                 | Y                                                            | Y                                                |
| Das-Munshi, 2017  | Y                                                                                | N                                                               | Y                                                                                        | N                                                        | Y                              | CT                                          | N                                                        | CT                                                                                                                                 | CT                                                           | CT                                               |
| Daumit, 2010      | CT                                                                               | N                                                               | CT                                                                                       | N                                                        | Y                              | Y                                           | N                                                        | CT                                                                                                                                 | Y                                                            | N                                                |
| Dutta, 2012       | Y                                                                                | N                                                               | Y                                                                                        | N                                                        | Y                              | N                                           | N                                                        | CT                                                                                                                                 | CT                                                           | CT                                               |
| Fors, 2007        | Y                                                                                | Y                                                               | Y                                                                                        | N                                                        | Y                              | CT                                          | N                                                        | CT                                                                                                                                 | Y                                                            | Y                                                |
| Giel, 1978        | N                                                                                | N                                                               | CT                                                                                       | N                                                        | CT                             | N                                           | N                                                        | N                                                                                                                                  | N                                                            | N                                                |
| Girardi, 2021     | Y                                                                                | N                                                               | Y                                                                                        | N                                                        | Y                              | N                                           | N                                                        | CT                                                                                                                                 | Y                                                            | CT                                               |
| Grigoletti, 2009  | Y                                                                                | N                                                               | Y                                                                                        | N                                                        | CT                             | N                                           | N                                                        | CT                                                                                                                                 | Y                                                            | N                                                |
| Hansen, 2001      | CT                                                                               | N                                                               | Y                                                                                        | N                                                        | Y                              | N                                           | N                                                        | CT                                                                                                                                 | CT                                                           | Y                                                |

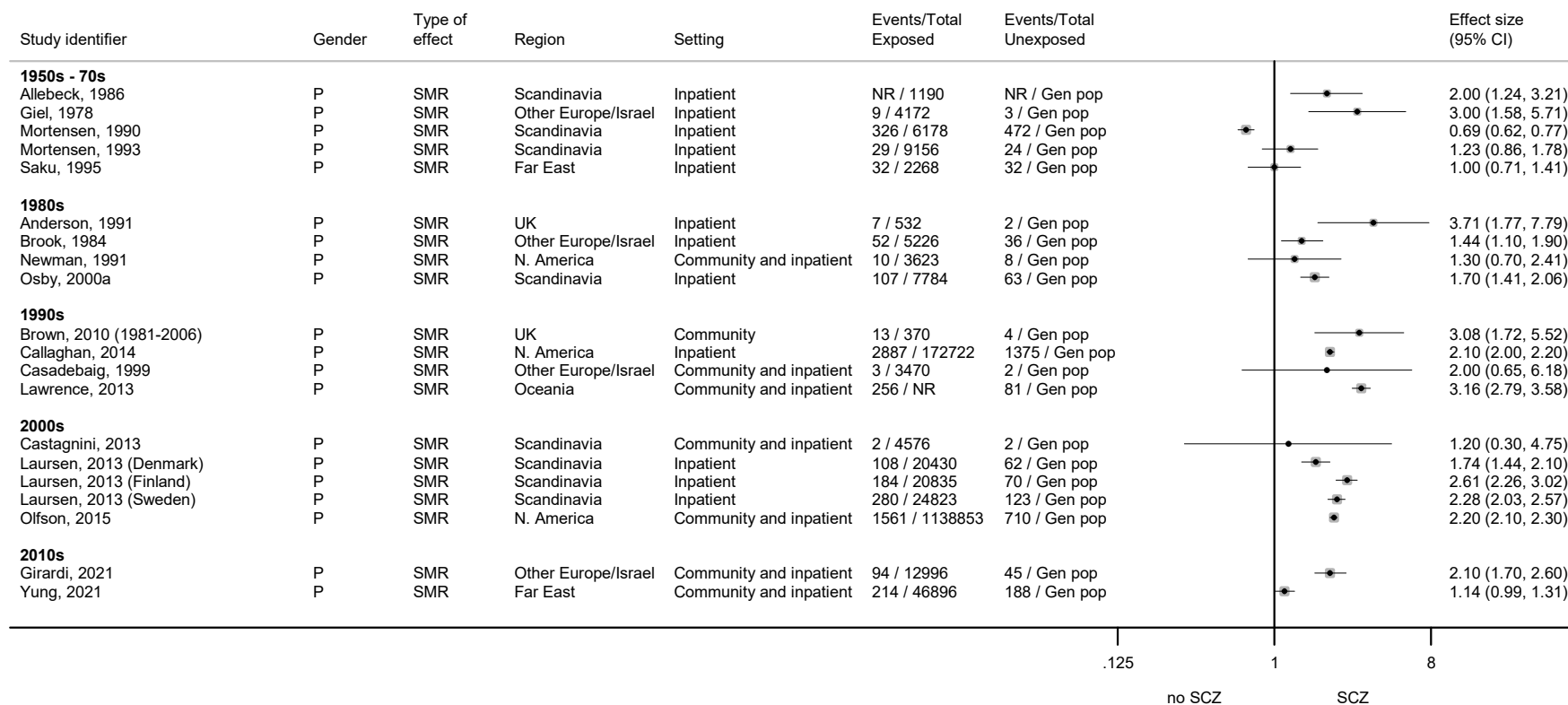
| Study ID            | Selection                                                                        |                                                                 |                                                                                          | Comparability                                            |                                |                                             |                                                           | Outcome                                                                                                                            |                                                              |                                                  |
|---------------------|----------------------------------------------------------------------------------|-----------------------------------------------------------------|------------------------------------------------------------------------------------------|----------------------------------------------------------|--------------------------------|---------------------------------------------|-----------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------|--------------------------------------------------|
|                     | Truly or somewhat representative of the average person with SMI in the community | Non-exposed drawn from the same community as the exposed cohort | Ascertainment of exposure from secure record e.g. medical record or structured interview | Demonstration that CVD was not present at start of study | Study controls for age and sex | Study controls for socio-demographic factor | Study controls for additional cardio-vascular risk factor | Outcome accurately measured & validated, similar methods used for cases and controls, reliable system for measuring CVD occurrence | Follow-up long enough for outcomes to occur (min of 5 years) | Adequacy of follow-up of SMI and non-SMI cohorts |
| Hayes, 2017         | Y                                                                                | Y                                                               | Y                                                                                        | N                                                        | Y                              | Y                                           | Y                                                         | CT                                                                                                                                 | N                                                            | N                                                |
| Heiberg, 2018       | CT                                                                               | N                                                               | Y                                                                                        | N                                                        | Y                              | N                                           | N                                                         | CT                                                                                                                                 | N                                                            | Y                                                |
| Heila, 2005         | CT                                                                               | N                                                               | Y                                                                                        | N                                                        | Y                              | N                                           | N                                                         | CT                                                                                                                                 | CT                                                           | Y                                                |
| Hiroeh, 2008        | CT                                                                               | CT                                                              | CT                                                                                       | N                                                        | Y                              | N                                           | N                                                         | CT                                                                                                                                 | Y                                                            | Y                                                |
| Hoang, 2011         | CT                                                                               | N                                                               | Y                                                                                        | N                                                        | Y                              | N                                           | N                                                         | CT                                                                                                                                 | N                                                            | N                                                |
| Hoye, 2011          | CT                                                                               | N                                                               | Y                                                                                        | N                                                        | Y                              | N                                           | N                                                         | CT                                                                                                                                 | Y                                                            | Y                                                |
| John, 2018          | Y                                                                                | N                                                               | Y                                                                                        | N                                                        | Y                              | N                                           | N                                                         | CT                                                                                                                                 | CT                                                           | N                                                |
| Kelly, 2010         | N                                                                                | N                                                               | Y                                                                                        | N                                                        | Y                              | CT                                          | N                                                         | CT                                                                                                                                 | Y                                                            | N                                                |
| Kilbourne, 2009     | N                                                                                | CT                                                              | Y                                                                                        | N                                                        | CT                             | Y                                           | Y                                                         | CT                                                                                                                                 | CT                                                           | N                                                |
| Kiviniemi, 2010     | CT                                                                               | N                                                               | Y                                                                                        | N                                                        | Y                              | CT                                          | N                                                         | CT                                                                                                                                 | Y                                                            | Y                                                |
| Kredentser, 2014    | CT                                                                               | N                                                               | Y                                                                                        | N                                                        | CT                             | N                                           | N                                                         | CT                                                                                                                                 | Y                                                            | N                                                |
| Lahti, 2012         | CT                                                                               | CT                                                              | Y                                                                                        | CT                                                       | Y                              | CT                                          | CT                                                        | CT                                                                                                                                 | Y                                                            | N                                                |
| Laursen, 2007       | CT                                                                               | CT                                                              | Y                                                                                        | N                                                        | Y                              | N                                           | N                                                         | CT                                                                                                                                 | Y                                                            | Y                                                |
| Laursen, 2010       | CT                                                                               | CT                                                              | Y                                                                                        | Y                                                        | Y                              | N                                           | N                                                         | CT                                                                                                                                 | CT                                                           | Y                                                |
| Laursen, 2013       | CT                                                                               | N                                                               | Y                                                                                        | N                                                        | Y                              | N                                           | N                                                         | CT                                                                                                                                 | CT                                                           | Y                                                |
| Laursen, 2014       | CT                                                                               | CT                                                              | Y                                                                                        | CT                                                       | Y                              | N                                           | CT                                                        | CT                                                                                                                                 | Y                                                            | Y                                                |
| Laursen, 2019       | Y                                                                                | CT                                                              | Y                                                                                        | N                                                        | Y                              | N                                           | N                                                         | CT                                                                                                                                 | Y                                                            | Y                                                |
| Lawrence, 2003      | Y                                                                                | N                                                               | Y                                                                                        | N                                                        | Y                              | N                                           | N                                                         | CT                                                                                                                                 | Y                                                            | N                                                |
| Lawrence, 2013      | Y                                                                                | N                                                               | Y                                                                                        | N                                                        | Y                              | N                                           | N                                                         | CT                                                                                                                                 | Y                                                            | N                                                |
| Lemogne, 2013       | N                                                                                | Y                                                               | CT                                                                                       | N                                                        | Y                              | CT                                          | Y                                                         | CT                                                                                                                                 | Y                                                            | Y                                                |
| Lesage, 2015        | CT                                                                               | CT                                                              | N                                                                                        | N                                                        | Y                              | N                                           | N                                                         | CT                                                                                                                                 | CT                                                           | N                                                |
| Lumme, 2016         | CT                                                                               | N                                                               | Y                                                                                        | N                                                        | Y                              | N                                           | N                                                         | CT                                                                                                                                 | CT                                                           | Y                                                |
| Manderbacka, 2012   | CT                                                                               | N                                                               | Y                                                                                        | N                                                        | Y                              | N                                           | N                                                         | CT                                                                                                                                 | Y                                                            | Y                                                |
| Morden, 2012        | N                                                                                | Y                                                               | Y                                                                                        | N                                                        | Y                              | N                                           | N                                                         | CT                                                                                                                                 | CT                                                           | N                                                |
| Mortensen, 1990     | N                                                                                | N                                                               | Y                                                                                        | N                                                        | Y                              | N                                           | N                                                         | CT                                                                                                                                 | Y                                                            | Y                                                |
| Mortensen, 1993     | CT                                                                               | N                                                               | Y                                                                                        | N                                                        | Y                              | N                                           | N                                                         | CT                                                                                                                                 | y                                                            | Y                                                |
| Murray-Thomas, 2013 | CT                                                                               | Y                                                               | Y                                                                                        | CT                                                       | Y                              | N                                           | N                                                         | CT                                                                                                                                 | N                                                            | CT                                               |
| Newman, 1991        | Y                                                                                | N                                                               | CT                                                                                       | N                                                        | Y                              | N                                           | N                                                         | CT                                                                                                                                 | CT                                                           | CT                                               |
| Nilsson, 1995       | N                                                                                | N                                                               | Y                                                                                        | N                                                        | Y                              | N                                           | N                                                         | CT                                                                                                                                 | Y                                                            | Y                                                |
| Nordentoft, 2013    | CT                                                                               | N                                                               | Y                                                                                        | N                                                        | Y                              | N                                           | N                                                         | CT                                                                                                                                 | N                                                            | Y                                                |
| Odegard, 1967       | N                                                                                | N                                                               | Y                                                                                        | N                                                        | Y                              | N                                           | N                                                         | N                                                                                                                                  | N                                                            | N                                                |
| Olfson, 2015        | CT                                                                               | N                                                               | CT                                                                                       | N                                                        | Y                              | CT                                          | N                                                         | CT                                                                                                                                 | N                                                            | CT                                               |

| Study ID             | Selection                                                                        |                                                                 |                                                                                          | Comparability                                            |                                |                                             | Outcome                                                  |                                                                                                                                    |                                                              |                                                  |
|----------------------|----------------------------------------------------------------------------------|-----------------------------------------------------------------|------------------------------------------------------------------------------------------|----------------------------------------------------------|--------------------------------|---------------------------------------------|----------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------|--------------------------------------------------|
|                      | Truly or somewhat representative of the average person with SMI in the community | Non-exposed drawn from the same community as the exposed cohort | Ascertainment of exposure from secure record e.g. medical record or structured interview | Demonstration that CVD was not present at start of study | Study controls for age and sex | Study controls for socio-demographic factor | Study controls for additional cardiovascular risk factor | Outcome accurately measured & validated, similar methods used for cases and controls, reliable system for measuring CVD occurrence | Follow-up long enough for outcomes to occur (min of 5 years) | Adequacy of follow-up of SMI and non-SMI cohorts |
| Osborn, 2007         | Y                                                                                | Y                                                               | Y                                                                                        | N                                                        | Y                              | CT                                          | CT                                                       | CT                                                                                                                                 | N                                                            | N                                                |
| Osby, 2000a          | CT                                                                               | N                                                               | Y                                                                                        | N                                                        | Y                              | N                                           | N                                                        | CT                                                                                                                                 | Y                                                            | Y                                                |
| Osby, 2000b          | CT                                                                               | N                                                               | Y                                                                                        | N                                                        | Y                              | N                                           | N                                                        | CT                                                                                                                                 | Y                                                            | Y                                                |
| Osby, 2001           | CT                                                                               | N                                                               | CT                                                                                       | N                                                        | Y                              | N                                           | N                                                        | CT                                                                                                                                 | CT                                                           | Y                                                |
| Osby, 2016           | CT                                                                               | N                                                               | Y                                                                                        | N                                                        | Y                              | N                                           | N                                                        | CT                                                                                                                                 | N                                                            | Y                                                |
| Pan, 2020            | Y                                                                                | CT                                                              | Y                                                                                        | N                                                        | Y                              | N                                           | N                                                        | CT                                                                                                                                 | N                                                            | Y                                                |
| Park, 2015           | CT                                                                               | N                                                               | Y                                                                                        | N                                                        | CT                             | N                                           | N                                                        | CT                                                                                                                                 | Y                                                            | CT                                               |
| Prior, 1996          | Y                                                                                | N                                                               | CT                                                                                       | N                                                        | Y                              | N                                           | N                                                        | CT                                                                                                                                 | CT                                                           | CT                                               |
| Saku, 1995           | N                                                                                | N                                                               | Y                                                                                        | N                                                        | Y                              | N                                           | N                                                        | CT                                                                                                                                 | Y                                                            | N                                                |
| Salazar-Fraile, 1998 | Y                                                                                | CT                                                              | Y                                                                                        | N                                                        | Y                              | N                                           | N                                                        | CT                                                                                                                                 | Y                                                            | Y                                                |
| Sanchez, 2021        | Y                                                                                | CT                                                              | Y                                                                                        | Y                                                        | Y                              | N                                           | Y                                                        | Y                                                                                                                                  | N                                                            | N                                                |
| Tanskanen, 2018      | CT                                                                               | N                                                               | Y                                                                                        | N                                                        | CT                             | N                                           | N                                                        | CT                                                                                                                                 | Y                                                            | Y                                                |
| Termorshuizen, 2013  | Y                                                                                | Y                                                               | CT                                                                                       | N                                                        | Y                              | CT                                          | N                                                        | CT                                                                                                                                 | CT                                                           | N                                                |
| Torniaainen, 2015    | Y                                                                                | Y                                                               | Y                                                                                        | N                                                        | Y                              | N                                           | N                                                        | CT                                                                                                                                 | Y                                                            | Y                                                |
| Tsuang, 1980         | N                                                                                | N                                                               | Y                                                                                        | N                                                        | Y                              | N                                           | N                                                        | CT                                                                                                                                 | Y                                                            | Y                                                |
| Vance, 2019          | N                                                                                | CT                                                              | Y                                                                                        | Y                                                        | Y                              | CT                                          | Y                                                        | Y                                                                                                                                  | N                                                            | N                                                |
| Weeke, 1986          | CT                                                                               | N                                                               | CT                                                                                       | N                                                        | Y                              | N                                           | N                                                        | CT                                                                                                                                 | Y                                                            | Y                                                |
| Weeke, 1987          | N                                                                                | N                                                               | Y                                                                                        | N                                                        | Y                              | N                                           | N                                                        | CT                                                                                                                                 | N                                                            | Y                                                |
| Westman, 2013        | CT                                                                               | CT                                                              | Y                                                                                        | CT                                                       | Y                              | N                                           | N                                                        | CT                                                                                                                                 | Y                                                            | Y                                                |
| Westman, 2017        | CT                                                                               | CT                                                              | Y                                                                                        | CT                                                       | Y                              | N                                           | N                                                        | CT                                                                                                                                 | Y                                                            | Y                                                |
| Yung, 2021           | Y                                                                                | N                                                               | Y                                                                                        | N                                                        | Y                              | N                                           | N                                                        | CT                                                                                                                                 | CT                                                           | CT                                               |
| Zilber, 1989         | N                                                                                | N                                                               | Y                                                                                        | N                                                        | Y                              | N                                           | N                                                        | CT                                                                                                                                 | N                                                            | N                                                |

Y – yes, N – no, CT – unclear. Cohort studies with low risk of bias were denoted by a rating of “yes” or “can’t tell” on the “selection” and “outcome” criteria (excluding selection criteria on representativeness of people with SMI), together with adjustment for age, sex and at least two other confounding factors in the “comparability” category

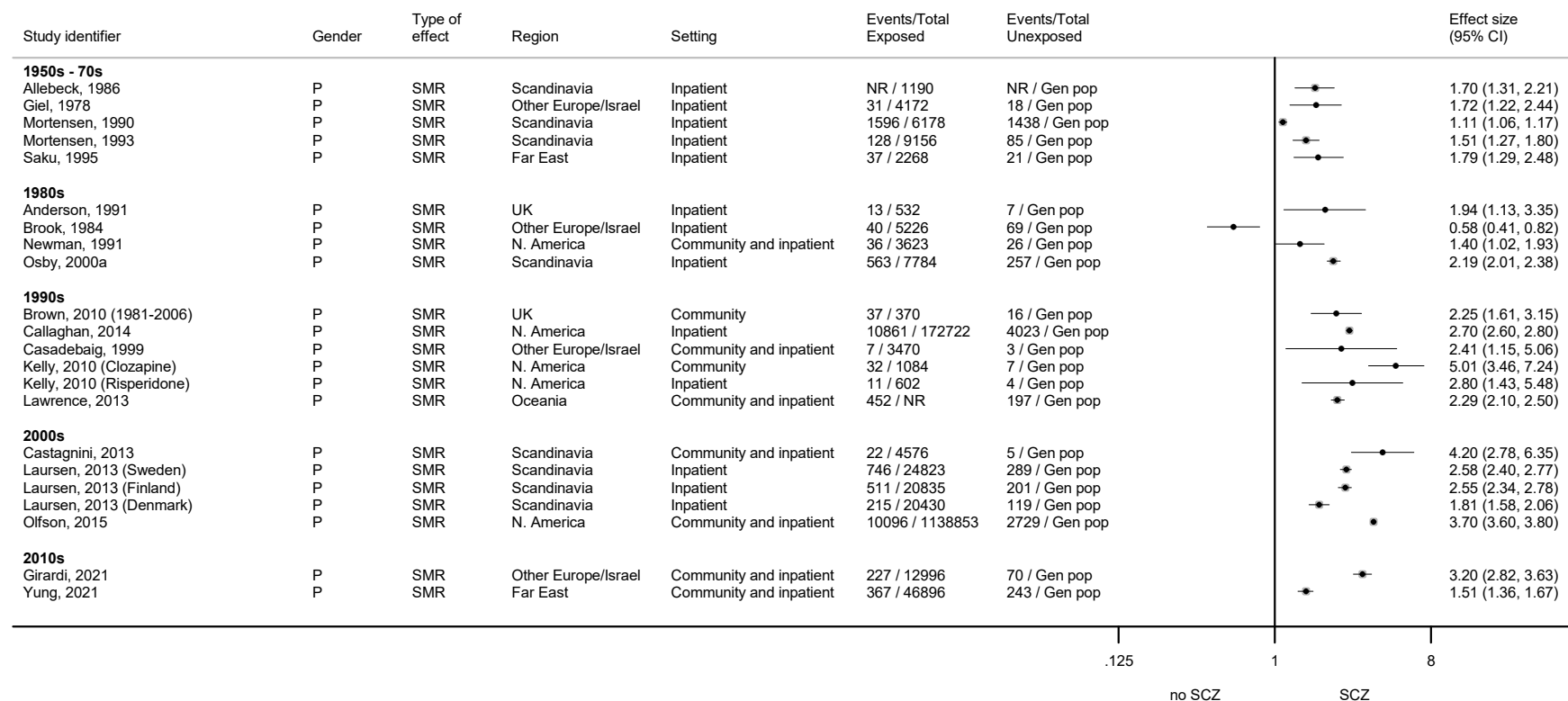


## APPENDIX XI FOREST PLOTS REPORTING CARDIOVASCULAR MORTALITY OUTCOMES



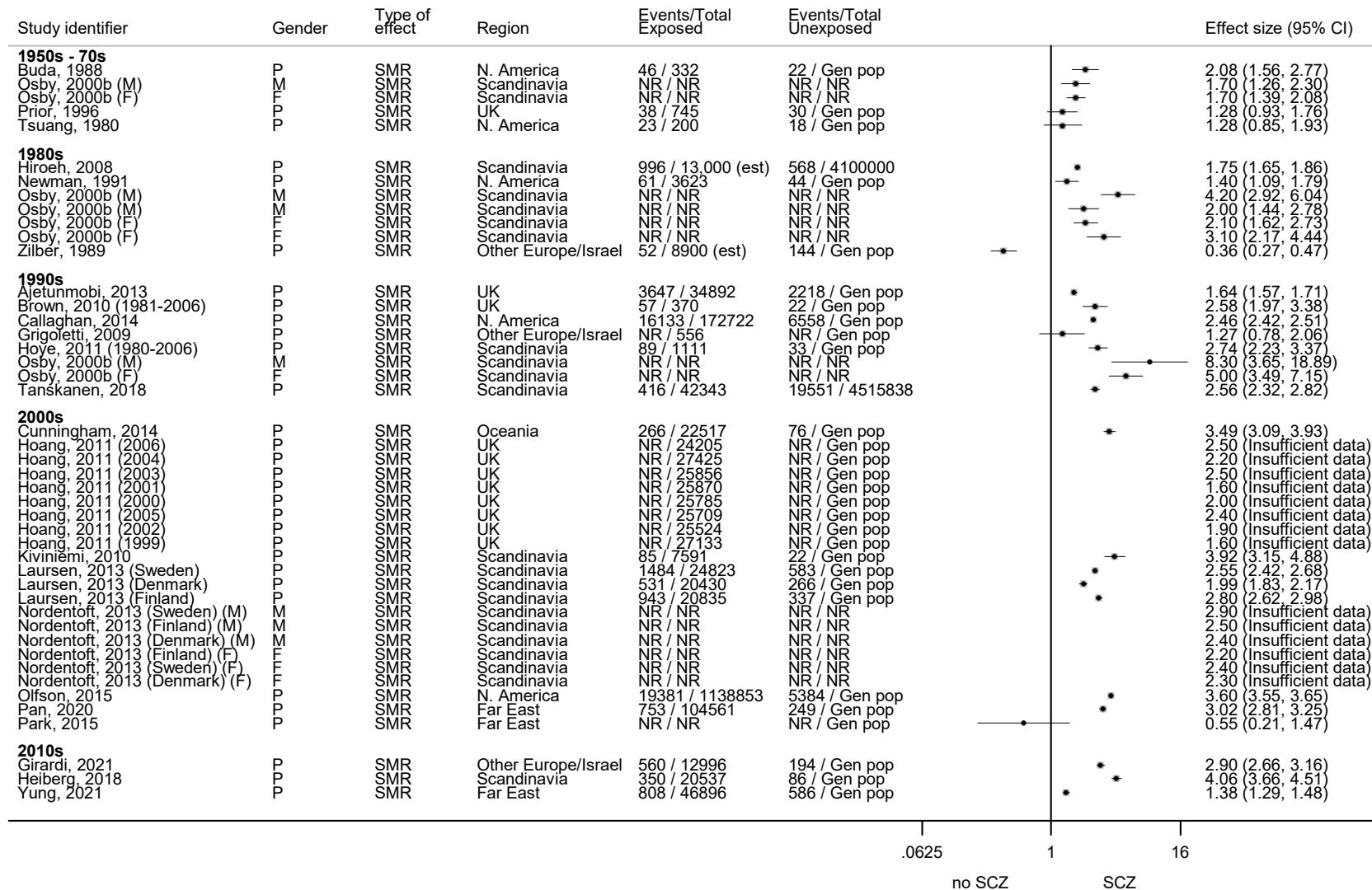
SCZ – schizophrenia, NR – not reported, HR – hazard ratio, RRatio – rate ratio, OR – odds ratio, RR – risk ratio, P – persons, M – males, F - females

**Appendix figure XI.1: Schizophrenia, mortality from cerebrovascular accident, standardised mortality ratios, across decades**



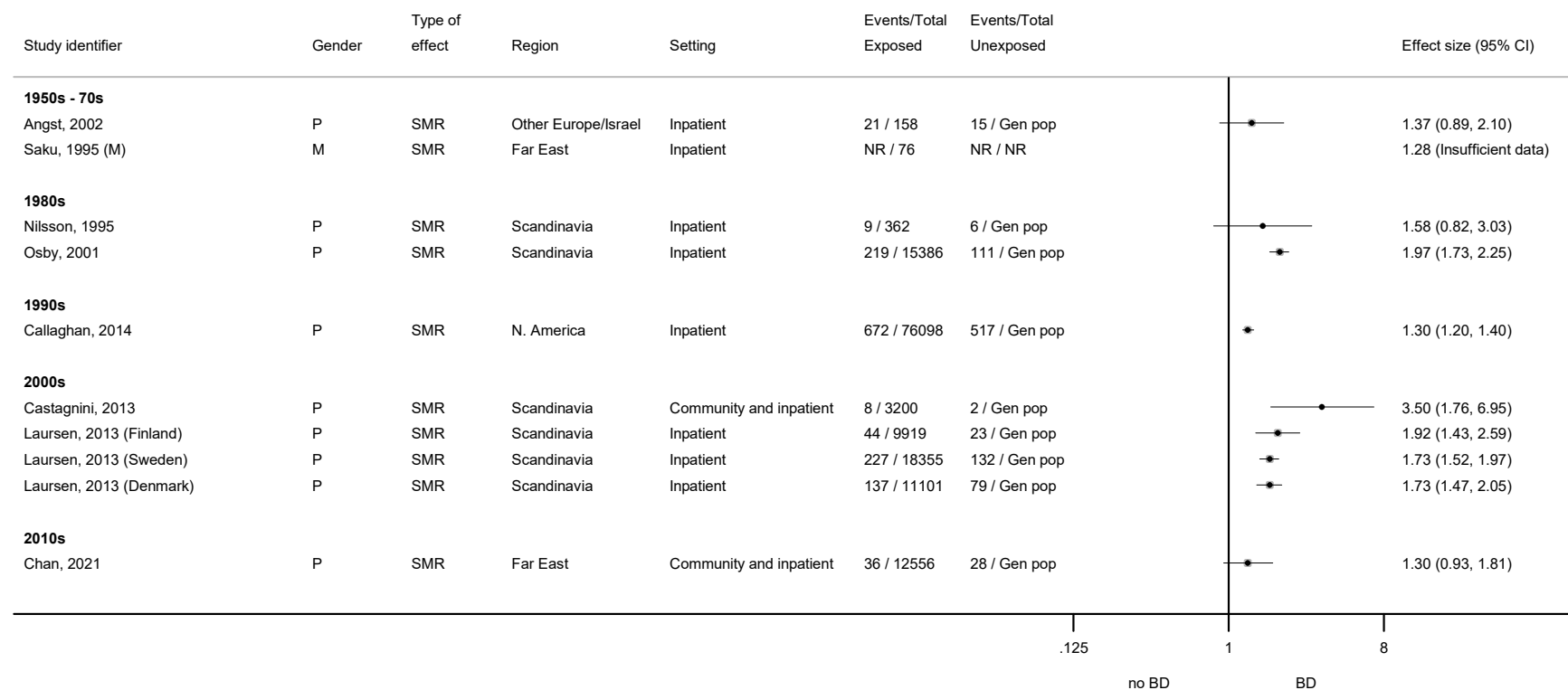
SCZ – schizophrenia, NR – not reported, gen pop – general population, SMR – standardised mortality ratio, P – persons

## Appendix figure XI.2: Schizophrenia, mortality from coronary heart disease, standardised mortality ratios, across decades



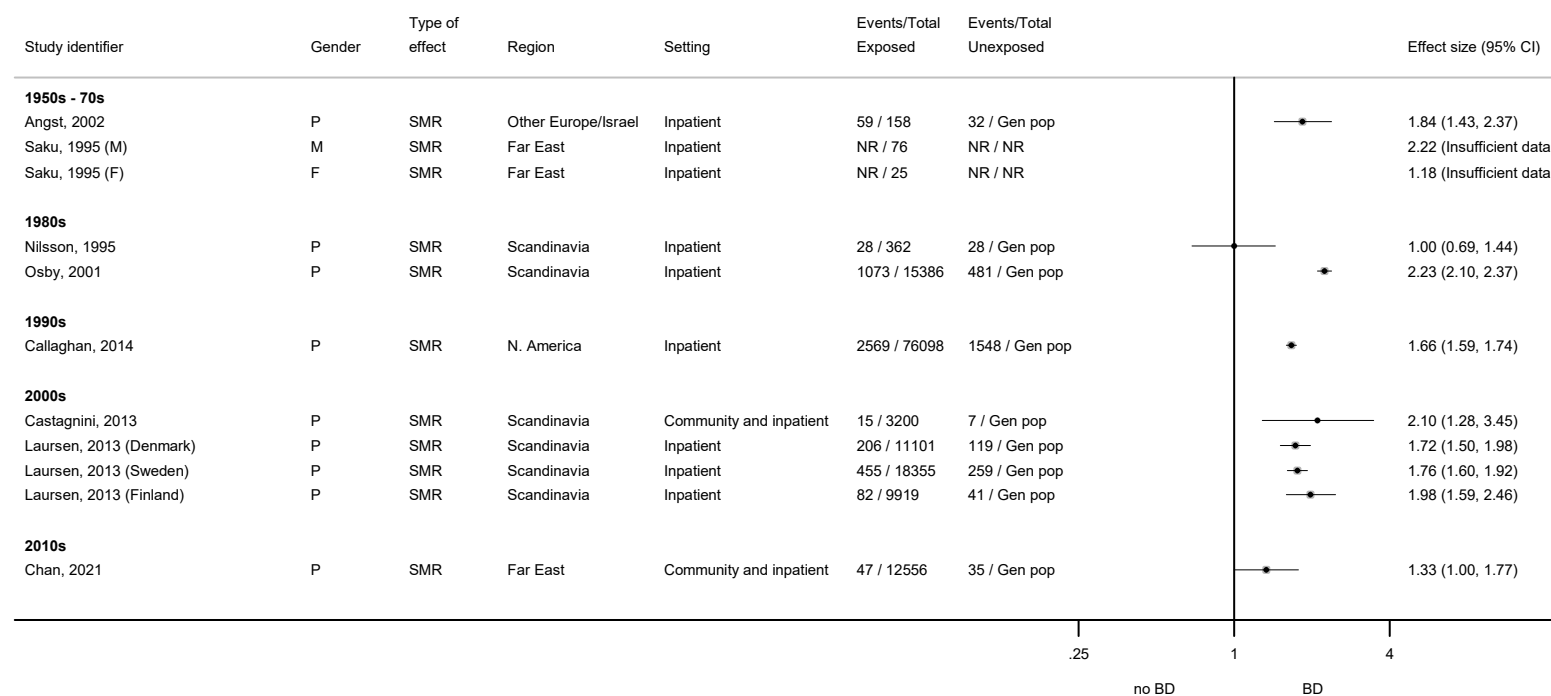
SCZ – schizophrenia, NR – not reported, gen pop – general population, SMR – standardised mortality ratio, P – persons, M – males, F – females

**Appendix figure XI.3: Schizophrenia, mortality from all circulatory disease, standardised mortality ratios, across decades**



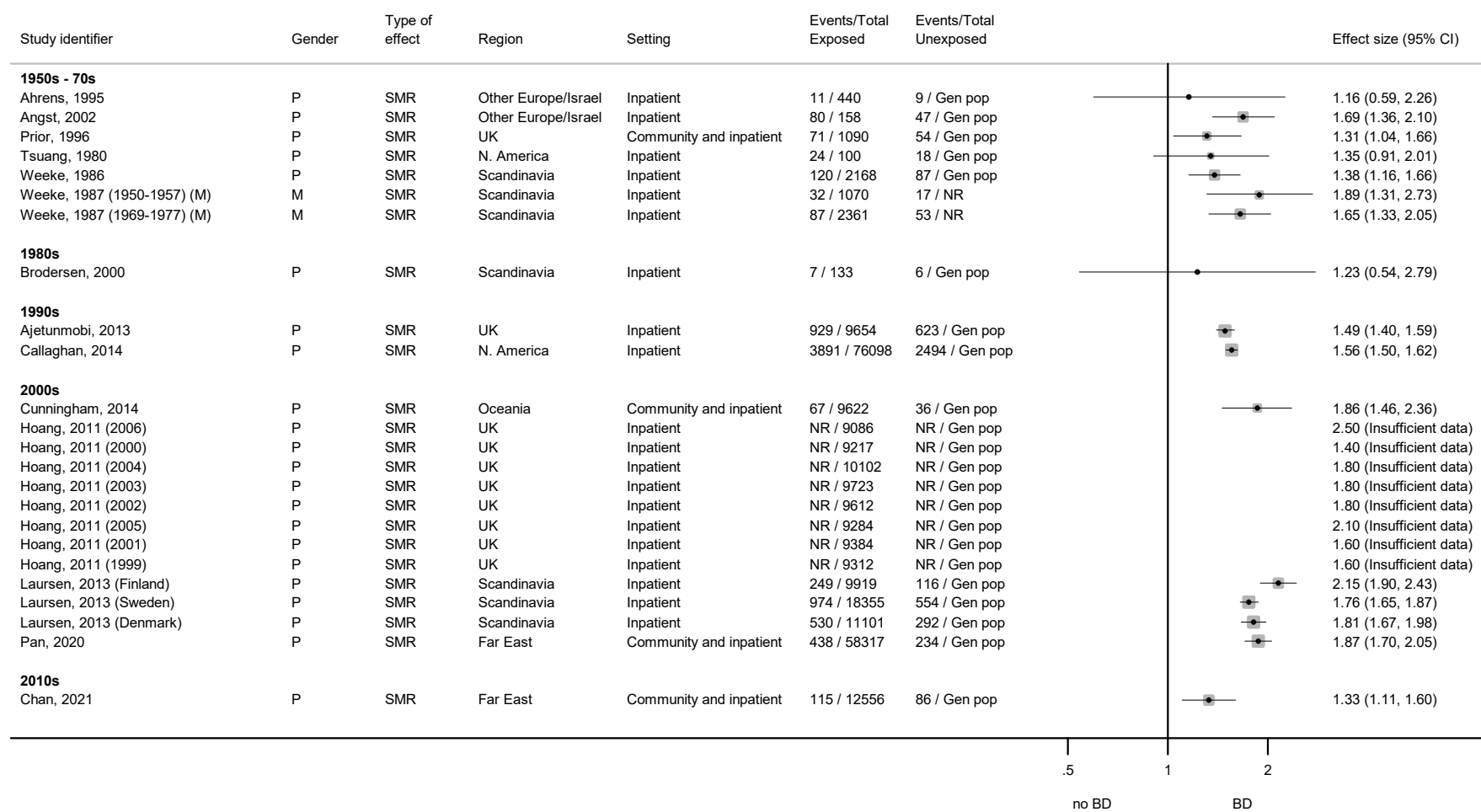
BD – bipolar disorder, NR – not reported, gen pop – general population, SMR – standardised mortality ratio, P – persons, M – males

**Appendix figure XI.4: Bipolar disorder, mortality from cerebrovascular accident, standardised mortality ratios, across decades**



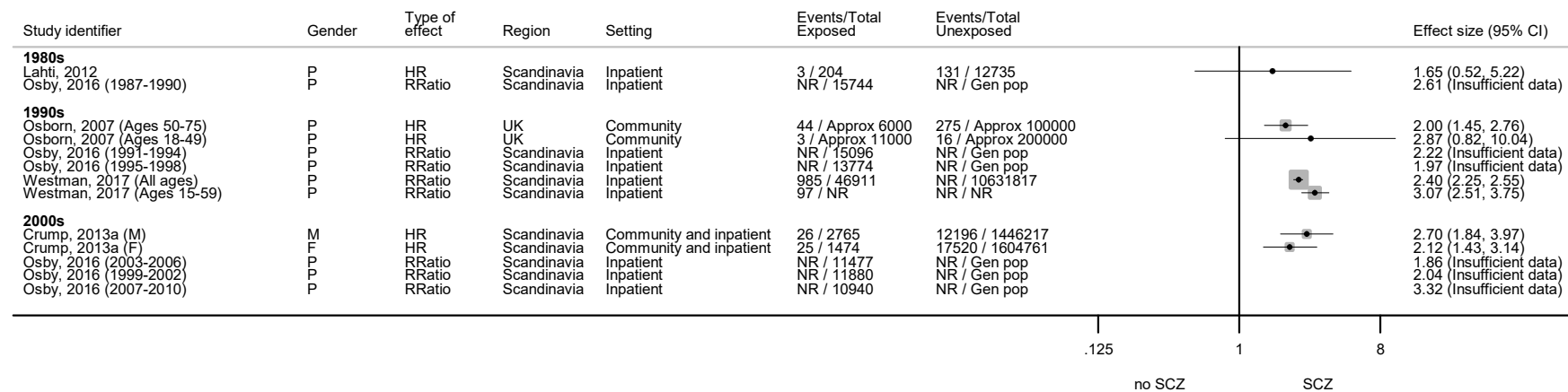
BD – bipolar disorder, NR – not reported, gen pop – general population, SMR – standardised mortality ratio, P – persons, M – males, F - females

**Appendix figure XI.5: Bipolar disorder, mortality from coronary heart disease, standardised mortality ratios, across decades**



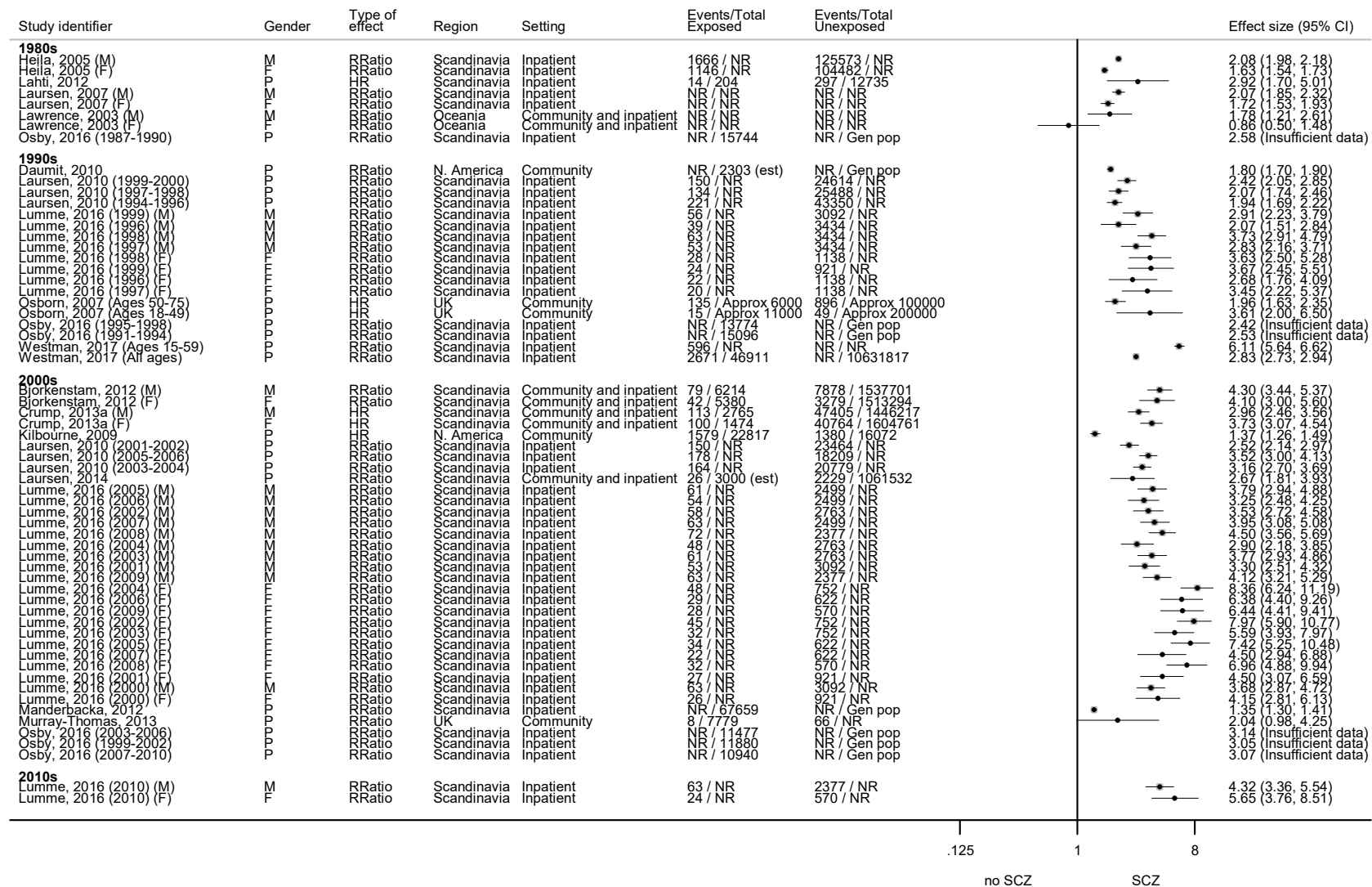
Bipolar disorder, NR – not reported, gen pop – general population, SMR – standardised mortality ratio, P – persons, M - males

**Appendix figure XI.6: Bipolar disorder, mortality from all circulatory disease, standardised mortality ratios, across decades**



SCZ – schizophrenia, NR – not reported, gen pop – general population, HR – hazard ratio, RRatio – rate ratio, P – persons, M – males, F – females

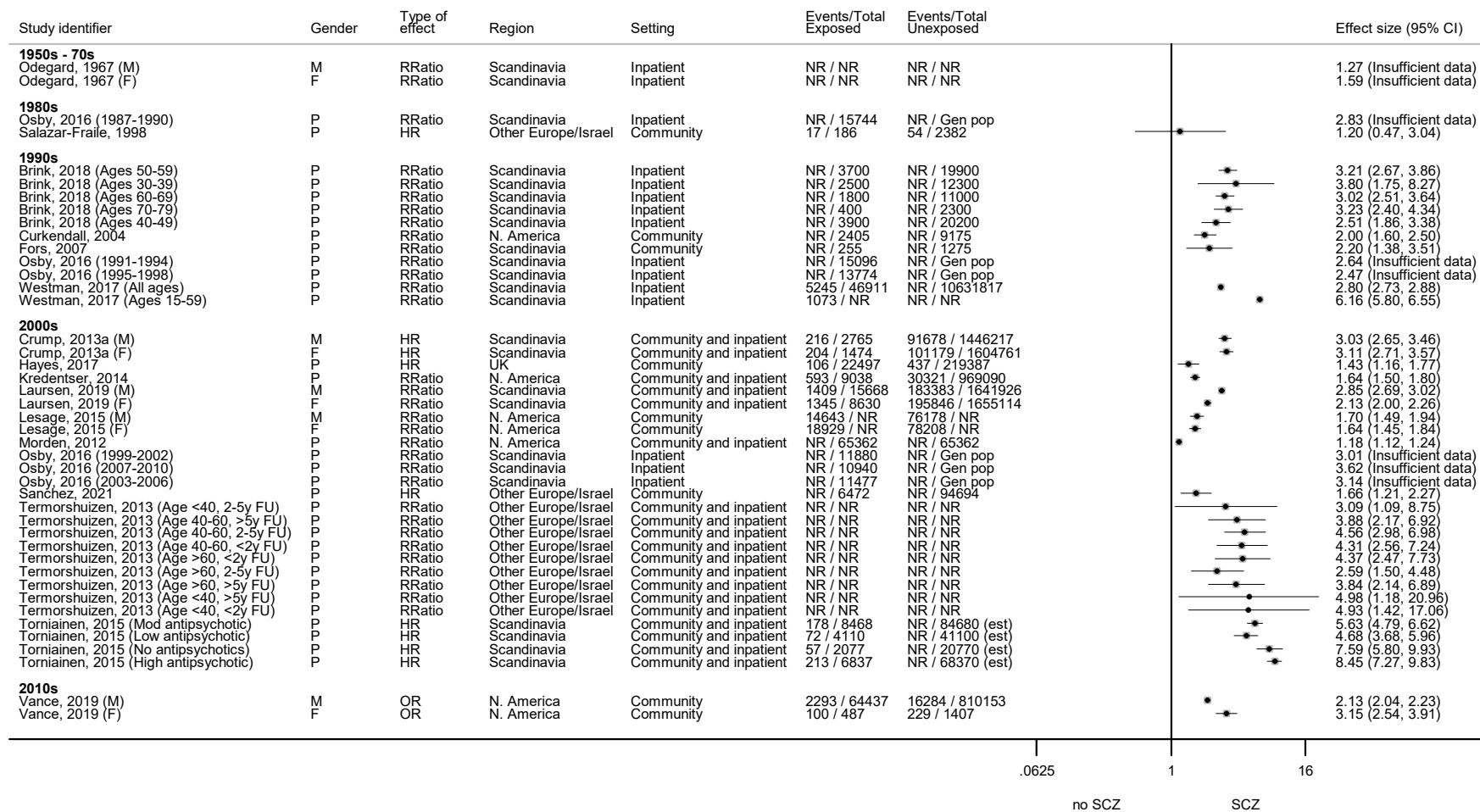
**Appendix figure XI.7: Schizophrenia, mortality from cerebrovascular accident, hazard ratios, rate ratios and odds ratios, across decades**



SCZ – schizophrenia, NR – not reported, gen pop – general population, HR – hazard ratio, RRatio – rate ratio, P – persons, M – males, F - females

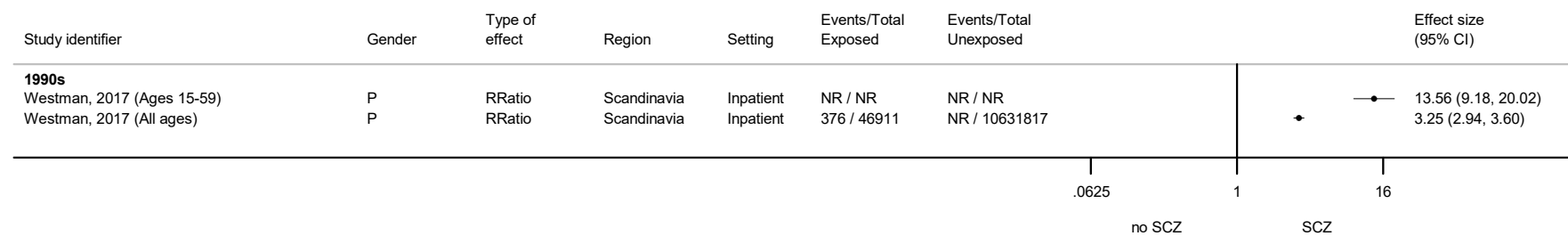
**Appendix figure XI.8: Schizophrenia, mortality from coronary heart disease, hazard ratios, rate ratios and odds ratios, across decades**





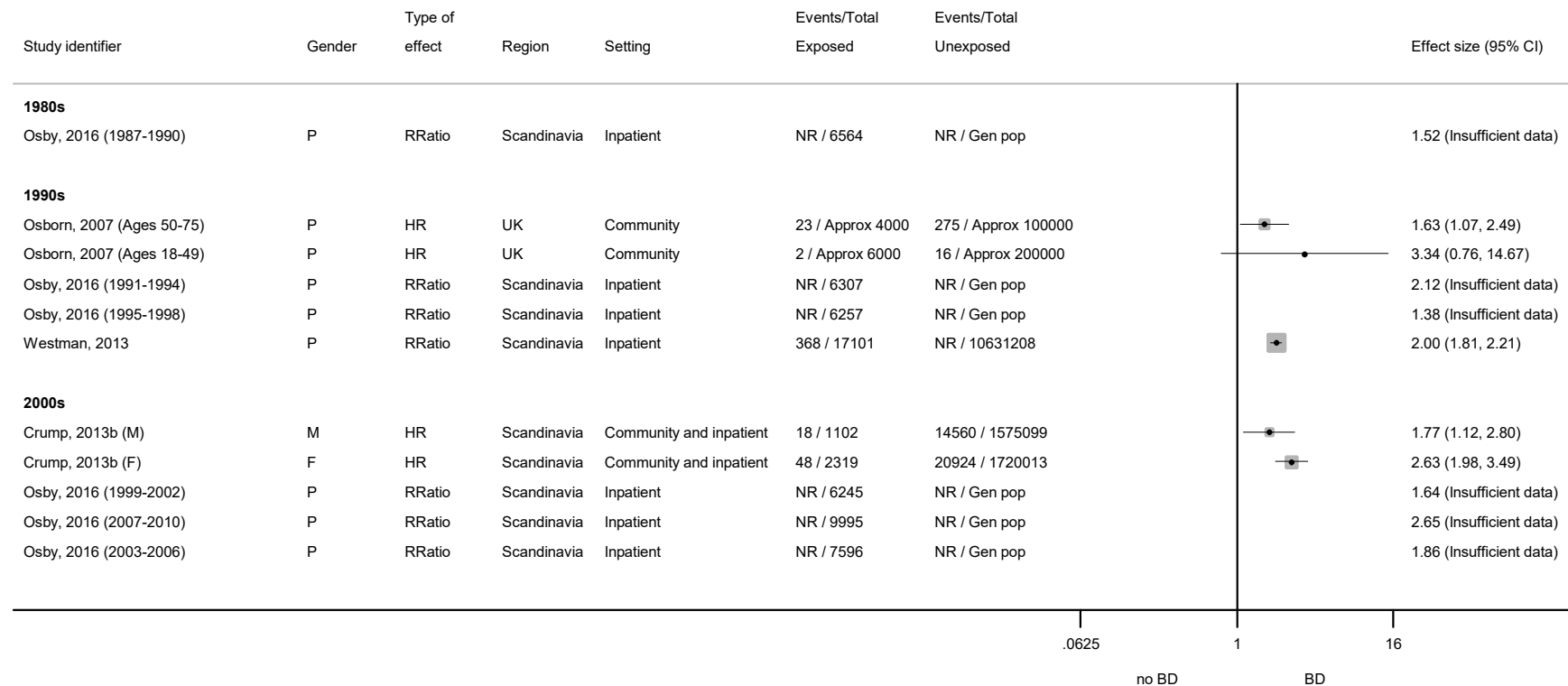
SCZ – schizophrenia, NR – not reported, gen pop – general population, est – estimated, HR – hazard ratio, RRatio – rate ratio, OR – odds ratio, P – persons, M – males, F – females, FU – follow-up

**Appendix figure XI.9: Schizophrenia, mortality from all circulatory disease, hazard ratios, rate ratios and odds ratios, across decades**



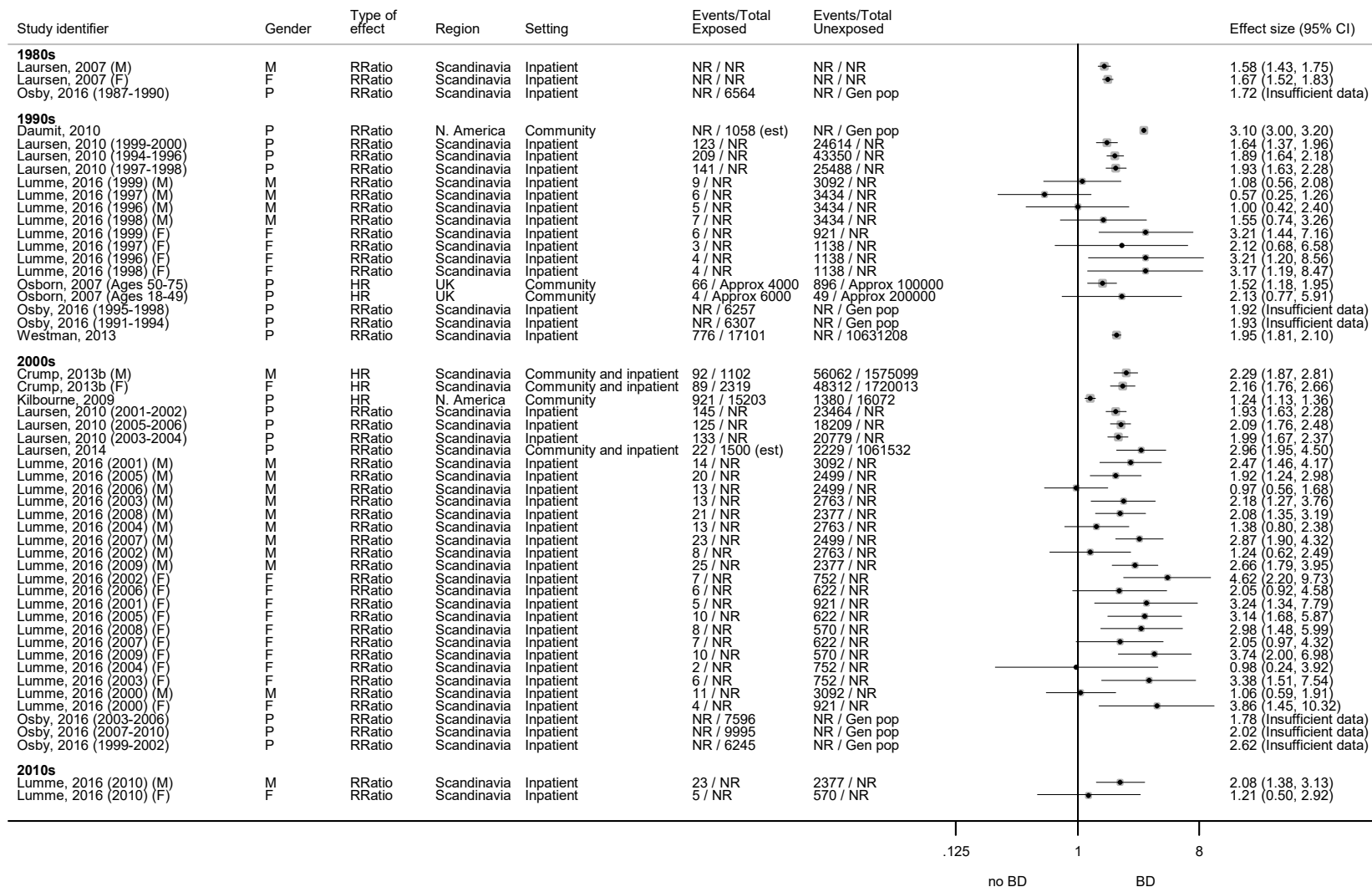
SCZ – schizophrenia, NR – not reported, RRatio – rate ratio, P – persons

**Appendix figure XI.10: Schizophrenia, mortality from heart failure, hazard ratios, rate ratios and odds ratios, across decades**



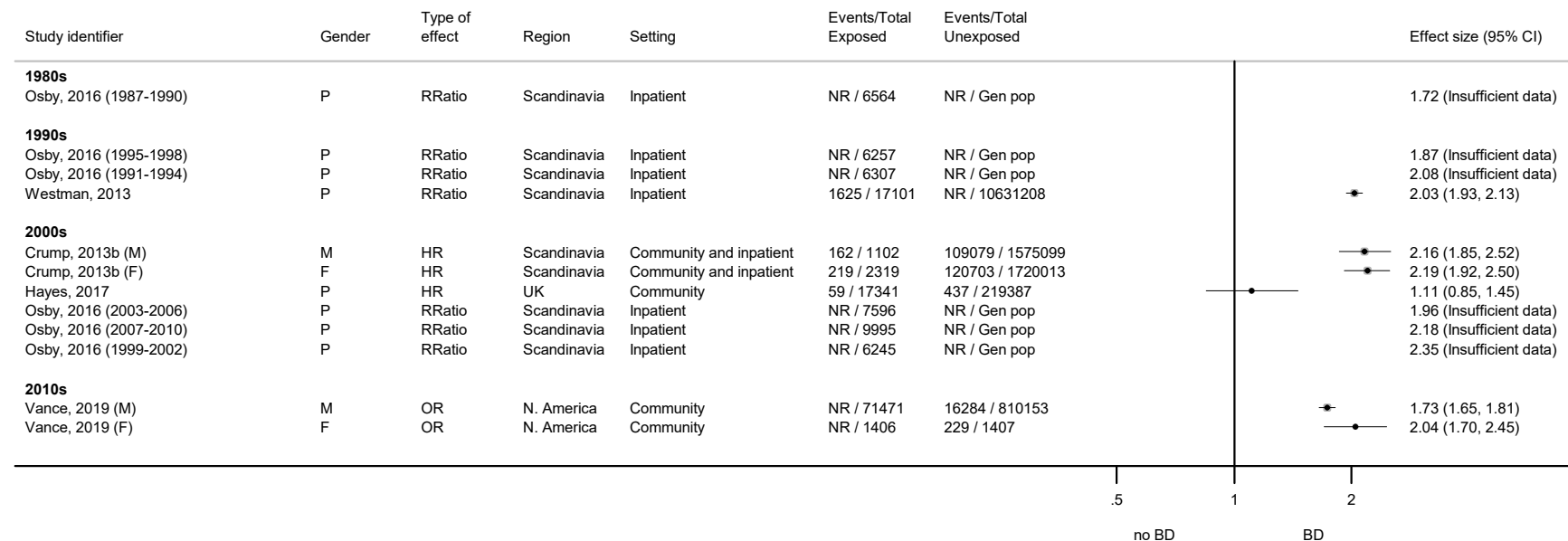
BD – bipolar disorder, NR – not reported, gen pop – general population, HR – hazard ratio, RRatio – rate ratio, P – persons, M – males, F - females

**Appendix figure XI.11: Bipolar disorder, mortality from cerebrovascular accident, hazard ratios, rate ratios and odds ratios, across decades**



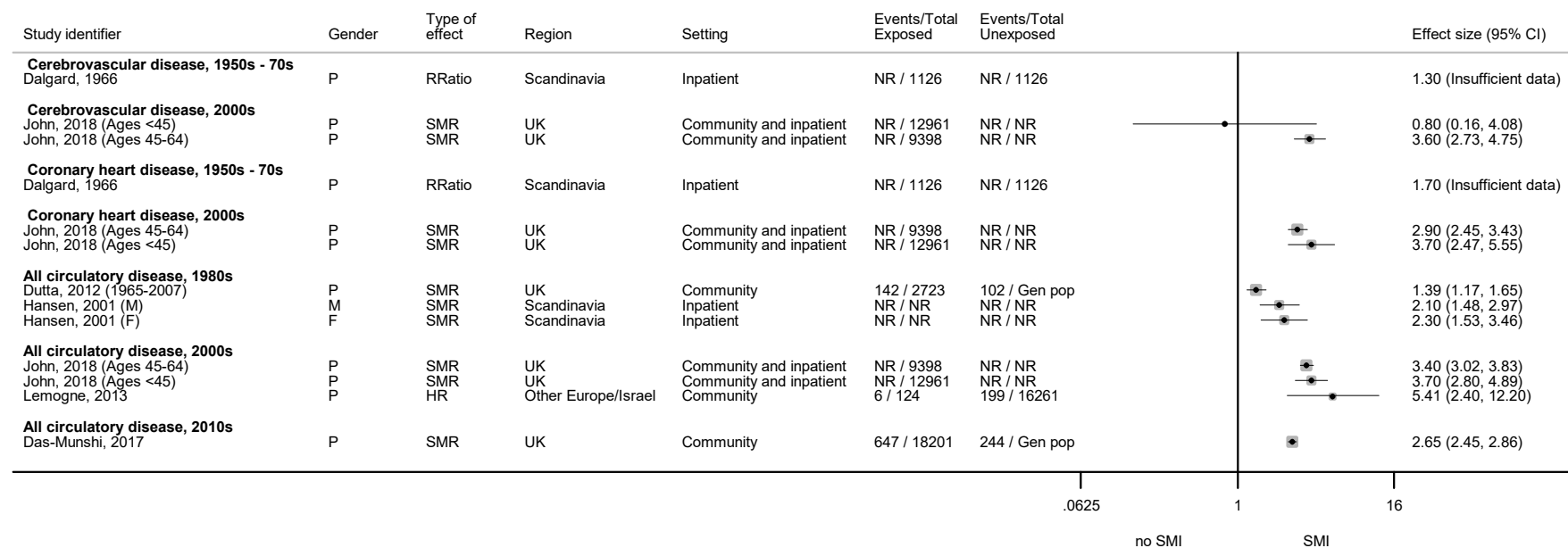
BD – bipolar disorder, NR – not reported, gen pop – general population, est – estimated, HR – hazard ratio, RRatio – rate ratio, P – persons, M – males, F - females

**Appendix figure XI.12: Bipolar disorder, mortality from coronary heart disease, hazard ratios, rate ratios and odds ratios, across decades**



BD – bipolar disorder, NR – not reported, gen pop – general population, HR – hazard ratio, RRatio – rate ratio, OR – odds ratio, P – persons, M – males, F - females

**Appendix figure XI.13: Bipolar disorder, mortality from all circulatory disease, hazard ratios, rate ratios and odds ratios, across decades**



SMI – severe mental illness, NR – not reported, gen pop – general population, HR – hazard ratio, RRatio – rate ratio, SMR – standardised mortality ratio, P – persons, M – males, F - females

**Appendix figure XI.14: Mixed SMI, mortality from cardiovascular diseases, hazard ratios, rate ratios, odds ratios, standardised mortality ratios, across decades**

## APPENDIX XII ANALYSIS OF TEMPORAL TRENDS: MORTALITY

**Table XII.1: Results of meta-regressions: estimates of increased effect size relative to the reference category by median 5-year calendar period of outcome, exponentiated regression coefficients (95% confidence intervals,) p values**

| Explanatory variable<br>(if no. of studies/results ≥10)              |                                                                      |                         | Schizophrenia                  |                            |                            | Bipolar disorder           |
|----------------------------------------------------------------------|----------------------------------------------------------------------|-------------------------|--------------------------------|----------------------------|----------------------------|----------------------------|
|                                                                      |                                                                      |                         | CVA                            | CHD                        | CVD                        | CVD                        |
| 5-year<br>calendar<br>period                                         | SMR                                                                  | 1950-69 (ref)           | 1                              | 1                          | 1                          | 1                          |
|                                                                      |                                                                      | 1970-74                 | 3.00 (0.85-10.54), 0.079       | 0.96 (0.25-3.71), 0.951    | -                          | 0.85 (0.55-1.33), 0.430    |
|                                                                      |                                                                      | 1975-79                 | 1.53 (0.60-3.92), 0.328        | 0.90 (0.29-2.81), 0.830    | 0.75 (0.20-2.85), 0.643    | 0.91 (0.60-1.38), 0.611    |
|                                                                      |                                                                      | 1980-84                 | 1.71 (0.69-4.24), 0.208        | 0.63 (0.21-1.90), 0.360    | 0.34 (0.08-1.42), 0.127    | -                          |
|                                                                      |                                                                      | 1985-89                 | -                              | -                          | -                          | -                          |
|                                                                      |                                                                      | 1990-94                 | 2.73 (0.91-8.22), 0.069        | 1.29 (0.38-4.34), 0.638    | 1.03 (0.27-3.94), 0.964    | -                          |
|                                                                      |                                                                      | 1995-99                 | <b>3.16</b> (1.18-8.44), 0.027 | 1.28 (0.35-4.65), 0.667    | 0.99 (0.24-4.00), 0.983    | 0.94 (0.65-1.37), 0.718    |
|                                                                      |                                                                      | 2000-04                 | 2.19 (0.97-4.95), 0.057        | 1.44 (0.51-4.10), 0.440    | 1.02 (0.28-3.77), 0.969    | 1.15 (0.80-1.67), 0.395    |
|                                                                      |                                                                      | 2005-09                 | -                              | -                          | 1.56 (0.38-6.35), 0.502    | 1.15 (0.78-1.70), 0.420    |
|                                                                      |                                                                      | 2010-14                 | 1.52 (0.63-3.68), 0.302        | 1.23 (0.40-3.81), 0.687    | 1.22 (0.32-4.59), 0.751    | 0.82 (0.52-1.28), 0.332    |
|                                                                      | <i>Model p-value, residual I<sup>2</sup>, adjusted R<sup>2</sup></i> |                         | <i>0.210, 81.4%, 45.8%</i>     | <i>0.394, 97.5%, 12.4%</i> | <i>0.244, 98.6%, 24.9%</i> | <i>0.067, 50.2%, 78.8%</i> |
|                                                                      | HR/rate ratio                                                        | 1980-84 (ref)           | Insufficient observations      | Insufficient observations  | 1                          | Insufficient observations  |
| 1985-89                                                              |                                                                      | -                       |                                |                            |                            |                            |
| 1990-94                                                              |                                                                      | -                       |                                |                            |                            |                            |
| 1995-99                                                              |                                                                      | 2.00 (0.46-8.59), 0.306 |                                |                            |                            |                            |
| 2000-04                                                              |                                                                      | 1.16 (0.27-4.95), 0.823 |                                |                            |                            |                            |
| 2005-09                                                              |                                                                      | 1.68 (0.42-6.77), 0.417 |                                |                            |                            |                            |
| 2010-14                                                              |                                                                      | -                       |                                |                            |                            |                            |
| <i>Model p-value, residual I<sup>2</sup>, adjusted R<sup>2</sup></i> |                                                                      |                         |                                | <i>0.328, 95.6%, 19.3%</i> |                            |                            |
| <i>Random effects meta-analysis I<sup>2</sup></i>                    |                                                                      |                         |                                |                            |                            |                            |
|                                                                      | SMRs                                                                 | 91.5%                   | 98.0%                          | 99.2%                      | 80.4%                      |                            |
|                                                                      | HR/rate ratio                                                        |                         |                                | 98.9%                      |                            |                            |

CVA – cerebrovascular accident, CHD – coronary heart disease, CVD – all circulatory disease, SMR – standardised mortality ratio, HR – hazard ratio, ref – reference group. Results where 95% confidence intervals exclude the null highlighted in bold. Models adjusted for age and sex and minimum number of additional factors. Results where 95% confidence intervals exclude the null highlighted in **bold**

**Table XII.2: Meta-analysis: pooled results by severe mental illness and decade, cardiovascular mortality**

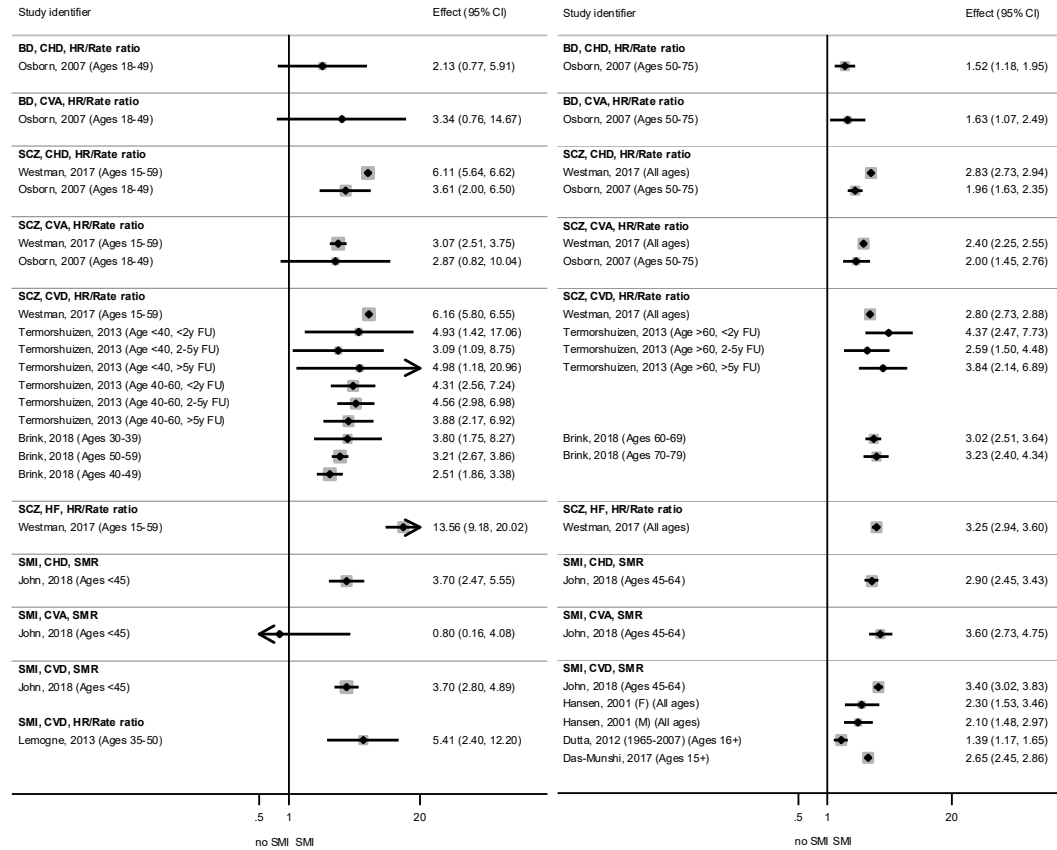
| SMI | Outcome | Measure   | Decade   | Studies | Results | Effect      | 95% CI          | p      | Lower prediction interval | Upper prediction interval | I <sup>2</sup> | Q     | Q df |
|-----|---------|-----------|----------|---------|---------|-------------|-----------------|--------|---------------------------|---------------------------|----------------|-------|------|
| SCZ | CVA     | HR/RRatio | 1980s    | 1       | 1       | 1.65        | ( 0.52 - 5.22 ) | 0.394  | .                         | .                         | .              | 0.0   | 0    |
| SCZ | CVA     | HR/RRatio | 1990s    | 2       | 2       | <b>2.40</b> | ( 2.26 - 2.56 ) | <0.001 | .                         | .                         | 0.0            | 0.1   | 1    |
| SCZ | CVA     | SMR       | 1950-70s | 4       | 4       | <b>1.56</b> | ( 1.01 - 2.40 ) | 0.045  | 0.2                       | 10.1                      | 74.2           | 11.6  | 3    |
| SCZ | CVA     | SMR       | 1980s    | 3       | 3       | <b>1.78</b> | ( 1.05 - 3.00 ) | 0.032  | 0.0                       | 620.7                     | 66.1           | 5.9   | 2    |
| SCZ | CVA     | SMR       | 1990s    | 3       | 3       | <b>3.14</b> | ( 2.78 - 3.55 ) | <0.001 | 1.4                       | 6.9                       | 0.0            | 0.6   | 2    |
| SCZ | CVA     | SMR       | 2000s    | 2       | 4       | <b>2.21</b> | ( 1.98 - 2.48 ) | <0.001 | 1.4                       | 3.6                       | 74.4           | 11.7  | 3    |
| SCZ | CVA     | SMR       | 2010s    | 2       | 2       | 1.54        | ( 0.85 - 2.80 ) | 0.158  | .                         | .                         | 95.6           | 22.5  | 1    |
| SCZ | CHD     | HR/RRatio | 1980s    | 3       | 6       | <b>1.78</b> | ( 1.55 - 2.05 ) | <0.001 | 1.1                       | 2.8                       | 90.6           | 53.1  | 5    |
| SCZ | CHD     | HR/RRatio | 1990s    | 2       | 2       | <b>2.83</b> | ( 2.73 - 2.94 ) | <0.001 | .                         | .                         | 0.0            | 0.7   | 1    |
| SCZ | CHD     | HR/RRatio | 2000s    | 2       | 2       | <b>1.35</b> | ( 1.31 - 1.41 ) | <0.001 | .                         | .                         | 0.0            | 0.1   | 1    |
| SCZ | CHD     | SMR       | 1950-70s | 4       | 4       | <b>1.62</b> | ( 1.43 - 1.83 ) | <0.001 | 1.2                       | 2.1                       | 0.0            | 1.2   | 3    |
| SCZ | CHD     | SMR       | 1980s    | 3       | 3       | 1.14        | ( 0.57 - 2.30 ) | 0.710  | 0.0                       | 6779.8                    | 89.6           | 19.3  | 2    |
| SCZ | CHD     | SMR       | 1990s    | 3       | 3       | <b>2.29</b> | ( 2.11 - 2.49 ) | <0.001 | 1.3                       | 3.9                       | 0.0            | 0.0   | 2    |
| SCZ | CHD     | SMR       | 2000s    | 2       | 4       | <b>2.59</b> | ( 1.93 - 3.47 ) | <0.001 | 0.6                       | 10.8                      | 98.7           | 222.9 | 3    |
| SCZ | CHD     | SMR       | 2010s    | 2       | 2       | <b>2.20</b> | ( 1.05 - 4.59 ) | 0.036  | .                         | .                         | 98.8           | 82.3  | 1    |
| SCZ | CVD     | HR/RRatio | 1980s    | 1       | 1       | 1.20        | ( 0.47 - 3.04 ) | 0.700  | .                         | .                         | .              | 0.0   | 0    |
| SCZ | CVD     | HR/RRatio | 1990s    | 2       | 2       | <b>2.41</b> | ( 1.74 - 3.35 ) | <0.001 | .                         | .                         | 88.4           | 8.6   | 1    |
| SCZ | CVD     | HR/RRatio | 2000s    | 7       | 9       | <b>1.86</b> | ( 1.44 - 2.40 ) | <0.001 | 0.7                       | 4.8                       | 98.4           | 512.9 | 8    |
| SCZ | CVD     | OR        | 2010s    | 1       | 2       | <b>2.55</b> | ( 1.74 - 3.74 ) | <0.001 | .                         | .                         | 91.8           | 12.1  | 1    |
| SCZ | CVD     | SMR       | 1950-70s | 3       | 4       | <b>1.68</b> | ( 1.41 - 2.00 ) | <0.001 | 0.9                       | 3.1                       | 39.1           | 4.9   | 3    |
| SCZ | CVD     | SMR       | 1980s    | 2       | 2       | 0.71        | ( 0.19 - 2.69 ) | 0.616  | .                         | .                         | 98.1           | 51.6  | 1    |
| SCZ | CVD     | SMR       | 1990s    | 5       | 5       | <b>2.13</b> | ( 1.59 - 2.84 ) | <0.001 | 0.7                       | 6.3                       | 95.7           | 93.1  | 4    |
| SCZ | CVD     | SMR       | 2000s    | 5       | 6       | <b>2.68</b> | ( 2.15 - 3.34 ) | <0.001 | 1.2                       | 5.8                       | 98.6           | 357.9 | 5    |
| SCZ | CVD     | SMR       | 2010s    | 3       | 3       | <b>2.53</b> | ( 1.32 - 4.84 ) | 0.005  | 0.0                       | 11000.0                   | 99.4           | 350.0 | 2    |
| SCZ | HF      | HR/RRatio | 1990s    | 1       | 1       | <b>3.25</b> | ( 2.94 - 3.60 ) | <0.001 | .                         | .                         | .              | 0.0   | 0    |
| BD  | CVA     | HR/RRatio | 1990s    | 2       | 2       | <b>2.01</b> | ( 1.81 - 2.22 ) | <0.001 | .                         | .                         | 0.0            | 0.5   | 1    |
| BD  | CVA     | SMR       | 1950-70s | 1       | 1       | 1.37        | ( 0.89 - 2.10 ) | 0.151  | .                         | .                         | .              | 0.0   | 0    |
| BD  | CVA     | SMR       | 1980s    | 1       | 1       | 1.58        | ( 0.82 - 3.03 ) | 0.172  | .                         | .                         | .              | 0.0   | 0    |
| BD  | CVA     | SMR       | 1990s    | 1       | 1       | <b>1.30</b> | ( 1.20 - 1.40 ) | <0.001 | .                         | .                         | .              | 0.0   | 0    |
| BD  | CVA     | SMR       | 2000s    | 1       | 3       | <b>1.75</b> | ( 1.59 - 1.93 ) | <0.001 | 0.9                       | 3.3                       | 0.0            | 0.5   | 2    |
| BD  | CVA     | SMR       | 2010s    | 1       | 1       | 1.30        | ( 0.94 - 1.81 ) | 0.119  | .                         | .                         | .              | 0.0   | 0    |
| BD  | CHD     | HR/RRatio | 1980s    | 1       | 2       | <b>1.63</b> | ( 1.52 - 1.74 ) | <0.001 | .                         | .                         | 0.0            | 0.6   | 1    |
| BD  | CHD     | HR/RRatio | 1990s    | 3       | 4       | <b>1.93</b> | ( 1.59 - 2.35 ) | <0.001 | 1.1                       | 3.5                       | 7.7            | 3.3   | 3    |
| BD  | CHD     | HR/RRatio | 2000s    | 1       | 1       | <b>1.24</b> | ( 1.13 - 1.36 ) | <0.001 | .                         | .                         | .              | 0.0   | 0    |
| BD  | CHD     | SMR       | 1950-70s | 1       | 1       | <b>1.84</b> | ( 1.43 - 2.37 ) | <0.001 | .                         | .                         | .              | 0.0   | 0    |



| SMI | Outcome | Measure   | Decade   | Studies | Results | Effect      | 95% CI           | p      | Lower prediction interval | Upper prediction interval | I <sup>2</sup> | Q   | Q df |
|-----|---------|-----------|----------|---------|---------|-------------|------------------|--------|---------------------------|---------------------------|----------------|-----|------|
| BD  | CHD     | SMR       | 1980s    | 1       | 1       | 1.00        | ( 0.69 - 1.44 )  | 0.980  | .                         | .                         | .              | 0.0 | 0    |
| BD  | CHD     | SMR       | 1990s    | 1       | 1       | <b>1.66</b> | ( 1.59 - 1.74 )  | <0.001 | .                         | .                         | .              | 0.0 | 0    |
| BD  | CHD     | SMR       | 2000s    | 1       | 3       | <b>1.77</b> | ( 1.65 - 1.90 )  | <0.001 | 1.1                       | 2.8                       | 0.0            | 1.2 | 2    |
| BD  | CHD     | SMR       | 2010s    | 1       | 1       | 1.33        | ( 1.00 - 1.77 )  | 0.052  | .                         | .                         | .              | 0.0 | 0    |
| BD  | CVD     | HR/RRatio | 1990s    | 1       | 1       | <b>2.03</b> | ( 1.93 - 2.13 )  | <0.001 | .                         | .                         | .              | 0.0 | 0    |
| BD  | CVD     | HR/RRatio | 2000s    | 1       | 1       | 1.11        | ( 0.85 - 1.46 )  | 0.450  | .                         | .                         | .              | 0.0 | 0    |
| BD  | CVD     | OR        | 2010s    | 1       | 2       | <b>1.83</b> | ( 1.57 - 2.14 )  | <0.001 | .                         | .                         | 65.2           | 2.9 | 1    |
| BD  | CVD     | SMR       | 1950-70s | 6       | 6       | <b>1.47</b> | ( 1.31 - 1.65 )  | <0.001 | 1.2                       | 1.8                       | 7.4            | 5.4 | 5    |
| BD  | CVD     | SMR       | 1990s    | 2       | 2       | <b>1.54</b> | ( 1.47 - 1.60 )  | <0.001 | .                         | .                         | 31.7           | 1.5 | 1    |
| BD  | CVD     | SMR       | 2000s    | 3       | 5       | <b>1.86</b> | ( 1.75 - 1.99 )  | <0.001 | 1.5                       | 2.3                       | 52.1           | 8.4 | 4    |
| BD  | CVD     | SMR       | 2010s    | 1       | 1       | <b>1.33</b> | ( 1.11 - 1.60 )  | 0.002  | .                         | .                         | .              | 0.0 | 0    |
| SMI | CHD     | SMR       | 2000s    | 1       | 1       | <b>3.70</b> | ( 2.47 - 5.55 )  | <0.001 | .                         | .                         | .              | 0.0 | 0    |
| SMI | CVA     | SMR       | 2000s    | 1       | 1       | 0.80        | ( 0.16 - 4.08 )  | 0.788  | .                         | .                         | .              | 0.0 | 0    |
| SMI | CVD     | HR/RRatio | 2000s    | 1       | 1       | <b>5.41</b> | ( 2.40 - 12.20 ) | <0.001 | .                         | .                         | .              | 0.0 | 0    |
| SMI | CVD     | SMR       | 1980s    | 2       | 3       | <b>1.82</b> | ( 1.28 - 2.58 )  | 0.001  | 0.0                       | 105.6                     | 75.1           | 8.0 | 2    |
| SMI | CVD     | SMR       | 2000s    | 1       | 1       | <b>3.70</b> | ( 2.80 - 4.90 )  | <0.001 | .                         | .                         | .              | 0.0 | 0    |
| SMI | CVD     | SMR       | 2010s    | 1       | 1       | <b>2.65</b> | ( 2.45 - 2.86 )  | <0.001 | .                         | .                         | .              | 0.0 | 0    |

SCZ – schizophrenia, BD – bipolar disorder, SMI – mixed severe mental illness, HR – hazard ratio, RRatio – rate ratio, SMR – standardised mortality ratio, OR – odds ratio, CVA – cerebrovascular accident, CHD – coronary heart disease, CVD – all circulatory disease, HF – heart failure. Results where 95% confidence intervals exclude the null highlighted in **bold**

## APPENDIX XIII SUBGROUP ANALYSIS: MORTALITY STUDIES

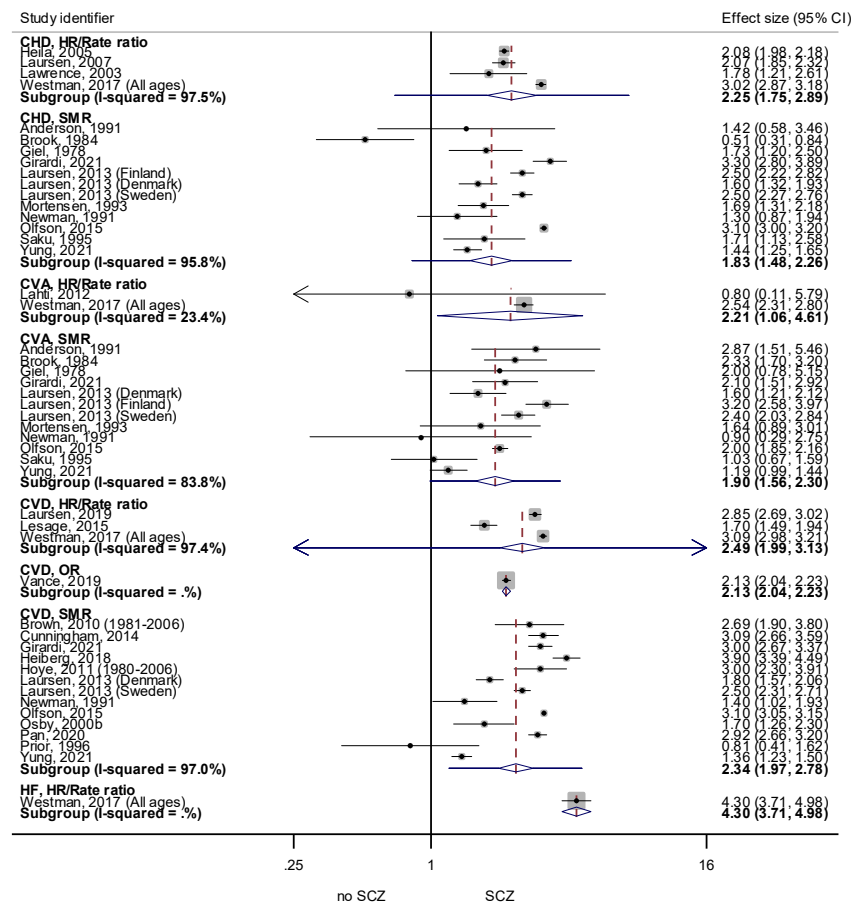


a)

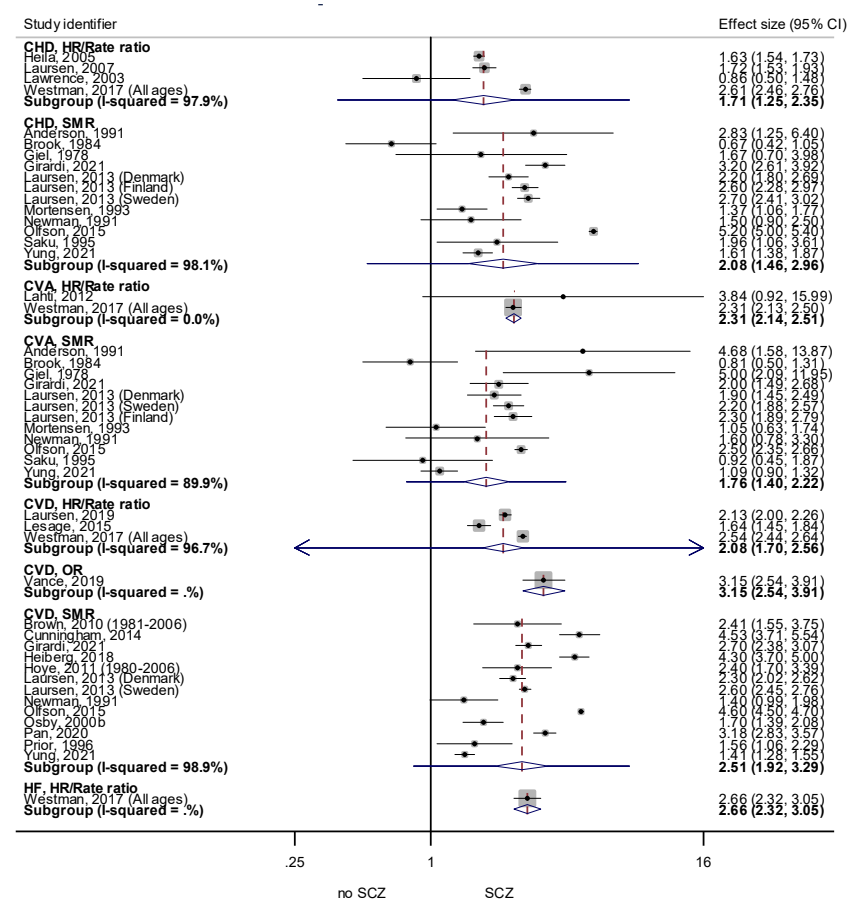
b)

BD – bipolar disorder, SCZ – schizophrenia, SMI – mixed severe mental illness, CHD – coronary heart disease, CVA – cerebrovascular accident, CVD – all circulatory disease, HF – heart failure, HR – hazard ratio, SMR – standardised mortality ratio, FU – follow-up

**Appendix figure XIII.1: Forest plots showing studies reporting CVD mortality risk for severe mental illness vs controls for a) age groups ≤60; b) older age groups or all ages**



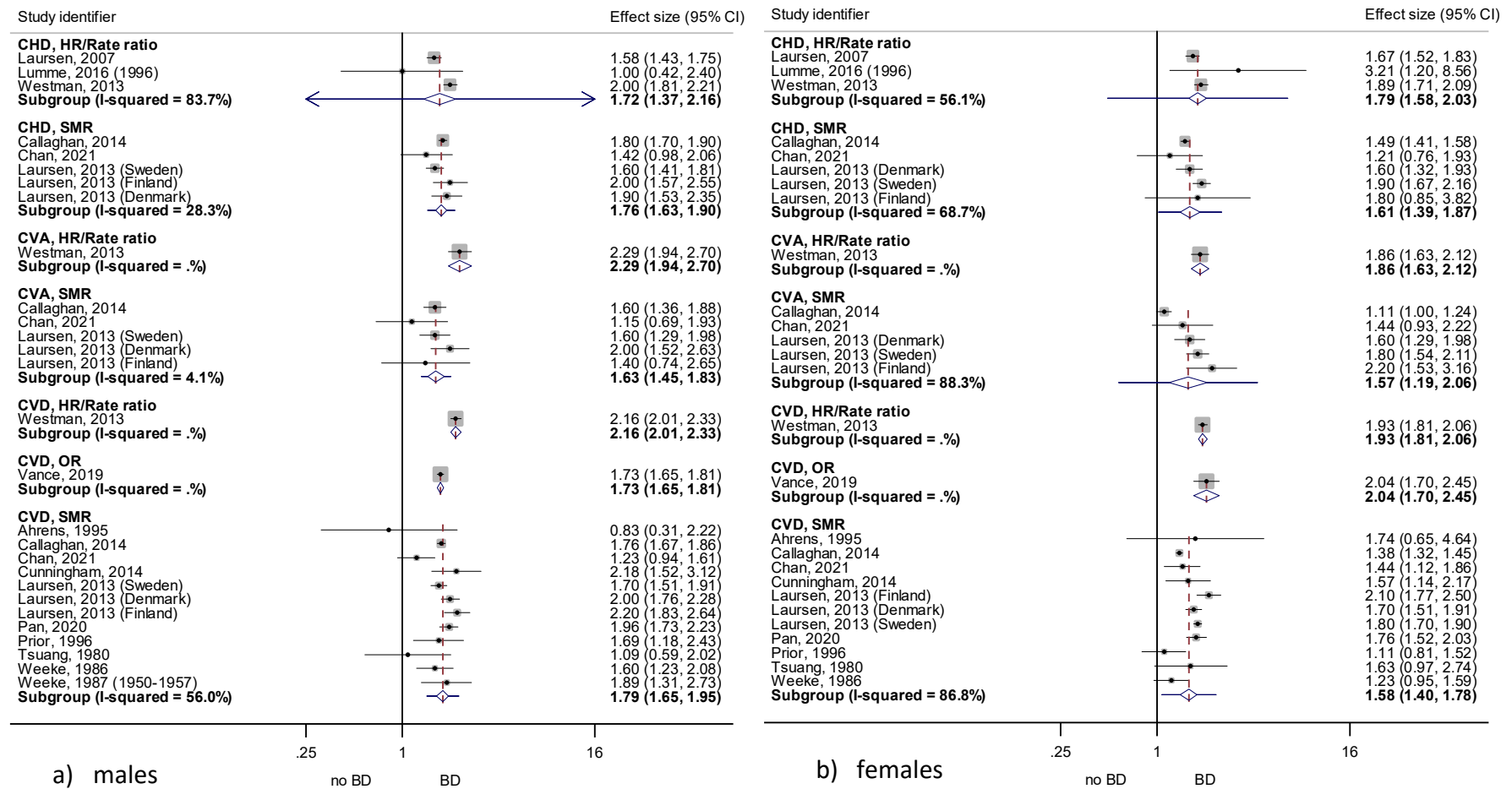
a) males



b) females

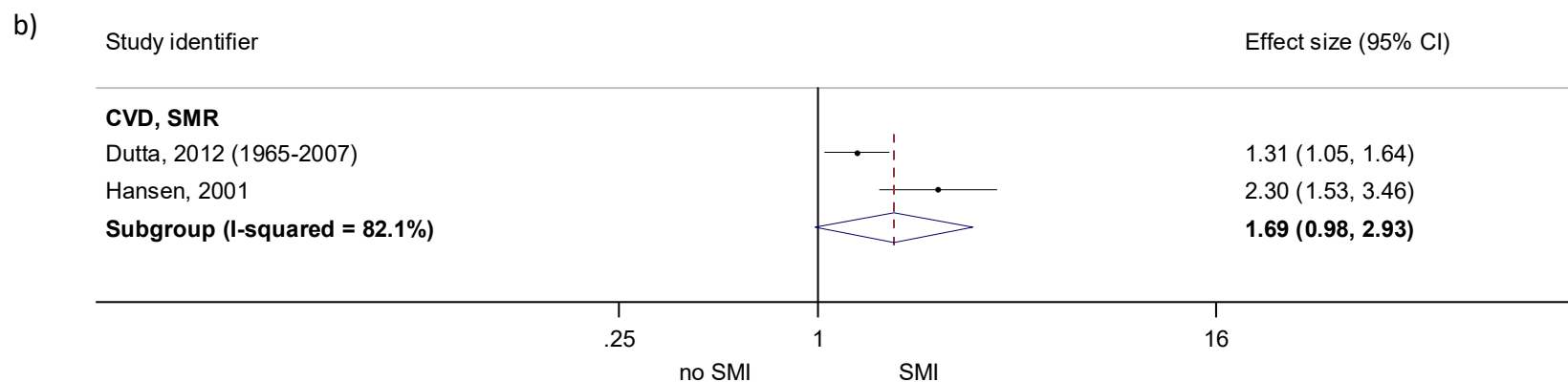
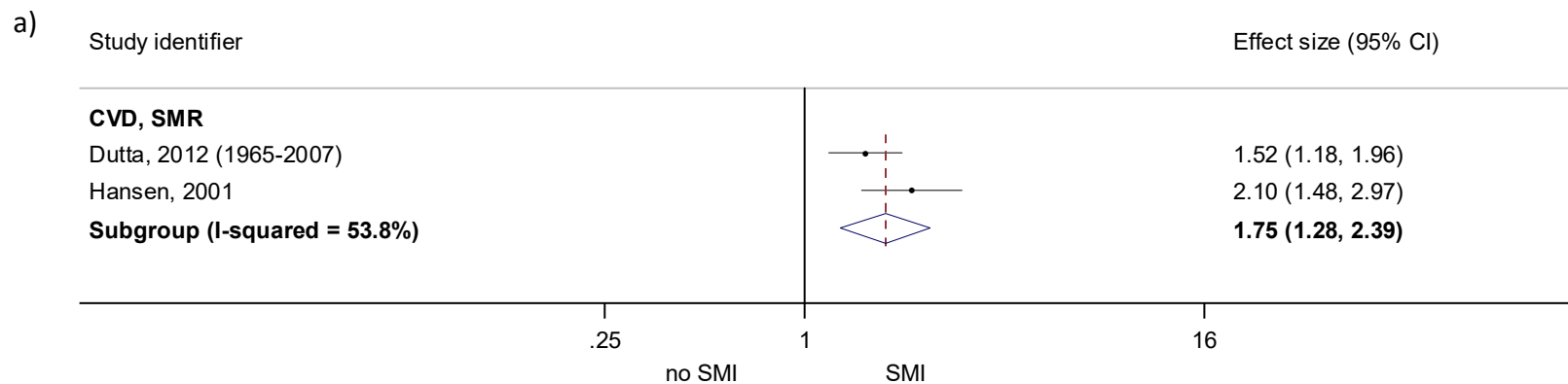
SCZ – schizophrenia, HR – hazard ratio, SMR – standardised mortality ratio, OR – odds ratio, CHD – coronary heart disease, CVA – cerebrovascular accident, CVD – all circulatory disease, HF – heart failure

**Appendix figure XIII.2: Forest plots showing relative risk of CVD mortality in those with vs without schizophrenia, studies included in meta-analysis for a) males; b) females**



BD – bipolar disorder, HR – hazard ratio, SMR – standardised mortality ratio, OR – odds ratio, CHD – coronary heart disease, CVA – cerebrovascular accident, CVD – all circulatory disease

**Appendix figure XIII.3: Forest plots showing relative risk of CVD mortality in those with vs without bipolar disorder, studies included in meta-analysis for a) males; b) females**



SMI – severe mental illness, SMR – standardised mortality ratio, CVD – all circulatory disease

**Appendix figure XIII.4: Forest plots showing relative risk of CVD mortality in those with vs without mixed SMI, studies included in meta-analysis for a) males; b) females**

## APPENDIX XIV SENSITIVITY ANALYSIS

### **Studies excluded from meta-analysis**

Results of some studies not included in the meta-analysis were outside the prediction intervals of included studies. Studies excluded from the meta-analysis due to overlapping periods of recruitment or multiple results from the same study are considered in sensitivity analyses (see Appendix table XIV.1 and Appendix table XIV.2 below).

Seven additional studies (one reporting incidence (Bent-Ennakhil, 2018), and six reporting CVD mortality (Hoang, 2011, Nordentoft, 2013, Saku, 1995, Ösby, 2016, Odegard, 1967, Dalgard, 1966) that were excluded from the meta-analysis due to unreported confidence intervals for effect estimates are considered here. For schizophrenia, there were six reported rate ratios that were within the prediction intervals of studies included in the meta-analysis for both CVA and CHD, also nine rate ratios and 14 SMRs within the prediction intervals for CVD. For bipolar disorder, there were six rate ratios for CVA with unreported confidence intervals with effect sizes between 1.38 and 2.65. No prediction interval was able to be calculated as there were only two studies included in this meta-analysis. However, the effect sizes for the excluded studies extend beyond both the upper and lower confidence interval of the pooled estimate. Similarly, no prediction interval was calculated for the incidence of major CVD events but the effect size of one study (Bent-Ennakhil, 2018) was above the range of the pooled confidence interval. There was one SMR with unreported confidence intervals for CVA and six rate ratios for CHD that fell within the prediction intervals of the respective meta-analyses. SMRs for one study (Saku, 1995) fell below the prediction interval of the pooled estimate for females and above for males. For all circulatory disease mortality, there were six rate ratios with unreported confidence intervals: all were within the confidence

interval of the pooled estimate. Of the eight SMRs with unreported confidence intervals for all CVD, one (Hoang, 2011) was above the prediction interval. One study (Dalgard, 1966) reported CVA and CHD rate ratios for mixed SMI that were within the confidence intervals for SMRs of the respective outcomes.

### **Borderline studies**

The decision to exclude studies at full-text screening was, in some cases, borderline due to lack of clarity in the methodology (Bresee, 2012, Wood, 1985, Schwalb, 1980), definition of SMI (Kondo, 2017), outcome (Cohen, 2012) or a high proportion with CVD at baseline (Enger, 2004, Joukamaa, 2001). However, results were similar to those for included studies, *i.e* higher relative risks of CVD mortality for people with SMI.

**Appendix table XIV.1: Sensitivity analyses showing effect of replacing included with excluded results, studies reporting mortality outcomes**

| SMI | Mortality outcome | Effect type | Change                                                                            | Meta-analysis pooled effect (95% CI) | New pooled effect (95% CI) | Comment                                                        |
|-----|-------------------|-------------|-----------------------------------------------------------------------------------|--------------------------------------|----------------------------|----------------------------------------------------------------|
| SCZ | CVA               | HR/RRatio   | Replace Westman with Crump                                                        | <b>2.40</b> (2.25-2.55)              | <b>2.37</b> (1.82-3.08)    | Slightly smaller effect size, but wider CI                     |
| SCZ | CVA               | HR/RRatio   | Replace Osborn ages 18-49 with ages 50-75                                         | <b>2.40</b> (2.25-2.55)              | <b>2.38</b> (2.24-2.53)    | No difference in scale or direction of effect                  |
| SCZ | CVA               | HR/RRatio   | Replace Westman all ages with ages 15-59                                          | <b>2.40</b> (2.25-2.55)              | <b>3.01</b> (2.48-3.66)    | Larger effect size, but wider CI                               |
| SCZ | CVA               | SMR         | Replace Mortensen, 1993 with Mortensen, 1990                                      | <b>1.93</b> (1.63-2.28)              | <b>1.86</b> (1.44-2.40)    | Slightly smaller effect size, but wider CI                     |
| SCZ | CVA               | SMR         | Replace Laursen (Denmark) with Castagnini                                         | <b>1.93</b> (1.63-2.28)              | <b>1.94</b> (1.62-2.31)    | No difference in scale or direction of effect                  |
| SCZ | CVA               | SMR         | Replace Allebeck with Ösby, 2000                                                  | <b>1.93</b> (1.63-2.28)              | <b>1.91</b> (1.62-2.25)    | No difference in scale or direction of effect                  |
| SCZ | CVA               | SMR         | Retain Callaghan as well as Olfson                                                | <b>1.93</b> (1.63-2.28)              | <b>1.95</b> (1.71-2.21)    | No difference in scale or direction of effect                  |
| SCZ | CHD               | HR/RRatio   | Replace Laursen, 2007 with Laursen, 2010 (1994-96)                                | <b>1.79</b> (1.43-2.24)              | <b>1.79</b> (1.40-2.28)    | No difference in scale or direction of effect                  |
| SCZ | CHD               | HR/RRatio   | Replace Laursen, 2007 with Laursen, 2010 (2005-2006)                              | <b>1.79</b> (1.43-2.24)              | <b>1.92</b> (1.49-2.47)    | Slightly larger effect size, but wider CI                      |
| SCZ | CHD               | HR/RRatio   | Replace Laursen, 2007 with Laursen, 2014                                          | <b>1.79</b> (1.43-2.24)              | <b>1.84</b> (1.43-2.37)    | No difference in scale or direction of effect                  |
| SCZ | CHD               | HR/RRatio   | Replace Heila and Manderbacka with Lahti                                          | <b>1.79</b> (1.43-2.24)              | <b>1.95</b> (1.47-2.63)    | Slightly larger effect size, but wider CI                      |
| SCZ | CHD               | HR/RRatio   | Replace Heila with Lumme (1990-96)                                                | <b>1.79</b> (1.43-2.24)              | <b>1.88</b> (1.41-2.49)    | Slightly larger effect size, but wider CI                      |
| SCZ | CHD               | HR/RRatio   | Replace Helia with last year of Lumme                                             | <b>1.79</b> (1.43-2.24)              | <b>2.17</b> (1.62-2.91)    | Slightly larger effect size, but wider CI                      |
| SCZ | CHD               | HR/RRatio   | Replace Westman with Crump                                                        | <b>1.79</b> (1.43-2.24)              | <b>1.92</b> (1.63-2.27)    | Slightly larger effect size and narrower CI                    |
| SCZ | CHD               | HR/RRatio   | Replace Westman with Bjorkenstam                                                  | <b>1.79</b> (1.43-2.24)              | <b>1.98</b> (1.67-2.35)    | Slightly larger effect size                                    |
| SCZ | CHD               | HR/RRatio   | Replace Osborn ages 18-49 with ages 50-75                                         | <b>1.79</b> (1.43-2.24)              | <b>1.74</b> (1.40-2.16)    | No difference in scale or direction of effect                  |
| SCZ | CHD               | HR/RRatio   | Replace Osborn with Murray-Thomas                                                 | <b>1.79</b> (1.43-2.24)              | <b>1.73</b> (1.38-2.16)    | No difference in scale or direction of effect                  |
| SCZ | CHD               | HR/RRatio   | Replace Kilbourne with Daumit                                                     | <b>1.79</b> (1.43-2.24)              | <b>1.85</b> (1.51-2.28)    | No difference in scale or direction of effect                  |
| SCZ | CHD               | HR/RRatio   | Replace Westman all ages with ages 15-59                                          | <b>1.79</b> (1.43-2.24)              | <b>1.95</b> (1.44-2.63)    | Slightly larger effect size, but wider CI                      |
| SCZ | CHD               | HR/RRatio   | Replace Heila follow-up >10 years with 0-5 years                                  | <b>1.79</b> (1.43-2.24)              | <b>1.90</b> (1.45-2.48)    | Slightly larger effect size, but wider CI                      |
| SCZ | CHD               | SMR         | Replace Mortensen, 1993 with Mortensen, 1990                                      | <b>1.94</b> (1.58-2.37)              | <b>1.88</b> (1.42-2.51)    | No difference in scale or direction of effect, but wider CI    |
| SCZ | CHD               | SMR         | Replace Laursen (Denmark) with Castagnini                                         | <b>1.94</b> (1.58-2.37)              | <b>2.03</b> (1.66-2.49)    | Slightly larger effect size                                    |
| SCZ | CHD               | SMR         | Replace Allebeck with Ösby, 2000                                                  | <b>1.94</b> (1.58-2.37)              | <b>1.97</b> (1.62-2.40)    | No difference in scale or direction of effect                  |
| SCZ | CHD               | SMR         | Replace Olfson with Callaghan and Kelly (Clozapine)                               | <b>1.94</b> (1.58-2.37)              | <b>2.01</b> (1.75-2.31)    | Slightly larger effect size and narrower CI                    |
| SCZ | CHD               | SMR         | Replace Olfson with Callaghan and Kelly (Risperidone)                             | <b>1.94</b> (1.58-2.37)              | <b>1.94</b> (1.69-2.22)    | No difference in scale or direction of effect, but narrower CI |
| SCZ | CVD               | HR/RRatio   | Replace Westman with Crump and Fors                                               | <b>1.91</b> (1.52-2.41)              | <b>2.01</b> (1.63-2.49)    | Slightly larger effect size and narrower CI                    |
| SCZ | CVD               | HR/RRatio   | Replace Westman with Crump, Fors and Tornainen (moderate level of antipsychotics) | <b>1.91</b> (1.52-2.41)              | <b>2.17</b> (1.73-2.72)    | Larger effect size                                             |
| SCZ | CVD               | HR/RRatio   | Replace Westman with Crump, Fors and Tornainen (no antipsychotics)                | <b>1.91</b> (1.52-2.41)              | <b>2.20</b> (1.77-2.74)    | Larger effect size                                             |
| SCZ | CVD               | HR/RRatio   | Replace Westman with Crump, Fors and Tornainen (low level of antipsychotics)      | <b>1.91</b> (1.52-2.41)              | <b>2.13</b> (1.73-2.64)    | Larger effect size                                             |
| SCZ | CVD               | HR/RRatio   | Replace Westman with Crump, Fors and Tornainen (moderate level of antipsychotics) | <b>1.91</b> (1.52-2.41)              | <b>2.23</b> (1.74-2.86)    | Larger effect size                                             |
| SCZ | CVD               | HR/RRatio   | Replace Westman all ages with ages 15-59                                          | <b>1.91</b> (1.52-2.41)              | <b>2.05</b> (1.43-2.93)    | Slightly larger effect size, but wider CI                      |
| SCZ | CVD               | HR/RRatio   | Replace Laursen, 2019 with Brink ages 50-59                                       | <b>1.91</b> (1.52-2.41)              | <b>1.91</b> (1.42-2.57)    | No difference in scale or direction of effect, but wider CI    |



| SMI | Mortality outcome | Effect type | Change                                                                | Meta-analysis pooled effect (95% CI) | New pooled effect (95% CI) | Comment                                                     |
|-----|-------------------|-------------|-----------------------------------------------------------------------|--------------------------------------|----------------------------|-------------------------------------------------------------|
| SCZ | CVD               | HR/RRatio   | Replace Brink ages 50-59 with ages 40-49                              | <b>1.91</b> (1.52-2.41)              | <b>1.87</b> (1.39-2.51)    | No difference in scale or direction of effect, but wider CI |
| SCZ | CVD               | HR/RRatio   | Replace Brink ages 50-59 with ages 30-39                              | <b>1.91</b> (1.52-2.41)              | <b>1.90</b> (1.40-2.57)    | No difference in scale or direction of effect, but wider CI |
| SCZ | CVD               | HR/RRatio   | Replace Brink ages 50-59 with ages 60-69                              | <b>1.91</b> (1.52-2.41)              | <b>1.90</b> (1.42-2.55)    | No difference in scale or direction of effect, but wider CI |
| SCZ | CVD               | HR/RRatio   | Replace Brink ages 50-59 with ages 70-79                              | <b>1.91</b> (1.52-2.41)              | <b>1.91</b> (1.42-2.57)    | No difference in scale or direction of effect, but wider CI |
| SCZ | CVD               | HR/RRatio   | Replace Termorshuizen with min effect size for age/follow-up category | <b>1.91</b> (1.52-2.41)              | <b>1.85</b> (1.47-2.33)    | No difference in scale or direction of effect               |
| SCZ | CVD               | HR/RRatio   | Replace Termorshuizen with max effect size for age/follow-up category | <b>1.91</b> (1.52-2.41)              | <b>1.85</b> (1.46-2.34)    | No difference in scale or direction of effect               |
| SCZ | CVD               | SMR         | Replace Laursen (Denmark with Hiroeh)                                 | <b>2.02</b> (1.69-2.41)              | <b>2.00</b> (1.67-2.40)    | No difference in scale or direction of effect               |
| SCZ | CVD               | SMR         | Replace Tanskanen with Kiviniemi                                      | <b>2.02</b> (1.69-2.41)              | <b>2.05</b> (1.71-2.46)    | No difference in scale or direction of effect               |
| SCZ | CVD               | SMR         | Replace Tanskanen with Laursen 2013 (Finland)                         | <b>2.02</b> (1.69-2.41)              | <b>2.03</b> (1.70-2.42)    | No difference in scale or direction of effect               |
| SCZ | CVD               | SMR         | Replace Laursen, 2013 (Sweden) with Ösby, 2000 (1991-95)              | <b>2.02</b> (1.69-2.41)              | <b>2.19</b> (1.80-2.66)    | Slightly larger effect size, but wider CI                   |
| SCZ | CVD               | SMR         | Replace Buda with Tsuang                                              | <b>2.02</b> (1.69-2.41)              | <b>1.98</b> (1.65-2.37)    | No difference in scale or direction of effect               |
| SCZ | CVD               | SMR         | Retain Callaghan as well as Olsson                                    | <b>2.02</b> (1.69-2.41)              | <b>2.06</b> (1.79-2.38)    | No difference in scale or direction of effect               |
| SCZ | CVD               | SMR         | Replace Tanskanen data for 2014 with 1984                             | <b>2.02</b> (1.69-2.41)              | <b>2.00</b> (1.67-2.39)    | No difference in scale or direction of effect               |
| SCZ | CVD               | SMR         | Replace Høye data for 1980-1992 with 1993-2006                        | <b>2.02</b> (1.69-2.41)              | <b>2.03</b> (1.70-2.43)    | No difference in scale or direction of effect               |
| BD  | CVA               | HR/RRatio   | Replace Osborn ages 18-49 with ages 50-75                             | <b>2.00</b> (1.81-2.22)              | <b>1.98</b> (1.79-2.18)    | No difference in scale or direction of effect               |
| BD  | CVA               | HR/RRatio   | Replace Westman with Crump                                            | <b>2.00</b> (1.81-2.22)              | <b>2.35</b> (1.78-3.09)    | Larger effect size, but wider CI                            |
| BD  | CVA               | SMR         | Replace Laursen (Sweden) and Nilsson with Ösby                        | <b>1.55</b> (1.33-1.81)              | <b>1.59</b> (1.30-1.95)    | No difference in scale or direction of effect               |
| BD  | CVA               | SMR         | Retain Ösby as well as Laursen (Sweden)                               | <b>1.55</b> (1.33-1.81)              | <b>1.61</b> (1.38-1.89)    | No difference in scale or direction of effect               |
| BD  | CVA               | SMR         | Replace Laursen with Castagnini                                       | <b>1.55</b> (1.33-1.81)              | <b>1.59</b> (1.32-1.92)    | No difference in scale or direction of effect               |
| BD  | CHD               | HR/RRatio   | Replace Laursen, 2007 with Laursen, 2010 (1994-96)                    | <b>1.61</b> (1.34-1.94)              | <b>1.69</b> (1.28-2.23)    | No difference in scale or direction of effect               |
| BD  | CHD               | HR/RRatio   | Replace Laursen, 2007 with Laursen, 2010 (2005-2006)                  | <b>1.61</b> (1.34-1.94)              | <b>1.73</b> (1.29-2.33)    | Slightly larger effect size, but wider CI                   |
| BD  | CHD               | HR/RRatio   | Replace Laursen, 2007 with Laursen, 2014                              | <b>1.61</b> (1.34-1.94)              | <b>1.84</b> (1.32-2.56)    | Slightly larger effect size, but wider CI                   |
| BD  | CHD               | HR/RRatio   | Replace first year of Lumme with last year                            | <b>1.61</b> (1.34-1.94)              | <b>1.63</b> (1.37-1.94)    | No difference in scale or direction of effect               |
| BD  | CHD               | HR/RRatio   | Replace Westman with Crump                                            | <b>1.61</b> (1.34-1.94)              | <b>1.72</b> (1.44-2.07)    | Slightly larger effect size                                 |
| BD  | CHD               | HR/RRatio   | Replace Osborn ages 18-49 with ages 50-75                             | <b>1.61</b> (1.34-1.94)              | <b>1.59</b> (1.34-1.88)    | No difference in scale or direction of effect               |
| BD  | CHD               | HR/RRatio   | Replace Kilbourne with Daumit                                         | <b>1.61</b> (1.34-1.94)              | <b>1.96</b> (1.42-2.72)    | Larger effect size, but wider CI                            |
| BD  | CHD               | SMR         | Replace Laursen with Castagnini                                       | <b>1.67</b> (1.54-1.82)              | <b>1.67</b> (1.51-1.85)    | No difference in scale or direction of effect               |
| BD  | CHD               | SMR         | Replace Laursen (Sweden) and Nilsson with Ösby                        | <b>1.67</b> (1.54-1.82)              | <b>1.80</b> (1.54-2.11)    | Slightly larger effect size, but wider CI                   |
| BD  | CHD               | SMR         | Retain Ösby as well as Laursen (Sweden)                               | <b>1.67</b> (1.54-1.82)              | <b>1.80</b> (1.58-2.04)    | Slightly larger effect size, but wider CI                   |
| BD  | CVD               | HR/RRatio   | Replace Westman with Crump                                            | 1.52 (0.84-2.75)                     | <b>1.78</b> (1.28-2.47)    | Larger effect size, achieved statistical significance       |
| BD  | CVD               | SMR         | Replace Ahrens with Brodersen                                         | <b>1.68</b> (1.58-1.79)              | <b>1.68</b> (1.58-1.79)    | No difference in scale or direction of effect               |

SMI – severe mental illness, SCZ – schizophrenia, BD – bipolar disorder, HR – hazard ratio, RRatio – rate ratio, SMR – standardised mortality ratio, CI – confidence interval, CVA – cerebrovascular accident, CHD – coronary heart disease, CVD – all circulatory disease. Results where 95% confidence intervals exclude the null highlighted in **bold**

**Appendix table XIV.2: Sensitivity analyses showing effect of replacing included with excluded results, studies reporting incidence outcomes**

| SMI | Incidence outcome | Effect type | Change                                                | Meta-analysis pooled effect (95% CI) | New pooled effect (95% CI) | Comment                                         |
|-----|-------------------|-------------|-------------------------------------------------------|--------------------------------------|----------------------------|-------------------------------------------------|
| SCZ | CVA               | HR/RRatio   | Replace Momen with Laursen, 2011 and Munk-Jorgensen   | <b>1.65</b> (1.36-2.02)              | <b>1.48</b> (1.14-1.91)    | Slightly smaller effect, but wider CI           |
| SCZ | CVA               | HR/RRatio   | Replace Westman with Crump                            | <b>1.65</b> (1.36-2.02)              | <b>1.61</b> (1.38-1.87)    | No difference in scale or direction of effect   |
| SCZ | CVA               | RR          | Replace Tsai with Chen                                | <b>1.40</b> (1.31-1.49)              | <b>1.63</b> (1.17-2.27)    | Slightly larger effect, but wider CI            |
| SCZ | CHD               | HR/RRatio   | Replace Momen with Munk-Jorgensen and Laursen, 2011   | 1.15 (0.99-1.35)                     | 1.11 (0.93-1.33)           | Slightly smaller effect, CI further from null   |
| SCZ | CHD               | HR/RRatio   | Replace Momen with Jakobsen                           | 1.15 (0.99-1.35)                     | 1.09 (0.89-1.32)           | Slightly smaller effect, CI further from null   |
| SCZ | CHD               | HR/RRatio   | Replace Laursen, 2011, with Laursen, 2010 (1994-96)   | 1.15 (0.99-1.35)                     | 1.06 (0.89-1.26)           | Slightly smaller effect, CI further from null   |
| SCZ | CHD               | HR/RRatio   | Replace Laursen, 2011, with Laursen, 2010 (2005-2006) | 1.15 (0.99-1.35)                     | 1.10 (0.93-1.31)           | Slightly smaller effect, CI further from null   |
| SCZ | CHD               | HR/RRatio   | Replace Westman by Crump and Gale                     | 1.15 (0.99-1.35)                     | <b>1.20</b> (1.05-1.38)    | Increased effect size, CI now excludes the null |
| SCZ | CHD               | HR/RRatio   | Replace Wu, 2015 with Lin, 2010                       | 1.15 (0.99-1.35)                     | <b>1.19</b> (1.01-1.40)    | Increased effect size, CI now excludes the null |
| SCZ | CHD               | RR          | Replace Curkendall IHD outcome with MI                | 0.91 (0.72-1.14)                     | 0.83 (0.65-1.06)           | No difference in scale or direction of effect   |
| SCZ | CVD               | HR/RRatio   | Replace Brink ages 50-59 with ages 40-49              | <b>1.25</b> (1.04-1.51)              | 1.22 (0.96-1.54)           | Reduced effect size, CI now includes the null   |
| SCZ | CVD               | HR/RRatio   | Replace with ages 30-39                               | <b>1.25</b> (1.04-1.51)              | <b>1.38</b> (1.03-1.61)    | Slightly larger effect, but wider CI            |
| BD  | CVA               | HR/RRatio   | Replace Westman with Crump                            | <b>1.60</b> (1.41-1.81)              | <b>1.63</b> (1.47-1.81)    | No difference in scale or direction of effect   |
| BD  | CVA               | HR/RRatio   | Replace Wium-Andersen with Laursen, 2011              | <b>1.60</b> (1.41-1.81)              | <b>1.74</b> (1.43-2.10)    | Slightly larger effect, but wider CI            |
| BD  | CHD               | HR/RRatio   | Replace Kessing with Wium-Andersen                    | <b>1.47</b> (1.16-1.87)              | <b>1.45</b> (1.11-1.88)    | No difference in scale or direction of effect   |
| BD  | CHD               | HR/RRatio   | Replace Kessing with Laursen, 2011                    | <b>1.47</b> (1.16-1.87)              | <b>1.52</b> (1.01-2.06)    | Slightly larger effect, but wider CI            |
| BD  | CHD               | HR/RRatio   | Replace Kessing, with Laursen, 2010 (1994-96)         | <b>1.47</b> (1.16-1.87)              | <b>1.45</b> (1.10-1.92)    | No difference in scale or direction of effect   |
| BD  | CHD               | HR/RRatio   | Replace Kessing, with Laursen, 2010 (2005-2006)       | <b>1.47</b> (1.16-1.87)              | <b>1.50</b> (1.15-1.96)    | No difference in scale or direction of effect   |
| BD  | CHD               | HR/RRatio   | Replace Westman by Crump and Gale                     | <b>1.47</b> (1.16-1.87)              | <b>1.46</b> (1.22-1.75)    | No difference in scale or direction of effect   |
| BD  | CHD               | HR/RRatio   | Replace Wu, 2015 with Hsu (all ages)                  | <b>1.47</b> (1.16-1.87)              | <b>1.49</b> (1.16-1.90)    | No difference in scale or direction of effect   |
| BD  | CHD               | HR/RRatio   | Replace Wu, 2015 with Hsu (ages 40-59)                | <b>1.47</b> (1.16-1.87)              | <b>1.53</b> (1.18-1.98)    | Slightly larger effect, but wider CI            |
| BD  | CHD               | HR/RRatio   | Replace Wu, 2015 with Hsu (ages 18-39)                | <b>1.47</b> (1.16-1.87)              | <b>1.60</b> (1.21-2.10)    | Slightly larger effect, but wider CI            |
| BD  | CVD               | HR/RRatio   | Replace Prieto with Foroughi, 2021                    | <b>1.47</b> (1.32-1.63)              | <b>1.52</b> (1.30-1.77)    | No difference in scale or direction of effect   |
| BD  | CVD               | HR/RRatio   | Replace Prieto with Foroughi, 2018                    | <b>1.47</b> (1.32-1.63)              | <b>1.45</b> (1.30-1.60)    | No difference in scale or direction of effect   |
| BD  | CVD               | OR          | Replace Goldstein BD I with BD II                     | <b>1.88</b> (1.34-2.66)              | <b>1.85</b> (1.31-2.62)    | No difference in scale or direction of effect   |

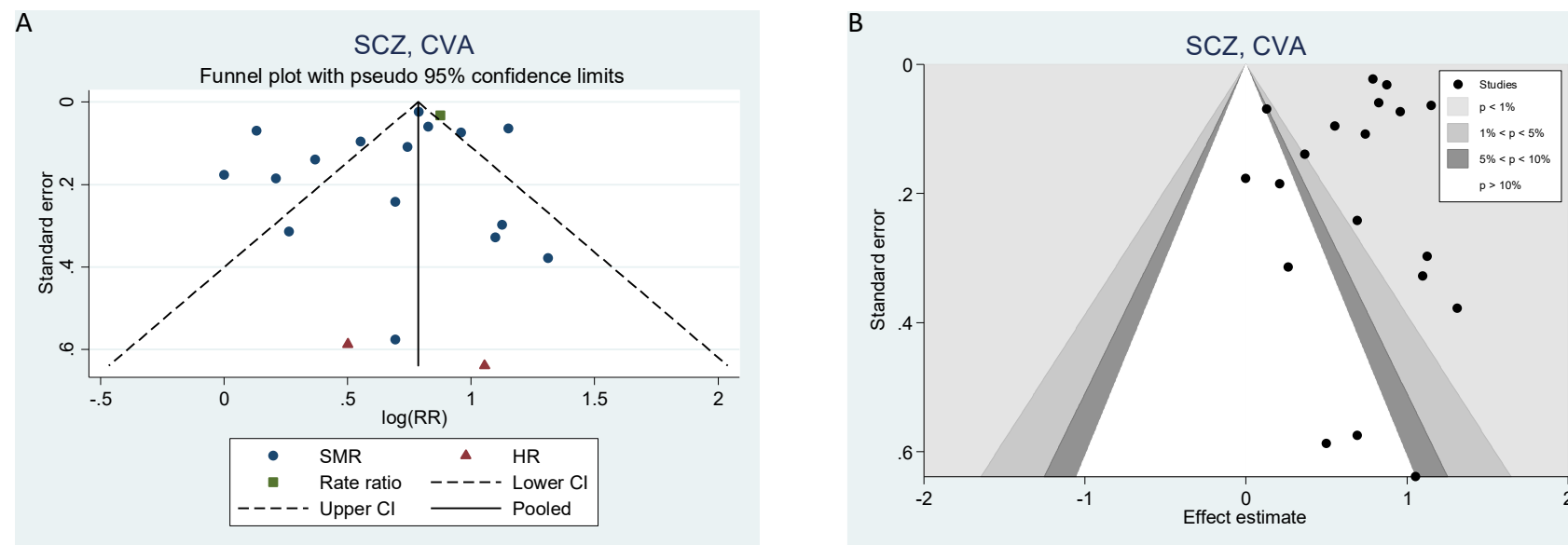
SMI – severe mental illness, SCZ – schizophrenia, BD – bipolar disorder, HR – hazard ratio, RRatio – rate ratio, RR – risk ratio, OR – odds ratio, CI – confidence interval, CVA – cerebrovascular accident, CHD – coronary heart disease, CVD – major cardiovascular events. Results where 95% confidence intervals exclude the null highlighted in **bold**

**Appendix table XIV.3: Pooled relative risks of cardiovascular incidence by SMI and CVD outcome, comparison of minimally adjusted and fully adjusted models reported by included studies**

| SMI              | Incidence outcome | Models adjusted for age and sex only, or min number of factors |                                        |        | Models adjusted for more factors |                                        |        |
|------------------|-------------------|----------------------------------------------------------------|----------------------------------------|--------|----------------------------------|----------------------------------------|--------|
|                  |                   | No. of studies/results                                         | Pooled effect (95% CI)                 | p      | No. of studies/results           | Pooled effect (95% CI)                 | p      |
| Schizophrenia    | CVA               | 4/5                                                            | HR/Rate ratio: <b>1.66</b> (1.36-2.02) | <0.001 | 5/6                              | HR/Rate ratio: <b>1.46</b> (1.27-1.66) | <0.001 |
|                  |                   | 2/2                                                            | OR: <b>1.88</b> (1.31-2.70)            | 0.001  | 2/2                              | OR: <b>1.70</b> (1.15-2.52)            | 0.008  |
|                  |                   | 3/3                                                            | RR: <b>1.40</b> (1.31-1.49)            | <0.001 | 3/3                              | RR: <b>1.40</b> (1.31-1.49)            | <0.001 |
| Schizophrenia    | CHD               | 8/10                                                           | HR/Rate ratio: 1.15 (0.99-1.35)        | 0.077  | 8/10                             | HR/Rate ratio: 1.11 (0.97-1.27)        | 0.117  |
|                  |                   | 2/2                                                            | OR: <b>0.76</b> (0.61-0.96)            | 0.022  | 2/2                              | OR: <b>0.76</b> (0.61-0.96)            | 0.022  |
|                  |                   | 3/3                                                            | RR: 0.91 (0.72-1.14)                   | 0.403  | 3/3                              | RR: 0.90 (0.71-1.14)                   | 0.379  |
|                  |                   | 1/2                                                            | SIR: <b>1.48</b> (1.30-1.69)           | <0.001 | 1/2                              | SIR: <b>1.15</b> (1.07-1.26)           | 0.001  |
| Schizophrenia    | CVD               | 3/3                                                            | HR/Rate ratio: <b>1.25</b> (1.04-1.51) | 0.016  | 3/3                              | HR/Rate ratio: <b>1.18</b> (1.09-1.27) | <0.001 |
|                  |                   | 1/2                                                            | OR: <b>1.80</b> (1.24-2.62)            | 0.002  | 1/2                              | OR: <b>1.52</b> (1.15-2.01)            | 0.003  |
| Bipolar disorder | CVA               | 4/5                                                            | HR/Rate Ratio: <b>1.60</b> (1.41-1.81) | <0.001 | 4/5                              | HR/Rate Ratio: <b>1.51</b> (1.33-1.71) | <0.001 |
|                  |                   | 1/1                                                            | OR: <b>3.39</b> (1.91-6.01)            | <0.001 | 1/1                              | OR: <b>2.23</b> (1.06-4.68)            | 0.034  |
|                  |                   | 2/2                                                            | RR: <b>1.31</b> (1.18-1.45)            | <0.001 | 1/1                              | RR: 1.19 (0.34-4.16)                   | 0.785  |
| Bipolar disorder | CHD               | 5/6                                                            | HR/Rate ratio: <b>1.47</b> (1.16-1.87) | 0.002  | 5/6                              | HR/Rate ratio: <b>1.46</b> (1.14-1.87) | 0.003  |
|                  |                   | 1/1                                                            | OR: <b>2.68</b> (1.51-4.76)            | 0.001  | 1/1                              | OR: <b>2.50</b> (1.32-4.73)            | 0.005  |
|                  |                   | 1/1                                                            | RR: 0.97 (0.50-1.88)                   | 0.928  | 1/1                              | RR: 0.97 (0.50-1.88)                   | 0.928  |
| Bipolar disorder | CVD               | 2/2                                                            | HR/Rate ratio: <b>1.47</b> (1.32-1.63) | <0.001 | 2/2                              | HR/Rate ratio: <b>1.26</b> (1.12-1.40) | <0.001 |
|                  |                   | 2/3                                                            | OR: <b>1.88</b> (1.34-2.66)            | <0.001 | 2/3                              | OR: <b>1.65</b> (1.20-2.25)            | 0.002  |

SMI – severe mental illness, CVA – cerebrovascular accident, CHD – coronary heart disease, CVD – all circulatory disease, HR – hazard ratio, OR – odds ratio, RR – risk ratio, SIR – standardised incidence ratio. Results where 95% confidence intervals exclude the null highlighted in **bold**

## APPENDIX XV ASSESSMENT OF PUBLICATION BIAS: MORTALITY STUDIES



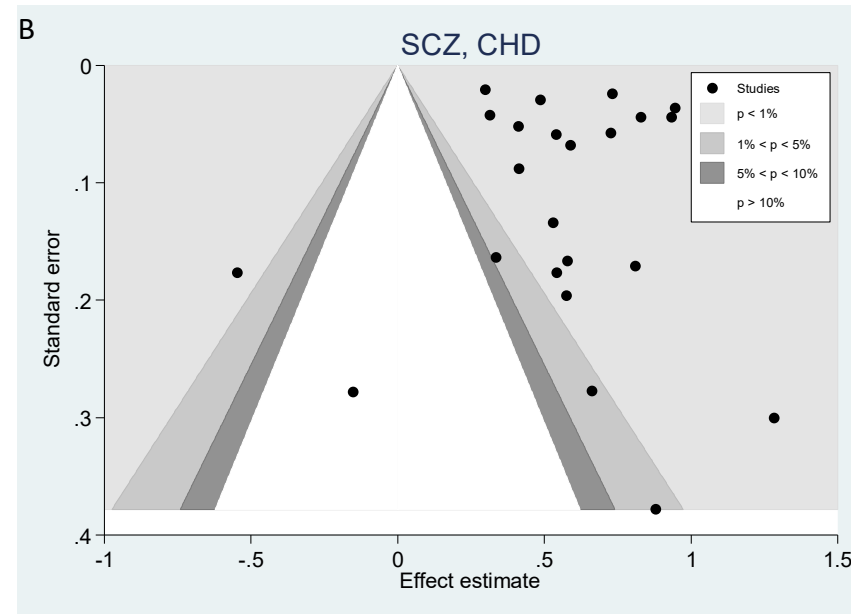
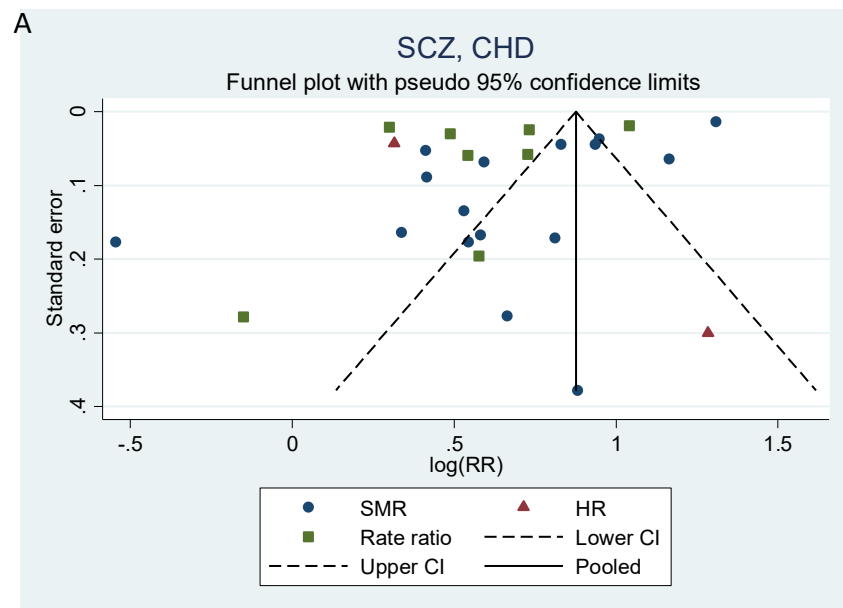
SCZ – schizophrenia, CVA – cerebrovascular accident, SMR – standardised mortality ratio, HR – hazard ratio

### Appendix figure XV.1: Funnel plots visual assessment of publication bias for studies reporting relative risk of CVD mortality for schizophrenia compared with controls, cerebrovascular accident

There is some asymmetry in studies reporting SMRs on the upper right-hand side of the funnel plot (A), suggesting missing studies falling outside the pseudo 95% confidence limits. In the contour-enhanced funnel plot (B) the “missing” studies would be in the shaded area of the graph, so would be expected to report significant effects, thus publication bias is unlikely.<sup>1</sup> Further, Egger’s test<sup>2</sup> (Appendix table XV.1) is non-significant. Publication bias is therefore not suspected.

<sup>1</sup> Peters JL, Sutton AJ, Jones DR, Abrams KR, Rushton L. Contour-enhanced meta-analysis funnel plots help distinguish publication bias from other causes of asymmetry. *Journal of Clinical Epidemiology*. 2008;61(10):991-6.

<sup>2</sup> Page MJ, Higgins JPT, Sterne JAC. Chapter 13: Assessing risk of bias due to missing results in a synthesis. 2019. In: *Cochrane Handbook for Systematic Reviews of Interventions*, Version 6.0. Cochrane, [accessed June 12, 2020]. Available from: [www.training.cochrane.org/handbook](http://www.training.cochrane.org/handbook).

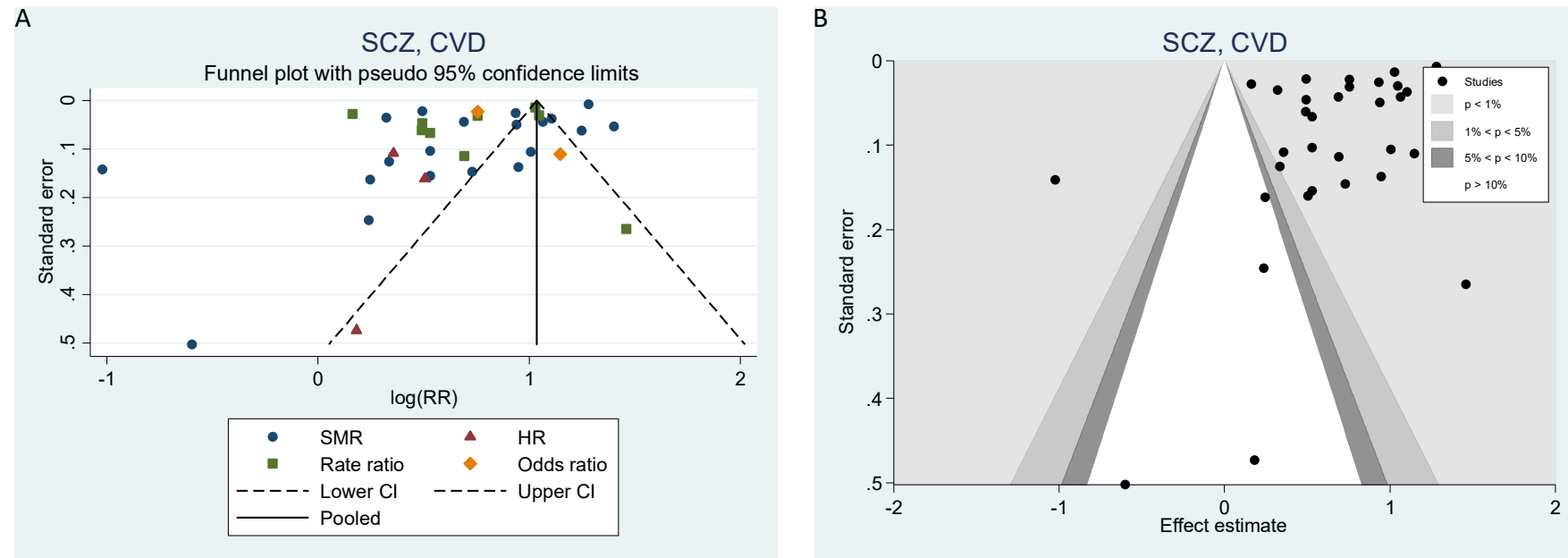


SCZ – schizophrenia, CHD – coronary heart disease, SMR – standardised mortality ratio, HR – hazard ratio

## Appendix figure XV.2: Funnel plots visual assessment of publication bias for studies reporting relative risk of CVD mortality for schizophrenia compared with controls, coronary heart disease

There is asymmetry on the right-hand side of the funnel plot (A), affecting SMRs and rate ratios outside the pseudo 95% confidence limits and SMRs inside the limits, suggesting missing studies. In the contour-enhanced funnel plot (B) the “missing” studies would be in the shaded area of the graph, so would be expected to report significant effects, therefore publication bias is unlikely. However, Egger’s test (Appendix table XV.1) for publication bias is significant for studies reporting SMRs *i.e.* the confidence interval for the intercept does not include zero (bias: -7.01, 95% CI: -10.51 to -3.50,  $p=0.001$ ). Applying a trim and fill procedure<sup>1</sup> (Appendix figure XV.7) suggests five missing unpublished studies reporting the association between CHD mortality and schizophrenia.

<sup>1</sup> Sterne JAC, Egger M, Moher D. Chapter 10: Addressing reporting biases. In: Higgins J, Green S, editors. Cochrane Handbook for Systematic Reviews of Interventions. Version 5.1.0 [updated March 2011] ed: The Cochrane Collaboration; 2011.

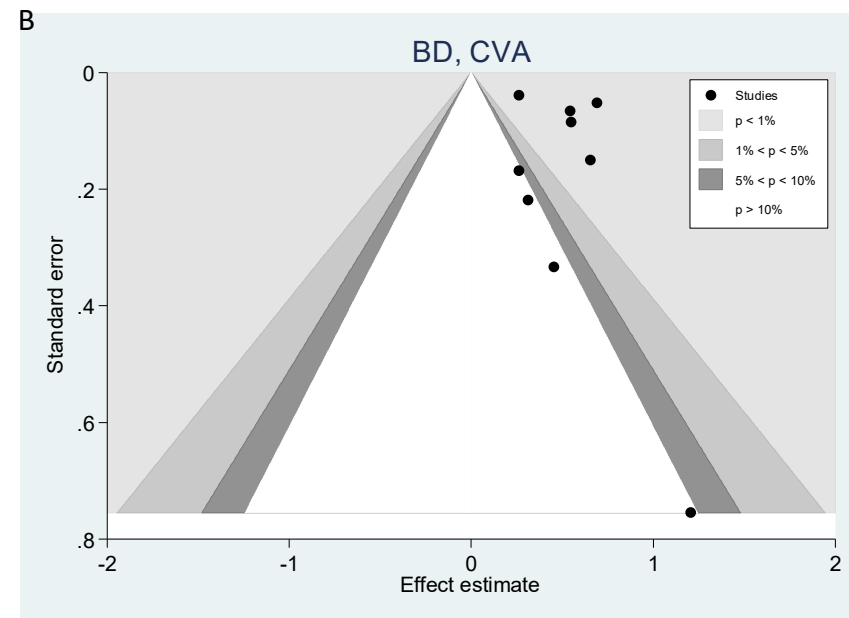
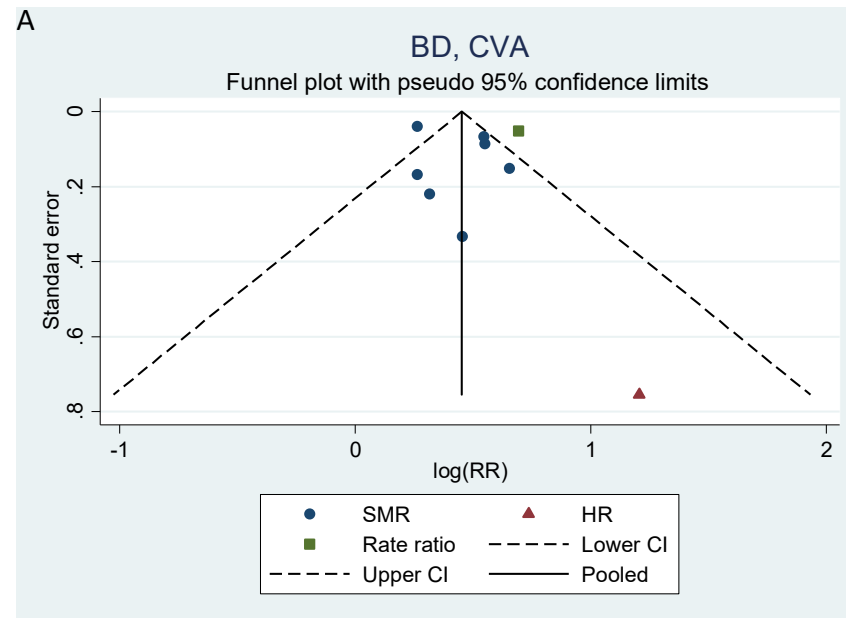


SCZ – schizophrenia, CVD – all circulatory disease, SMR – standardised mortality ratio, HR – hazard ratio

### Appendix figure XV.3: Funnel plots visual assessment of publication bias for studies reporting relative risk of CVD mortality for schizophrenia compared with controls, all circulatory disease

There is asymmetry on the right-hand side of the funnel plot (A), affecting SMRs and rate ratios outside the pseudo 95% confidence limits, suggesting missing studies. In the contour-enhanced funnel plot (B) the “missing” studies would be in the shaded area of the graph, so would be expected to report significant effects, therefore publication bias is unlikely. However, Egger’s test for publication bias is significant for studies reporting SMRs and for studies reporting all effect types *i.e.* the confidence interval for the intercept does not include zero (bias for SMR studies: -7.76, 95% CI: -13.43 to -2.09,  $p=0.01$ ). Two additional studies were found when a trim and fill procedure<sup>1</sup> was conducted (Appendix figure XV.8).

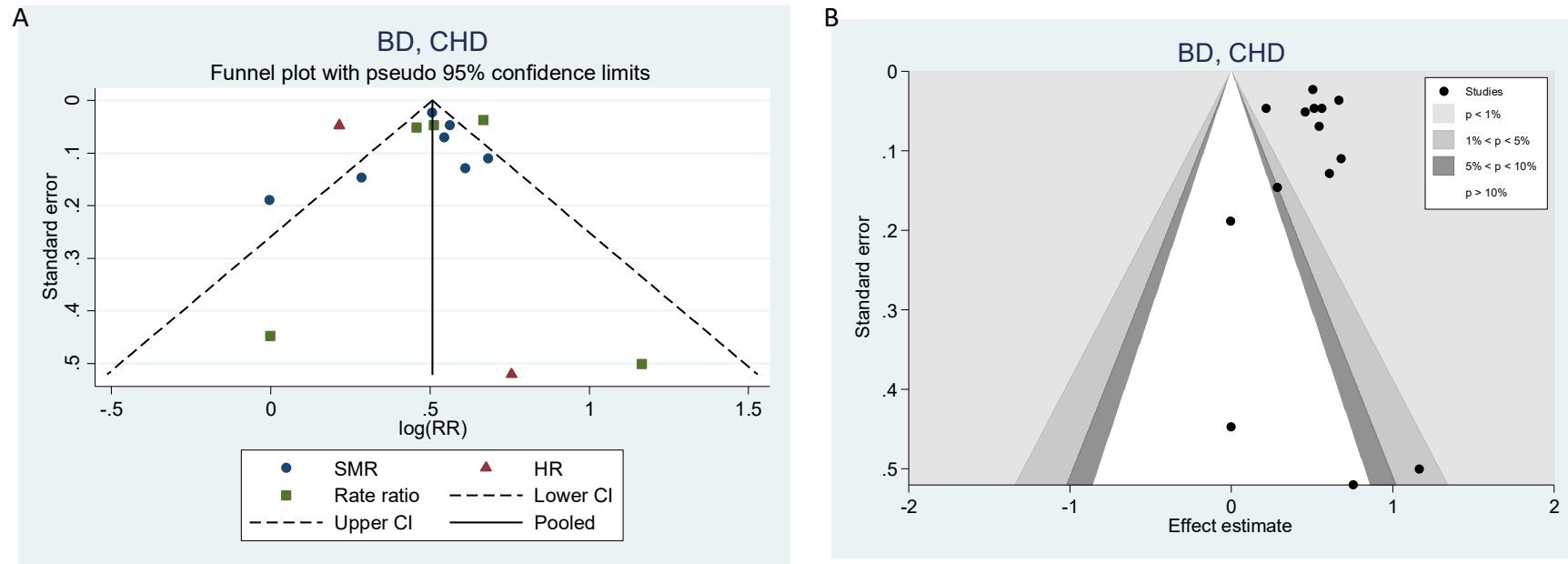
<sup>1</sup> Sterne JAC, Egger M, Moher D. Chapter 10: Addressing reporting biases. In: Higgins J, Green S, editors. Cochrane Handbook for Systematic Reviews of Interventions. Version 5.1.0 [updated March 2011] ed: The Cochrane Collaboration; 2011.



BD – bipolar disorder, CVA – cerebrovascular accident, SMR – standardised mortality ratio, HR – hazard ratio

**Appendix figure XV.4: Funnel plots visual assessment of publication bias for studies reporting relative risk of CVD mortality for bipolar disorder compared with controls, cerebrovascular accident**

There are too few studies to assess publication bias.

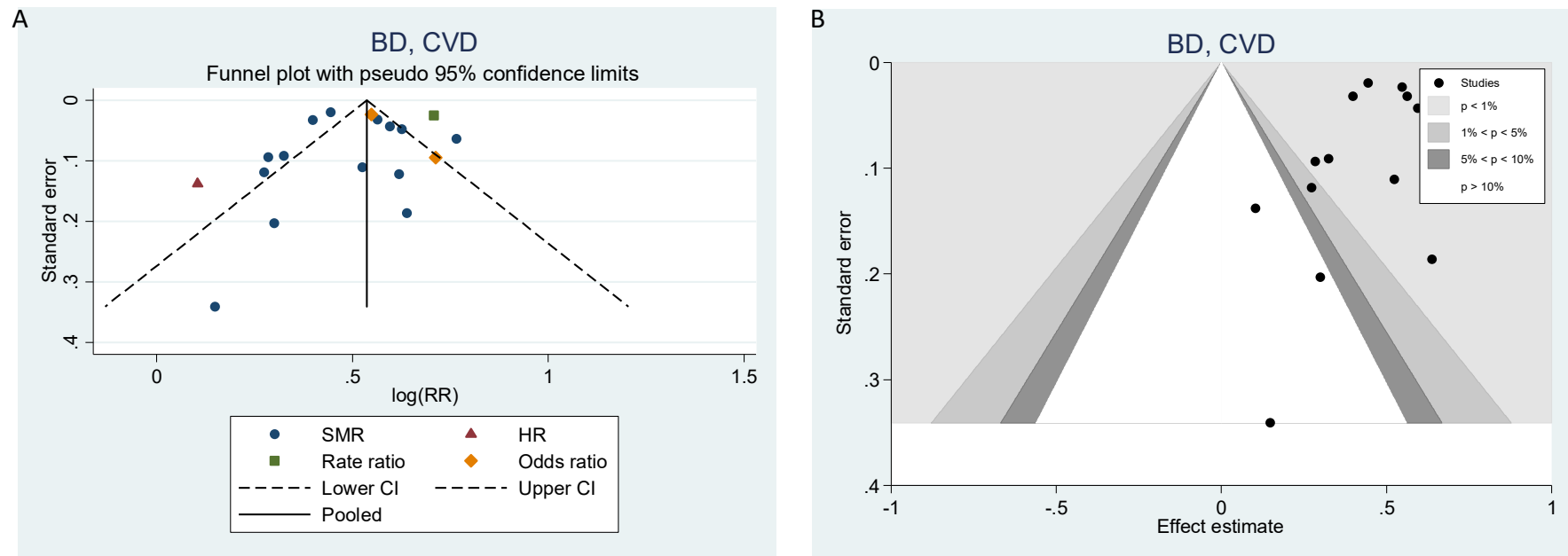


BD – bipolar disorder, CHD – coronary heart disease, SMR – standardised mortality ratio, HR – hazard ratio

**Appendix figure XV.5: Funnel plots visual assessment of publication bias for studies reporting relative risk of CVD mortality for bipolar disorder compared with controls, coronary heart disease**

Plot A shows little asymmetry, so publication bias is not suspected.





BD – bipolar disorder, CVD all circulatory disease, SMR – standardised mortality ratio, HR – hazard ratio

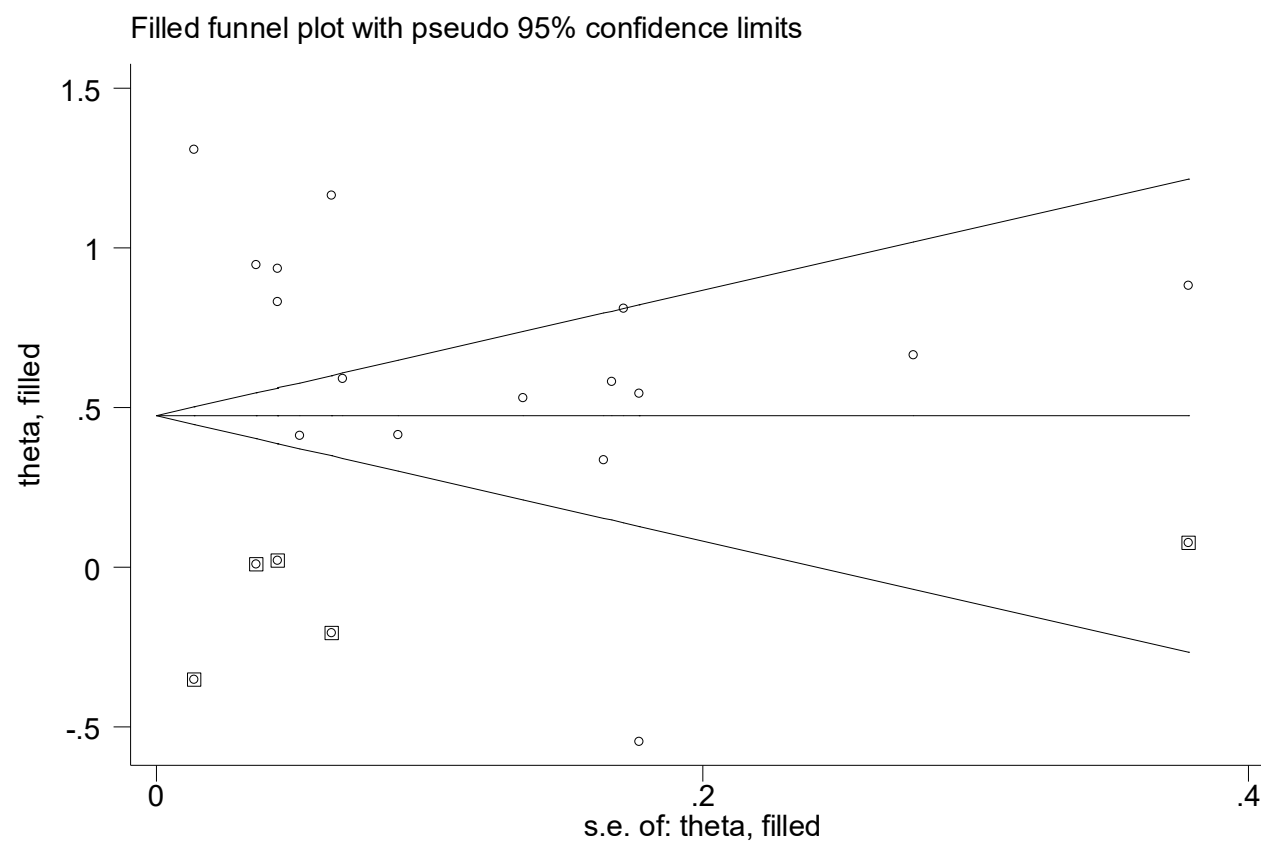
**Appendix figure XV.6: Funnel plots for visual assessment of publication bias for studies reporting relative risk of CVD mortality for bipolar disorder compared with controls, all circulatory disease**

Plot A shows little asymmetry, so publication bias is not suspected.

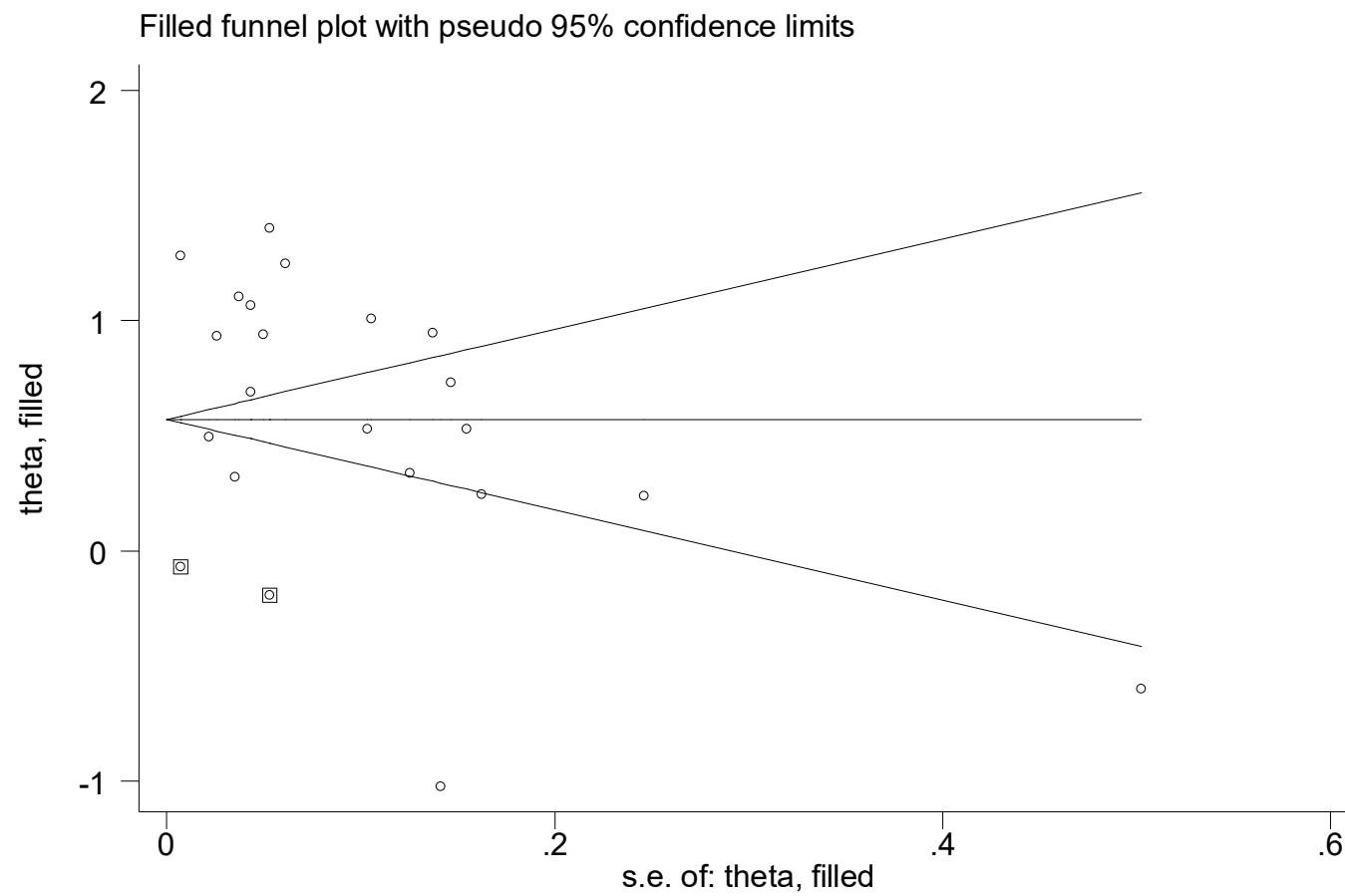
**Appendix table XV.1: Results of Egger's tests for publication bias, mortality outcomes**

| SMI              | Mortality outcome        | Effect type      | Bias (95% CI)                | p-value |
|------------------|--------------------------|------------------|------------------------------|---------|
| Schizophrenia    | Cerebrovascular accident | SMR              | -1.04 (-3.68, 1.60)          | 0.412   |
| Schizophrenia    | Cerebrovascular accident | HR/Rate ratio    | Too few studies              |         |
| Schizophrenia    | Cerebrovascular accident | All effect types | -1.01 (-3.17, 1.16)          | 0.340   |
| Schizophrenia    | Coronary heart disease   | SMR              | <b>-7.01</b> (-10.51, -3.50) | 0.001   |
| Schizophrenia    | Coronary heart disease   | HR/Rate ratio    | -2.63 (-15.18, 9.92)         | 0.642   |
| Schizophrenia    | Coronary heart disease   | All effect types | -5.19 (-10.87, 0.50)         | 0.072   |
| Schizophrenia    | All circulatory disease  | SMR              | <b>-7.76</b> (-13.43, -2.09) | 0.010   |
| Schizophrenia    | All circulatory disease  | HR/Rate ratio    | -4.32 (-11.99, 3.36)         | 0.244   |
| Schizophrenia    | All circulatory disease  | All effect types | <b>-7.67</b> (-12.22, -3.11) | 0.002   |
| Bipolar disorder | Cerebrovascular accident | SMR              | Too few studies              | -       |
| Bipolar disorder | Cerebrovascular accident | HR/Rate ratio    | Too few studies              | -       |
| Bipolar disorder | Cerebrovascular accident | All effect types | Too few studies              | -       |
| Bipolar disorder | Coronary heart disease   | SMR              | Too few studies              | -       |
| Bipolar disorder | Coronary heart disease   | HR/Rate ratio    | Too few studies              | -       |
| Bipolar disorder | Coronary heart disease   | All effect types | -0.41 (-2.76, 1.94)          | 0.712   |
| Bipolar disorder | All circulatory disease  | SMR              | 0.22 (-2.00, 2.44)           | 0.833   |
| Bipolar disorder | All circulatory disease  | HR/Rate ratio    | Too few studies              | -       |
| Bipolar disorder | All circulatory disease  | All effect types | -0.54 (-2.95, 1.88)          | 0.644   |

SMI – severe mental illness, SMR – standardised mortality ratio, HR – hazard ratio, CI – confidence intervals. Results where 95% confidence intervals exclude the null highlighted in **bold**

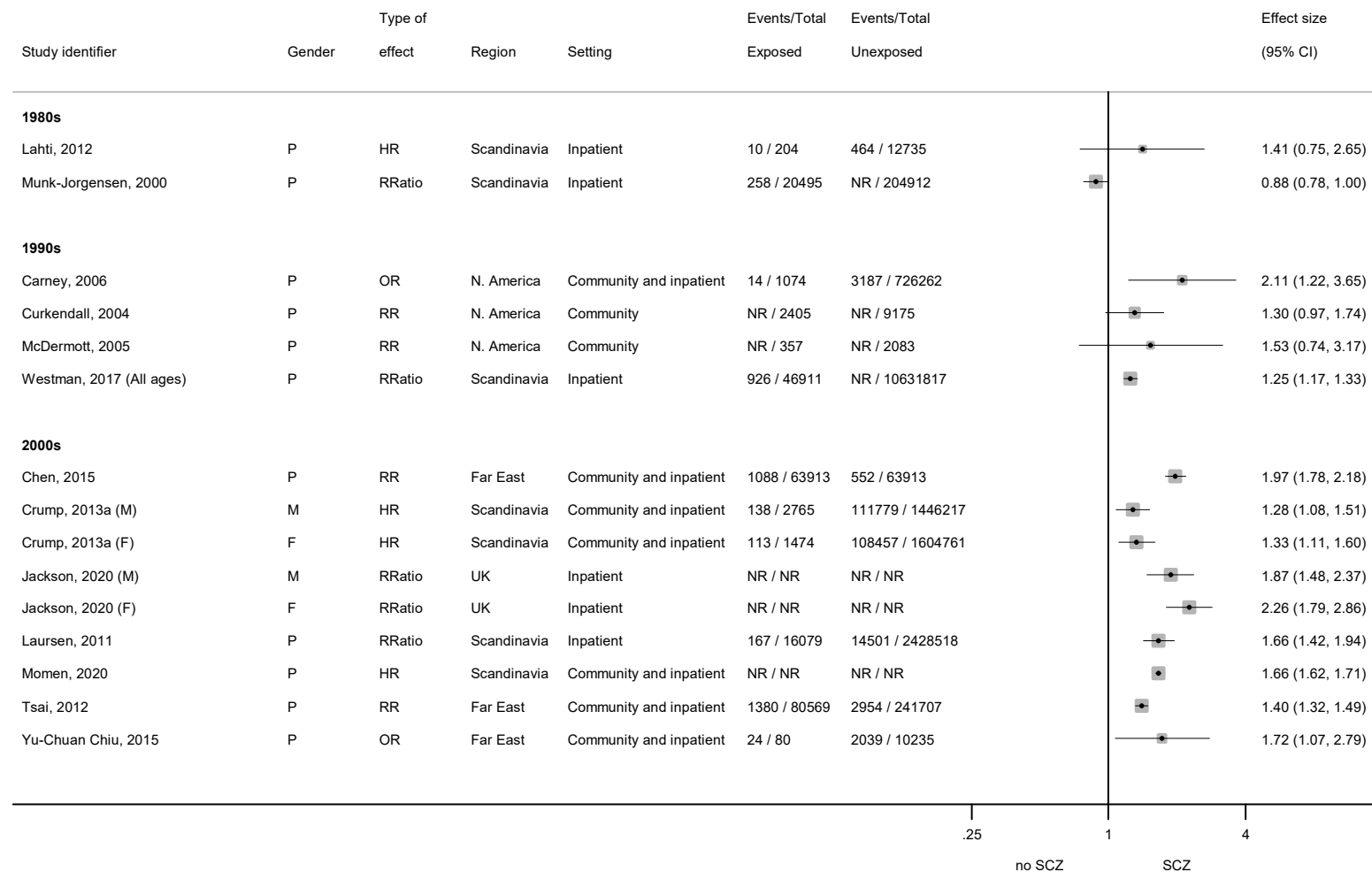


**Appendix figure XV.7: Funnel plot of schizophrenia and coronary heart disease mortality including five unpublished studies estimated from trim and fill**



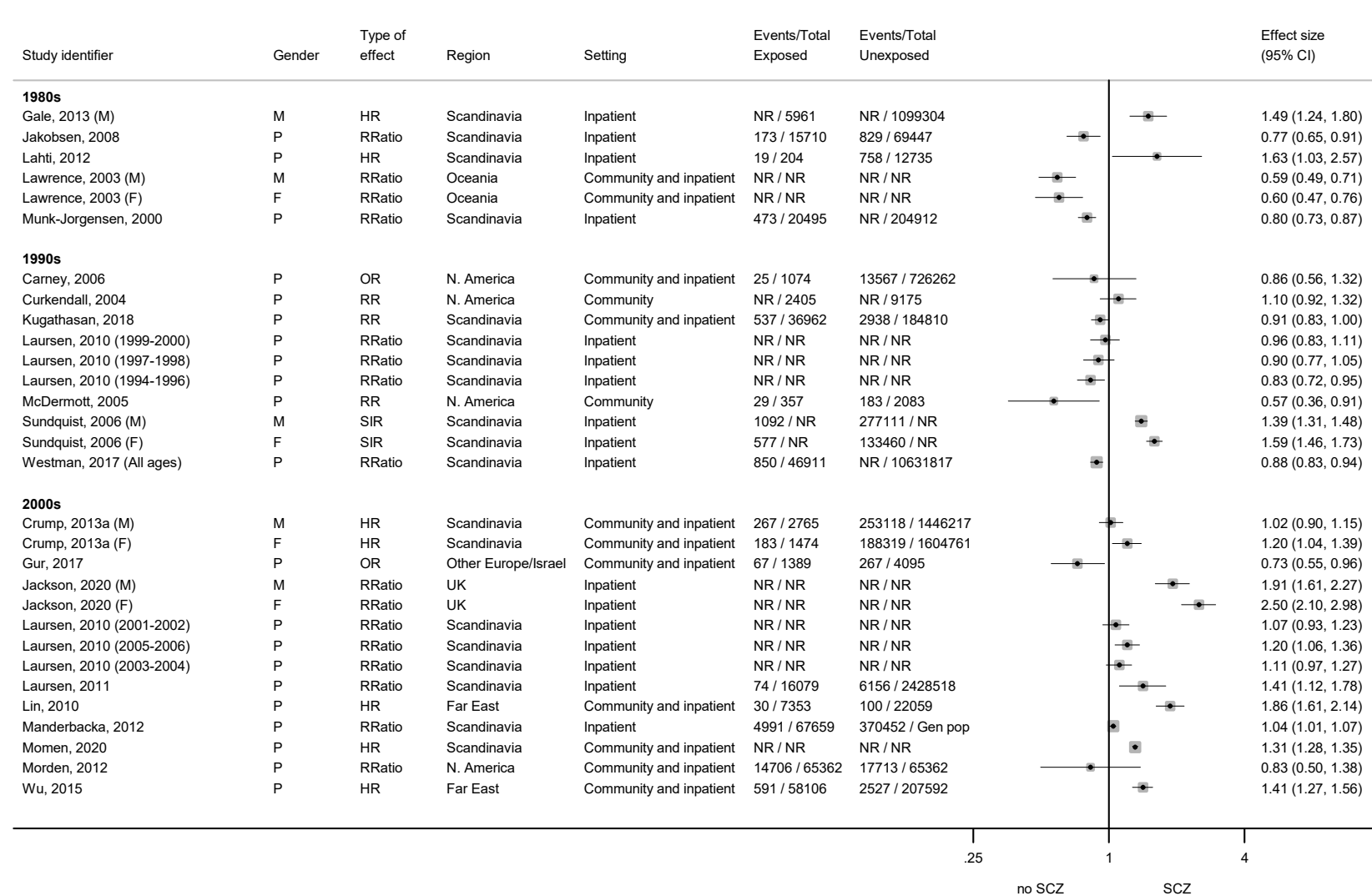
**Appendix figure XV.8: Funnel plot of schizophrenia and all circulatory disease mortality including two unpublished studies estimated from trim and fill**

## APPENDIX XVI FOREST PLOTS REPORTING CARDIOVASCULAR INCIDENCE OUTCOMES



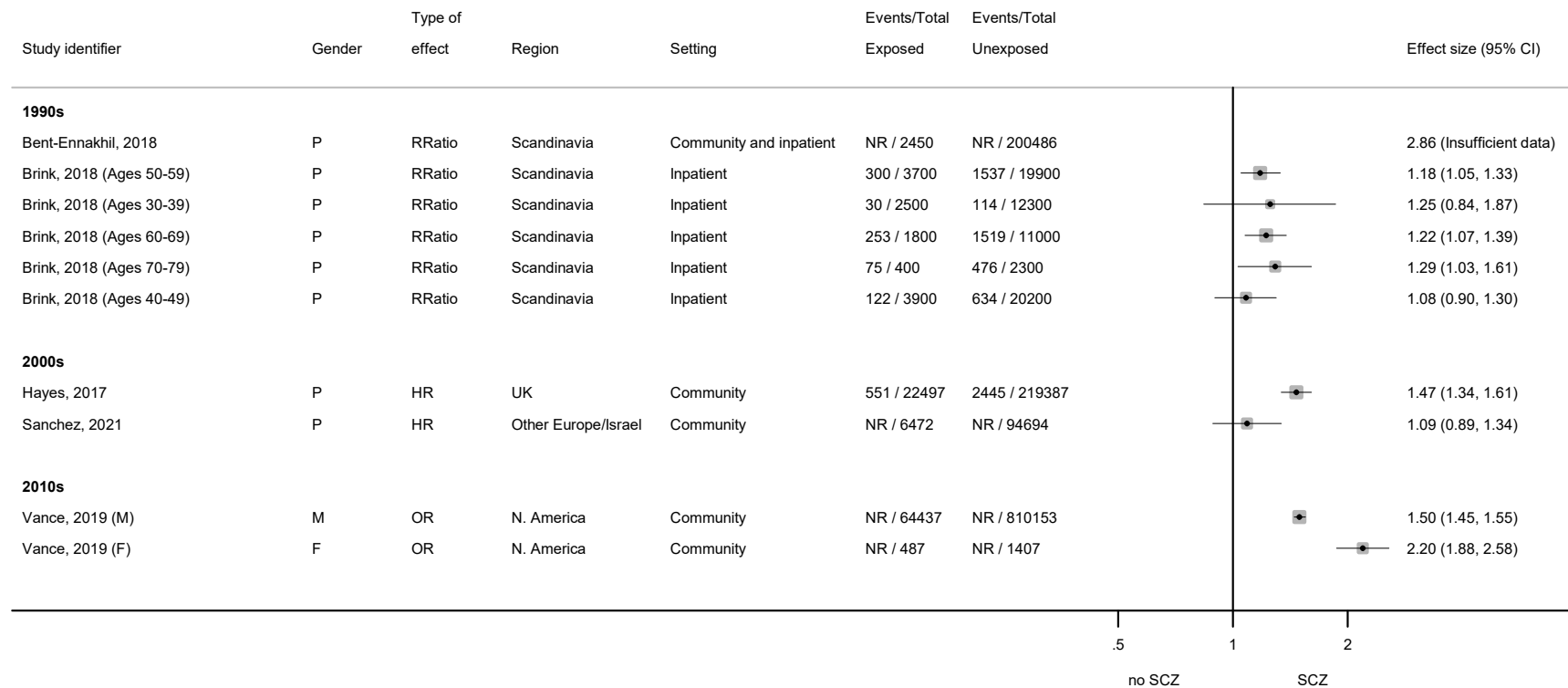
SCZ – schizophrenia, NR – not reported, HR – hazard ratio, RRatio – rate ratio, OR – odds ratio, RR – risk ratio, P – persons, M – males, F - females

**Appendix figure XVI.1: Schizophrenia, incidence of cerebrovascular accident, hazard ratios, rate ratios and odds ratios, across decades**



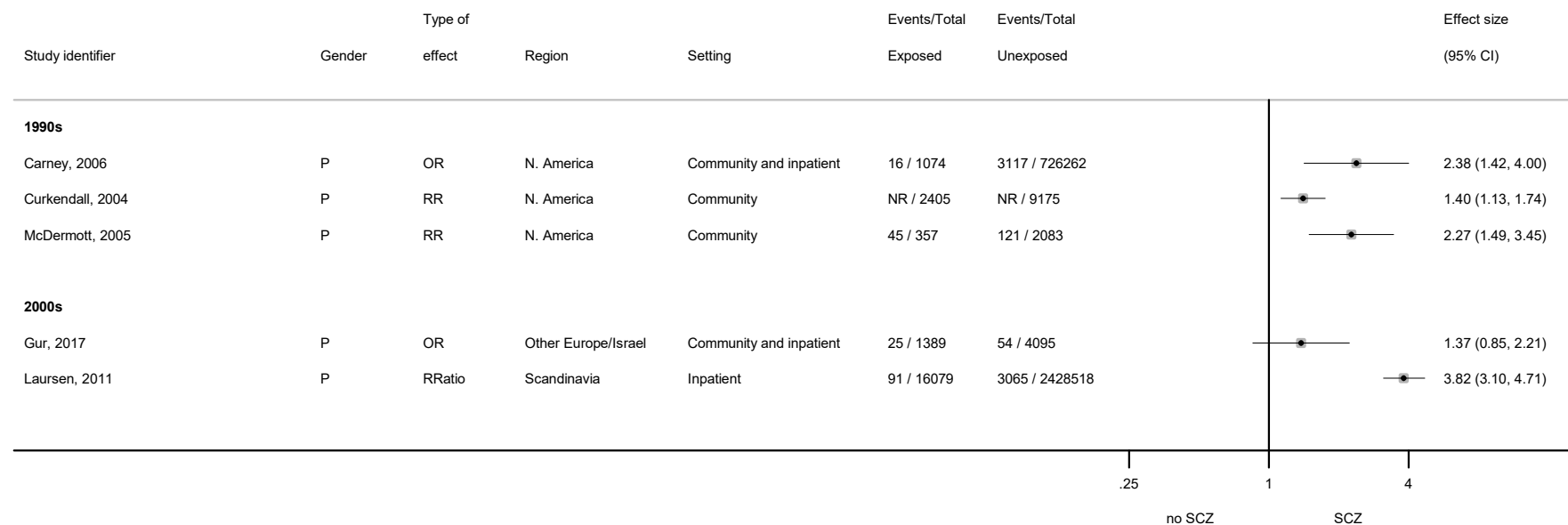
SCZ – schizophrenia, NR – not reported, gen pop – general population, HR – hazard ratio, RRatio – rate ratio, OR – odds ratio, RR – risk ratio, SIR – standardised incidence ratio, P – persons, M – males, F – females

**Appendix figure XVI.2: Schizophrenia, incidence of coronary heart disease, hazard ratios, rate ratios and odds ratios, across decades**



SCZ – schizophrenia, NR – not reported, HR – hazard ratio, RRatio – rate ratio, OR – odds ratio, P – persons, M – males, F - females

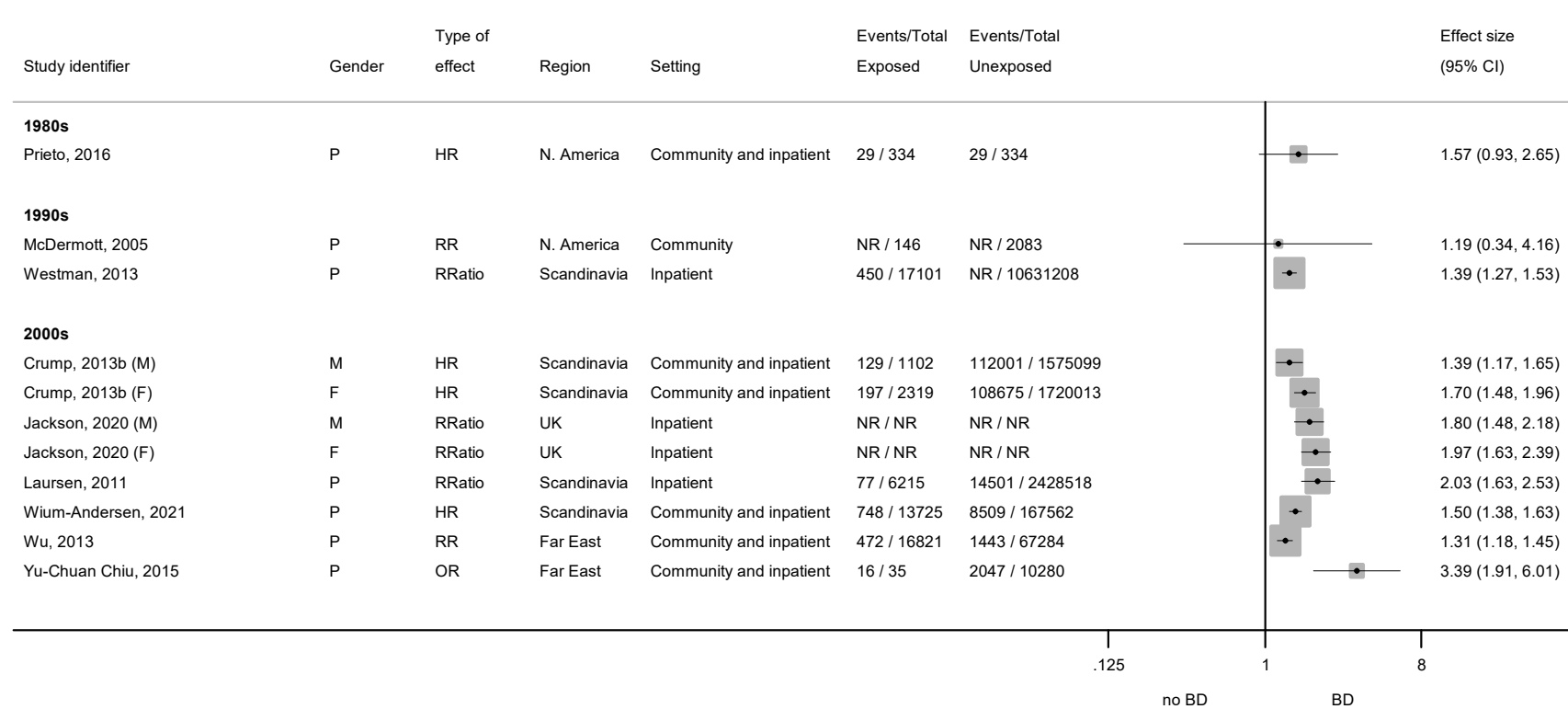
**Appendix figure XVI.3: Schizophrenia, incidence of major cardiovascular events, hazard ratios, rate ratios and odds ratios, across decades**



SCZ – schizophrenia, NR – not reported, RRatio – rate ratio, OR – odds ratio, RR – risk ratio, P – persons

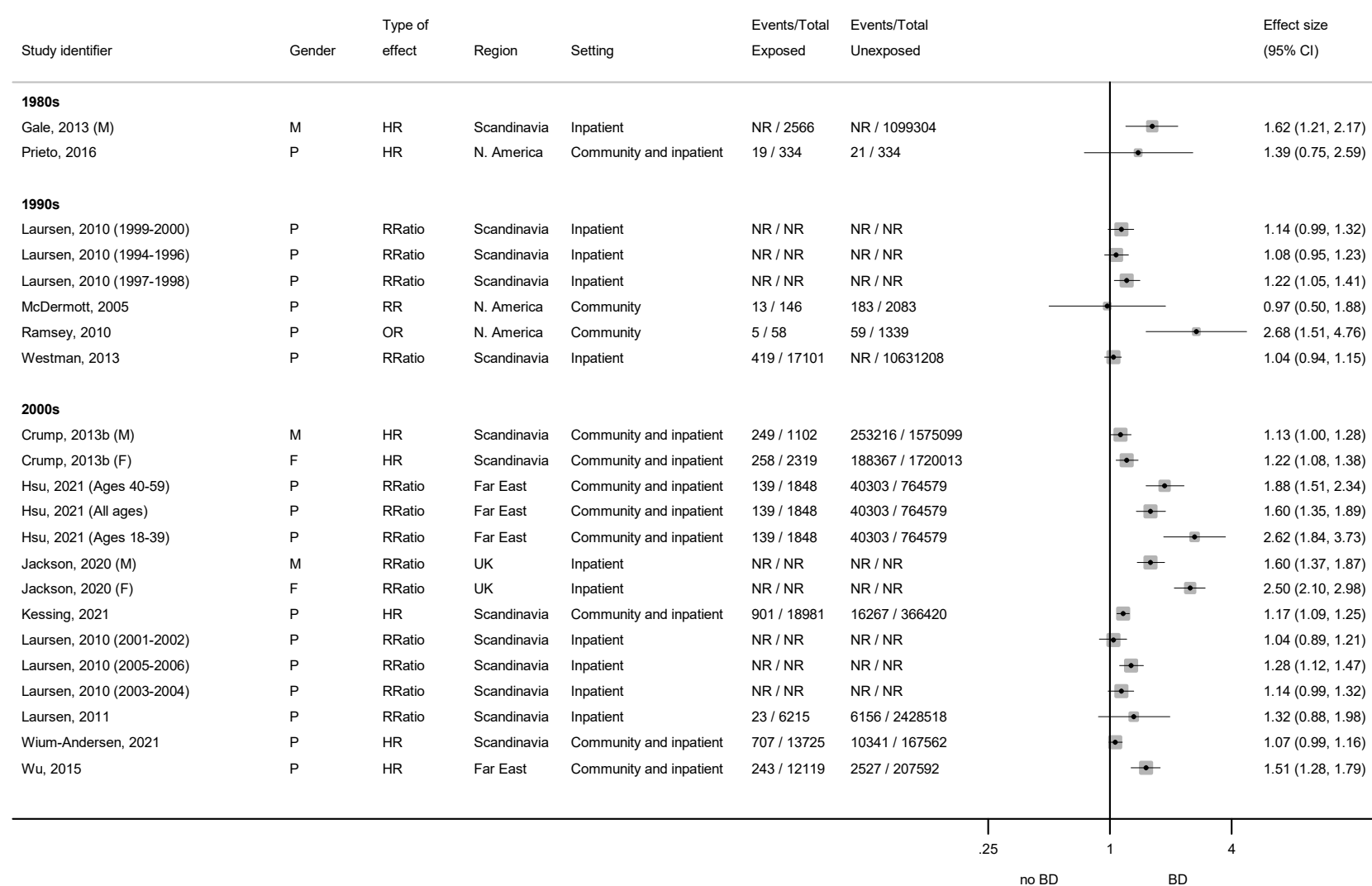
**Appendix figure XVI.4: Schizophrenia, incidence of heart failure, hazard ratios, rate ratios and rate ratios, across decades**





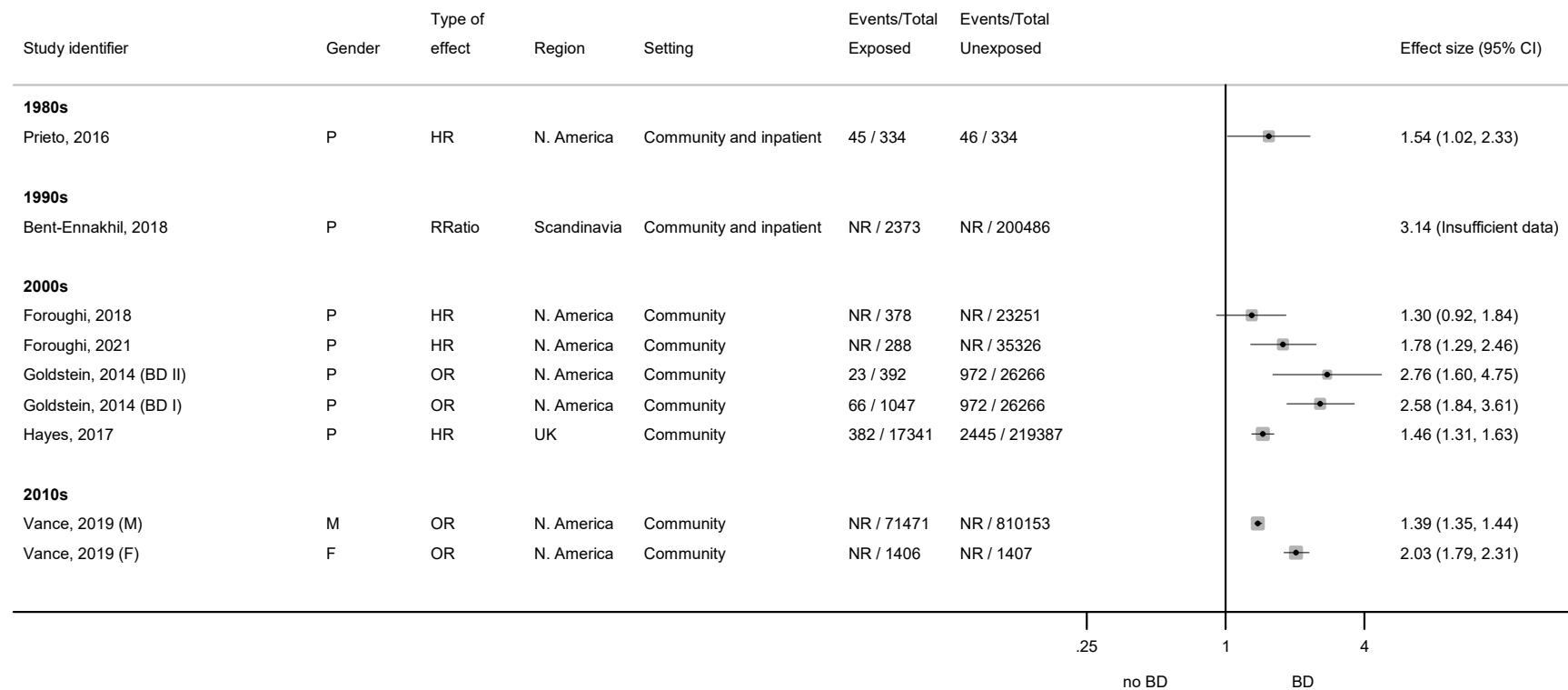
BD – bipolar disorder, NR – not reported, HR – hazard ratio, RRatio – rate ratio, OR – odds ratio, RR – risk ratio, P – persons, M – males, F - females

**Appendix figure XVI.5: Bipolar disorder, incidence of cerebrovascular accident, hazard ratios, rate ratios, and odds ratios across decades**



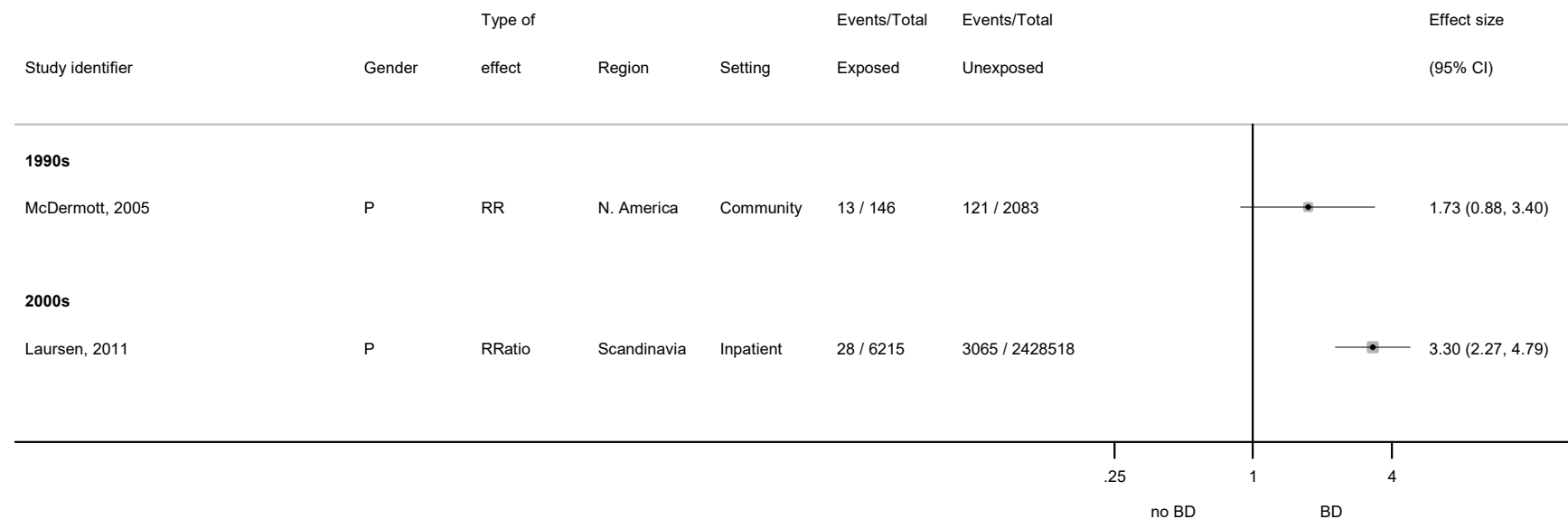
BD – bipolar disorder, NR – not reported, HR – hazard ratio, RRatio – rate ratio, OR – odds ratio, RR – risk ratio, P – persons, M – males, F - females

**Appendix figure XVI.6: Bipolar disorder, incidence of coronary heart disease, hazard ratios, rate ratios and odds ratios, across decades**



BD – bipolar disorder, NR – not reported, HR – hazard ratio, RRatio – rate ratio, OR – odds ratio, P – persons, M – males, F - females

**Appendix figure XVI.7: Bipolar disorder, incidence of major cardiovascular events, hazard ratios, rate ratios and odds ratios, across decades**



BD – bipolar disorder, RRatio – rate ratio, RR – risk ratio, P – persons

**Appendix figure XVI.8: Bipolar disorder, incidence of heart failure, hazard ratios, rate ratios and odds ratios, across decades**

## APPENDIX XVII RISK OF BIAS ASSESSMENT FOR INCLUDED INCIDENCE STUDIES

**Appendix table XVII.1: Risk of bias assessment of studies reporting cardiovascular incidence outcomes, cohort studies**

| Study ID            | Selection                                                                        |                                                                 | Comparability                                                                                   |                                                          |                                |                                              |                                                           | Outcome                                                                                                                            |                                                              |                                                  |
|---------------------|----------------------------------------------------------------------------------|-----------------------------------------------------------------|-------------------------------------------------------------------------------------------------|----------------------------------------------------------|--------------------------------|----------------------------------------------|-----------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------|--------------------------------------------------|
|                     | Truly or somewhat representative of the average person with SMI in the community | Non-exposed drawn from the same community as the exposed cohort | Ascertainment of exposure from secure record <i>e.g.</i> medical record or structured interview | Demonstration that CVD was not present at start of study | Study controls for age and sex | Study controls for socio-demographic factors | Study controls for additional cardiovascular risk factors | Outcome accurately measured & validated, similar methods used for cases and controls, reliable system for measuring CVD occurrence | Follow-up long enough for outcomes to occur (min of 5 years) | Adequacy of follow-up of SMI and non-SMI cohorts |
| Bent-Ennakhil, 2018 | Y                                                                                | CT                                                              | Y                                                                                               | Y                                                        | Y                              | N                                            | N                                                         | Y                                                                                                                                  | Y                                                            | Y                                                |
| Brink, 2018         | CT                                                                               | Y                                                               | Y                                                                                               | Y                                                        | Y                              | Y                                            | CT                                                        | Y                                                                                                                                  | Y                                                            | CT                                               |
| Carney, 2006        | CT                                                                               | Y                                                               | CT                                                                                              | N                                                        | Y                              | Y                                            | N                                                         | CT                                                                                                                                 | N                                                            | N                                                |
| Chen, 2015          | Y                                                                                | Y                                                               | Y                                                                                               | CT                                                       | Y                              | N                                            | N                                                         | CT                                                                                                                                 | CT                                                           | Y                                                |
| Crump, 2013a        | Y                                                                                | CT                                                              | Y                                                                                               | CT                                                       | Y                              | Y                                            | Y                                                         | CT                                                                                                                                 | Y                                                            | Y                                                |
| Crump, 2013b        | Y                                                                                | CT                                                              | Y                                                                                               | CT                                                       | Y                              | Y                                            | Y                                                         | CT                                                                                                                                 | Y                                                            | Y                                                |
| Curkendall, 2004    | CT                                                                               | Y                                                               | CT                                                                                              | CT                                                       | Y                              | N                                            | Y                                                         | CT                                                                                                                                 | N                                                            | N                                                |
| Foroughi, 2018      | Y                                                                                | Y                                                               | CT                                                                                              | CT                                                       | Y                              | N                                            | N                                                         | CT                                                                                                                                 | Y                                                            | N                                                |
| Foroughi, 2021      | Y                                                                                | CT                                                              | Y                                                                                               | Y                                                        | Y                              | N                                            | Y                                                         | Y                                                                                                                                  | Y                                                            | CT                                               |
| Gale, 2013          | N                                                                                | Y                                                               | Y                                                                                               | CT                                                       | Y                              | Y                                            | Y                                                         | CT                                                                                                                                 | Y                                                            | CT                                               |
| Goldstein, 2014     | CT                                                                               | Y                                                               | N                                                                                               | CT                                                       | CT                             | CT                                           | Y                                                         | N                                                                                                                                  | N                                                            | N                                                |
| Gur, 2017           | Y                                                                                | Y                                                               | Y                                                                                               | N                                                        | Y                              | CT                                           | N                                                         | Y                                                                                                                                  | CT                                                           | N                                                |
| Hayes, 2017         | Y                                                                                | Y                                                               | Y                                                                                               | N                                                        | Y                              | Y                                            | Y                                                         | CT                                                                                                                                 | N                                                            | N                                                |
| Hsu, 2021           | Y                                                                                | CT                                                              | Y                                                                                               | CT                                                       | CT                             | Y                                            | N                                                         | CT                                                                                                                                 | N                                                            | Y                                                |
| Jackson, 2020       | CT                                                                               | CT                                                              | Y                                                                                               | CT                                                       | Y                              | CT                                           | N                                                         | CT                                                                                                                                 | Y                                                            | N                                                |
| Jakobsen, 2008      | CT                                                                               | Y                                                               | Y                                                                                               | Y                                                        | Y                              | N                                            | N                                                         | CT                                                                                                                                 | Y                                                            | Y                                                |
| Kessing, 2021       | Y                                                                                | Y                                                               | Y                                                                                               | CT                                                       | Y                              | CT                                           | N                                                         | CT                                                                                                                                 | Y                                                            | Y                                                |
| Kugathasan, 2018    | Y                                                                                | Y                                                               | Y                                                                                               | CT                                                       | Y                              | N                                            | N                                                         | CT                                                                                                                                 | Y                                                            | Y                                                |
| Lahti, 2012         | CT                                                                               | CT                                                              | Y                                                                                               | CT                                                       | Y                              | CT                                           | CT                                                        | CT                                                                                                                                 | Y                                                            | N                                                |
| Laursen, 2010       | CT                                                                               | CT                                                              | Y                                                                                               | Y                                                        | Y                              | N                                            | N                                                         | CT                                                                                                                                 | CT                                                           | Y                                                |
| Laursen, 2011       | CT                                                                               | CT                                                              | Y                                                                                               | CT                                                       | Y                              | N                                            | N                                                         | CT                                                                                                                                 | Y                                                            | Y                                                |
| Lawrence, 2003      | Y                                                                                | N                                                               | Y                                                                                               | N                                                        | Y                              | N                                            | N                                                         | CT                                                                                                                                 | Y                                                            | N                                                |
| Lin, 2010           | CT                                                                               | CT                                                              | Y                                                                                               | CT                                                       | Y                              | Y                                            | Y                                                         | CT                                                                                                                                 | Y                                                            | Y                                                |
| Manderbacka, 2012   | CT                                                                               | N                                                               | Y                                                                                               | N                                                        | Y                              | N                                            | N                                                         | CT                                                                                                                                 | Y                                                            | Y                                                |
| McDermott, 2005     | Y                                                                                | Y                                                               | Y                                                                                               | N                                                        | Y                              | CT                                           | Y                                                         | CT                                                                                                                                 | CT                                                           | N                                                |

| Study ID             | Selection                                                                        |                                                                 | Comparability                                                                                   |                                                          |                                |                                              | Outcome                                                   |                                                                                                                                    |                                                              |                                                  |
|----------------------|----------------------------------------------------------------------------------|-----------------------------------------------------------------|-------------------------------------------------------------------------------------------------|----------------------------------------------------------|--------------------------------|----------------------------------------------|-----------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------|--------------------------------------------------|
|                      | Truly or somewhat representative of the average person with SMI in the community | Non-exposed drawn from the same community as the exposed cohort | Ascertainment of exposure from secure record <i>e.g.</i> medical record or structured interview | Demonstration that CVD was not present at start of study | Study controls for age and sex | Study controls for socio-demographic factors | Study controls for additional cardiovascular risk factors | Outcome accurately measured & validated, similar methods used for cases and controls, reliable system for measuring CVD occurrence | Follow-up long enough for outcomes to occur (min of 5 years) | Adequacy of follow-up of SMI and non-SMI cohorts |
| Momen, 2020          | Y                                                                                | Y                                                               | Y                                                                                               | CT                                                       | Y                              | N                                            | N                                                         | CT                                                                                                                                 | Y                                                            | Y                                                |
| Morden, 2012         | N                                                                                | Y                                                               | Y                                                                                               | N                                                        | Y                              | N                                            | N                                                         | CT                                                                                                                                 | CT                                                           | N                                                |
| Munk-Jorgensen, 2000 | CT                                                                               | Y                                                               | Y                                                                                               | N                                                        | Y                              | N                                            | N                                                         | N                                                                                                                                  | Y                                                            | Y                                                |
| Prieto, 2016         | Y                                                                                | Y                                                               | Y                                                                                               | CT                                                       | Y                              | N                                            | Y                                                         | Y                                                                                                                                  | Y                                                            | CT                                               |
| Ramsey, 2010         | CT                                                                               | Y                                                               | N                                                                                               | CT                                                       | Y                              | CT                                           | Y                                                         | N                                                                                                                                  | Y                                                            | N                                                |
| Sanchez, 2021        | Y                                                                                | CT                                                              | Y                                                                                               | Y                                                        | Y                              | N                                            | Y                                                         | Y                                                                                                                                  | N                                                            | N                                                |
| Sundquist, 2006      | CT                                                                               | CT                                                              | Y                                                                                               | CT                                                       | Y                              | Y                                            | CT                                                        | CT                                                                                                                                 | Y                                                            | Y                                                |
| Tsai, 2012           | CT                                                                               | Y                                                               | Y                                                                                               | CT                                                       | Y                              | Y                                            | Y                                                         | CT                                                                                                                                 | N                                                            | Y                                                |
| Vance, 2019          | N                                                                                | CT                                                              | Y                                                                                               | Y                                                        | Y                              | CT                                           | Y                                                         | Y                                                                                                                                  | N                                                            | N                                                |
| Westman, 2013        | CT                                                                               | CT                                                              | Y                                                                                               | CT                                                       | Y                              | N                                            | N                                                         | CT                                                                                                                                 | Y                                                            | Y                                                |
| Westman, 2017        | CT                                                                               | CT                                                              | Y                                                                                               | CT                                                       | Y                              | N                                            | N                                                         | CT                                                                                                                                 | Y                                                            | Y                                                |
| Wium-Andersen, 2021  | Y                                                                                | Y                                                               | Y                                                                                               | CT                                                       | Y                              | Y                                            | CT                                                        | CT                                                                                                                                 | CT                                                           | Y                                                |
| Wu, 2013             | CT                                                                               | Y                                                               | Y                                                                                               | CT                                                       | Y                              | Y                                            | Y                                                         | CT                                                                                                                                 | N                                                            | Y                                                |
| Wu, 2015             | Y                                                                                | CT                                                              | Y                                                                                               | N                                                        | Y                              | Y                                            | Y                                                         | CT                                                                                                                                 | Y                                                            | Y                                                |

Y= yes, N – no, CT – can't tell. Cohort studies with low risk of bias were denoted by a rating of "yes" or "can't tell" on the "selection" and "outcome" criteria (excluding selection criteria on representativeness of people with SMI), together with adjustment for age, sex and at least two other confounding factors in the "comparability" category

**Appendix table XVII.2: Risk of bias assessment of studies reporting cardiovascular incidence outcomes, case-control studies**

| Selection           |                                       |                                                                                                      |                                   |                                                             | Comparability                  |                                                        |                                                 | Exposure                                                                                        |                                        |                                                     |                   |
|---------------------|---------------------------------------|------------------------------------------------------------------------------------------------------|-----------------------------------|-------------------------------------------------------------|--------------------------------|--------------------------------------------------------|-------------------------------------------------|-------------------------------------------------------------------------------------------------|----------------------------------------|-----------------------------------------------------|-------------------|
| Study ID            | Adequate definition of cases with CVD | Cases with CVD are representative of defined population and reliable system used for selecting cases | Selection of controls without CVD | Definition of controls - demonstration of no history of CVD | Study controls for age and sex | Study controls for additional sociodemographic factors | Study controls for additional lifestyle factors | Ascertainment of exposure from secure record <i>e.g.</i> medical record or structured interview | Does SMI exposure precede CVD outcome? | Same method of ascertainment for cases and controls | Non-response rate |
| Yu-Chuan Chiu, 2015 | Y                                     | CT                                                                                                   | Y                                 | CT                                                          | Y                              | Y                                                      | Y                                               | Y                                                                                               | Y                                      | Y                                                   | CT                |

Y= yes, N – no, CT – can't tell. Case-control studies with low risk of bias were denoted by "yes" or "can't tell" in "selection" and "exposure" categories, plus adjustment for age, sex and at least two other confounding factors in the "comparability" category

# APPENDIX XVIII ANALYSIS OF TEMPORAL TRENDS: INCIDENCE

**Appendix table XVIII.1: Meta-analysis: pooled results by severe mental illness and cardiovascular incidence**

| SMI | Outcome | Measure   | Decade | Studies | Results | Effect      | 95% CI          | p      | Lower prediction interval | Upper prediction interval | I <sup>2</sup> | Q     | Q df |
|-----|---------|-----------|--------|---------|---------|-------------|-----------------|--------|---------------------------|---------------------------|----------------|-------|------|
| SCZ | CVA     | HR/RRatio | 1980s  | 1       | 1       | 1.41        | ( 0.75 - 2.65 ) | 0.285  | .                         | .                         | .              | 0.0   | 0    |
| SCZ | CVA     | HR/RRatio | 1990s  | 1       | 1       | <b>1.25</b> | ( 1.17 - 1.33 ) | <0.001 | .                         | .                         | .              | 0.0   | 0    |
| SCZ | CVA     | HR/RRatio | 2000s  | 2       | 3       | <b>1.86</b> | ( 1.54 - 2.25 ) | <0.001 | 0.2                       | 16.4                      | 73.3           | 7.5   | 2    |
| SCZ | CVA     | OR        | 1990s  | 1       | 1       | <b>2.11</b> | ( 1.22 - 3.65 ) | 0.008  | .                         | .                         | .              | 0.0   | 0    |
| SCZ | CVA     | OR        | 2000s  | 1       | 1       | <b>1.72</b> | ( 1.07 - 2.79 ) | 0.027  | .                         | .                         | .              | 0.0   | 0    |
| SCZ | CVA     | RR        | 1990s  | 2       | 2       | <b>1.33</b> | ( 1.01 - 1.75 ) | 0.040  | .                         | .                         | 0.0            | 0.2   | 1    |
| SCZ | CVA     | RR        | 2000s  | 1       | 1       | <b>1.40</b> | ( 1.32 - 1.49 ) | <0.001 | .                         | .                         | .              | 0.0   | 0    |
| SCZ | CHD     | HR/RRatio | 1980s  | 2       | 3       | 0.79        | ( 0.50 - 1.24 ) | 0.307  | 0.0                       | 205.5                     | 88.2           | 17.0  | 2    |
| SCZ | CHD     | HR/RRatio | 1990s  | 1       | 1       | <b>0.88</b> | ( 0.83 - 0.94 ) | <0.001 | .                         | .                         | .              | 0.0   | 0    |
| SCZ | CHD     | HR/RRatio | 2000s  | 5       | 6       | <b>1.46</b> | ( 1.22 - 1.74 ) | <0.001 | 0.8                       | 2.7                       | 98.0           | 243.4 | 5    |
| SCZ | CHD     | OR        | 1990s  | 1       | 1       | 0.86        | ( 0.56 - 1.32 ) | 0.487  | .                         | .                         | .              | 0.0   | 0    |
| SCZ | CHD     | OR        | 2000s  | 1       | 1       | <b>0.73</b> | ( 0.55 - 0.96 ) | 0.023  | .                         | .                         | .              | 0.0   | 0    |
| SCZ | CHD     | RR        | 1990s  | 3       | 3       | 0.91        | ( 0.72 - 1.14 ) | 0.403  | 0.1                       | 11.5                      | 73.7           | 7.6   | 2    |
| SCZ | CHD     | SIR       | 1990s  | 1       | 2       | <b>1.48</b> | ( 1.30 - 1.69 ) | <0.001 | .                         | .                         | 85.0           | 6.7   | 1    |
| SCZ | CVD     | HR/RRatio | 1990s  | 1       | 1       | <b>1.18</b> | ( 1.05 - 1.33 ) | 0.006  | .                         | .                         | .              | 0.0   | 0    |
| SCZ | CVD     | HR/RRatio | 2000s  | 2       | 2       | 1.29        | ( 0.96 - 1.72 ) | 0.092  | .                         | .                         | 84.9           | 6.6   | 1    |
| SCZ | CVD     | OR        | 2010s  | 1       | 2       | <b>1.80</b> | ( 1.24 - 2.62 ) | 0.002  | .                         | .                         | 95.3           | 21.4  | 1    |
| SCZ | HF      | HR/RRatio | 2000s  | 1       | 1       | <b>3.82</b> | ( 3.10 - 4.71 ) | <0.001 | .                         | .                         | .              | 0.0   | 0    |
| SCZ | HF      | OR        | 1990s  | 1       | 1       | <b>2.38</b> | ( 1.42 - 4.00 ) | 0.001  | .                         | .                         | .              | 0.0   | 0    |
| SCZ | HF      | OR        | 2000s  | 1       | 1       | 1.37        | ( 0.85 - 2.21 ) | 0.195  | .                         | .                         | .              | 0.0   | 0    |
| SCZ | HF      | RR        | 1990s  | 2       | 2       | <b>1.72</b> | ( 1.08 - 2.75 ) | 0.023  | .                         | .                         | 75.1           | 4.0   | 1    |
| BD  | CVA     | HR/RRatio | 1980s  | 1       | 1       | 1.57        | ( 0.93 - 2.65 ) | 0.090  | .                         | .                         | .              | 0.0   | 0    |
| BD  | CVA     | HR/RRatio | 1990s  | 1       | 1       | <b>1.39</b> | ( 1.27 - 1.53 ) | <0.001 | .                         | .                         | .              | 0.0   | 0    |
| BD  | CVA     | HR/RRatio | 2000s  | 2       | 3       | <b>1.72</b> | ( 1.43 - 2.06 ) | <0.001 | 0.2                       | 14.2                      | 76.3           | 8.4   | 2    |
| BD  | CVA     | OR        | 2000s  | 1       | 1       | <b>3.39</b> | ( 1.91 - 6.01 ) | <0.001 | .                         | .                         | .              | 0.0   | 0    |
| BD  | CVA     | RR        | 1990s  | 1       | 1       | 1.19        | ( 0.34 - 4.16 ) | 0.785  | .                         | .                         | .              | 0.0   | 0    |
| BD  | CVA     | RR        | 2000s  | 1       | 1       | <b>1.31</b> | ( 1.18 - 1.45 ) | <0.001 | .                         | .                         | .              | 0.0   | 0    |
| BD  | CHD     | HR/RRatio | 1980s  | 1       | 1       | 1.39        | ( 0.75 - 2.59 ) | 0.299  | .                         | .                         | .              | 0.0   | 0    |

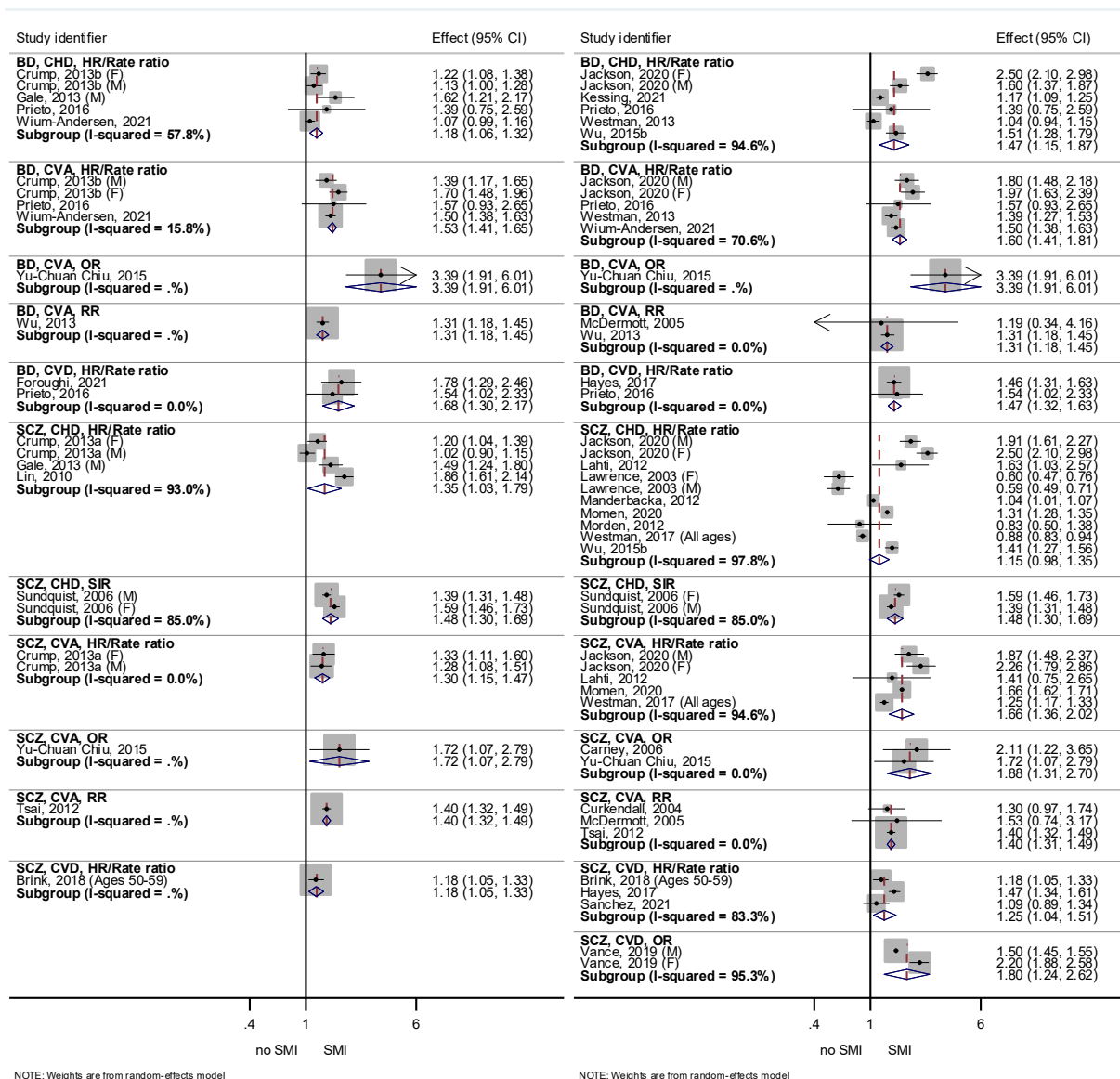


| SMI | Outcome | Measure   | Decade | Studies | Results | Effect      | 95% CI          | p      | Lower prediction interval | Upper prediction interval | I <sup>2</sup> | Q    | Q df |
|-----|---------|-----------|--------|---------|---------|-------------|-----------------|--------|---------------------------|---------------------------|----------------|------|------|
| BD  | CHD     | HR/RRatio | 1990s  | 1       | 1       | 1.04        | ( 0.94 - 1.15 ) | 0.425  | .                         | .                         | .              | 0.0  | 0    |
| BD  | CHD     | HR/RRatio | 2000s  | 3       | 4       | <b>1.62</b> | ( 1.17 - 2.24 ) | 0.004  | 0.3                       | 7.7                       | 95.8           | 70.7 | 3    |
| BD  | CHD     | OR        | 1990s  | 1       | 1       | <b>2.68</b> | ( 1.51 - 4.76 ) | 0.001  | .                         | .                         | .              | 0.0  | 0    |
| BD  | CHD     | RR        | 1990s  | 1       | 1       | 0.97        | ( 0.50 - 1.88 ) | 0.928  | .                         | .                         | .              | 0.0  | 0    |
| BD  | CVD     | HR/RRatio | 1980s  | 1       | 1       | <b>1.54</b> | ( 1.02 - 2.33 ) | 0.040  | .                         | .                         | .              | 0.0  | 0    |
| BD  | CVD     | HR/RRatio | 2000s  | 1       | 1       | <b>1.46</b> | ( 1.31 - 1.63 ) | <0.001 | .                         | .                         | .              | 0.0  | 0    |
| BD  | CVD     | OR        | 2000s  | 1       | 1       | <b>2.58</b> | ( 1.84 - 3.61 ) | <0.001 | .                         | .                         | .              | 0.0  | 0    |
| BD  | CVD     | OR        | 2010s  | 1       | 2       | <b>1.67</b> | ( 1.15 - 2.42 ) | 0.007  | .                         | .                         | 96.9           | 31.8 | 1    |
| BD  | HF      | HR/RRatio | 2000s  | 1       | 1       | <b>3.30</b> | ( 2.27 - 4.79 ) | <0.001 | .                         | .                         | .              | 0.0  | 0    |
| BD  | HF      | RR        | 1990s  | 1       | 1       | 1.73        | ( 0.88 - 3.40 ) | 0.111  | .                         | .                         | .              | 0.0  | 0    |

SCZ – schizophrenia, BD – bipolar disorder, SMI – mixed severe mental illness, HR – hazard ratio, RRatio – rate ratio, OR – odds ratio, RR – risk ratio, SIR – standardised incidence ratio, CVA – cerebrovascular accident, CHD – coronary heart disease, CVD – major cardiovascular events, HF – heart failure. Results where 95% confidence intervals exclude the null highlighted in **bold**



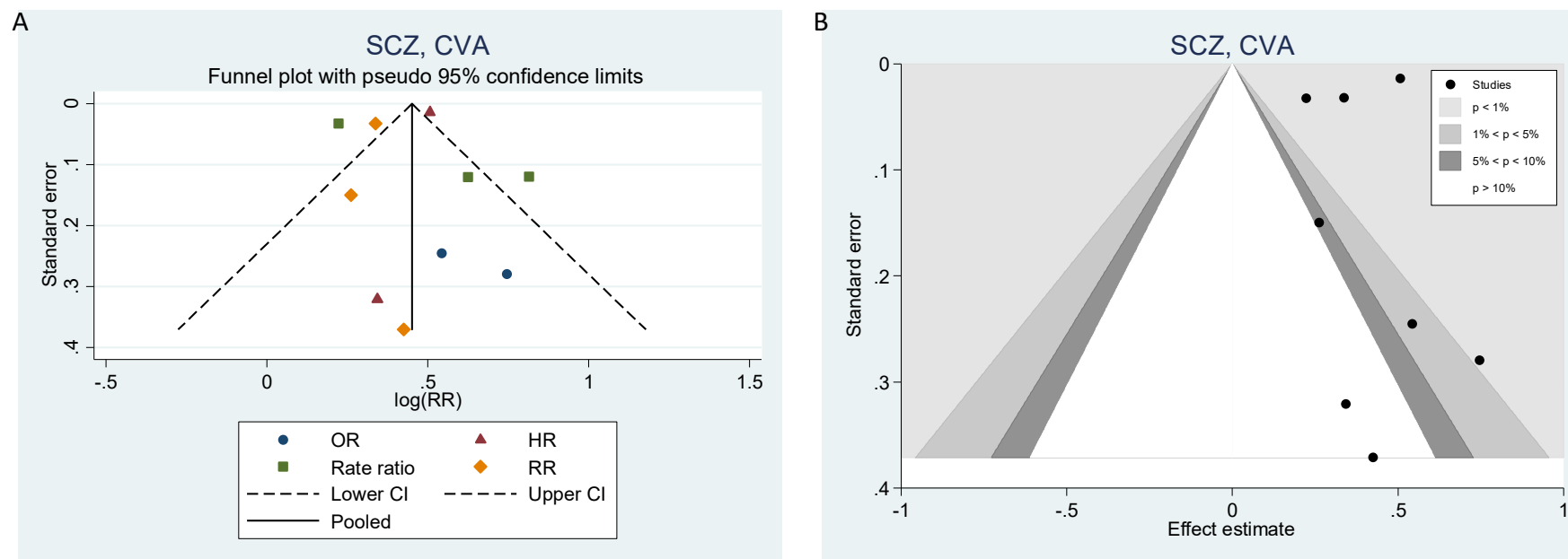
## APPENDIX XIX SUBGROUP ANALYSIS: INCIDENCE STUDIES



BD – bipolar disorder, SCZ – schizophrenia, CHD – coronary heart disease, CVA – cerebrovascular accident, CVD – major cardiovascular events, HR – hazard ratio, OR – odds ratio, SIR – standardised incidence ratio

**Appendix figure XIX.1: Forest plots of CVD incidence for a) studies with low risk of bias, b) all studies included in meta-analysis, schizophrenia and bipolar disorder**

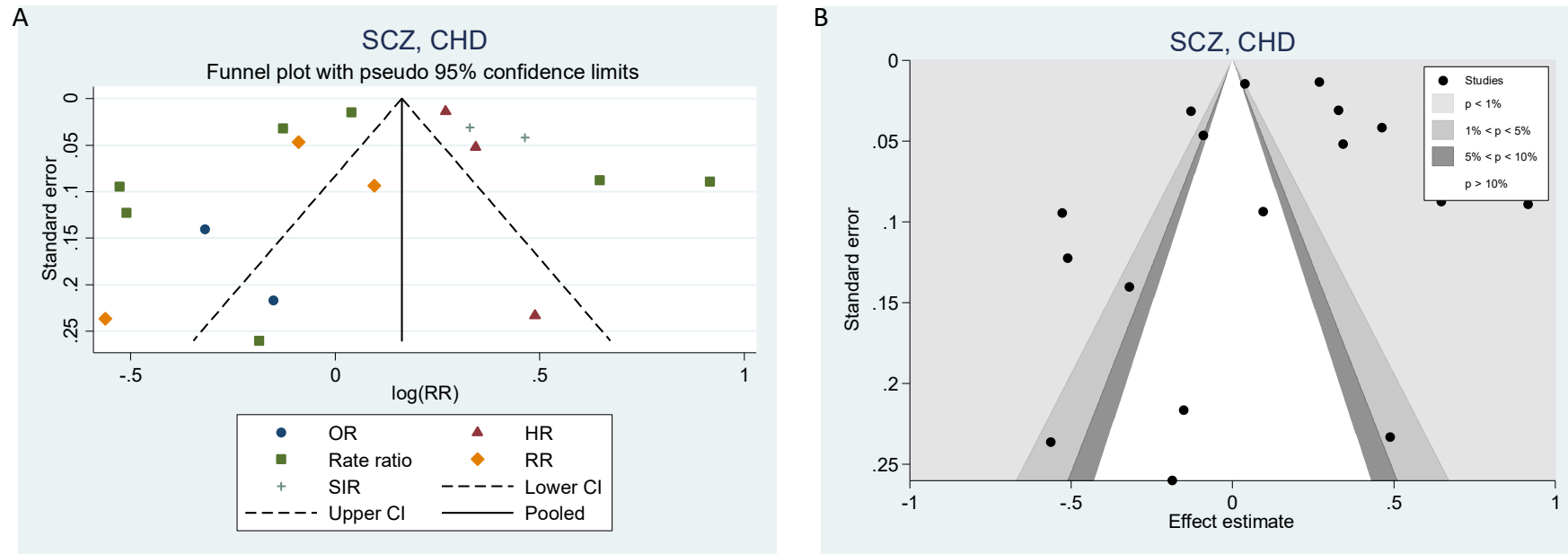
## APPENDIX XX ASSESSMENT OF PUBLICATION BIAS: INCIDENCE STUDIES



SCZ – schizophrenia, CVA – cerebrovascular accident, OR – odds ratio, HR – hazard ratio, RR – risk ratio

**Appendix figure XX.1: Funnel plots for visual assessment of publication bias for studies reporting relative risk of CVD incidence for schizophrenia compared with controls, cerebrovascular accident**

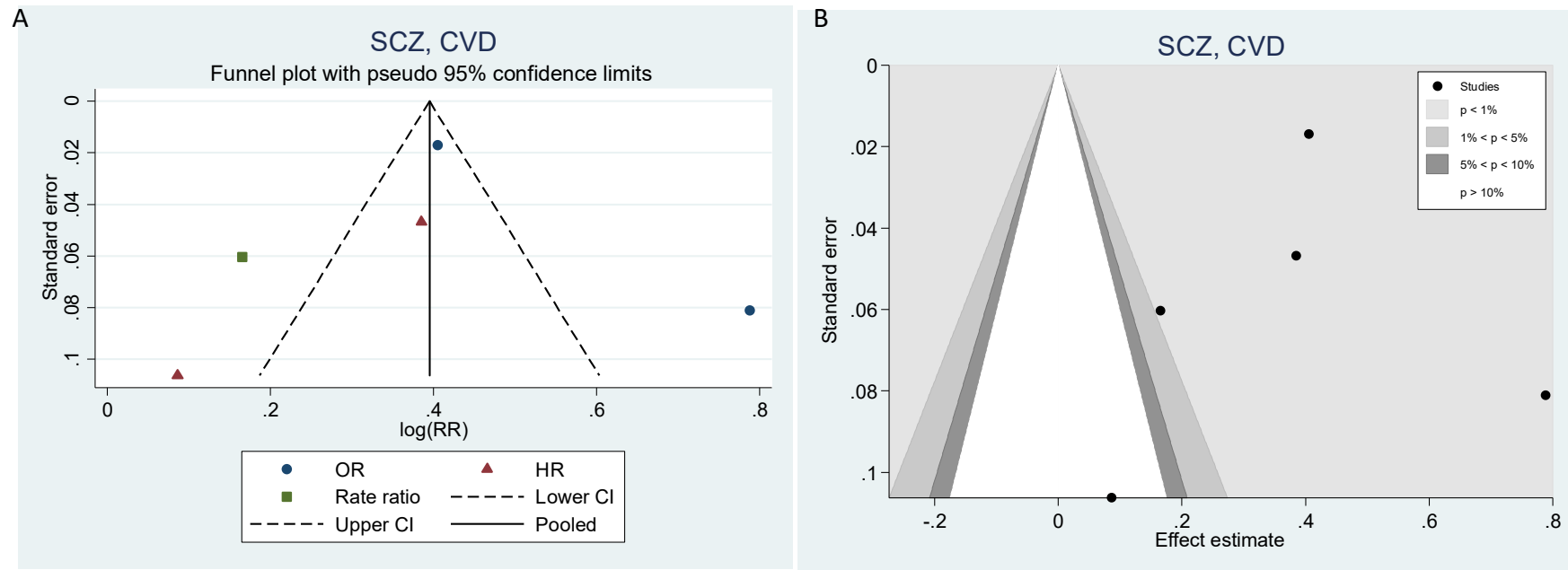
Plot A shows little asymmetry, so publication bias is not suspected.



SCZ – schizophrenia, CVA – cerebrovascular accident, OR – odds ratio, HR – hazard ratio, RR – risk ratio

**Appendix figure XX.2: Funnel plots for visual assessment of publication bias for studies reporting relative risk of CVD incidence for schizophrenia compared with controls, coronary heart disease**

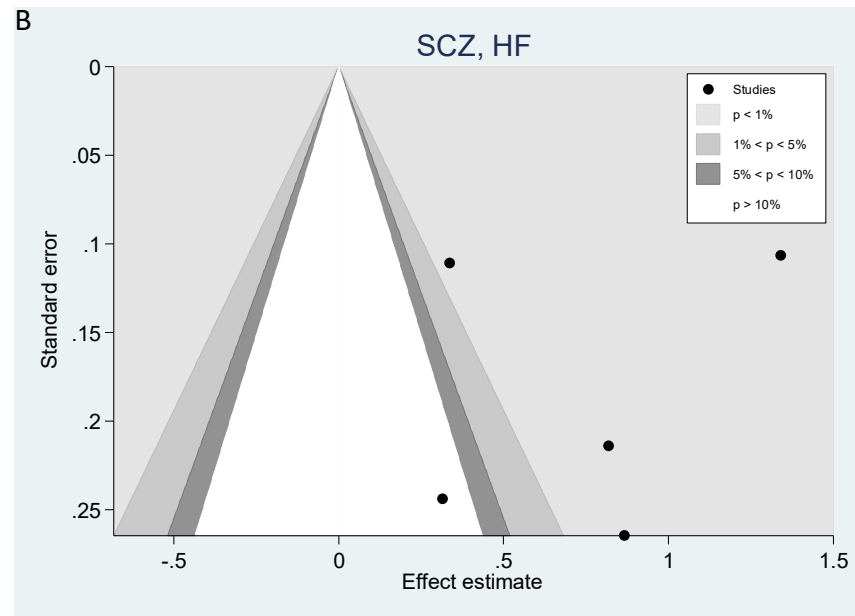
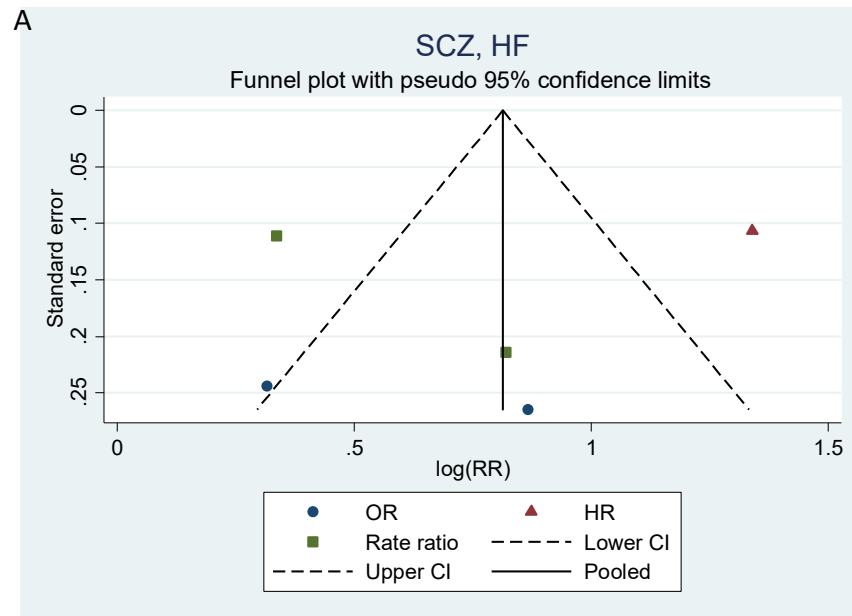
There is some asymmetry on the lower right-hand side of the funnel plot (A), suggesting missing studies falling outside the pseudo 95% confidence limits. In the contour-enhanced funnel plot (B) the “missing” studies would be in the shaded area of the graph, so would be expected to report significant effects. Further, Egger’s test is non-significant. Publication bias is therefore not suspected.



SCZ – schizophrenia, CVD – major cardiovascular events, OR – odds ratio, HR – hazard ratio, RR- risk ratio

**Appendix figure XX.3: Funnel plots for visual assessment of publication bias for studies reporting relative risk of CVD incidence for schizophrenia compared with controls, major cardiovascular events**

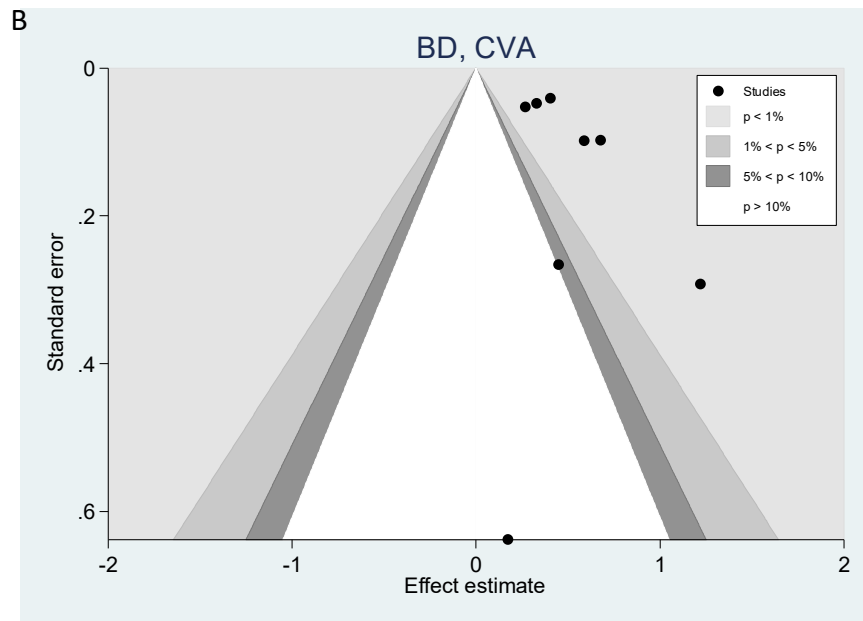
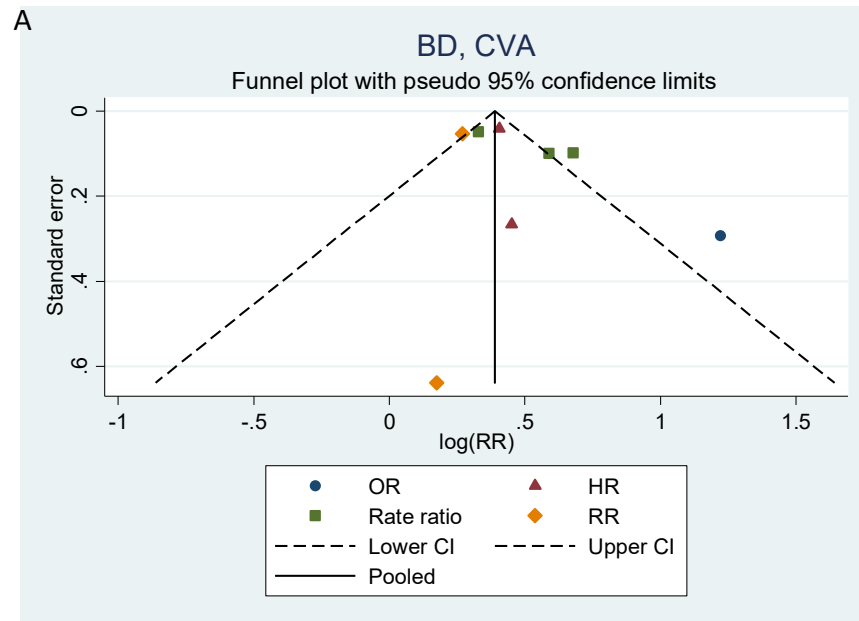
There are too few studies to assess publication bias.



SCZ – schizophrenia, HF – heart failure, OR – odds ratio, HR – hazard ratio, RR- risk ratio

**Appendix figure XX.4: Funnel plots for visual assessment of publication bias for studies reporting relative risk of CVD incidence for schizophrenia compared with controls, heart failure**

There are too few studies to assess publication bias.

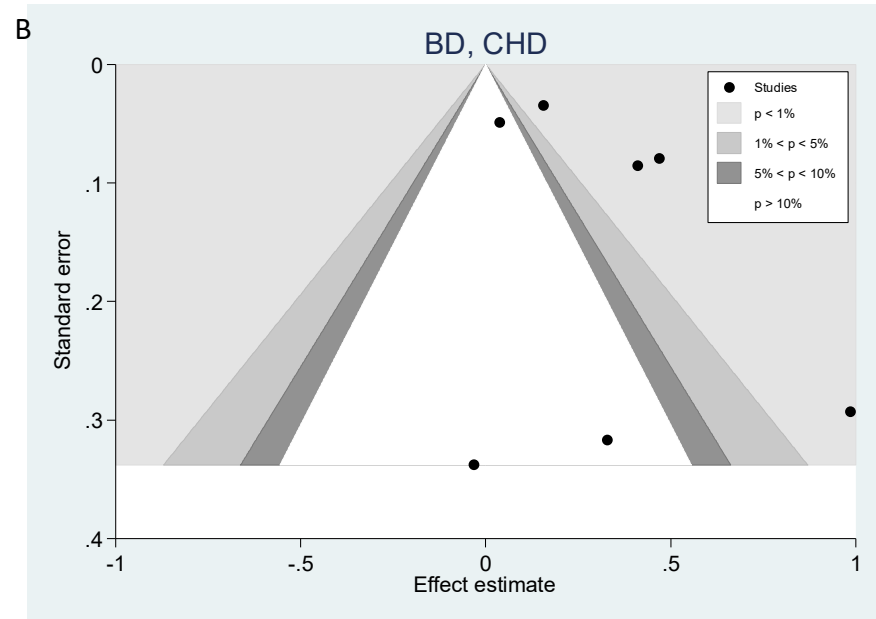
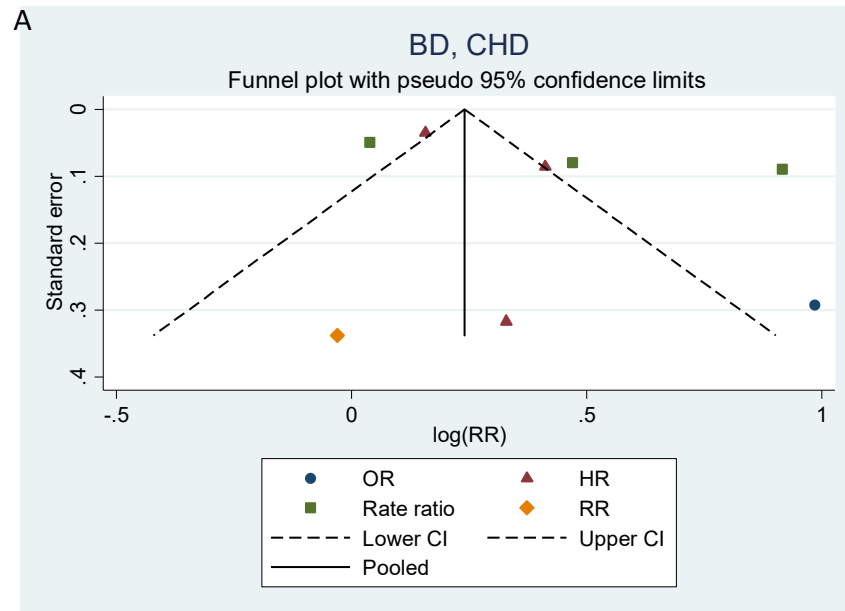


BD – bipolar disorder, CVA – cerebrovascular accident, OR – odds ratio, HR – hazard ratio, RR- risk ratio

**Appendix figure XX.5: Funnel plots for visual assessment of publication bias for studies reporting relative risk of CVD incidence for bipolar disorder compared with controls, cerebrovascular accident**

There are too few studies to assess publication bias.

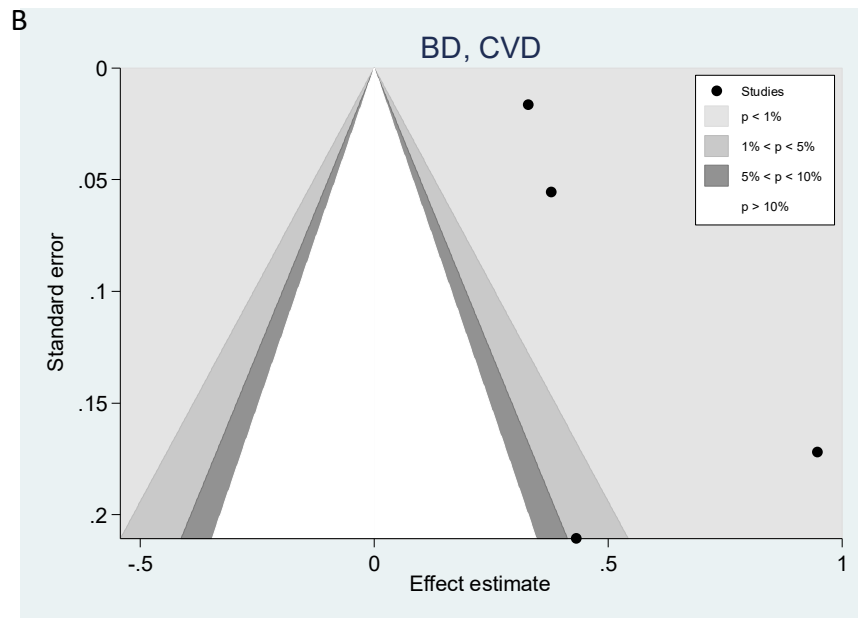
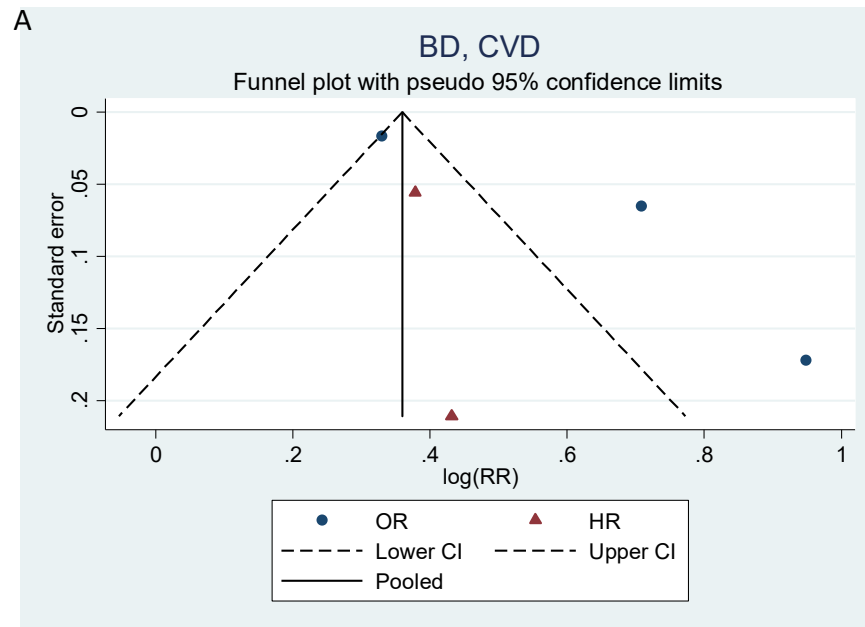




BD – bipolar disorder, CHD – coronary heart disease, OR – odds ratio, HR – hazard ratio, RR- risk ratio

**Appendix figure XX.6: Funnel plots for visual assessment of publication bias for studies reporting relative risk of CVD incidence for bipolar disorder compared with controls, coronary heart disease**

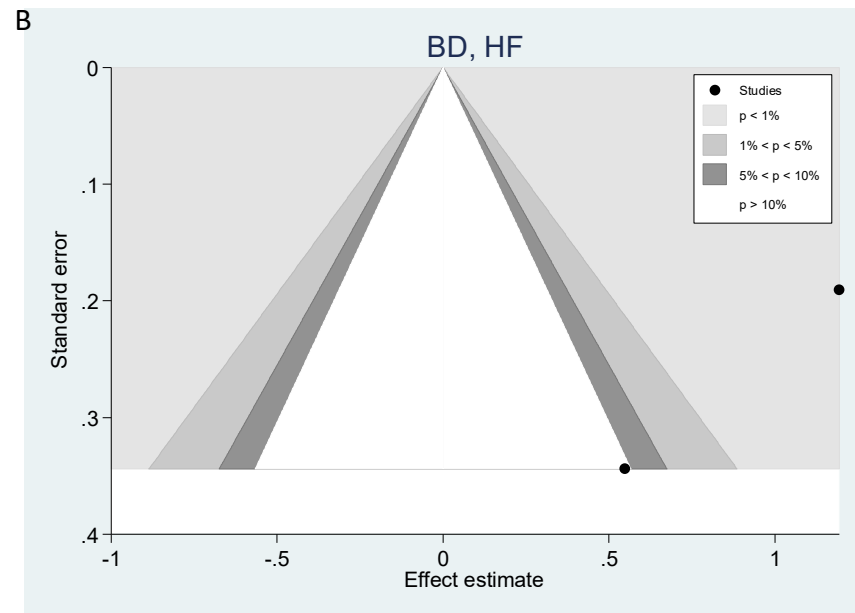
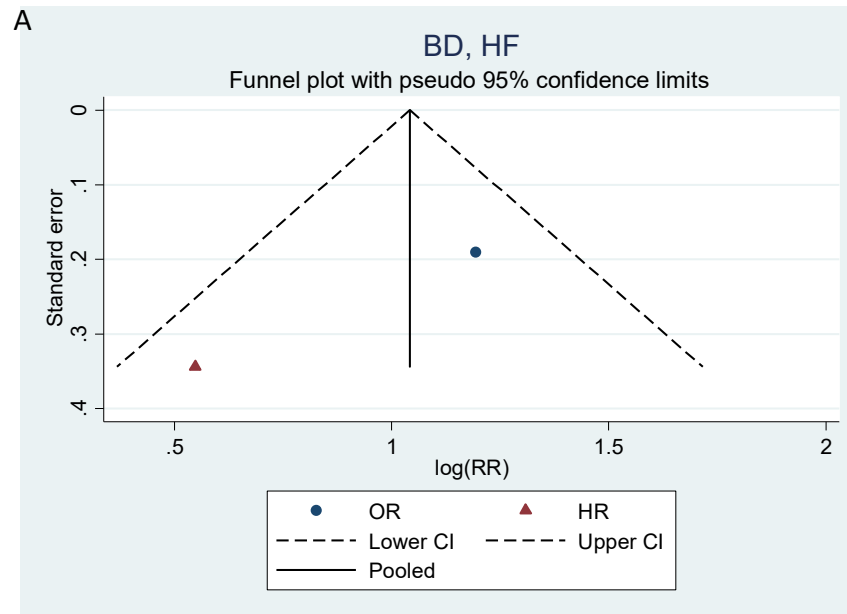
There are too few studies to assess publication bias.



BD – bipolar disorder, CVD – major cardiovascular events, OR – odds ratio, HR – hazard ratio, RR- risk ratio

**Appendix figure XX.7: Funnel plots for visual assessment of publication bias for studies reporting relative risk of CVD incidence for bipolar disorder compared with controls, major cardiovascular events**

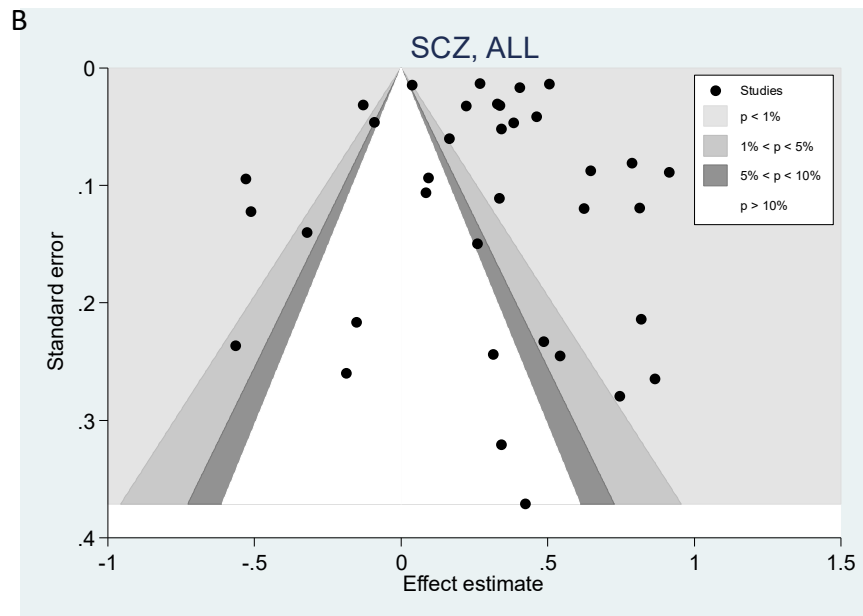
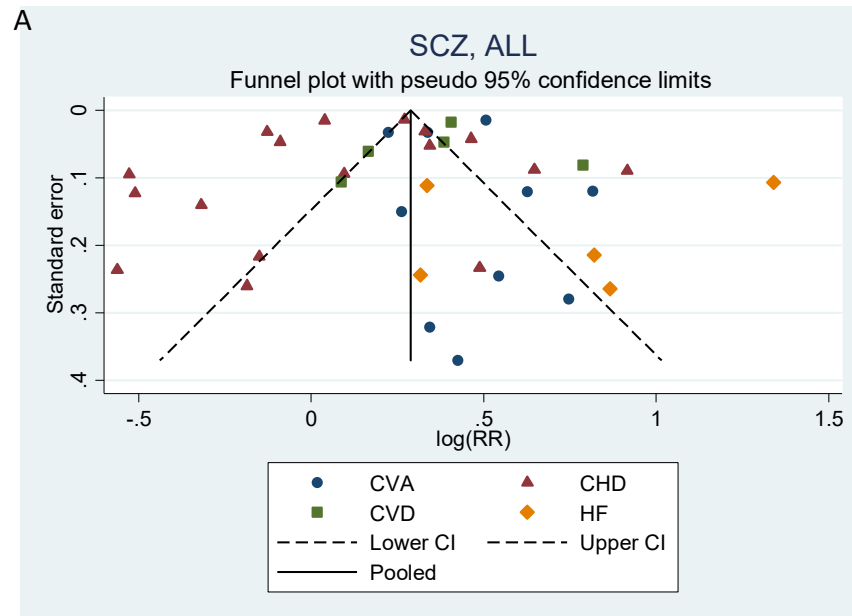
There are too few studies to assess publication bias.



BD – bipolar disorder, HF – heart failure, OR – odds ratio, HR – hazard ratio, RR- risk ratio

**Appendix figure XX.8: Funnel plots for visual assessment of publication bias for studies reporting relative risk of CVD incidence for bipolar disorder compared with controls, heart failure**

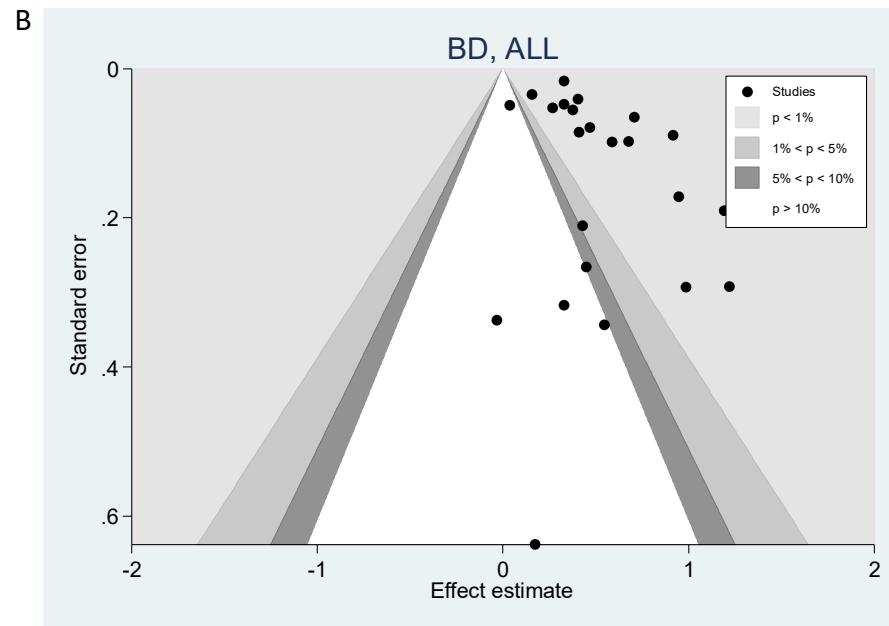
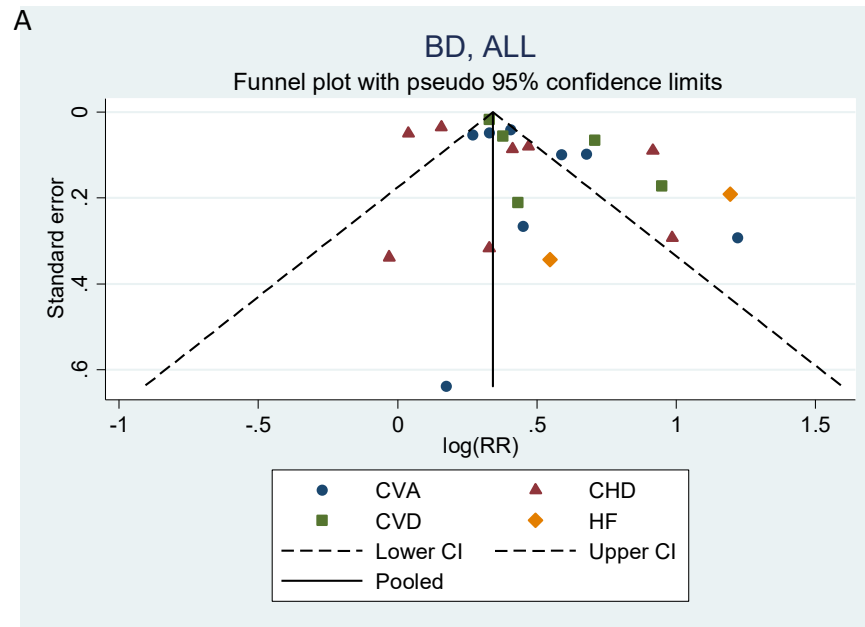
There are too few studies to assess publication bias.



SCZ - schizophrenia, CVA – cerebrovascular accident, CHD – coronary heart disease, CVD – major cardiovascular events, HF – heart failure

### Appendix figure XX.9: Funnel plots for visual assessment of publication bias for studies reporting relative risk of CVD incidence for schizophrenia compared with controls, all cardiovascular disease

The funnel plot (A) suggests some asymmetry in the bottom left-hand corner, which could be missing small studies. These would fall inside the White (non-significant) area of the contour-enhanced funnel plot (B), so could indicate possible publication bias. However, the results of Egger's test (0.08, 95% CI: -2.64 to 2.81,  $p=0.951$ ) were non-significant for small study effects.

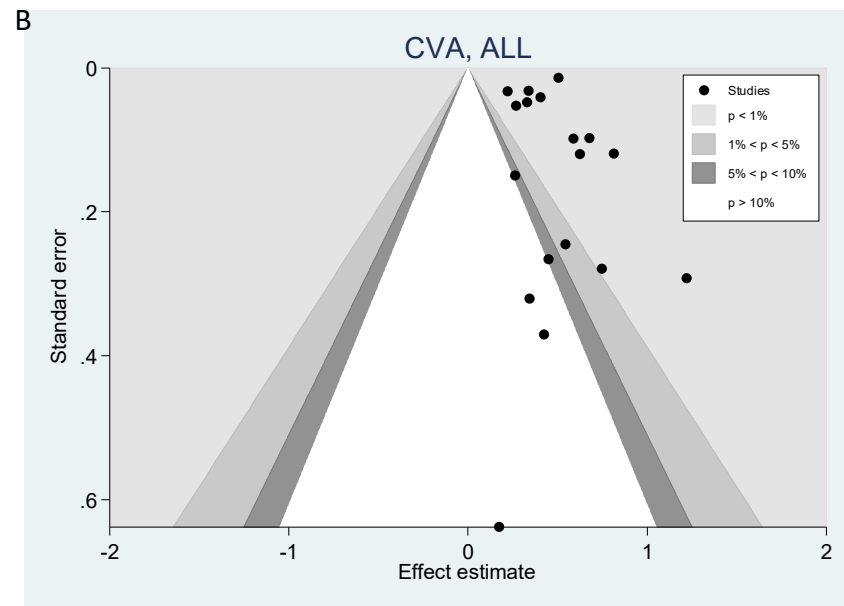
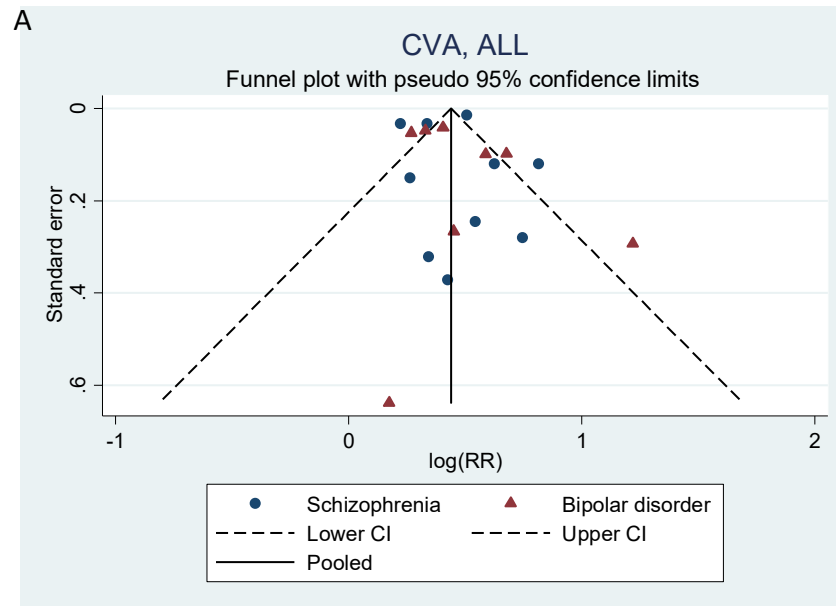


BD – bipolar disorder, CVA – cerebrovascular accident, CHD – coronary heart disease, CVD – major cardiovascular events, HF – heart failure

### Appendix figure XX.10: Funnel plots for visual assessment of publication bias for studies reporting relative risk of CVD incidence for bipolar disorder compared with controls, all cardiovascular disease

There is some asymmetry in the upper left-hand side of the funnel plot (A), outside the pseudo 95% confidence limits, which could suggest missing studies. In the contour-enhanced funnel plot (B) the “missing” studies would fall mainly in the White (non-significant) area of the graph, so publication bias is a possibility. Further, Egger’s test indicates a significant small study effect bias (1.94, 95% CI: 0.16 to 3.72,  $p=0.034$ ), therefore publication bias may exist. Also, some of the smaller studies fall into the significant (shaded) areas of plot B, suggesting that publication bias may not be the only cause of asymmetry in the plots<sup>1</sup>. However, applying trim and fill methodology indicates does not add any additional unpublished studies.

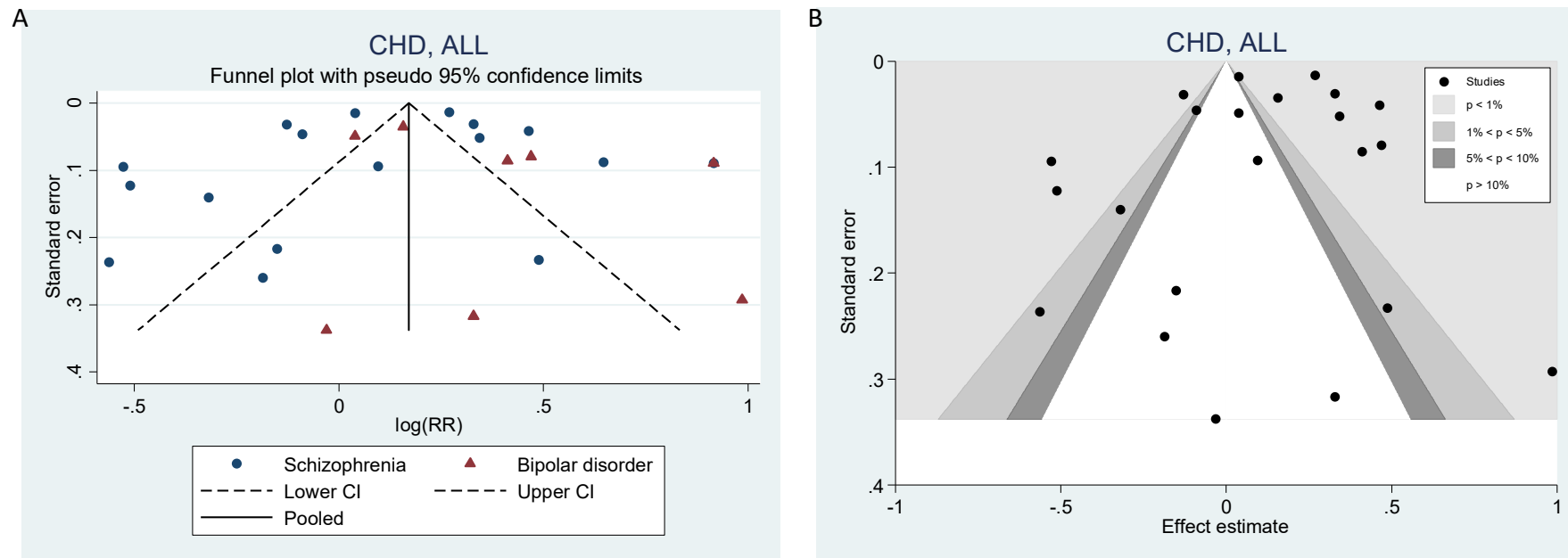
<sup>1</sup> Chaimani A, Mavridis D, Salanti G. A hands-on practical tutorial on performing meta-analysis with Stata. *Evidence Based Mental Health*. 2014;17(4):111.



CVA – cerebrovascular accident

**Appendix figure XX.11: Funnel plots for visual assessment of publication bias for studies reporting relative risk of CVD incidence for schizophrenia and bipolar disorder compared with controls, cerebrovascular accident**

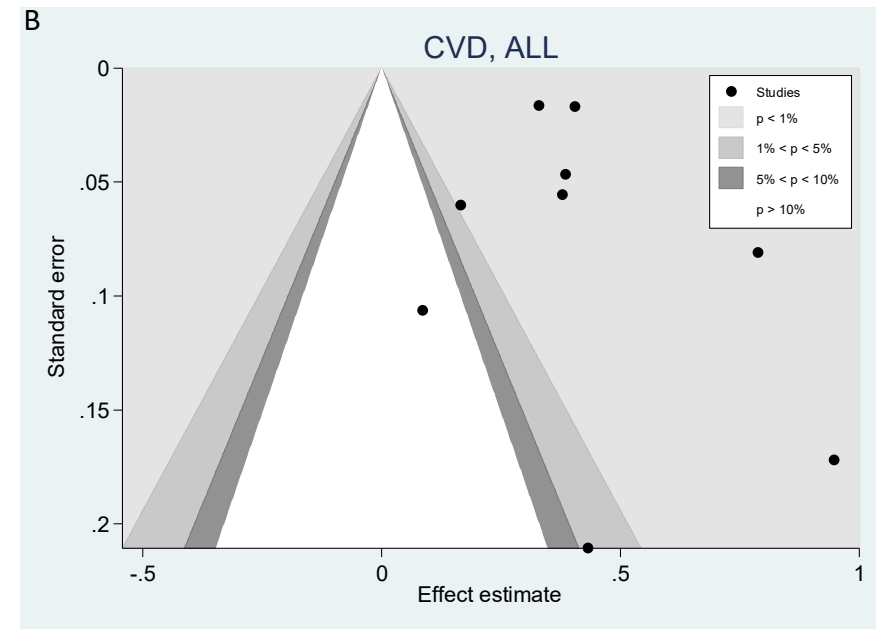
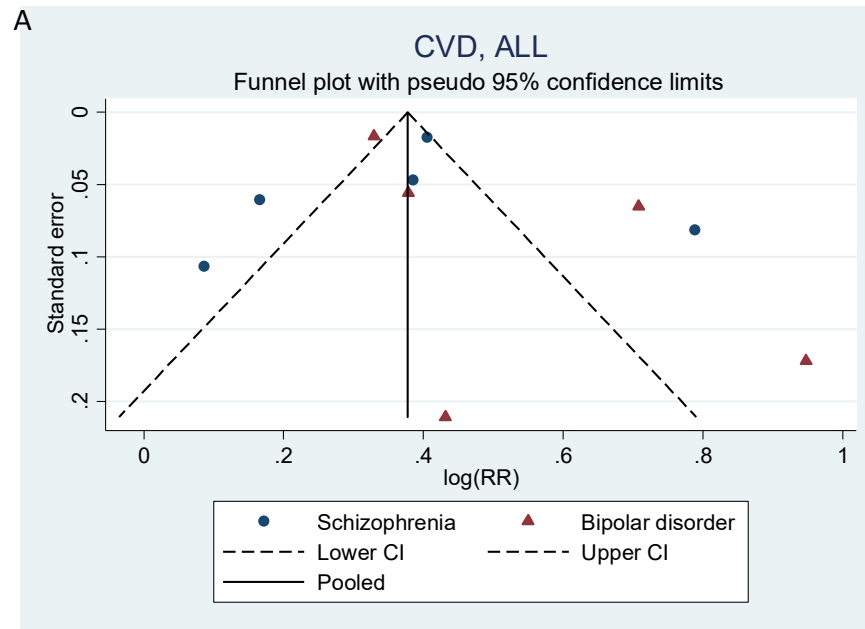
The funnel plot (A) suggests some asymmetry on the left-hand side, within the pseudo 95% confidence limits, which could be missing smaller studies. These would fall inside the White (non-significant) area of the contour-enhanced funnel plot (B), so could indicate possible publication bias. However, the results of Egger's test ( $-0.05$ , 95% CI:  $-1.89$  to  $1.80$ ,  $p=0.0.957$ ) were non-significant for small study effects.



CHD – coronary heart disease

**Appendix figure XX.12: Funnel plots for visual assessment of publication bias for studies reporting relative risk of CVD incidence for schizophrenia and bipolar disorder compared with controls, coronary heart disease**

There is some asymmetry in the upper right-hand side of the funnel plot (A), outside the pseudo 95% confidence limits, which could suggest missing studies. In the contour-enhanced funnel plot (B) the “missing” studies would fall into the shaded area, indicating that publication bias is unlikely.

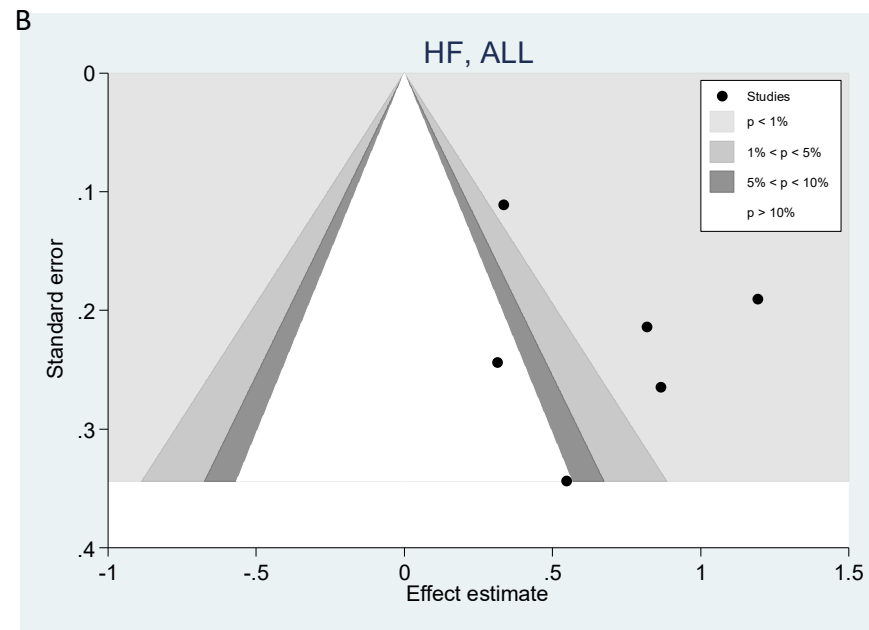
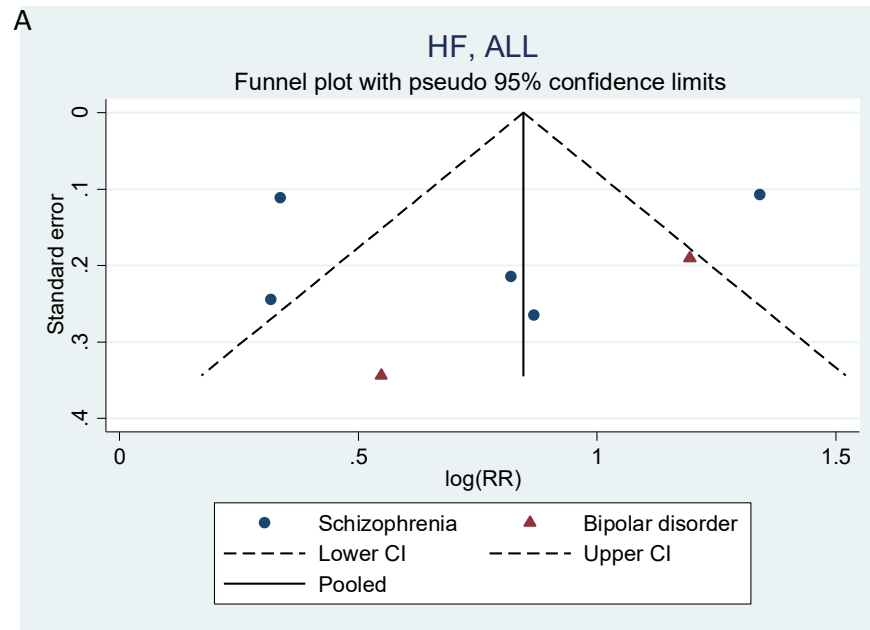


CVD – major cardiovascular events

**Appendix figure XX.13: Funnel plots for visual assessment of publication bias for studies reporting relative risk of CVD incidence for schizophrenia and bipolar disorder compared with controls, major cardiovascular events**

Plot A shows little asymmetry, so publication bias is not suspected.

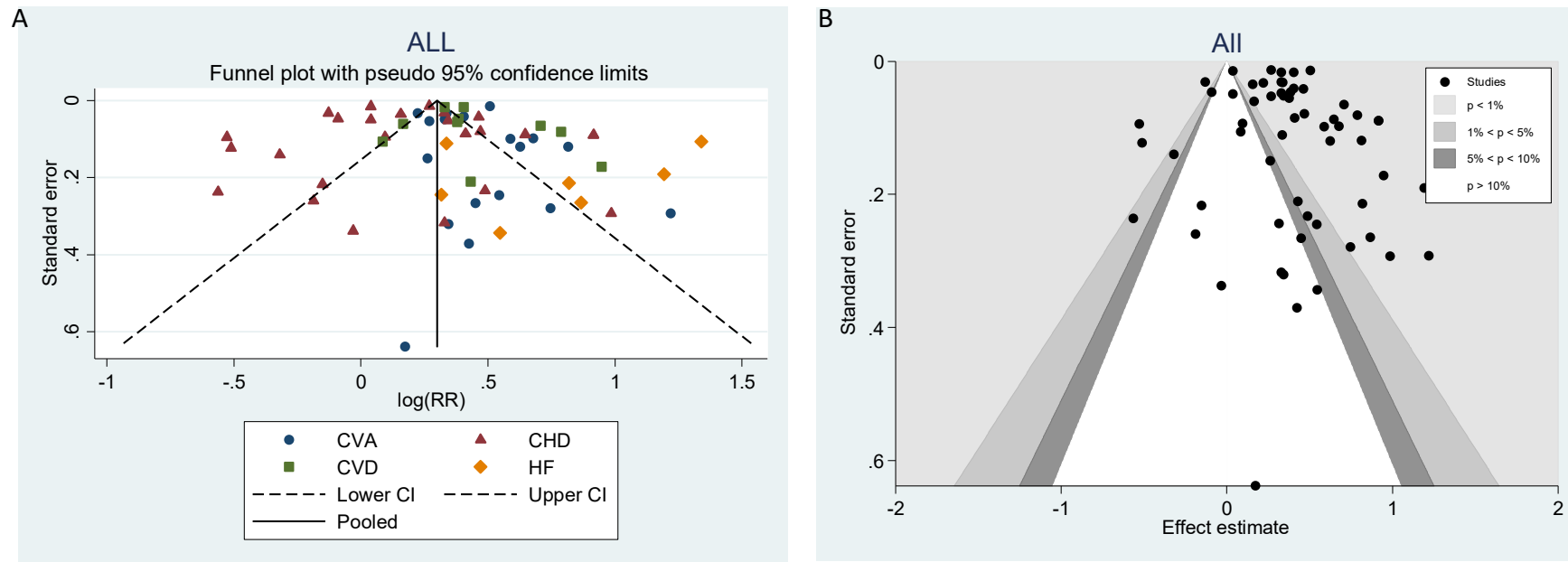




HF – heart failure

**Appendix figure XX.14: Funnel plots for visual assessment of publication bias for studies reporting relative risk of CVD incidence for schizophrenia and bipolar disorder compared with controls, heart failure**

There are too few studies to assess publication bias.



CVA – cerebrovascular accident, CHD – coronary heart disease, CVD – major cardiovascular events, HF – heart failure

# **Appendix figure XX.15: Funnel plots for visual assessment of publication bias for studies reporting relative risk of CVD incidence for schizophrenia and bipolar disorder compared with controls, all cardiovascular disease**

When included results from all studies are considered together, the funnel plot (A) suggests some asymmetry on the left-hand side, within the pseudo 95% confidence limits, which could be missing smaller studies. These would fall inside the White (non-significant) area of the contour-enhanced funnel plot (B), so could suggest publication bias. However, the results of Egger's test (0.86, 95% CI: -0.91 to 2.63,  $p=0.336$ ) were non-significant for small study effects.

**Appendix table XX.1: Results of Egger's tests for publication bias, incidence outcomes**

| <b>SMI</b>       | <b>Incidence outcome</b>       | <b>Bias (95% CI)</b>     | <b>p-value</b> |
|------------------|--------------------------------|--------------------------|----------------|
| Schizophrenia    | Cerebrovascular accident       | -0.37 (-3.53, 2.79)      | 0.796          |
| Schizophrenia    | Coronary heart disease         | -0.77 (-5.17, 3.64)      | 0.716          |
| Schizophrenia    | All circulatory disease events | Too few studies          | -              |
| Schizophrenia    | Heart failure                  | Too few studies          | -              |
| Bipolar disorder | Cerebrovascular accident       | Too few studies          | -              |
| Bipolar disorder | Coronary heart disease         | Too few studies          | -              |
| Bipolar disorder | All circulatory disease events | Too few studies          | -              |
| Bipolar disorder | Heart failure                  | Too few studies          | -              |
| All SMI          | Cerebrovascular accident       | -0.05 (-1.90, 1.80)      | 0.957          |
| All SMI          | Coronary heart disease         | 0.40 (-2.69, 3.50)       | 0.791          |
| All SMI          | All circulatory disease events | 1.48 (-2.13, 5.09)       | 0.374          |
| All SMI          | Heart failure                  | Too few studies          | -              |
| Schizophrenia    | All CVD incidence outcomes     | 0.08 (-2.64, 2.81)       | 0.951          |
| Bipolar disorder | All CVD incidence outcomes     | <b>1.94</b> (0.16, 3.72) | 0.034          |
| All SMI          | All CVD incidence outcomes     | 0.86 (-0.91, 2.63)       | 0.336          |

SMI – severe mental illness. Results where 95% confidence intervals exclude the null highlighted in **bold**

## APPENDIX XXI INCLUDED READ CODES FOR SEVERE MENTAL ILLNESS

**Appendix table XXI.1: Read codes for bipolar disorder**

| <b>Read code</b> | <b>Description</b>                                            | <b>Incident or prevalent</b> |
|------------------|---------------------------------------------------------------|------------------------------|
| E11..00          | Affective psychoses                                           | incident                     |
| E11..11          | Bipolar psychoses                                             | incident                     |
| E11..12          | Depressive psychoses                                          | incident                     |
| E11..13          | Manic psychoses                                               | incident                     |
| E110.00          | Manic disorder, single episode                                | incident                     |
| E110.11          | Hypomanic psychoses                                           | incident                     |
| E110000          | Single manic episode, unspecified                             | incident                     |
| E110100          | Single manic episode, mild                                    | incident                     |
| E110200          | Single manic episode, moderate                                | incident                     |
| E110300          | Single manic episode, severe without mention of psychosis     | incident                     |
| E110400          | Single manic episode, severe, with psychosis                  | incident                     |
| E110z00          | Manic disorder, single episode NOS                            | incident                     |
| E114.00          | Bipolar affective disorder, currently manic                   | incident                     |
| E114.11          | Manic-depressive - now manic                                  | incident                     |
| E114000          | Bipolar affective disorder, currently manic, unspecified      | incident                     |
| E114100          | Bipolar affective disorder, currently manic, mild             | incident                     |
| E114200          | Bipolar affective disorder, currently manic, moderate         | incident                     |
| E114300          | Bipolar affect disord, currently manic, severe, no psychosis  | incident                     |
| E114400          | Bipolar affect disord, currently manic, severe with psychosis | incident                     |
| E114z00          | Bipolar affective disorder, currently manic, NOS              | incident                     |
| E115.00          | Bipolar affective disorder, currently depressed               | incident                     |
| E115.11          | Manic-depressive - now depressed                              | incident                     |
| E115000          | Bipolar affective disorder, currently depressed, unspecified  | incident                     |
| E115100          | Bipolar affective disorder, currently depressed, mild         | incident                     |
| E115200          | Bipolar affective disorder, currently depressed, moderate     | incident                     |
| E115300          | Bipolar affect disord, now depressed, severe, no psychosis    | incident                     |
| E115400          | Bipolar affect disord, now depressed, severe with psychosis   | incident                     |
| E115z00          | Bipolar affective disorder, currently depressed, NOS          | incident                     |
| E116.00          | Mixed bipolar affective disorder                              | incident                     |
| E116000          | Mixed bipolar affective disorder, unspecified                 | incident                     |
| E116100          | Mixed bipolar affective disorder, mild                        | incident                     |
| E116200          | Mixed bipolar affective disorder, moderate                    | incident                     |
| E116300          | Mixed bipolar affective disorder, severe, without psychosis   | incident                     |
| E116400          | Mixed bipolar affective disorder, severe, with psychosis      | incident                     |
| E116z00          | Mixed bipolar affective disorder, NOS                         | incident                     |
| E117.00          | Unspecified bipolar affective disorder                        | incident                     |
| E117000          | Unspecified bipolar affective disorder, unspecified           | incident                     |
| E117100          | Unspecified bipolar affective disorder, mild                  | incident                     |
| E117200          | Unspecified bipolar affective disorder, moderate              | incident                     |
| E117300          | Unspecified bipolar affective disorder, severe, no psychosis  | incident                     |
| E117400          | Unspecified bipolar affective disorder, severe with psychosis | incident                     |
| E117z00          | Unspecified bipolar affective disorder, NOS                   | incident                     |
| E11y.00          | Other and unspecified manic-depressive psychoses              | incident                     |
| E11y000          | Unspecified manic-depressive psychoses                        | incident                     |
| E11y100          | Atypical manic disorder                                       | incident                     |
| E11y300          | Other mixed manic-depressive psychoses                        | incident                     |
| E11yz00          | Other and unspecified manic-depressive psychoses NOS          | incident                     |
| E11z.00          | Other and unspecified affective psychoses                     | incident                     |
| E11z000          | Unspecified affective psychoses NOS                           | incident                     |
| E11zz00          | Other affective psychosis NOS                                 | incident                     |
| Eu30.00          | [X]Manic episode                                              | incident                     |
| Eu30.11          | [X]Bipolar disorder, single manic episode                     | incident                     |
| Eu30000          | [X]Hypomania                                                  | incident                     |
| Eu30100          | [X]Mania without psychotic symptoms                           | incident                     |

| Read code | Description                                                  | Incident or prevalent |
|-----------|--------------------------------------------------------------|-----------------------|
| Eu30200   | [X]Mania with psychotic symptoms                             | incident              |
| Eu30211   | [X]Mania with mood-congruent psychotic symptoms              | incident              |
| Eu30212   | [X]Mania with mood-incongruent psychotic symptoms            | incident              |
| Eu30213   | [X]Manic stupor                                              | incident              |
| Eu30y00   | [X]Other manic episodes                                      | incident              |
| Eu30z00   | [X]Manic episode, unspecified                                | incident              |
| Eu30z11   | [X]Mania NOS                                                 | incident              |
| Eu31.00   | [X]Bipolar affective disorder                                | incident              |
| Eu31.11   | [X]Manic-depressive illness                                  | incident              |
| Eu31.12   | [X]Manic-depressive psychosis                                | incident              |
| Eu31000   | [X]Bipolar affective disorder, current episode hypomanic     | incident              |
| Eu31100   | [X]Bipolar affect disorder cur epi manic wout psychotic symp | incident              |
| Eu31200   | [X]Bipolar affect disorder cur epi manic with psychotic symp | incident              |
| Eu31300   | [X]Bipolar affect disorder cur epi mild or moderate depressn | incident              |
| Eu31400   | [X]Bipol aff disord, curr epis sev depress, no psychot symp  | incident              |
| Eu31500   | [X]Bipolar affect dis cur epi severe depres with psyc symp   | incident              |
| Eu31600   | [X]Bipolar affective disorder, current episode mixed         | incident              |
| Eu31800   | [X]Bipolar affective disorder type I                         | incident              |
| Eu31900   | [X]Bipolar affective disorder type II                        | incident              |
| Eu31911   | [X]Bipolar II disorder                                       | incident              |
| Eu31y00   | [X]Other bipolar affective disorders                         | incident              |
| Eu31y11   | [X]Bipolar II disorder                                       | incident              |
| Eu31z00   | [X]Bipolar affective disorder, unspecified                   | incident              |
| Eu33213   | [X]Manic-depress psychosis,depressd,no psychotic symptoms    | incident              |
| Eu33312   | [X]Manic-depress psychosis,depressed type+psychotic symptoms | incident              |
| Eu3z.11   | [X]Affective psychosis NOS                                   | incident              |
| 146D.00   | H/O: manic depressive disorder                               | prevalent             |
| 212V.00   | Bipolar affective disorder resolved                          | prevalent             |
| E110500   | Single manic episode in partial or unspecified remission     | prevalent             |
| E110600   | Single manic episode in full remission                       | prevalent             |
| E111.00   | Recurrent manic episodes                                     | prevalent             |
| E111000   | Recurrent manic episodes, unspecified                        | prevalent             |
| E111100   | Recurrent manic episodes, mild                               | prevalent             |
| E111200   | Recurrent manic episodes, moderate                           | prevalent             |
| E111300   | Recurrent manic episodes, severe without mention psychosis   | prevalent             |
| E111400   | Recurrent manic episodes, severe, with psychosis             | prevalent             |
| E111500   | Recurrent manic episodes, partial or unspecified remission   | prevalent             |
| E111600   | Recurrent manic episodes, in full remission                  | prevalent             |
| E111z00   | Recurrent manic episode NOS                                  | prevalent             |
| E113400   | Recurrent major depressive episodes, severe, with psychosis  | prevalent             |
| E114500   | Bipolar affect disord,currently manic, part/unspec remission | prevalent             |
| E114600   | Bipolar affective disorder, currently manic, full remission  | prevalent             |
| E115500   | Bipolar affect disord, now depressed, part/unspec remission  | prevalent             |
| E115600   | Bipolar affective disorder, now depressed, in full remission | prevalent             |
| E116500   | Mixed bipolar affective disorder, partial/unspec remission   | prevalent             |
| E116600   | Mixed bipolar affective disorder, in full remission          | prevalent             |
| E117500   | Unspecified bipolar affect disord, partial/unspec remission  | prevalent             |
| E117600   | Unspecified bipolar affective disorder, in full remission    | prevalent             |
| Eu31700   | [X]Bipolar affective disorder, currently in remission        | prevalent             |
| Eu31y12   | [X]Recurrent manic episodes                                  | prevalent             |
| ZV11111   | [V]Personal history of manic-depressive psychosis            | prevalent             |
| ZV11112   | [V]Personal history of manic-depressive psychosis            | prevalent             |

**Appendix table XXI.2: Read codes for schizophrenia**

| <b>Read code</b> | <b>Description</b>                                      | <b>Incident or prevalent</b> |
|------------------|---------------------------------------------------------|------------------------------|
| 285..11          | Psychotic condition, insight present                    | incident                     |
| 286..11          | Poor insight into psychotic condition                   | incident                     |
| 8G13100          | CBTp - cognitive behavioural therapy for psychosis      | incident                     |
| 8HHs.00          | Referral to psychosis early intervention service        | incident                     |
| E1...00          | Non-organic psychoses                                   | incident                     |
| E10..00          | Schizophrenic disorders                                 | incident                     |
| E100.00          | Simple schizophrenia                                    | incident                     |
| E100.11          | Schizophrenia simplex                                   | incident                     |
| E100000          | Unspecified schizophrenia                               | incident                     |
| E100z00          | Simple schizophrenia NOS                                | incident                     |
| E101.00          | Hebephrenic schizophrenia                               | incident                     |
| E101000          | Unspecified hebephrenic schizophrenia                   | incident                     |
| E101z00          | Hebephrenic schizophrenia NOS                           | incident                     |
| E102.00          | Catatonic schizophrenia                                 | incident                     |
| E102000          | Unspecified catatonic schizophrenia                     | incident                     |
| E102z00          | Catatonic schizophrenia NOS                             | incident                     |
| E103.00          | Paranoid schizophrenia                                  | incident                     |
| E103000          | Unspecified paranoid schizophrenia                      | incident                     |
| E103z00          | Paranoid schizophrenia NOS                              | incident                     |
| E104.00          | Acute schizophrenic episode                             | incident                     |
| E105.00          | Latent schizophrenia                                    | incident                     |
| E105000          | Unspecified latent schizophrenia                        | incident                     |
| E105z00          | Latent schizophrenia NOS                                | incident                     |
| E107.00          | Schizo-affective schizophrenia                          | incident                     |
| E107.11          | Cyclic schizophrenia                                    | incident                     |
| E107000          | Unspecified schizo-affective schizophrenia              | incident                     |
| E107z00          | Schizo-affective schizophrenia NOS                      | incident                     |
| E10y.00          | Other schizophrenia                                     | incident                     |
| E10y.11          | Cenesthopathic schizophrenia                            | incident                     |
| E10y000          | Atypical schizophrenia                                  | incident                     |
| E10y100          | Coenesthopathic schizophrenia                           | incident                     |
| E10yz00          | Other schizophrenia NOS                                 | incident                     |
| E10z.00          | Schizophrenia NOS                                       | incident                     |
| E112400          | Single major depressive episode, severe, with psychosis | incident                     |
| E12..00          | Paranoid states                                         | incident                     |
| E120.00          | Simple paranoid state                                   | incident                     |
| E121.00          | Chronic paranoid psychosis                              | incident                     |
| E121.11          | Sander's disease                                        | incident                     |
| E122.00          | Paraphrenia                                             | incident                     |
| E123.00          | Shared paranoid disorder                                | incident                     |
| E123.11          | Folie a deux                                            | incident                     |
| E12y.00          | Other paranoid states                                   | incident                     |
| E12y000          | Paranoia querulans                                      | incident                     |
| E12yz00          | Other paranoid states NOS                               | incident                     |
| E12z.00          | Paranoid psychosis NOS                                  | incident                     |
| E13..00          | Other nonorganic psychoses                              | incident                     |
| E133.00          | Acute paranoid reaction                                 | incident                     |
| E133.11          | Bouffee delirante                                       | incident                     |
| E134.00          | Psychogenic paranoid psychosis                          | incident                     |
| E13z.00          | Nonorganic psychosis NOS                                | incident                     |
| E13z.11          | Psychotic episode NOS                                   | incident                     |
| E1y..00          | Other specified non-organic psychoses                   | incident                     |
| E1z..00          | Non-organic psychosis NOS                               | incident                     |
| Eu2..00          | [X]Schizophrenia, schizotypal and delusional disorders  | incident                     |
| Eu20.00          | [X]Schizophrenia                                        | incident                     |
| Eu20000          | [X]Paranoid schizophrenia                               | incident                     |
| Eu20011          | [X]Paraphrenic schizophrenia                            | incident                     |

| <b>Read code</b> | <b>Description</b>                                           | <b>Incident or prevalent</b> |
|------------------|--------------------------------------------------------------|------------------------------|
| Eu20100          | [X]Hebephrenic schizophrenia                                 | incident                     |
| Eu20111          | [X]Disorganised schizophrenia                                | incident                     |
| Eu20200          | [X]Catatonic schizophrenia                                   | incident                     |
| Eu20211          | [X]Catatonic stupor                                          | incident                     |
| Eu20212          | [X]Schizophrenic catalepsy                                   | incident                     |
| Eu20213          | [X]Schizophrenic catatonia                                   | incident                     |
| Eu20214          | [X]Schizophrenic flexibilatis cerea                          | incident                     |
| Eu20300          | [X]Undifferentiated schizophrenia                            | incident                     |
| Eu20311          | [X]Atypical schizophrenia                                    | incident                     |
| Eu20600          | [X]Simple schizophrenia                                      | incident                     |
| Eu20y00          | [X]Other schizophrenia                                       | incident                     |
| Eu20y11          | [X]Cenesthopathic schizophrenia                              | incident                     |
| Eu20y12          | [X]Schizophreniform disord NOS                               | incident                     |
| Eu20y13          | [X]Schizophrenifrm psychos NOS                               | incident                     |
| Eu20z00          | [X]Schizophrenia, unspecified                                | incident                     |
| Eu21.11          | [X]Latent schizophrenic reaction                             | incident                     |
| Eu21.12          | [X]Borderline schizophrenia                                  | incident                     |
| Eu21.13          | [X]Latent schizophrenia                                      | incident                     |
| Eu21.14          | [X]Prepsychotic schizophrenia                                | incident                     |
| Eu21.16          | [X]Pseudoneurotic schizophrenia                              | incident                     |
| Eu21.17          | [X]Pseudopsychopathic schizophrenia                          | incident                     |
| Eu22.00          | [X]Persistent delusional disorders                           | incident                     |
| Eu22000          | [X]Delusional disorder                                       | incident                     |
| Eu22011          | [X]Paranoid psychosis                                        | incident                     |
| Eu22012          | [X]Paranoid state                                            | incident                     |
| Eu22013          | [X]Paraphrenia - late                                        | incident                     |
| Eu22014          | [X]Sensitiver Beziehungswahn                                 | incident                     |
| Eu22015          | [X]Paranoia                                                  | incident                     |
| Eu22100          | [X]Delusional misidentification syndrome                     | incident                     |
| Eu22111          | [X]Capgras syndrome                                          | incident                     |
| Eu22200          | [X]Cotard syndrome                                           | incident                     |
| Eu22y11          | [X]Delusional dysmorphophobia                                | incident                     |
| Eu22y12          | [X]Involutional paranoid state                               | incident                     |
| Eu22y13          | [X]Paranoia querulans                                        | incident                     |
| Eu22z00          | [X]Persistent delusional disorder, unspecified               | incident                     |
| Eu23.00          | [X]Acute and transient psychotic disorders                   | incident                     |
| Eu23000          | [X]Acute polymorphic psychot disord without symp of schizoph | incident                     |
| Eu23011          | [X]Bouffee delirante                                         | incident                     |
| Eu23012          | [X]Cycloid psychosis                                         | incident                     |
| Eu23100          | [X]Acute polymorphic psychot disord with symp of schizophren | incident                     |
| Eu23111          | [X]Bouffee delirante with symptoms of schizophrenia          | incident                     |
| Eu23112          | [X]Cycloid psychosis with symptoms of schizophrenia          | incident                     |
| Eu23200          | [X]Acute schizophrenia-like psychotic disorder               | incident                     |
| Eu23211          | [X]Brief schizophreniform disorder                           | incident                     |
| Eu23212          | [X]Brief schizophrenifrm psych                               | incident                     |
| Eu23300          | [X]Other acute predominantly delusional psychotic disorders  | incident                     |
| Eu23312          | [X]Psychogenic paranoid psychosis                            | incident                     |
| Eu23y00          | [X]Other acute and transient psychotic disorders             | incident                     |
| Eu23z00          | [X]Acute and transient psychotic disorder, unspecified       | incident                     |
| Eu24.00          | [X]Induced delusional disorder                               | incident                     |
| Eu24.11          | [X]Folie a deux                                              | incident                     |
| Eu24.12          | [X]Induced paranoid disorder                                 | incident                     |
| Eu24.13          | [X]Induced psychotic disorder                                | incident                     |
| Eu25.00          | [X]Schizoaffective disorders                                 | incident                     |
| Eu25000          | [X]Schizoaffective disorder, manic type                      | incident                     |
| Eu25011          | [X]Schizoaffective psychosis, manic type                     | incident                     |
| Eu25012          | [X]Schizophreniform psychosis, manic type                    | incident                     |
| Eu25100          | [X]Schizoaffective disorder, depressive type                 | incident                     |

| <b>Read code</b> | <b>Description</b>                                           | <b>Incident or prevalent</b> |
|------------------|--------------------------------------------------------------|------------------------------|
| Eu25111          | [X]Schizoaffective psychosis, depressive type                | incident                     |
| Eu25112          | [X]Schizophreniform psychosis, depressive type               | incident                     |
| Eu25200          | [X]Schizoaffective disorder, mixed type                      | incident                     |
| Eu25211          | [X]Cyclic schizophrenia                                      | incident                     |
| Eu25212          | [X]Mixed schizophrenic and affective psychosis               | incident                     |
| Eu25y00          | [X]Other schizoaffective disorders                           | incident                     |
| Eu25z00          | [X]Schizoaffective disorder, unspecified                     | incident                     |
| Eu25z11          | [X]Schizoaffective psychosis NOS                             | incident                     |
| Eu2y.00          | [X]Other nonorganic psychotic disorders                      | incident                     |
| Eu2y.11          | [X]Chronic hallucinatory psychosis                           | incident                     |
| Eu2z.00          | [X]Unspecified nonorganic psychosis                          | incident                     |
| Eu2z.11          | [X]Psychosis NOS                                             | incident                     |
| Eu32300          | [X]Severe depressive episode with psychotic symptoms         | incident                     |
| Eu32311          | [X]Single episode of major depression and psychotic symptoms | incident                     |
| Eu32312          | [X]Single episode of psychogenic depressive psychosis        | incident                     |
| Eu32313          | [X]Single episode of psychotic depression                    | incident                     |
| Eu32800          | [X]Major depression, severe with psychotic symptoms          | incident                     |
| Eu32900          | [X]Single major depr ep, severe with psych, psych in remiss  | incident                     |
| Eu33311          | [X]Endogenous depression with psychotic symptoms             | incident                     |
| 1464.00          | H/O: schizophrenia                                           | prevalent                    |
| 146H.00          | H/O: psychosis                                               | prevalent                    |
| 212W.00          | Schizophrenia resolved                                       | prevalent                    |
| 212X.00          | Psychosis resolved                                           | prevalent                    |
| E100100          | Subchronic schizophrenia                                     | prevalent                    |
| E100200          | Chronic schizophrenic                                        | prevalent                    |
| E100300          | Acute exacerbation of subchronic schizophrenia               | prevalent                    |
| E100400          | Acute exacerbation of chronic schizophrenia                  | prevalent                    |
| E100500          | Schizophrenia in remission                                   | prevalent                    |
| E101100          | Subchronic hebephrenic schizophrenia                         | prevalent                    |
| E101200          | Chronic hebephrenic schizophrenia                            | prevalent                    |
| E101300          | Acute exacerbation of subchronic hebephrenic schizophrenia   | prevalent                    |
| E101400          | Acute exacerbation of chronic hebephrenic schizophrenia      | prevalent                    |
| E101500          | Hebephrenic schizophrenia in remission                       | prevalent                    |
| E102100          | Subchronic catatonic schizophrenia                           | prevalent                    |
| E102200          | Chronic catatonic schizophrenia                              | prevalent                    |
| E102300          | Acute exacerbation of subchronic catatonic schizophrenia     | prevalent                    |
| E102400          | Acute exacerbation of chronic catatonic schizophrenia        | prevalent                    |
| E102500          | Catatonic schizophrenia in remission                         | prevalent                    |
| E103100          | Subchronic paranoid schizophrenia                            | prevalent                    |
| E103200          | Chronic paranoid schizophrenia                               | prevalent                    |
| E103300          | Acute exacerbation of subchronic paranoid schizophrenia      | prevalent                    |
| E103400          | Acute exacerbation of chronic paranoid schizophrenia         | prevalent                    |
| E103500          | Paranoid schizophrenia in remission                          | prevalent                    |
| E105100          | Subchronic latent schizophrenia                              | prevalent                    |
| E105200          | Chronic latent schizophrenia                                 | prevalent                    |
| E105300          | Acute exacerbation of subchronic latent schizophrenia        | prevalent                    |
| E105400          | Acute exacerbation of chronic latent schizophrenia           | prevalent                    |
| E105500          | Latent schizophrenia in remission                            | prevalent                    |
| E106.00          | Residual schizophrenia                                       | prevalent                    |
| E106.11          | Restzustand - schizophrenia                                  | prevalent                    |
| E107100          | Subchronic schizo-affective schizophrenia                    | prevalent                    |
| E107200          | Chronic schizo-affective schizophrenia                       | prevalent                    |
| E107300          | Acute exacerbation subchronic schizo-affective schizophrenia | prevalent                    |
| E107400          | Acute exacerbation of chronic schizo-affective schizophrenia | prevalent                    |
| E107500          | Schizo-affective schizophrenia in remission                  | prevalent                    |
| Eu20400          | [X]Post-schizophrenic depression                             | prevalent                    |
| Eu20500          | [X]Residual schizophrenia                                    | prevalent                    |
| Eu20511          | [X]Chronic undifferentiated schizophrenia                    | prevalent                    |



| <b>Read code</b> | <b>Description</b>                                           | <b>Incident or prevalent</b> |
|------------------|--------------------------------------------------------------|------------------------------|
| Eu20512          | [X]Restzustand schizophrenic                                 | prevalent                    |
| Eu22300          | [X]Paranoid state in remission                               | prevalent                    |
| Eu22y00          | [X]Other persistent delusional disorders                     | prevalent                    |
| Eu26.00          | [X]Nonorganic psychosis in remission                         | prevalent                    |
| Eu32A00          | [X]Recurr major depr ep, severe with psych, psych in remiss  | prevalent                    |
| Eu33300          | [X]Recurrent depress disorder cur epi severe with psyc symp  | prevalent                    |
| Eu33313          | [X]Recurr severe episodes/major depression+psychotic symptom | prevalent                    |
| Eu33314          | [X]Recurr severe episodes/psychogenic depressive psychosis   | prevalent                    |
| Eu33315          | [X]Recurrent severe episodes of psychotic depression         | prevalent                    |
| ZV11000          | [V]Personal history of schizophrenia                         | prevalent                    |

## APPENDIX XXII INCLUDED READ CODES FOR CARDIOVASCULAR DISEASE

**Appendix table XXII.1: Read codes for myocardial infarction**

| Read code | Description                                                | Incident or prevalent |
|-----------|------------------------------------------------------------|-----------------------|
| 14A3.00   | H/O: myocardial infarct <60                                | prevalent             |
| 14A4.00   | H/O: myocardial infarct >60                                | prevalent             |
| 14AH.00   | H/O: Myocardial infarction in last year                    | prevalent             |
| 14AT.00   | History of myocardial infarction                           | prevalent             |
| 323..00   | ECG: myocardial infarction                                 | incident              |
| 3232.00   | ECG: old myocardial infarction                             | prevalent             |
| 3233.00   | ECG: antero-septal infarct.                                | incident              |
| 3234.00   | ECG:posterior/inferior infarct                             | incident              |
| 3235.00   | ECG: subendocardial infarct                                | incident              |
| 3236.00   | ECG: lateral infarction                                    | incident              |
| 323Z.00   | ECG: myocardial infarct NOS                                | prevalent             |
| 889A.00   | Diab mellit insulin-glucose infus acute myocardial infarct | incident              |
| 8B3a.00   | Door to needle time                                        | incident              |
| 8B3g.00   | Pain to thrombolysis time                                  | incident              |
| G30..00   | Acute myocardial infarction                                | incident              |
| G30..11   | Attack - heart                                             | incident              |
| G30..12   | Coronary thrombosis                                        | incident              |
| G30..13   | Cardiac rupture following myocardial infarction (MI)       | incident              |
| G30..14   | Heart attack                                               | incident              |
| G30..15   | MI - acute myocardial infarction                           | incident              |
| G30..16   | Thrombosis - coronary                                      | incident              |
| G30..17   | Silent myocardial infarction                               | incident              |
| G300.00   | Acute anterolateral infarction                             | incident              |
| G301.00   | Other specified anterior myocardial infarction             | incident              |
| G301000   | Acute anteroapical infarction                              | incident              |
| G301100   | Acute anteroapical infarction                              | incident              |
| G301200   | Anterior myocardial infarction NOS                         | incident              |
| G302.00   | Acute inferolateral infarction                             | incident              |
| G303.00   | Acute inferoposterior infarction                           | incident              |
| G304.00   | Posterior myocardial infarction NOS                        | incident              |
| G305.00   | Lateral myocardial infarction NOS                          | incident              |
| G306.00   | True posterior myocardial infarction                       | incident              |
| G307.00   | Acute subendocardial infarction                            | incident              |
| G307000   | Acute non-Q wave infarction                                | incident              |
| G307100   | Acute non-ST segment elevation myocardial infarction       | incident              |
| G308.00   | Inferior myocardial infarction NOS                         | incident              |
| G309.00   | Acute Q-wave infarct                                       | incident              |
| G30B.00   | Acute posterolateral myocardial infarction                 | incident              |
| G30X.00   | Acute transmural myocardial infarction of unspecif site    | incident              |
| G30X000   | Acute ST segment elevation myocardial infarction           | incident              |
| G30y.00   | Other acute myocardial infarction                          | incident              |
| G30y000   | Acute atrial infarction                                    | incident              |
| G30y100   | Acute papillary muscle infarction                          | incident              |
| G30y200   | Acute septal infarction                                    | incident              |
| G30yz00   | Other acute myocardial infarction NOS                      | incident              |
| G30z.00   | Acute myocardial infarction NOS                            | incident              |
| G310.00   | Postmyocardial infarction syndrome                         | prevalent             |
| G310.11   | Dressler's syndrome                                        | prevalent             |
| G32..00   | Old myocardial infarction                                  | prevalent             |
| G32..11   | Healed myocardial infarction                               | prevalent             |
| G32..12   | Personal history of myocardial infarction                  | prevalent             |
| G33z500   | Post infarct angina                                        | prevalent             |

| Read code | Description                                                  | Incident or prevalent |
|-----------|--------------------------------------------------------------|-----------------------|
| G35..00   | Subsequent myocardial infarction                             | prevalent             |
| G350.00   | Subsequent myocardial infarction of anterior wall            | prevalent             |
| G351.00   | Subsequent myocardial infarction of inferior wall            | prevalent             |
| G353.00   | Subsequent myocardial infarction of other sites              | prevalent             |
| G35X.00   | Subsequent myocardial infarction of unspecified site         | prevalent             |
| G36..00   | Certain current complication follow acute myocardial infarct | prevalent             |
| G360.00   | Haemopericardium/current comp folow acut myocard infarct     | prevalent             |
| G361.00   | Atrial septal defect/curr comp folow acut myocardal infarct  | prevalent             |
| G362.00   | Ventric septal defect/curr comp fol acut myocardal infarctn  | prevalent             |
| G363.00   | Ruptur cardiac wall w'out haemopericard/cur comp fol ac MI   | prevalent             |
| G364.00   | Ruptur chordae tendinae/curr comp fol acute myocard infarct  | prevalent             |
| G365.00   | Rupture papillary muscle/curr comp fol acute myocard infarct | prevalent             |
| G366.00   | Thrombosis atrium,auric append&vent/curr comp foll acute MI  | prevalent             |
| G38..00   | Postoperative myocardial infarction                          | incident              |
| G380.00   | Postoperative transmural myocardial infarction anterior wall | incident              |
| G381.00   | Postoperative transmural myocardial infarction inferior wall | incident              |
| G382.00   | Postoperative transmural myocardial infarction other sites   | incident              |
| G383.00   | Postoperative transmural myocardial infarction unspec site   | incident              |
| G384.00   | Postoperative subendocardial myocardial infarction           | incident              |
| G38z.00   | Postoperative myocardial infarction, unspecified             | incident              |
| G501.00   | Post infarction pericarditis                                 | prevalent             |
| Gyu3100   | [X]Other current complicatns following acute myocard infarct | prevalent             |
| Gyu3400   | [X]Acute transmural myocardial infarction of unspecif site   | incident              |
| Gyu3500   | [X]Subsequent myocardial infarction of other sites           | prevalent             |
| Gyu3600   | [X]Subsequent myocardial infarction of unspecified site      | prevalent             |

**Appendix table XXII.2: Read codes for revascularisation**

| Read code | Description                                                 | Incident or prevalent |
|-----------|-------------------------------------------------------------|-----------------------|
| 792..00   | Coronary artery operations                                  | incident              |
| 792..11   | Coronary artery bypass graft operations                     | incident              |
| 7920.00   | Saphenous vein graft replacement of coronary artery         | incident              |
| 7920.11   | Saphenous vein graft bypass of coronary artery              | incident              |
| 7920000   | Saphenous vein graft replacement of one coronary artery     | incident              |
| 7920100   | Saphenous vein graft replacement of two coronary arteries   | incident              |
| 7920200   | Saphenous vein graft replacement of three coronary arteries | incident              |
| 7920300   | Saphenous vein graft replacement of four+ coronary arteries | incident              |
| 7920y00   | Saphenous vein graft replacement of coronary artery OS      | incident              |
| 7920z00   | Saphenous vein graft replacement coronary artery NOS        | incident              |
| 7921.00   | Other autograft replacement of coronary artery              | incident              |
| 7921.11   | Other autograft bypass of coronary artery                   | incident              |
| 7921000   | Autograft replacement of one coronary artery NEC            | incident              |
| 7921100   | Autograft replacement of two coronary arteries NEC          | incident              |
| 7921200   | Autograft replacement of three coronary arteries NEC        | incident              |
| 7921300   | Autograft replacement of four or more coronary arteries NEC | incident              |
| 7921y00   | Other autograft replacement of coronary artery OS           | incident              |
| 7921z00   | Other autograft replacement of coronary artery NOS          | incident              |
| 7922.00   | Allograft replacement of coronary artery                    | incident              |
| 7922.11   | Allograft bypass of coronary artery                         | incident              |
| 7922000   | Allograft replacement of one coronary artery                | incident              |
| 7922100   | Allograft replacement of two coronary arteries              | incident              |
| 7922200   | Allograft replacement of three coronary arteries            | incident              |
| 7922300   | Allograft replacement of four or more coronary arteries     | incident              |
| 7922y00   | Other specified allograft replacement of coronary artery    | incident              |
| 7922z00   | Allograft replacement of coronary artery NOS                | incident              |
| 7923.00   | Prosthetic replacement of coronary artery                   | incident              |
| 7923.11   | Prosthetic bypass of coronary artery                        | incident              |

| Read code | Description                                                  | Incident or prevalent |
|-----------|--------------------------------------------------------------|-----------------------|
| 7923000   | Prosthetic replacement of one coronary artery                | incident              |
| 7923100   | Prosthetic replacement of two coronary arteries              | incident              |
| 7923200   | Prosthetic replacement of three coronary arteries            | incident              |
| 7923300   | Prosthetic replacement of four or more coronary arteries     | incident              |
| 7923y00   | Other specified prosthetic replacement of coronary artery    | incident              |
| 7923z00   | Prosthetic replacement of coronary artery NOS                | incident              |
| 7924.00   | Revision of bypass for coronary artery                       | prevalent             |
| 7924000   | Revision of bypass for one coronary artery                   | prevalent             |
| 7924100   | Revision of bypass for two coronary arteries                 | prevalent             |
| 7924200   | Revision of bypass for three coronary arteries               | prevalent             |
| 7924300   | Revision of bypass for four or more coronary arteries        | prevalent             |
| 7924400   | Revision of connection of thoracic artery to coronary artery | prevalent             |
| 7924500   | Revision of implantation of thoracic artery into heart       | prevalent             |
| 7924y00   | Other specified revision of bypass for coronary artery       | prevalent             |
| 7924z00   | Revision of bypass for coronary artery NOS                   | prevalent             |
| 7925.00   | Connection of mammary artery to coronary artery              | incident              |
| 7925.11   | Creation of bypass from mammary artery to coronary artery    | incident              |
| 7925000   | Double anastomosis of mammary arteries to coronary arteries  | incident              |
| 7925011   | LIMA sequential anastomosis                                  | incident              |
| 7925012   | RIMA sequential anastomosis                                  | incident              |
| 7925100   | Double implant of mammary arteries into coronary arteries    | incident              |
| 7925200   | Single anast mammary art to left ant descend coronary art    | incident              |
| 7925300   | Single anastomosis of mammary artery to coronary artery NEC  | incident              |
| 7925311   | LIMA single anastomosis                                      | incident              |
| 7925312   | RIMA single anastomosis                                      | incident              |
| 7925400   | Single implantation of mammary artery into coronary artery   | incident              |
| 7925y00   | Connection of mammary artery to coronary artery OS           | incident              |
| 7925z00   | Connection of mammary artery to coronary artery NOS          | incident              |
| 7926.00   | Connection of other thoracic artery to coronary artery       | incident              |
| 7926000   | Double anastom thoracic arteries to coronary arteries NEC    | incident              |
| 7926100   | Double implant thoracic arteries into coronary arteries NEC  | incident              |
| 7926200   | Single anastomosis of thoracic artery to coronary artery NEC | incident              |
| 7926300   | Single implantation thoracic artery into coronary artery NEC | incident              |
| 7926y00   | Connection of other thoracic artery to coronary artery OS    | incident              |
| 7926z00   | Connection of other thoracic artery to coronary artery NOS   | incident              |
| 7927.00   | Other open operations on coronary artery                     | incident              |
| 7927000   | Repair of arteriovenous fistula of coronary artery           | incident              |
| 7927100   | Repair of aneurysm of coronary artery                        | incident              |
| 7927200   | Transection of muscle bridge of coronary artery              | incident              |
| 7927300   | Transposition of coronary artery NEC                         | incident              |
| 7927400   | Exploration of coronary artery                               | incident              |
| 7927500   | Open angioplasty of coronary artery                          | incident              |
| 7927y00   | Other specified other open operation on coronary artery      | incident              |
| 7927z00   | Other open operation on coronary artery NOS                  | incident              |
| 7928.00   | Transluminal balloon angioplasty of coronary artery          | incident              |
| 7928.11   | Percutaneous balloon coronary angioplasty                    | incident              |
| 7928000   | Percut transluminal balloon angioplasty one coronary artery  | incident              |
| 7928100   | Percut translum balloon angioplasty mult coronary arteries   | incident              |
| 7928200   | Percut translum balloon angioplasty bypass graft coronary a  | incident              |
| 7928300   | Percut translum cutting balloon angioplasty coronary artery  | incident              |
| 7928y00   | Transluminal balloon angioplasty of coronary artery OS       | incident              |
| 7928z00   | Transluminal balloon angioplasty of coronary artery NOS      | incident              |
| 7929.00   | Other therapeutic transluminal operations on coronary artery | incident              |
| 7929000   | Percutaneous transluminal laser coronary angioplasty         | incident              |
| 7929100   | Percut transluminal coronary thrombolysis with streptokinase | incident              |
| 7929111   | Percut translum coronary thrombolytic therapy- streptokinase | incident              |
| 7929200   | Percut translum inject therap subst to coronary artery NEC   | incident              |
| 7929300   | Rotary blade coronary angioplasty                            | incident              |

| Read code | Description                                                  | Incident or prevalent |
|-----------|--------------------------------------------------------------|-----------------------|
| 7929400   | Insertion of coronary artery stent                           | incident              |
| 7929500   | Insertion of drug-eluting coronary artery stent              | incident              |
| 7929600   | Percutaneous transluminal atherectomy of coronary artery     | incident              |
| 7929y00   | Other therapeutic transluminal op on coronary artery OS      | incident              |
| 7929z00   | Other therapeutic transluminal op on coronary artery NOS     | incident              |
| 792A.00   | Diagnostic transluminal operations on coronary artery        | incident              |
| 792A000   | Percutaneous transluminal angioscopy                         | incident              |
| 792A100   | Intravascular ultrasound of coronary artery                  | incident              |
| 792Ay00   | Diagnostic transluminal operation on coronary artery OS      | incident              |
| 792Az00   | Diagnostic transluminal operation on coronary artery NOS     | incident              |
| 792B.00   | Repair of coronary artery NEC                                | incident              |
| 792B000   | Endarterectomy of coronary artery NEC                        | incident              |
| 792By00   | Other specified repair of coronary artery                    | incident              |
| 792Bz00   | Repair of coronary artery NOS                                | incident              |
| 792C.00   | Other replacement of coronary artery                         | incident              |
| 792C000   | Replacement of coronary arteries using multiple methods      | incident              |
| 792Cy00   | Other specified replacement of coronary artery               | incident              |
| 792Cz00   | Replacement of coronary artery NOS                           | incident              |
| 792D.00   | Other bypass of coronary artery                              | incident              |
| 792Dy00   | Other specified other bypass of coronary artery              | incident              |
| 792Dz00   | Other bypass of coronary artery NOS                          | incident              |
| 792E.00   | Percutaneous coronary intervention                           | incident              |
| 792E000   | Emergency percutaneous coronary intervention                 | incident              |
| 792y.00   | Other specified operations on coronary artery                | incident              |
| 792z.00   | Coronary artery operations NOS                               | incident              |
| 793G.00   | Perc translumin balloon angioplasty stenting coronary artery | incident              |
| 793G000   | Perc translum ball angio insert 1-2 drug elut stents cor art | incident              |
| 793G100   | Perc tran ball angio ins 3 or more drug elut stents cor art  | incident              |
| 793G200   | Perc translum balloon angioplasty insert 1-2 stents cor art  | incident              |
| 793G300   | Percutaneous cor balloon angiop 3 more stents cor art NEC    | incident              |
| 793Gy00   | OS perc translumina balloon angioplast stenting coronary art | incident              |
| 793Gz00   | Perc translum balloon angioplasty stenting coronary art NOS  | incident              |
| SP00300   | Mechanical complication of coronary bypass                   | prevalent             |
| SP07600   | Coronary artery bypass graft occlusion                       | prevalent             |
| ZV45800   | [V]Presence of coronary angioplasty implant and graft        | prevalent             |
| ZV45K00   | [V]Presence of coronary artery bypass graft                  | prevalent             |
| ZV45K11   | [V]Presence of coronary artery bypass graft - CABG           | prevalent             |
| ZV45L00   | [V]Status following coronary angioplasty NOS                 | prevalent             |

**Appendix table XXII.3: Read codes for other CHD**

| Read code | Description                                    | Incident or prevalent |
|-----------|------------------------------------------------|-----------------------|
| 14A5.00   | H/O: angina pectoris                           | prevalent             |
| 14AJ.00   | H/O: Angina in last year                       | prevalent             |
| 14AL.00   | H/O: Treatment for ischaemic heart disease     | prevalent             |
| 14AW.00   | H/O acute coronary syndrome                    | prevalent             |
| 187..00   | Frequency of angina                            | prevalent             |
| 322..00   | ECG: myocardial ischaemia                      | incident              |
| 3222.00   | ECG:shows myocardial ischaemia                 | incident              |
| 322Z.00   | ECG: myocardial ischaemia NOS                  | incident              |
| 8B27.00   | Antianginal therapy                            | incident              |
| 8H2V.00   | Admit ischaemic heart disease emergency        | incident              |
| 8L40.00   | Coronary artery bypass graft operation planned | prevalent             |
| 8L41.00   | Coronary angioplasty planned                   | prevalent             |
| G3...00   | Ischaemic heart disease                        | incident              |
| G3...11   | Arteriosclerotic heart disease                 | incident              |

| Read code | Description                                                | Incident or prevalent |
|-----------|------------------------------------------------------------|-----------------------|
| G3...12   | Atherosclerotic heart disease                              | incident              |
| G3...13   | IHD - Ischaemic heart disease                              | incident              |
| G31..00   | Other acute and subacute ischaemic heart disease           | incident              |
| G311.00   | Preinfarction syndrome                                     | incident              |
| G311.11   | Crescendo angina                                           | incident              |
| G311.12   | Impending infarction                                       | incident              |
| G311.13   | Unstable angina                                            | incident              |
| G311.14   | Angina at rest                                             | incident              |
| G311000   | Myocardial infarction aborted                              | prevalent             |
| G311011   | MI - myocardial infarction aborted                         | prevalent             |
| G311100   | Unstable angina                                            | incident              |
| G311200   | Angina at rest                                             | incident              |
| G311300   | Refractory angina                                          | incident              |
| G311400   | Worsening angina                                           | prevalent             |
| G311500   | Acute coronary syndrome                                    | incident              |
| G311z00   | Preinfarction syndrome NOS                                 | incident              |
| G312.00   | Coronary thrombosis not resulting in myocardial infarction | incident              |
| G31y.00   | Other acute and subacute ischaemic heart disease           | incident              |
| G31y000   | Acute coronary insufficiency                               | incident              |
| G31y100   | Microinfarction of heart                                   | incident              |
| G31y200   | Subendocardial ischaemia                                   | incident              |
| G31y300   | Transient myocardial ischaemia                             | incident              |
| G31yz00   | Other acute and subacute ischaemic heart disease NOS       | incident              |
| G33..00   | Angina pectoris                                            | incident              |
| G330.00   | Angina decubitus                                           | incident              |
| G330000   | Nocturnal angina                                           | incident              |
| G330z00   | Angina decubitus NOS                                       | incident              |
| G331.00   | Prinzmetal's angina                                        | incident              |
| G331.11   | Variant angina pectoris                                    | incident              |
| G33z.00   | Angina pectoris NOS                                        | incident              |
| G33z000   | Status anginosus                                           | incident              |
| G33z100   | Stenocardia                                                | incident              |
| G33z200   | Syncope anginosa                                           | incident              |
| G33z300   | Angina on effort                                           | incident              |
| G33z400   | Ischaemic chest pain                                       | incident              |
| G33z600   | New onset angina                                           | incident              |
| G33z700   | Stable angina                                              | incident              |
| G33zz00   | Angina pectoris NOS                                        | incident              |
| G34..00   | Other chronic ischaemic heart disease                      | prevalent             |
| G340.00   | Coronary atherosclerosis                                   | incident              |
| G340.11   | Triple vessel disease of the heart                         | incident              |
| G340.12   | Coronary artery disease                                    | incident              |
| G340000   | Single coronary vessel disease                             | incident              |
| G340100   | Double coronary vessel disease                             | incident              |
| G342.00   | Atherosclerotic cardiovascular disease                     | incident              |
| G343.00   | Ischaemic cardiomyopathy                                   | incident              |
| G344.00   | Silent myocardial ischaemia                                | incident              |
| G34y.00   | Other specified chronic ischaemic heart disease            | prevalent             |
| G34y000   | Chronic coronary insufficiency                             | prevalent             |
| G34y100   | Chronic myocardial ischaemia                               | prevalent             |
| G34yz00   | Other specified chronic ischaemic heart disease NOS        | prevalent             |
| G34z.00   | Other chronic ischaemic heart disease NOS                  | prevalent             |
| G34z000   | Asymptomatic coronary heart disease                        | incident              |
| G37..00   | Cardiac syndrome X                                         | incident              |
| G39..00   | Coronary microvascular disease                             | incident              |
| G3y..00   | Other specified ischaemic heart disease                    | incident              |
| G3z..00   | Ischaemic heart disease NOS                                | incident              |
| Gyu3.00   | [X]Ischaemic heart diseases                                | incident              |

| Read code | Description                                       | Incident or prevalent |
|-----------|---------------------------------------------------|-----------------------|
| Gyu3000   | [X]Other forms of angina pectoris                 | incident              |
| Gyu3200   | [X]Other forms of acute ischaemic heart disease   | incident              |
| Gyu3300   | [X]Other forms of chronic ischaemic heart disease | prevalent             |

**Appendix table XXII.4: Read codes for haemorrhagic stroke**

| Read code | Description                                                  | Incident or prevalent |
|-----------|--------------------------------------------------------------|-----------------------|
| G61..00   | Intracerebral haemorrhage                                    | incident              |
| G61..11   | CVA - cerebrovascular accid due to intracerebral haemorrhage | incident              |
| G61..12   | Stroke due to intracerebral haemorrhage                      | incident              |
| G610.00   | Cortical haemorrhage                                         | incident              |
| G611.00   | Internal capsule haemorrhage                                 | incident              |
| G612.00   | Basal nucleus haemorrhage                                    | incident              |
| G613.00   | Cerebellar haemorrhage                                       | incident              |
| G614.00   | Pontine haemorrhage                                          | incident              |
| G615.00   | Bulbar haemorrhage                                           | incident              |
| G616.00   | External capsule haemorrhage                                 | incident              |
| G618.00   | Intracerebral haemorrhage, multiple localized                | incident              |
| G619.00   | Lobar cerebral haemorrhage                                   | incident              |
| G61X.00   | Intracerebral haemorrhage in hemisphere, unspecified         | incident              |
| G61X000   | Left sided intracerebral haemorrhage, unspecified            | incident              |
| G61X100   | Right sided intracerebral haemorrhage, unspecified           | incident              |
| G61z.00   | Intracerebral haemorrhage NOS                                | incident              |
| G681.00   | Sequelae of intracerebral haemorrhage                        | prevalent             |
| G683.00   | Sequelae of cerebral infarction                              | prevalent             |
| Gyu6200   | [X]Other intracerebral haemorrhage                           | incident              |
| Gyu6B00   | [X]Sequelae of other nontraumatic intracranial haemorrhage   | prevalent             |
| Gyu6F00   | [X]Intracerebral haemorrhage in hemisphere, unspecified      | incident              |

**Appendix table XXII.5: Read codes for non-haemorrhagic stroke**

| Read code | Description                                                 | Incident or prevalent |
|-----------|-------------------------------------------------------------|-----------------------|
| 1477.00   | H/O: cerebrovascular disease                                | prevalent             |
| 14A7.00   | H/O: CVA/stroke                                             | prevalent             |
| 14A7.11   | H/O: CVA                                                    | prevalent             |
| 14A7.12   | H/O: stroke                                                 | prevalent             |
| 14AK.00   | H/O: Stroke in last year                                    | prevalent             |
| 1M4..00   | Central post-stroke pain                                    | prevalent             |
| 662M200   | Stroke initial post discharge review                        | incident              |
| 7P24200   | Delivery of rehabilitation for stroke                       | incident              |
| 8HBJ.00   | Stroke / transient ischaemic attack referral                | incident              |
| 8HTQ.00   | Referral to stroke clinic                                   | incident              |
| 8IEC.00   | Ref multidisciplinary stroke function improvement declined  | incident              |
| 9N0p.00   | Seen in stroke clinic                                       | incident              |
| 9N4X.00   | DNA - Did not attend stroke clinic                          | prevalent             |
| F11x200   | Cerebral degeneration due to cerebrovascular disease        | prevalent             |
| Fyu5700   | [X]Other vascular syndroms/brain in cerebrovasculr diseases | prevalent             |
| G6...00   | Cerebrovascular disease                                     | incident              |
| G63y000   | Cerebral infarct due to thrombosis of precerebral arteries  | incident              |
| G63y100   | Cerebral infarction due to embolism of precerebral arteries | incident              |
| G64..00   | Cerebral arterial occlusion                                 | incident              |
| G64..11   | CVA - cerebral artery occlusion                             | incident              |
| G64..12   | Infarction - cerebral                                       | incident              |

| Read code | Description                                                  | Incident or prevalent |
|-----------|--------------------------------------------------------------|-----------------------|
| G64..13   | Stroke due to cerebral arterial occlusion                    | incident              |
| G640.00   | Cerebral thrombosis                                          | incident              |
| G640000   | Cerebral infarction due to thrombosis of cerebral arteries   | incident              |
| G641.00   | Cerebral embolism                                            | incident              |
| G641.11   | Cerebral embolus                                             | incident              |
| G641000   | Cerebral infarction due to embolism of cerebral arteries     | incident              |
| G64z.00   | Cerebral infarction NOS                                      | incident              |
| G64z.11   | Brainstem infarction NOS                                     | incident              |
| G64z.12   | Cerebellar infarction                                        | incident              |
| G64z000   | Brainstem infarction                                         | incident              |
| G64z100   | Wallenberg syndrome                                          | incident              |
| G64z111   | Lateral medullary syndrome                                   | incident              |
| G64z200   | Left sided cerebral infarction                               | incident              |
| G64z300   | Right sided cerebral infarction                              | incident              |
| G64z400   | Infarction of basal ganglia                                  | incident              |
| G66..00   | Stroke and cerebrovascular accident unspecified              | incident              |
| G66..11   | CVA unspecified                                              | incident              |
| G66..12   | Stroke unspecified                                           | incident              |
| G66..13   | CVA - Cerebrovascular accident unspecified                   | incident              |
| G660.00   | Middle cerebral artery syndrome                              | incident              |
| G661.00   | Anterior cerebral artery syndrome                            | incident              |
| G662.00   | Posterior cerebral artery syndrome                           | incident              |
| G663.00   | Brain stem stroke syndrome                                   | incident              |
| G664.00   | Cerebellar stroke syndrome                                   | incident              |
| G665.00   | Pure motor lacunar syndrome                                  | incident              |
| G666.00   | Pure sensory lacunar syndrome                                | incident              |
| G667.00   | Left sided CVA                                               | incident              |
| G668.00   | Right sided CVA                                              | incident              |
| G676000   | Cereb infarct due cerebral venous thrombosis, nonpyogenic    | incident              |
| G68..00   | Late effects of cerebrovascular disease                      | prevalent             |
| G68X.00   | Sequelae of stroke,not specfd as h'morrhage or infarction    | prevalent             |
| G6W..00   | Cereb infarct due unsp occlus/stenos precerebr arteries      | incident              |
| G6X..00   | Cerebrl infarctn due/unspcf occlusn or sten/cerebrl artr     | incident              |
| G6z..00   | Cerebrovascular disease NOS                                  | incident              |
| Gyu6.00   | [X]Cerebrovascular diseases                                  | incident              |
| Gyu6300   | [X]Cerebrl infarctn due/unspcf occlusn or sten/cerebrl artr  | incident              |
| Gyu6400   | [X]Other cerebral infarction                                 | incident              |
| Gyu6500   | [X]Occlusion and stenosis of other precerebral arteries      | incident              |
| Gyu6600   | [X]Occlusion and stenosis of other cerebral arteries         | incident              |
| Gyu6C00   | [X]Sequelae of stroke,not specfd as h'morrhage or infarction | prevalent             |
| Gyu6D00   | [X]Sequelae/other + unspecified cerebrovascular diseases     | prevalent             |
| Gyu6G00   | [X]Cereb infarct due unsp occlus/stenos precerebr arteries   | incident              |
| ZLEP.00   | Discharge from stroke serv                                   | prevalent             |
| ZV12511   | [V]Personal history of stroke                                | prevalent             |
| ZV12512   | [V]Personal history of cerebrovascular accident (CVA)        | prevalent             |

**Appendix table XXII.6: Read codes for transient ischaemic attack**

| Read code | Description                                                  | Incident or prevalent |
|-----------|--------------------------------------------------------------|-----------------------|
| 14AB.00   | H/O: TIA                                                     | prevalent             |
| F423600   | Amaurosis fugax                                              | incident              |
| Fyu5500   | [X]Other transnt cerebral ischaemic attacks+related syndroms | incident              |
| G65..00   | Transient cerebral ischaemia                                 | incident              |
| G65..12   | Transient ischaemic attack                                   | incident              |
| G65..13   | Vertebro-basilar insufficiency                               | incident              |
| G650.00   | Basilar artery syndrome                                      | incident              |



| Read code | Description                                         | Incident or prevalent |
|-----------|-----------------------------------------------------|-----------------------|
| G650.11   | Insufficiency - basilar artery                      | incident              |
| G651.00   | Vertebral artery syndrome                           | incident              |
| G651000   | Vertebro-basilar artery syndrome                    | incident              |
| G652.00   | Subclavian steal syndrome                           | incident              |
| G653.00   | Carotid artery syndrome hemispheric                 | incident              |
| G654.00   | Multiple and bilateral precerebral artery syndromes | incident              |
| G656.00   | Vertebrobasilar insufficiency                       | incident              |
| G657.00   | Carotid territory transient ischaemic attack        | incident              |
| G65y.00   | Other transient cerebral ischaemia                  | incident              |
| G65z.00   | Transient cerebral ischaemia NOS                    | incident              |
| G65z000   | Impending cerebral ischaemia                        | incident              |
| G65z100   | Intermittent cerebral ischaemia                     | incident              |
| G65zz00   | Transient cerebral ischaemia NOS                    | incident              |
| G679.00   | Small vessel cerebrovascular disease                | incident              |
| ZV12D00   | [V]Personal history of transient ischaemic attack   | prevalent             |

**Appendix table XXII.7: Read codes for peripheral arterial disease**

| Read code | Description                                                  | Incident or prevalent |
|-----------|--------------------------------------------------------------|-----------------------|
| 14NB.00   | H/O: Peripheral vascular disease procedure                   | prevalent             |
| 16l..00   | Claudication distance                                        | incident              |
| 1M11000   | Ischaemic foot pain at rest                                  | incident              |
| 1M11100   | Ischaemic foot pain when walking                             | incident              |
| 2G63.00   | Ischaemic toe                                                | incident              |
| 9N4h.00   | DNA - Did not attend peripheral vascular disease clinic      | prevalent             |
| C107.00   | Diabetes mellitus with peripheral circulatory disorder       | incident              |
| C107000   | Diabetes mellitus; juvenile +peripheral circulatory disorder | incident              |
| C107100   | Diabetes mellitus; adult; + peripheral circulatory disorder  | incident              |
| C107300   | IDDM with peripheral circulatory disorder                    | incident              |
| C107400   | NIDDM with peripheral circulatory disorder                   | incident              |
| C107y00   | Other specified diabetes mellitus with periph circ comps     | incident              |
| C107z00   | Diabetes mellitus NOS with peripheral circulatory disorder   | incident              |
| C108G00   | Insulin dependent diab mell with peripheral angiopathy       | incident              |
| C108G11   | Type I diabetes mellitus with peripheral angiopathy          | incident              |
| C108G12   | Type 1 diabetes mellitus with peripheral angiopathy          | incident              |
| C109F00   | Non-insulin-dependent d m with peripheral angiopath          | incident              |
| C109F11   | Type II diabetes mellitus with peripheral angiopathy         | incident              |
| C109F12   | Type 2 diabetes mellitus with peripheral angiopathy          | incident              |
| C10EG00   | Type 1 diabetes mellitus with peripheral angiopathy          | incident              |
| C10EG11   | Type I diabetes mellitus with peripheral angiopathy          | incident              |
| C10EG12   | Insulin dependent diab mell with peripheral angiopathy       | incident              |
| C10FF00   | Type 2 diabetes mellitus with peripheral angiopathy          | incident              |
| C10FF11   | Type II diabetes mellitus with peripheral angiopathy         | incident              |
| G73..00   | Other peripheral vascular disease                            | incident              |
| G73..11   | Peripheral ischaemic vascular disease                        | incident              |
| G73..12   | Ischaemia of legs                                            | incident              |
| G73..13   | Peripheral ischaemia                                         | incident              |
| G733.00   | Ischaemic foot                                               | incident              |
| G734.00   | Peripheral arterial disease                                  | incident              |
| G73y.00   | Other specified peripheral vascular disease                  | incident              |
| G73y000   | Diabetic peripheral angiopathy                               | incident              |
| G73y100   | Peripheral angiopathic disease EC NOS                        | incident              |
| G73yz00   | Other specified peripheral vascular disease NOS              | incident              |
| G73z.00   | Peripheral vascular disease NOS                              | incident              |
| G73z000   | Intermittent claudication                                    | incident              |
| G73z011   | Claudication                                                 | incident              |

| <b>Read code</b> | <b>Description</b>                              | <b>Incident or prevalent</b> |
|------------------|-------------------------------------------------|------------------------------|
| G73z012          | Vascular claudication                           | incident                     |
| G73zz00          | Peripheral vascular disease NOS                 | incident                     |
| Gyu7400          | [X]Other specified peripheral vascular diseases | incident                     |
| M271.12          | Ischaemic leg ulcer                             | incident                     |
| M271000          | Ischaemic ulcer diabetic foot                   | incident                     |

#### **Appendix table XXII.8: Read code for other cardiovascular disease**

| <b>Read code</b> | <b>Description</b>          | <b>Incident or prevalent</b> |
|------------------|-----------------------------|------------------------------|
| 14A..00          | H/O: cardiovascular disease | prevalent                    |

## APPENDIX XXIII INCLUDED READ AND DRUG CODES FOR OTHER COVARIATES

**Appendix table XXIII.1: Read codes for dementia**

| Read code | Description                                                  |
|-----------|--------------------------------------------------------------|
| 1461.00   | H/O: dementia                                                |
| E00..00   | Senile and presenile organic psychotic conditions            |
| E00..11   | Senile dementia                                              |
| E00..12   | Senile/presenile dementia                                    |
| E000.00   | Uncomplicated senile dementia                                |
| E001.00   | Presenile dementia                                           |
| E001000   | Uncomplicated presenile dementia                             |
| E001100   | Presenile dementia with delirium                             |
| E001200   | Presenile dementia with paranoia                             |
| E001300   | Presenile dementia with depression                           |
| E001z00   | Presenile dementia NOS                                       |
| E002.00   | Senile dementia with depressive or paranoid features         |
| E002000   | Senile dementia with paranoia                                |
| E002100   | Senile dementia with depression                              |
| E002z00   | Senile dementia with depressive or paranoid features NOS     |
| E003.00   | Senile dementia with delirium                                |
| E004.00   | Arteriosclerotic dementia                                    |
| E004.11   | Multi infarct dementia                                       |
| E004000   | Uncomplicated arteriosclerotic dementia                      |
| E004100   | Arteriosclerotic dementia with delirium                      |
| E004200   | Arteriosclerotic dementia with paranoia                      |
| E004300   | Arteriosclerotic dementia with depression                    |
| E004z00   | Arteriosclerotic dementia NOS                                |
| E00y.00   | Other senile and presenile organic psychoses                 |
| E00y.11   | Presbyophrenic psychosis                                     |
| E00z.00   | Senile or presenile psychoses NOS                            |
| E012.00   | Other alcoholic dementia                                     |
| E012.11   | Alcoholic dementia NOS                                       |
| E041.00   | Dementia in conditions EC                                    |
| Eu00.00   | [X]Dementia in Alzheimer's disease                           |
| Eu00000   | [X]Dementia in Alzheimer's disease with early onset          |
| Eu00011   | [X]Presenile dementia,Alzheimer's type                       |
| Eu00012   | [X]Primary degen dementia, Alzheimer's type, presenile onset |
| Eu00013   | [X]Alzheimer's disease type 2                                |
| Eu00100   | [X]Dementia in Alzheimer's disease with late onset           |
| Eu00111   | [X]Alzheimer's disease type 1                                |
| Eu00112   | [X]Senile dementia,Alzheimer's type                          |
| Eu00113   | [X]Primary degen dementia of Alzheimer's type, senile onset  |
| Eu00200   | [X]Dementia in Alzheimer's dis, atypical or mixed type       |
| Eu00z00   | [X]Dementia in Alzheimer's disease, unspecified              |
| Eu00z11   | [X]Alzheimer's dementia unspec                               |
| Eu01.00   | [X]Vascular dementia                                         |
| Eu01.11   | [X]Arteriosclerotic dementia                                 |
| Eu01000   | [X]Vascular dementia of acute onset                          |
| Eu01100   | [X]Multi-infarct dementia                                    |
| Eu01111   | [X]Predominantly cortical dementia                           |
| Eu01200   | [X]Subcortical vascular dementia                             |
| Eu01300   | [X]Mixed cortical and subcortical vascular dementia          |
| Eu01y00   | [X]Other vascular dementia                                   |
| Eu01z00   | [X]Vascular dementia, unspecified                            |
| Eu02.00   | [X]Dementia in other diseases classified elsewhere           |

| <b>Read code</b> | <b>Description</b>                                        |
|------------------|-----------------------------------------------------------|
| Eu02000          | [X]Dementia in Pick's disease                             |
| Eu02100          | [X]Dementia in Creutzfeldt-Jakob disease                  |
| Eu02200          | [X]Dementia in Huntington's disease                       |
| Eu02300          | [X]Dementia in Parkinson's disease                        |
| Eu02400          | [X]Dementia in human immunodef virus [HIV] disease        |
| Eu02500          | [X]Lewy body dementia                                     |
| Eu02y00          | [X]Dementia in other specified diseases classif elsewhere |
| Eu02z00          | [X] Unspecified dementia                                  |
| Eu02z11          | [X] Presenile dementia NOS                                |
| Eu02z12          | [X] Presenile psychosis NOS                               |
| Eu02z13          | [X] Primary degenerative dementia NOS                     |
| Eu02z14          | [X] Senile dementia NOS                                   |
| Eu02z15          | [X] Senile psychosis NOS                                  |
| Eu02z16          | [X] Senile dementia, depressed or paranoid type           |
| Eu04100          | [X]Delirium superimposed on dementia                      |
| Eu10711          | [X]Alcoholic dementia NOS                                 |
| F110.00          | Alzheimer's disease                                       |
| F110000          | Alzheimer's disease with early onset                      |
| F110100          | Alzheimer's disease with late onset                       |
| F111.00          | Pick's disease                                            |
| F112.00          | Senile degeneration of brain                              |
| F116.00          | Lewy body disease                                         |
| Fyu3000          | [X]Other Alzheimer's disease                              |

## Appendix table XXIII.2: Read codes for type 1 diabetes mellitus

| <b>Read code</b> | <b>Description</b>                                           |
|------------------|--------------------------------------------------------------|
| 13B1000          | Diabetic carbohydrate counting diet                          |
| 66An.00          | Diabetes type 1 review                                       |
| 66At000          | Type I diabetic dietary review                               |
| 66At011          | Type 1 diabetic dietary review                               |
| 8CP2.00          | Transition of diabetes care options discussed                |
| 8Hj3.00          | Referral to DAFNE diabetes structured education programme    |
| 8I82.00          | Did not complete DAFNE diabetes structured educati           |
| 8IEa.00          | Referral to DAFNE diabetes structured educn prog declined    |
| 9NIC.00          | Did not attend DAFNE diabetes structured education           |
| 9OLH.00          | Attended DAFNE diabetes structured education progr           |
| 9OLJ.00          | DAFNE diabetes structured education programme comp           |
| C100000          | Diabetes mellitus; juvenile type; no mention of co           |
| C101000          | Diabetes mellitus, juvenile type, with ketoacidosis          |
| C102000          | Diabetes mellitus; juvenile type; with hyperosmolar coma     |
| C103000          | Diabetes mellitus; juvenile type; with ketoacidotic coma     |
| C104000          | Diabetes mellitus, juvenile type, with renal manifestation   |
| C105000          | Diabetes mellitus; juvenile type; + ophthalmic manifestation |
| C106000          | Diabetes mellitus; juvenile; + neurological manifestation    |
| C107000          | Diabetes mellitus, juvenile +peripheral circulatory disorder |
| C108.12          | Type 1 diabetes mellitus                                     |
| C108.13          | Type I diabetes mellitus                                     |
| C108011          | Type I diabetes mellitus with renal complications            |
| C108012          | Type 1 diabetes mellitus with renal complications            |
| C108111          | Type I diabetes mellitus with ophthalmic complications       |
| C108112          | Type 1 diabetes mellitus with ophthalmic complications       |
| C108211          | Type I diabetes mellitus with neurological complic           |
| C108212          | Type 1 diabetes mellitus with neurological complic           |
| C108311          | Type I diabetes mellitus with multiple complicatio           |
| C108312          | Type 1 diabetes mellitus with multiple complications         |

| Read code | Description                                              |
|-----------|----------------------------------------------------------|
| C108411   | Unstable type I diabetes mellitus                        |
| C108412   | Unstable type 1 diabetes mellitus                        |
| C108511   | Type I diabetes mellitus with ulcer                      |
| C108512   | Type 1 diabetes mellitus with ulcer                      |
| C108611   | Type I diabetes mellitus with gangrene                   |
| C108612   | Type 1 diabetes mellitus with gangrene                   |
| C108711   | Type I diabetes mellitus with retinopathy                |
| C108712   | Type 1 diabetes mellitus with retinopathy                |
| C108811   | Type I diabetes mellitus - poor control                  |
| C108812   | Type 1 diabetes mellitus - poor control                  |
| C108911   | Type I diabetes mellitus maturity onset                  |
| C108912   | Type 1 diabetes mellitus maturity onset                  |
| C108A11   | Type I diabetes mellitus without complication            |
| C108A12   | Type 1 diabetes mellitus without complication            |
| C108B11   | Type I diabetes mellitus with mononeuropathy             |
| C108B12   | Type 1 diabetes mellitus with mononeuropathy             |
| C108C11   | Type I diabetes mellitus with polyneuropathy             |
| C108C12   | Type 1 diabetes mellitus with polyneuropathy             |
| C108D11   | Type I diabetes mellitus with nephropathy                |
| C108D12   | Type 1 diabetes mellitus with nephropathy                |
| C108E11   | Type I diabetes mellitus with hypoglycaemic coma         |
| C108E12   | Type 1 diabetes mellitus with hypoglycaemic coma         |
| C108F11   | Type I diabetes mellitus with diabetic cataract          |
| C108F12   | Type 1 diabetes mellitus with diabetic cataract          |
| C108G11   | Type I diabetes mellitus with peripheral angiopathy      |
| C108G12   | Type 1 diabetes mellitus with peripheral angiopathy      |
| C108H11   | Type I diabetes mellitus with arthropathy                |
| C108H12   | Type 1 diabetes mellitus with arthropathy                |
| C108J11   | Type I diabetes mellitus with neuropathic arthropathy    |
| C108J12   | Type 1 diabetes mellitus with neuropathic arthropathy    |
| C10E.00   | Type 1 diabetes mellitus                                 |
| C10E.11   | Type I diabetes mellitus                                 |
| C10E000   | Type 1 diabetes mellitus with renal complications        |
| C10E011   | Type I diabetes mellitus with renal complications        |
| C10E100   | Type 1 diabetes mellitus with ophthalmic complications   |
| C10E111   | Type I diabetes mellitus with ophthalmic complications   |
| C10E200   | Type 1 diabetes mellitus with neurological complications |
| C10E211   | Type I diabetes mellitus with neurological complications |
| C10E300   | Type 1 diabetes mellitus with multiple complications     |
| C10E311   | Type I diabetes mellitus with multiple complications     |
| C10E400   | Unstable type 1 diabetes mellitus                        |
| C10E411   | Unstable type I diabetes mellitus                        |
| C10E500   | Type 1 diabetes mellitus with ulcer                      |
| C10E511   | Type I diabetes mellitus with ulcer                      |
| C10E600   | Type 1 diabetes mellitus with gangrene                   |
| C10E611   | Type I diabetes mellitus with gangrene                   |
| C10E700   | Type 1 diabetes mellitus with retinopathy                |
| C10E711   | Type I diabetes mellitus with retinopathy                |
| C10E800   | Type 1 diabetes mellitus - poor control                  |
| C10E811   | Type I diabetes mellitus - poor control                  |
| C10E900   | Type 1 diabetes mellitus maturity onset                  |
| C10E911   | Type I diabetes mellitus maturity onset                  |
| C10EA00   | Type 1 diabetes mellitus without complication            |
| C10EA11   | Type I diabetes mellitus without complication            |
| C10EB00   | Type 1 diabetes mellitus with mononeuropathy             |
| C10EB11   | Type I diabetes mellitus with mononeuropathy             |
| C10EC00   | Type 1 diabetes mellitus with polyneuropathy             |
| C10EC11   | Type I diabetes mellitus with polyneuropathy             |

| <b>Read code</b> | <b>Description</b>                                           |
|------------------|--------------------------------------------------------------|
| C10ED00          | Type 1 diabetes mellitus with nephropathy                    |
| C10ED11          | Type I diabetes mellitus with nephropathy                    |
| C10EE00          | Type 1 diabetes mellitus with hypoglycaemic coma             |
| C10EE11          | Type I diabetes mellitus with hypoglycaemic coma             |
| C10EF00          | Type 1 diabetes mellitus with diabetic cataract              |
| C10EF11          | Type I diabetes mellitus with diabetic cataract              |
| C10EG00          | Type 1 diabetes mellitus with peripheral angiopathy          |
| C10EG11          | Type I diabetes mellitus with peripheral angiopathy          |
| C10EH00          | Type 1 diabetes mellitus with arthropathy                    |
| C10EH11          | Type I diabetes mellitus with arthropathy                    |
| C10EJ00          | Type 1 diabetes mellitus with neuropathic arthropathy        |
| C10EJ11          | Type I diabetes mellitus with neuropathic arthropathy        |
| C10EK00          | Type 1 diabetes mellitus with persistent proteinuria         |
| C10EK11          | Type I diabetes mellitus with persistent proteinuria         |
| C10EL00          | Type 1 diabetes mellitus with persistent microalbuminuria    |
| C10EL11          | Type I diabetes mellitus with persistent microalbuminuria    |
| C10EM00          | Type 1 diabetes mellitus with ketoacidosis                   |
| C10EM11          | Type I diabetes mellitus with ketoacidosis                   |
| C10EN00          | Type 1 diabetes mellitus with ketoacidotic coma              |
| C10EN11          | Type I diabetes mellitus with ketoacidotic coma              |
| C10EP00          | Type 1 diabetes mellitus with exudative maculopathy          |
| C10EP11          | Type I diabetes mellitus with exudative maculopathy          |
| C10EQ00          | Type 1 diabetes mellitus with gastroparesis                  |
| C10EQ11          | Type I diabetes mellitus with gastroparesis                  |
| C10ER00          | Latent autoimmune diabetes mellitus in adult                 |
| C10FS00          | Maternally inherited diabetes mellitus                       |
| C10J.00          | Insulin autoimmune syndrome                                  |
| C10J000          | Insulin autoimmune syndrome without complication             |
| C10P000          | Type I diabetes mellitus in remission                        |
| C10P011          | Type 1 diabetes mellitus in remission                        |
| C10y000          | Diabetes mellitus, juvenile, + other specified manifestation |
| C10z000          | Diabetes mellitus; juvenile type; + unspecified co           |
| ZC2C900          | Dietary advice for type I diabetes                           |

**Appendix table XXIII.3: Read codes for non-type 1 diabetes mellitus**

| <b>Read code</b> | <b>Description</b>                                    |
|------------------|-------------------------------------------------------|
| 13AB.00          | Diabetic lipid lowering diet                          |
| 13AC.00          | Diabetic weight reducing diet                         |
| 13B1.00          | Diabetic diet                                         |
| 1434.00          | H/O: diabetes mellitus                                |
| 14F4.00          | H/O: Admission in last year for diabetes foot prob    |
| 1IA..00          | No evidence of diabetic nephropathy                   |
| 1M8..00          | Diabetic peripheral neuropathic pain                  |
| 2126300          | Diabetes resolved                                     |
| 212H.00          | Diabetes resolved                                     |
| 2BBF.00          | Retinal abnormality - diabetes related                |
| 2BBJ.00          | O/E - no right diabetic retinopathy                   |
| 2BBK.00          | O/E - no left diabetic retinopathy                    |
| 2BBL.00          | O/E - diabetic maculopathy present both eyes          |
| 2BBM.00          | O/E - diabetic maculopathy absent both eyes           |
| 2BBP.00          | O/E - right eye background diabetic retinopathy       |
| 2BBQ.00          | O/E - left eye background diabetic retinopathy        |
| 2BBR.00          | O/E - right eye preproliferative diabetic retinopathy |
| 2BBS.00          | O/E - left eye preproliferative diabetic retinopathy  |
| 2BBT.00          | O/E - right eye proliferative diabetic retinopathy    |
| 2BBV.00          | O/E - left eye proliferative diabetic retinopathy     |

| Read code | Description                                                |
|-----------|------------------------------------------------------------|
| 2BBW.00   | O/E - right eye diabetic maculopathy                       |
| 2BBX.00   | O/E - left eye diabetic maculopathy                        |
| 2BBk.00   | O/E - right eye stable treated prolif diabetic retinopathy |
| 2BBl.00   | O/E - left eye stable treated prolif diabetic retinopathy  |
| 2BBo.00   | O/E - sight threatening diabetic retinopathy               |
| 2BBr.00   | Impaired vision due to diabetic retinopathy                |
| 2G51000   | Foot abnormality - diabetes related                        |
| 2G5A.00   | O/E - Right diabetic foot at risk                          |
| 2G5B.00   | O/E - Left diabetic foot at risk                           |
| 2G5C.00   | Foot abnormality - diabetes related                        |
| 2G5E.00   | O/E - Right diabetic foot at low risk                      |
| 2G5F.00   | O/E - Right diabetic foot at moderate risk                 |
| 2G5G.00   | O/E - Right diabetic foot at high risk                     |
| 2G5H.00   | O/E - Right diabetic foot - ulcerated                      |
| 2G5I.00   | O/E - Left diabetic foot at low risk                       |
| 2G5J.00   | O/E - Left diabetic foot at moderate risk                  |
| 2G5K.00   | O/E - Left diabetic foot at high risk                      |
| 2G5L.00   | O/E - Left diabetic foot - ulcerated                       |
| 2G5V.00   | O/E - right chronic diabetic foot ulcer                    |
| 2G5W.00   | O/E - left chronic diabetic foot ulcer                     |
| 2G5d.00   | O/E - Left diabetic foot at increased risk                 |
| 2G5e.00   | O/E - Right diabetic foot at increased risk                |
| 3881.00   | Education score - diabetes                                 |
| 3882.00   | Diabetes well being questionnaire                          |
| 3883.00   | Diabetes treatment satisfaction questionnaire              |
| 42W..00   | Hb. A1C - diabetic control                                 |
| 42W1.00   | Hb. A1C < 7% - good control                                |
| 42W2.00   | Hb. A1C 7-10% - borderline                                 |
| 42W3.00   | Hb. A1C > 10% - bad control                                |
| 42WZ.00   | Hb. A1C - diabetic control NOS                             |
| 42c..00   | HbA1 - diabetic control                                    |
| 42c0.00   | HbA1 < 7% - good control                                   |
| 42c1.00   | HbA1 7 - 10% - borderline control                          |
| 42c2.00   | HbA1 > 10% - bad control                                   |
| 44V3.00   | Glucose tol. test diabetic                                 |
| 661M400   | Diabetes self-management plan agreed                       |
| 661N400   | Diabetes self-management plan review                       |
| 66A..00   | Diabetic monitoring                                        |
| 66A1.00   | Initial diabetic assessment                                |
| 66A2.00   | Follow-up diabetic assessment                              |
| 66A3.00   | Diabetic on diet only                                      |
| 66A4.00   | Diabetic on oral treatment                                 |
| 66A5.00   | Diabetic on insulin                                        |
| 66A6.00   | Last hypo. attack                                          |
| 66A7.00   | Frequency of hypo. attacks                                 |
| 66A7000   | Frequency of hospital treated hypoglycaemia                |
| 66A7100   | Frequency of GP or paramedic treated hypoglycaemia         |
| 66A8.00   | Has seen dietician - diabetes                              |
| 66A9.00   | Understands diet - diabetes                                |
| 66AA.00   | Injection sites                                            |
| 66AA.11   | Injection sites - diabetic                                 |
| 66AD.00   | Fundoscopy - diabetic check                                |
| 66AG.00   | Diabetic drug side effects                                 |
| 66AH.00   | Diabetic treatment changed                                 |
| 66AH000   | Conversion to insulin                                      |
| 66AH200   | Conversion to insulin by diabetes specialist nurse         |
| 66AI.00   | Diabetic - good control                                    |
| 66AJ.00   | Diabetic - poor control                                    |
| 66AJ.11   | Unstable diabetes                                          |

| Read code | Description                                              |
|-----------|----------------------------------------------------------|
| 66AJ000   | Chronic hyperglycaemia                                   |
| 66AJ100   | Brittle diabetes                                         |
| 66AJ200   | Loss of hypoglycaemic warning                            |
| 66AJ300   | Recurrent severe hypos                                   |
| 66AJz00   | Diabetic - poor control NOS                              |
| 66AK.00   | Diabetic - cooperative patient                           |
| 66AL.00   | Diabetic-uncooperative patient                           |
| 66AM.00   | Diabetic - follow-up default                             |
| 66AN.00   | Date diabetic treatment start                            |
| 66AO.00   | Date diabetic treatment stopp.                           |
| 66AP.00   | Diabetes: practice programme                             |
| 66AQ.00   | Diabetes: shared care programme                          |
| 66AQ000   | Unsuitable for diabetes year of care programme           |
| 66AQ100   | Declined consent for diabetes year of care program       |
| 66AR.00   | Diabetes management plan given                           |
| 66AS.00   | Diabetic annual review                                   |
| 66AS000   | Diabetes Year of Care annual review                      |
| 66AT.00   | Annual diabetic blood test                               |
| 66AU.00   | Diabetes care by hospital only                           |
| 66AV.00   | Diabetic on insulin and oral treatment                   |
| 66AW.00   | Diabetic foot risk assessment                            |
| 66AX.00   | Diabetes: shared care in pregnancy - diabetol and obstet |
| 66AY.00   | Diabetic diet - good compliance                          |
| 66AZ.00   | Diabetic monitoring NOS                                  |
| 66Aa.00   | Diabetic diet - poor compliance                          |
| 66Ab.00   | Diabetic foot examination                                |
| 66Ac.00   | Diabetic peripheral neuropathy screening                 |
| 66Ad.00   | Hypoglycaemic attack requiring 3rd party assistance      |
| 66Af.00   | Patient diabetes education review                        |
| 66Ag.00   | Insulin needles changed daily                            |
| 66Ah.00   | Insulin needles changed for each injection               |
| 66Ai.00   | Diabetic 6 month review                                  |
| 66Aj.00   | Insulin needles changed less than once a day             |
| 66Ak.00   | Diabetic monitoring - lower risk albumin excretion       |
| 66Al.00   | Diabetic monitoring - higher risk albumin excretio       |
| 66Am.00   | Insulin dose changed                                     |
| 66Ao.00   | Diabetes type 2 review                                   |
| 66Ap.00   | Insulin treatment initiated                              |
| 66Aq.00   | Diabetic foot screen                                     |
| 66Ar.00   | Insulin treatment stopped                                |
| 66As.00   | Diabetic on subcutaneous treatment                       |
| 66At.00   | Diabetic dietary review                                  |
| 66At100   | Type II diabetic dietary review                          |
| 66At111   | Type 2 diabetic dietary review                           |
| 66Au.00   | Diabetic erectile dysfunction review                     |
| 66Av.00   | Diabetic assessment of erectile dysfunction              |
| 66Aw.00   | Insulin dose                                             |
| 66b1.00   | Diabetic monitoring not required                         |
| 66o..00   | Further diabetic monitoring                              |
| 66o1.00   | Enquiry about diabetic erectile dysfunction declin       |
| 66o2.00   | Diabetic on non-insulin injectable medication            |
| 66o5.00   | Diabetic on oral treatment and glucagon-like pepti       |
| 6761.00   | Diabetic pre-pregnancy counselling                       |
| 679L.00   | Health education - diabetes                              |
| 679L000   | Education in self management of diabetes                 |
| 679L200   | Education about diabetes and driving                     |
| 679L211   | Advice about diabetes and driving                        |
| 679L300   | Diabetic foot care education                             |
| 679R.00   | Patient offered diabetes structured education prog       |



| Read code | Description                                                 |
|-----------|-------------------------------------------------------------|
| 679I.00   | Diabetic injection administration education                 |
| 67D8.00   | Provision of diabetes clinical summary                      |
| 67HA.00   | Lifestyle education for diabetes                            |
| 67IJ100   | Pre-conception advice for diabetes mellitus                 |
| 67W1.00   | Recommendation self-refer for diabetes structured           |
| 68A7.00   | Diabetic retinopathy screening                              |
| 68A9.00   | Diabetic retinopathy screening offered                      |
| 68AB.00   | Diabetic digital retinopathy screening offered              |
| 7276.00   | Pan retinal photocoagulation for diabetes                   |
| 7L10000   | Continuous subcutaneous infusion of insulin                 |
| 7L19800   | Subcutaneous injection of insulin                           |
| 889A.00   | Diab mellit insulin-glucose infus acute myocardial          |
| 8A12.00   | Diabetic crisis monitoring                                  |
| 8A13.00   | Diabetic stabilisation                                      |
| 8B3I.00   | Diabetes medication review                                  |
| 8BL2.00   | Patient on maximal tolerated therapy for diabetes           |
| 8CA4100   | Pt advised re diabetic diet                                 |
| 8CMW700   | Diabetes clinical pathway                                   |
| 8CR2.00   | Diabetes clinical management plan                           |
| 8CS0.00   | Diabetes care plan agreed                                   |
| 8H2J.00   | Admit diabetic emergency                                    |
| 8H3O.00   | Non-urgent diabetic admission                               |
| 8H4F.00   | Referral to diabetologist                                   |
| 8H4e.00   | Referral to diabetes special interest general prac          |
| 8H7C.00   | Refer; diabetic liaison nurse                               |
| 8H7f.00   | Referral to diabetes nurse                                  |
| 8H7r.00   | Refer to diabetic foot screener                             |
| 8HBG.00   | Diabetic retinopathy 12 month review                        |
| 8HBH.00   | Diabetic retinopathy 6 month review                         |
| 8HHy.00   | Referral to diabetic register                               |
| 8HKE.00   | Diabetology D.V. requested                                  |
| 8HLE.00   | Diabetology Domiciliary. Visit. done                        |
| 8HME.00   | Listed for Diabetology admissn                              |
| 8HTE100   | Referral to community diabetes clinic                       |
| 8HTE.00   | Referral to diabetes preconception counselling clinic       |
| 8HTi.00   | Referral to multidisciplinary diabetic clinic               |
| 8HTk.00   | Referral to diabetic eye clinic                             |
| 8HVU.00   | Private referral to diabetologist                           |
| 8Hg4.00   | Discharged from care of diabetes specialist nurse           |
| 8HgC.00   | Discharged from diabetes shared care programme              |
| 8Hj0.00   | Referral to diabetes structured education programme         |
| 8Hj1.00   | Family/carer referral to diabetes structured educa          |
| 8Hj4.00   | Referral to DESMOND diabetes structured education programme |
| 8Hj5.00   | Referral to XPERT diabetes structured education programme   |
| 8HI1.00   | Referral for diabetic retinopathy screening                 |
| 8HI4.00   | Referral to community diabetes specialist nurse             |
| 8Hlc.00   | Referral to community diabetes service                      |
| 8I3W.00   | Diabetic foot examination declined                          |
| 8I3X.00   | Diabetic retinopathy screening refused                      |
| 8I3k.00   | Insulin therapy declined                                    |
| 8I57.00   | Patient held diabetic record declined                       |
| 8I6F.00   | Diabetic retinopathy screening not indicated                |
| 8I6G.00   | Diabetic foot examination not indicated                     |
| 8I81.00   | Did not complete diabetes structured education pro          |
| 8I83.00   | Did not complete DESMOND diabetes structured educa          |
| 8I84.00   | Did not complete XPERT diabetes structured educati          |
| 8I94.00   | Diabetes structured education programme not available       |
| 8IAs.00   | Diabetic dietary review declined                            |
| 8IE2.00   | Diabetes care plan declined                                 |

| Read code | Description                                             |
|-----------|---------------------------------------------------------|
| 8IE9.00   | Referral to DESMOND structured programme declined       |
| 8IEQ.00   | Referral to community diabetes specialist nurse de      |
| 8OA3.00   | Provision of written information about diabetes an      |
| 8OAH.00   | Provision of written information about diabetes an      |
| 8OAK.00   | Provsn written information about diabetes & high c      |
| 918T.00   | Diabetes key contact                                    |
| 9360.00   | Patient held diabetic record issued                     |
| 93C4.00   | Patient consent given for addition to diabetic register |
| 9M00.00   | Informed consent for diabetes national audit            |
| 9M10.00   | Informed dissent for diabetes national audit            |
| 9N0m.00   | Seen in diabetic nurse consultant clinic                |
| 9N0n.00   | Seen in community diabetes specialist clinic            |
| 9N0o.00   | Seen in community diabetic specialist nurse clinic      |
| 9N1Q.00   | Seen in diabetic clinic                                 |
| 9N1i.00   | Seen in diabetic foot clinic                            |
| 9N1o.00   | Seen in multidisciplinary diabetic clinic               |
| 9N1v.00   | Seen in diabetic eye clinic                             |
| 9N2d.00   | Seen by diabetologist                                   |
| 9N2i.00   | Seen by diabetic liaison nurse                          |
| 9N4I.00   | DNA - Did not attend diabetic clinic                    |
| 9N4p.00   | Did not attend diabetic retinopathy clinic              |
| 9NJy.00   | In-house diabetic foot screening                        |
| 9NM0.00   | Attending diabetes clinic                               |
| 9NN8.00   | Under care of diabetologist                             |
| 9NN9.00   | Under care of diabetes specialist nurse                 |
| 9NND.00   | Under care of diabetic foot screener                    |
| 9NST.00   | Not suitable for DESMOND programme                      |
| 9NiA.00   | Did not attend diabetes structured education progr      |
| 9NiD.00   | Did not attend DESMOND diabetes structured educati      |
| 9NiE.00   | Did not attend XPERT diabetes structured education      |
| 9NiZ.00   | Did not attend diabetes foot screening                  |
| 9N14.00   | Seen by general practitioner special interest in d      |
| 9OL..00   | Diabetes monitoring admin.                              |
| 9OL..11   | Diabetes clinic administration                          |
| 9OL1.00   | Attends diabetes monitoring                             |
| 9OL2.00   | Refuses diabetes monitoring                             |
| 9OL3.00   | Diabetes monitoring default                             |
| 9OL4.00   | Diabetes monitoring 1st letter                          |
| 9OL5.00   | Diabetes monitoring 2nd letter                          |
| 9OL6.00   | Diabetes monitoring 3rd letter                          |
| 9OL7.00   | Diabetes monitor.verbal invite                          |
| 9OL8.00   | Diabetes monitor.phone invite                           |
| 9OL9.00   | Diabetes monitoring deleted                             |
| 9OLA.00   | Diabetes monitor. check done                            |
| 9OLA.11   | Diabetes monitored                                      |
| 9OLB.00   | Attended diabetes structured education programme        |
| 9OLC.00   | Family/carer attended diabetes structured educatio      |
| 9OLD.00   | Diabetic patient unsuitable for digital retinal ph      |
| 9OLF.00   | Diabetes structured education programme completed       |
| 9OLG.00   | Attended XPERT diabetes structured education progr      |
| 9OLK.00   | DESMOND diabetes structured education programme co      |
| 9OLL.00   | XPERT diabetes structured education programme comp      |
| 9OLM.00   | Diabetes structured education programme declined        |
| 9OLN.00   | Diabetes monitor invitation by SMS (short message       |
| 9OLZ.00   | Diabetes monitoring admin.NOS                           |
| 9Oy..00   | Diabetes screening administration                       |
| 9Oy0.00   | Diabetes screening invitation                           |
| 9Oy0000   | Diabetic foot screening invitation                      |
| 9Oy0200   | Diabetic foot screening invitation first letter         |

| Read code | Description                                                   |
|-----------|---------------------------------------------------------------|
| 9Oy0300   | Diabetic foot screening invitation second letter              |
| 9Oy0400   | Diabetic foot screening invitation third letter               |
| 9b92000   | Diabetic medicine                                             |
| 9h4..00   | Exception reporting: diabetes quality indicators              |
| 9h41.00   | Excepted from diabetes qual indicators: Patient unsuitable    |
| 9h42.00   | Excepted from diabetes quality indicators: Informed dissent   |
| 9h43.00   | Excepted from diabetes qual indicators: service un            |
| 9m0..00   | Diabetic retinopathy screening administrative stat            |
| 9m00.00   | Eligible for diabetic retinopathy screening                   |
| 9m01.00   | Ineligible for diabetic retinopathy screening                 |
| 9m02.00   | Eligibility temporarily inactive for diabetic reti            |
| 9m03.00   | Eligibility permanently inactive for diabetic reti            |
| 9m04.00   | Excluded from diabetic retinopathy screening                  |
| 9m05.00   | Excluded from diabetic retinopathy screening as moved away    |
| 9m06.00   | Excluded from diabetic retinopathy screening as deceased      |
| 9m07.00   | Excluded diabetic retinop screen as under care opht           |
| 9m08.00   | Excluded from diabetic retinopathy screening as bl            |
| 9m09.00   | Excluded from diabetic retinop screen as no longer diabetic   |
| 9m0A.00   | Declined diabetic retinopathy screening                       |
| 9m0B.00   | Excluded frm diab retinop screen as no currnt contact details |
| 9m0C.00   | Excluded frm diabetic retinopathy screen as terminal illness  |
| 9m0D.00   | Excluded from diabetic retinophy screen as learn disability   |
| 9m0E.00   | Excluded from diabetic retinopathy screen physical disorder   |
| C10..00   | Diabetes mellitus                                             |
| C100.00   | Diabetes mellitus with no mention of complication             |
| C100011   | Insulin dependent diabetes mellitus                           |
| C100100   | Diabetes mellitus, adult onset, no mention of complication    |
| C100111   | Maturity onset diabetes                                       |
| C100112   | Non-insulin dependent diabetes mellitus                       |
| C100z00   | Diabetes mellitus NOS with no mention of complication         |
| C101.00   | Diabetes mellitus with ketoacidosis                           |
| C101100   | Diabetes mellitus, adult onset, with ketoacidosis             |
| C101y00   | Other specified diabetes mellitus with ketoacidosis           |
| C101z00   | Diabetes mellitus NOS with ketoacidosis                       |
| C102.00   | Diabetes mellitus with hyperosmolar coma                      |
| C102100   | Diabetes mellitus, adult onset, with hyperosmolar coma        |
| C102z00   | Diabetes mellitus NOS with hyperosmolar coma                  |
| C103.00   | Diabetes mellitus with ketoacidotic coma                      |
| C103100   | Diabetes mellitus; adult onset; with ketoacidotic             |
| C103y00   | Other specified diabetes mellitus with coma                   |
| C103z00   | Diabetes mellitus NOS with ketoacidotic coma                  |
| C104.00   | Diabetes mellitus with renal manifestation                    |
| C104.11   | Diabetic nephropathy                                          |
| C104100   | Diabetes mellitus; adult onset; with renal manifestation      |
| C104y00   | Other specified diabetes mellitus with renal complications    |
| C104z00   | Diabetes mellitis with nephropathy NOS                        |
| C105.00   | Diabetes mellitus with ophthalmic manifestation               |
| C105100   | Diabetes mellitus, adult onset, + ophthalmic manifestation    |
| C105y00   | Other specified diabetes mellitus with ophthalmic complicatn  |
| C105z00   | Diabetes mellitus NOS with ophthalmic manifestation           |
| C106.00   | Diabetes mellitus with neurological manifestation             |
| C106.11   | Diabetic amyotrophy                                           |
| C106.12   | Diabetes mellitus with neuropathy                             |
| C106.13   | Diabetes mellitus with polyneuropathy                         |
| C106100   | Diabetes mellitus; adult onset; + neurological manifestation  |
| C106y00   | Other specified diabetes mellitus with neurological comps     |
| C106z00   | Diabetes mellitus NOS with neurological manifestat            |
| C107.00   | Diabetes mellitus with peripheral circulatory diso            |
| C107.11   | Diabetes mellitus with gangrene                               |

| Read code | Description                                                  |
|-----------|--------------------------------------------------------------|
| C107.12   | Diabetes with gangrene                                       |
| C107100   | Diabetes mellitus; adult; + peripheral circulatory disorder  |
| C107200   | Diabetes mellitus; adult with gangrene                       |
| C107300   | IDDM with peripheral circulatory disorder                    |
| C107400   | NIDDM with peripheral circulatory disorder                   |
| C107y00   | Other specified diabetes mellitus with periph circ comps     |
| C107z00   | Diabetes mellitus NOS with peripheral circulatory disorder   |
| C108.00   | Insulin dependent diabetes mellitus                          |
| C108.11   | IDDM-Insulin dependent diabetes mellitus                     |
| C108000   | Insulin-dependent diabetes mellitus with renal complications |
| C108100   | Insulin-dependent diabetes mellitus with ophthalmi           |
| C108200   | Insulin-dependent diabetes mellitus with neurological comps  |
| C108300   | Insulin dependent diabetes mellitus with multiple complicatn |
| C108400   | Unstable insulin dependent diabetes mellitus                 |
| C108500   | Insulin dependent diabetes mellitus with ulcer               |
| C108600   | Insulin dependent diabetes mellitus with gangrene            |
| C108700   | Insulin dependent diabetes mellitus with retinopathy         |
| C108800   | Insulin dependent diabetes mellitus - poor control           |
| C108900   | Insulin dependent diabetes maturity onset                    |
| C108A00   | Insulin-dependent diabetes without complication              |
| C108B00   | Insulin dependent diabetes mellitus with mononeuropathy      |
| C108C00   | Insulin dependent diabetes mellitus with polyneuro           |
| C108D00   | Insulin dependent diabetes mellitus with nephropathy         |
| C108E00   | Insulin dependent diabetes mellitus with hypoglycaemic coma  |
| C108F00   | Insulin dependent diabetes mellitus with diabetic            |
| C108G00   | Insulin dependent diab mell with peripheral angiop           |
| C108H00   | Insulin dependent diabetes mellitus with arthropathy         |
| C108J00   | Insulin dependent diab mell with neuropathic arthr           |
| C108y00   | Other specified diabetes mellitus with multiple comps        |
| C108z00   | Unspecified diabetes mellitus with multiple complications    |
| C109.00   | Non-insulin-dependent diabetes mellitus                      |
| C109.11   | NIDDM - Non-insulin dependent diabetes mellitus              |
| C109.12   | Type 2 diabetes mellitus                                     |
| C109.13   | Type II diabetes mellitus                                    |
| C109000   | Non-insulin-dependent diabetes mellitus with renal           |
| C109011   | Type II diabetes mellitus with renal complications           |
| C109012   | Type 2 diabetes mellitus with renal complications            |
| C109100   | Non-insulin-dependent diabetes mellitus with ophthalm comps  |
| C109111   | Type II diabetes mellitus with ophthalmic complica           |
| C109112   | Type 2 diabetes mellitus with ophthalmic complicat           |
| C109200   | Non-insulin-dependent diabetes mellitus with neuro           |
| C109211   | Type II diabetes mellitus with neurological compli           |
| C109212   | Type 2 diabetes mellitus with neurological complications     |
| C109300   | Non-insulin-dependent diabetes mellitus with multi           |
| C109311   | Type II diabetes mellitus with multiple complications        |
| C109312   | Type 2 diabetes mellitus with multiple complications         |
| C109400   | Non-insulin dependent diabetes mellitus with ulcer           |
| C109411   | Type II diabetes mellitus with ulcer                         |
| C109412   | Type 2 diabetes mellitus with ulcer                          |
| C109500   | Non-insulin dependent diabetes mellitus with gangrene        |
| C109511   | Type II diabetes mellitus with gangrene                      |
| C109512   | Type 2 diabetes mellitus with gangrene                       |
| C109600   | Non-insulin-dependent diabetes mellitus with retin           |
| C109611   | Type II diabetes mellitus with retinopathy                   |
| C109612   | Type 2 diabetes mellitus with retinopathy                    |
| C109700   | Non-insulin dependant diabetes mellitus - poor control       |
| C109711   | Type II diabetes mellitus - poor control                     |
| C109712   | Type 2 diabetes mellitus - poor control                      |
| C109900   | Non-insulin-dependent diabetes mellitus without co           |

| Read code | Description                                                  |
|-----------|--------------------------------------------------------------|
| C109911   | Type II diabetes mellitus without complication               |
| C109912   | Type 2 diabetes mellitus without complication                |
| C109A00   | Non-insulin dependent diabetes mellitus with mononeuropathy  |
| C109A11   | Type II diabetes mellitus with mononeuropathy                |
| C109A12   | Type 2 diabetes mellitus with mononeuropathy                 |
| C109B00   | Non-insulin dependent diabetes mellitus with polyneuropathy  |
| C109B11   | Type II diabetes mellitus with polyneuropathy                |
| C109B12   | Type 2 diabetes mellitus with polyneuropathy                 |
| C109C00   | Non-insulin dependent diabetes mellitus with nephr           |
| C109C11   | Type II diabetes mellitus with nephropathy                   |
| C109C12   | Type 2 diabetes mellitus with nephropathy                    |
| C109D00   | Non-insulin dependent diabetes mellitus with hypog           |
| C109D11   | Type II diabetes mellitus with hypoglycaemic coma            |
| C109D12   | Type 2 diabetes mellitus with hypoglycaemic coma             |
| C109E00   | Non-insulin depend diabetes mellitus with diabetic           |
| C109E11   | Type II diabetes mellitus with diabetic cataract             |
| C109E12   | Type 2 diabetes mellitus with diabetic cataract              |
| C109F00   | Non-insulin-dependent d m with peripheral angiopath          |
| C109F11   | Type II diabetes mellitus with peripheral angiopat           |
| C109F12   | Type 2 diabetes mellitus with peripheral angiopathy          |
| C109G00   | Non-insulin dependent diabetes mellitus with arthr           |
| C109G11   | Type II diabetes mellitus with arthropathy                   |
| C109G12   | Type 2 diabetes mellitus with arthropathy                    |
| C109H00   | Non-insulin dependent d m with neuropathic arthropathy       |
| C109H11   | Type II diabetes mellitus with neuropathic arthropathy       |
| C109H12   | Type 2 diabetes mellitus with neuropathic arthropathy        |
| C109J00   | Insulin treated Type 2 diabetes mellitus                     |
| C109J11   | Insulin treated non-insulin dependent diabetes mellitus      |
| C109J12   | Insulin treated Type II diabetes mellitus                    |
| C109K00   | Hyperosmolar non-ketotic state in type 2 diabetes mellitus   |
| C10B.00   | Diabetes mellitus induced by steroids                        |
| C10B000   | Steroid induced diabetes mellitus without complication       |
| C10C.00   | Diabetes mellitus autosomal dominant                         |
| C10C.11   | Maturity onset diabetes in youth                             |
| C10C.12   | Maturity onset diabetes in youth type 1                      |
| C10D.00   | Diabetes mellitus autosomal dominant type 2                  |
| C10D.11   | Maturity onset diabetes in youth type 2                      |
| C10E.12   | Insulin dependent diabetes mellitus                          |
| C10E012   | Insulin-dependent diabetes mellitus with renal complications |
| C10E112   | Insulin-dependent diabetes mellitus with ophthalmic comps    |
| C10E212   | Insulin-dependent diabetes mellitus with neurological comps  |
| C10E312   | Insulin dependent diabetes mellitus with multiple complicat  |
| C10E412   | Unstable insulin dependent diabetes mellitus                 |
| C10E512   | Insulin dependent diabetes mellitus with ulcer               |
| C10E612   | Insulin dependent diabetes mellitus with gangrene            |
| C10E712   | Insulin dependent diabetes mellitus with retinopathy         |
| C10E812   | Insulin dependent diabetes mellitus - poor control           |
| C10E912   | Insulin dependent diabetes maturity onset                    |
| C10EA12   | Insulin-dependent diabetes without complication              |
| C10EB12   | Insulin dependent diabetes mellitus with mononeuropathy      |
| C10EC12   | Insulin dependent diabetes mellitus with polyneuropathy      |
| C10ED12   | Insulin dependent diabetes mellitus with nephropathy         |
| C10EE12   | Insulin dependent diabetes mellitus with hypoglycaemic coma  |
| C10EF12   | Insulin dependent diabetes mellitus with diabetic cataract   |
| C10EG12   | Insulin dependent diab mell with peripheral angiopathy       |
| C10EH12   | Insulin dependent diabetes mellitus with arthropathy         |
| C10EJ12   | Insulin dependent diab mell with neuropathic arthropathy     |
| C10F.00   | Type 2 diabetes mellitus                                     |
| C10F.11   | Type II diabetes mellitus                                    |

| Read code | Description                                                 |
|-----------|-------------------------------------------------------------|
| C10F000   | Type 2 diabetes mellitus with renal complications           |
| C10F011   | Type II diabetes mellitus with renal complications          |
| C10F100   | Type 2 diabetes mellitus with ophthalmic complications      |
| C10F111   | Type II diabetes mellitus with ophthalmic complications     |
| C10F200   | Type 2 diabetes mellitus with neurological complications    |
| C10F211   | Type II diabetes mellitus with neurological complications   |
| C10F300   | Type 2 diabetes mellitus with multiple complications        |
| C10F311   | Type II diabetes mellitus with multiple complications       |
| C10F400   | Type 2 diabetes mellitus with ulcer                         |
| C10F411   | Type II diabetes mellitus with ulcer                        |
| C10F500   | Type 2 diabetes mellitus with gangrene                      |
| C10F511   | Type II diabetes mellitus with gangrene                     |
| C10F600   | Type 2 diabetes mellitus with retinopathy                   |
| C10F611   | Type II diabetes mellitus with retinopathy                  |
| C10F700   | Type 2 diabetes mellitus - poor control                     |
| C10F711   | Type II diabetes mellitus - poor control                    |
| C10F900   | Type 2 diabetes mellitus without complication               |
| C10F911   | Type II diabetes mellitus without complication              |
| C10FA00   | Type 2 diabetes mellitus with mononeuropathy                |
| C10FA11   | Type II diabetes mellitus with mononeuropathy               |
| C10FB00   | Type 2 diabetes mellitus with polyneuropathy                |
| C10FB11   | Type II diabetes mellitus with polyneuropathy               |
| C10FC00   | Type 2 diabetes mellitus with nephropathy                   |
| C10FC11   | Type II diabetes mellitus with nephropathy                  |
| C10FD00   | Type 2 diabetes mellitus with hypoglycaemic coma            |
| C10FD11   | Type II diabetes mellitus with hypoglycaemic coma           |
| C10FE00   | Type 2 diabetes mellitus with diabetic cataract             |
| C10FE11   | Type II diabetes mellitus with diabetic cataract            |
| C10FF00   | Type 2 diabetes mellitus with peripheral angiopathy         |
| C10FF11   | Type II diabetes mellitus with peripheral angiopathy        |
| C10FG00   | Type 2 diabetes mellitus with arthropathy                   |
| C10FG11   | Type II diabetes mellitus with arthropathy                  |
| C10FH00   | Type 2 diabetes mellitus with neuropathic arthropathy       |
| C10FH11   | Type II diabetes mellitus with neuropathic arthropathy      |
| C10FJ00   | Insulin treated Type 2 diabetes mellitus                    |
| C10FJ11   | Insulin treated Type II diabetes mellitus                   |
| C10FK00   | Hyperosmolar non-ketotic state in type 2 diabetes mellitus  |
| C10FK11   | Hyperosmolar non-ketotic state in type II diabetes mellitus |
| C10FL00   | Type 2 diabetes mellitus with persistent proteinuria        |
| C10FL11   | Type II diabetes mellitus with persistent proteinuria       |
| C10FM00   | Type 2 diabetes mellitus with persistent microalbuminuria   |
| C10FM11   | Type II diabetes mellitus with persistent microalbuminuria  |
| C10FN00   | Type 2 diabetes mellitus with ketoacidosis                  |
| C10FN11   | Type II diabetes mellitus with ketoacidosis                 |
| C10FP00   | Type 2 diabetes mellitus with ketoacidotic coma             |
| C10FP11   | Type II diabetes mellitus with ketoacidotic coma            |
| C10FQ00   | Type 2 diabetes mellitus with exudative maculopathy         |
| C10FQ11   | Type II diabetes mellitus with exudative maculopathy        |
| C10FR00   | Type 2 diabetes mellitus with gastroparesis                 |
| C10FR11   | Type II diabetes mellitus with gastroparesis                |
| C10G.00   | Secondary pancreatic diabetes mellitus                      |
| C10G000   | Secondary pancreatic diabetes mellitus without complication |
| C10H.00   | Diabetes mellitus induced by non-steroid drugs              |
| C10H000   | DM induced by non-steroid drugs without complication        |
| C10L.00   | Fibrocalculus pancreatopathy                                |
| C10L000   | Fibrocalculus pancreatopathy without complication           |
| C10M.00   | Lipoatrophic diabetes mellitus                              |
| C10M000   | Lipoatrophic diabetes mellitus without complication         |
| C10N.00   | Secondary diabetes mellitus                                 |

| Read code | Description                                               |
|-----------|-----------------------------------------------------------|
| C10N000   | Secondary diabetes mellitus without complication          |
| C10N100   | Cystic fibrosis related diabetes mellitus                 |
| C10P.00   | Diabetes mellitus in remission                            |
| C10P100   | Type II diabetes mellitus in remission                    |
| C10P111   | Type 2 diabetes mellitus in remission                     |
| C10Q.00   | Maturity onset diabetes of the young type 5               |
| C10y.00   | Diabetes mellitus with other specified manifestation      |
| C10y100   | Diabetes mellitus, adult, + other specified manifestation |
| C10yy00   | Other specified diabetes mellitus with other spec comps   |
| C10yz00   | Diabetes mellitus NOS with other specified manifestation  |
| C10z.00   | Diabetes mellitus with unspecified complication           |
| C10z100   | Diabetes mellitus; adult onset; + unspecified comp        |
| C10zy00   | Other specified diabetes mellitus with unspecified comps  |
| C10zz00   | Diabetes mellitus NOS with unspecified complication       |
| C11y000   | Steroid induced diabetes                                  |
| Cyu2.00   | [X]Diabetes mellitus                                      |
| Cyu2000   | [X]Other specified diabetes mellitus                      |
| Cyu2300   | [X]Unspecified diabetes mellitus with renal compli        |
| F171100   | Autonomic neuropathy due to diabetes                      |
| F345000   | Diabetic mononeuritis multiplex                           |
| F35z000   | Diabetic mononeuritis NOS                                 |
| F372.00   | Polyneuropathy in diabetes                                |
| F372.11   | Diabetic polyneuropathy                                   |
| F372.12   | Diabetic neuropathy                                       |
| F372000   | Acute painful diabetic neuropathy                         |
| F372100   | Chronic painful diabetic neuropathy                       |
| F372200   | Asymptomatic diabetic neuropathy                          |
| F381300   | Myasthenic syndrome due to diabetic amyotrophy            |
| F381311   | Diabetic amyotrophy                                       |
| F3y0.00   | Diabetic mononeuropathy                                   |
| F420.00   | Diabetic retinopathy                                      |
| F420000   | Background diabetic retinopathy                           |
| F420100   | Proliferative diabetic retinopathy                        |
| F420200   | Preproliferative diabetic retinopathy                     |
| F420300   | Advanced diabetic maculopathy                             |
| F420400   | Diabetic maculopathy                                      |
| F420500   | Advanced diabetic retinal disease                         |
| F420600   | Non proliferative diabetic retinopathy                    |
| F420700   | High risk proliferative diabetic retinopathy              |
| F420800   | High risk non proliferative diabetic retinopathy          |
| F420z00   | Diabetic retinopathy NOS                                  |
| F440700   | Diabetic iritis                                           |
| F464000   | Diabetic cataract                                         |
| G73y000   | Diabetic peripheral angiopathy                            |
| K01x100   | Nephrotic syndrome in diabetes mellitus                   |
| K01x111   | Kimmelstiel - Wilson disease                              |
| K08yA00   | Proteinuric diabetic nephropathy                          |
| K08yA11   | Clinical diabetic nephropathy                             |
| K27y700   | Erectile dysfunction due to diabetes mellitus             |
| Kyu0300   | [X]Glomerular disorders in diabetes mellitus              |
| L180.00   | Diabetes mellitus during pregnancy/childbirth/puer        |
| L180000   | Diabetes mellitus - unspec whether in pregnancy/pu        |
| L180100   | Diabetes mellitus during pregnancy - baby delivere        |
| L180300   | Diabetes mellitus during pregnancy - baby not yet         |
| L180400   | Diabetes mellitus in puerperium - baby previously d       |
| L180500   | Pre-existing diabetes mellitus; insulin-dependent         |
| L180600   | Pre-existing diabetes mellitus, non-insulin-dependent     |
| L180700   | Pre-existing malnutrition-related diabetes mellitus       |
| L180800   | Diabetes mellitus arising in pregnancy                    |

| Read code | Description                                        |
|-----------|----------------------------------------------------|
| L180X00   | Pre-existing diabetes mellitus, unspecified        |
| L180z00   | Diabetes mellitus in pregnancy/childbirth/puerperi |
| Lyu2900   | [X]Pre-existing diabetes mellitus; unspecified     |
| M037200   | Cellulitis in diabetic foot                        |
| M21yC00   | Insulin lipohypertrophy                            |
| M21yC11   | Insulin site lipohypertrophy                       |
| M271000   | Ischaemic ulcer diabetic foot                      |
| M271100   | Neuropathic diabetic ulcer - foot                  |
| M271200   | Mixed diabetic ulcer - foot                        |
| N030000   | Diabetic cheiroarthropathy                         |
| N030011   | Diabetic cheiropathy                               |
| N030100   | Diabetic Charcot arthropathy                       |
| R054200   | [D]Gangrene of toe in diabetic                     |
| R054300   | [D]Widespread diabetic foot gangrene               |
| ZC2C800   | Dietary advice for diabetes mellitus               |
| ZC2C911   | Diet advice for insulin-dependent diabetes         |
| ZC2CA00   | Dietary advice for type II diabetes                |
| ZL22500   | Under care of diabetic liaison nurse               |
| ZL62500   | Referral to diabetes nurse                         |
| ZL62600   | Referral to diabetic liaison nurse                 |
| ZLA2500   | Seen by diabetic liaison nurse                     |
| ZLD7500   | Discharge by diabetic liaison nurse                |
| ZRB4.00   | Diabetes clinic satisfaction questionnaire         |
| ZRB4.11   | CSQ - Diabetes clinic satisfaction questionnaire   |
| ZRB5.00   | Diabetes treatment satisfaction questionnaire      |
| ZRB5.11   | DTSQ - Diabetes treatment satisfaction questionnai |
| ZRB6.00   | Diabetes wellbeing questionnaire                   |
| ZRB6.11   | DWBQ - Diabetes wellbeing questionnaire            |
| ZRBa.00   | Education score - diabetes                         |
| ZRBH.00   | Perceived control of insulin-dependent diabetes    |
| ZV65312   | [V]Dietary counselling in diabetes mellitus        |

**Appendix table XXIII.4: Drug codes for non-metformin diabetes mellitus medications**

| Drug code | Generic name                                                                                 |
|-----------|----------------------------------------------------------------------------------------------|
| 24146978  | International normalised ratio testing strips                                                |
| 34147978  | Sterile single use needle                                                                    |
| 37903978  | Lancets sterile single use 1.5mm/25gauge                                                     |
| 37946978  | Hypodermic insulin needles for pre-filled / reusable pen injectors screw on 4mm/32gauge      |
| 37960978  | Lancets sterile single use 0.31mm/30gauge                                                    |
| 37961978  | Lancets sterile single use 1.8mm/23gauge                                                     |
| 38535978  | Lancets sterile single use 0.2mm/33gauge                                                     |
| 38584978  | Lancets sterile single use 0.36mm/28gauge                                                    |
| 39144978  | Albiglutide 30mg powder and solvent for solution for injection pre-filled disposable devices |
| 39174978  | Urine testing strips                                                                         |
| 39175978  | Urine testing strips                                                                         |
| 39291978  | Lancets sterile single use 0.36mm/28gauge                                                    |
| 39422978  | Gliclazide 60mg modified-release tablets                                                     |
| 39657978  | Blood glucose biosensor testing strips                                                       |
| 39755978  | Gliclazide 30mg modified-release tablets                                                     |
| 39897978  | Lancets sterile single use 1.6mm/30gauge                                                     |
| 39914978  | Lancets sterile single use 2.2mm/23gauge                                                     |
| 39923978  | Hypodermic insulin needles for pre-filled / reusable pen injectors screw on 10mm/29gauge     |
| 39941978  | Hypodermic insulin needles for pre-filled / reusable pen injectors screw on 4mm/32gauge      |
| 39964978  | Lancets sterile single use 0.31mm/30gauge                                                    |
| 39965978  | Lancets sterile single use 1.8mm/28gauge                                                     |
| 42390978  | Lancets sterile single use 1.8mm/26gauge                                                     |



| Drug code | Generic name                                                                                                             |
|-----------|--------------------------------------------------------------------------------------------------------------------------|
| 42480978  | Hypodermic insulin needles for pre-filled / reusable pen injectors screw on 8mm/31gauge                                  |
| 42481978  | Hypodermic insulin needles for pre-filled / reusable pen injectors screw on 6mm/31gauge                                  |
| 42482978  | Hypodermic insulin needles for pre-filled / reusable pen injectors screw on 5mm/31gauge                                  |
| 42492978  | Blood glucose biosensor testing strips                                                                                   |
| 45821978  | Empagliflozin 5mg / Metformin 850mg tablets                                                                              |
| 45822978  | Empagliflozin 5mg / Metformin 850mg tablets                                                                              |
| 45823978  | Empagliflozin 5mg / Metformin 1g tablets                                                                                 |
| 45824978  | Empagliflozin 5mg / Metformin 1g tablets                                                                                 |
| 45825978  | Empagliflozin 12.5mg / Metformin 850mg tablets                                                                           |
| 45826978  | Empagliflozin 12.5mg / Metformin 850mg tablets                                                                           |
| 45827978  | Empagliflozin 12.5mg / Metformin 1g tablets                                                                              |
| 45828978  | Empagliflozin 12.5mg / Metformin 1g tablets                                                                              |
| 45845978  | Sterile subcutaneous drug delivery device 79cm tubing 9mm inserter/retractor                                             |
| 45849978  | Sterile subcutaneous drug delivery device 107cm tubing 6mm inserter/retractor                                            |
| 46211978  | Blood glucose biosensor testing strips                                                                                   |
| 46212978  | Blood glucose biosensor testing strips                                                                                   |
| 46282978  | Insulin glargine 100units/ml solution for injection 3ml pre-filled disposable devices                                    |
| 46283978  | Insulin glargine 100units/ml solution for injection 3ml cartridges                                                       |
| 46889978  | Insulin glargine 300units/ml solution for injection 1.5ml pre-filled disposable devices                                  |
| 46890978  | Insulin glargine 300units/ml solution for injection 1.5ml pre-filled disposable devices                                  |
| 47074978  | Insulin glulisine 100units/ml solution for injection 3ml pre-filled disposable devices                                   |
| 47511978  | Blood glucose colorimetric cassette                                                                                      |
| 47638978  | Blood glucose biosensor testing strips                                                                                   |
| 47640978  | Urine ketones testing strips                                                                                             |
| 47709978  | Pioglitazone 30mg tablets                                                                                                |
| 47997978  | Lancets sterile single use 2.2mm/23gauge                                                                                 |
| 48001978  | Lancets sterile single use 1.8mm/30gauge                                                                                 |
| 48012978  | Lancets sterile single use 1.8mm/28gauge                                                                                 |
| 50823978  | Lancets sterile single use 1.8mm/26gauge                                                                                 |
| 51006978  | Hypodermic insulin needles for pre-filled / reusable pen injectors screw on 4mm/32gauge                                  |
| 51014978  | Hypodermic insulin injection pen reusable for 3ml cartridge 0.5 unit dial up / range 1-30 units                          |
| 51015978  | Hypodermic insulin injection pen reusable for 3ml cartridge 0.5 unit dial up / range 1-30 units                          |
| 51016978  | Hypodermic insulin injection pen reusable for 3ml cartridge 0.5 unit dial up / range 1-30 units                          |
| 51053978  | Hypodermic insulin injection pen reusable for 3ml cartridge 1 unit dial up / range 1-60 units                            |
| 51054978  | Hypodermic insulin injection pen reusable for 3ml cartridge 1 unit dial up / range 1-60 units                            |
| 51055978  | Sterile single use needle                                                                                                |
| 51391978  | Insulin lispro 200units/ml solution for injection 3ml pre-filled disposable devices                                      |
| 52039979  | Lixisenatide 20micrograms/0.2ml solution for injection 3ml pre-filled disposable devices                                 |
| 52040979  | Lixisenatide 20micrograms/0.2ml solution for injection 3ml pre-filled disposable devices                                 |
| 52041979  | Lixisenatide 10micrograms/0.2ml solution for injection 3ml pre-filled disposable devices                                 |
| 52042979  | Lixisenatide 10micrograms/0.2ml solution for injection 3ml pre-filled disposable devices and Lixisenatide 20micrograms/0 |
| 52043979  | Lixisenatide 10micrograms/0.2ml solution for injection 3ml pre-filled disposable devices                                 |
| 52044979  | Lixisenatide 10micrograms/0.2ml solution for injection 3ml pre-filled disposable devices                                 |
| 52067979  | Insulin degludec 200units/ml solution for injection 3ml pre-filled disposable devices                                    |
| 52068979  | Insulin degludec 200units/ml solution for injection 3ml pre-filled disposable devices                                    |
| 52069979  | Insulin degludec 100units/ml solution for injection 3ml pre-filled disposable devices                                    |
| 52070979  | Insulin degludec 100units/ml solution for injection 3ml pre-filled disposable devices                                    |
| 52071979  | Insulin degludec 100units/ml solution for injection 3ml cartridges                                                       |
| 52072979  | Insulin degludec 100units/ml solution for injection 3ml cartridges                                                       |
| 52123979  | Lancets sterile single use 0.38mm/30gauge                                                                                |
| 52296979  | Blood glucose biosensor testing strips                                                                                   |
| 53004979  | Saxagliptin 2.5mg / Metformin 850mg tablets                                                                              |
| 53005979  | Saxagliptin 2.5mg / Metformin 850mg tablets                                                                              |
| 53006979  | Saxagliptin 2.5mg / Metformin 1g tablets                                                                                 |
| 53007979  | Saxagliptin 2.5mg / Metformin 1g tablets                                                                                 |
| 53029979  | Hypodermic insulin needles for pre-filled / reusable pen injectors screw on 8mm/32gauge                                  |
| 53031979  | Hypodermic insulin needles for pre-filled / reusable pen injectors screw on 6mm/32gauge                                  |

| Drug code | Generic name                                                                                                  |
|-----------|---------------------------------------------------------------------------------------------------------------|
| 53080979  | Hypodermic insulin needles for pre-filled / reusable pen injectors screw on 4mm/32gauge                       |
| 53153979  | Hypodermic insulin needles for pre-filled / reusable pen injectors screw on 8mm/31gauge                       |
| 53154979  | Hypodermic insulin needles for pre-filled / reusable pen injectors screw on 6mm/31gauge                       |
| 53155979  | Hypodermic insulin needles for pre-filled / reusable pen injectors screw on 5mm/31gauge                       |
| 53156979  | Hypodermic insulin needles for pre-filled / reusable pen injectors screw on 12mm/29gauge                      |
| 53325979  | Dapagliflozin 5mg tablets                                                                                     |
| 53326979  | Dapagliflozin 5mg tablets                                                                                     |
| 53327979  | Dapagliflozin 10mg tablets                                                                                    |
| 53328979  | Dapagliflozin 10mg tablets                                                                                    |
| 53431978  | Dulaglutide 1.5mg/0.5ml solution for injection pre-filled disposable devices                                  |
| 53432978  | Dulaglutide 1.5mg/0.5ml solution for injection pre-filled disposable devices                                  |
| 53433978  | Dulaglutide 0.75mg/0.5ml solution for injection pre-filled disposable devices                                 |
| 53434978  | Dulaglutide 0.75mg/0.5ml solution for injection pre-filled disposable devices                                 |
| 54904979  | Linagliptin 2.5mg / Metformin 850mg tablets                                                                   |
| 54905979  | Linagliptin 2.5mg / Metformin 850mg tablets                                                                   |
| 54906979  | Linagliptin 2.5mg / Metformin 1g tablets                                                                      |
| 54907979  | Linagliptin 2.5mg / Metformin 1g tablets                                                                      |
| 54980979  | Sterile subcutaneous drug delivery device 100cm tubing 4 x 10mm needle 27gauge                                |
| 54986979  | Sterile subcutaneous drug delivery device 100cm tubing 3 x 10mm needle 27gauge                                |
| 54988979  | Sterile subcutaneous drug delivery device 100cm tubing 2 x 8mm needle 27gauge                                 |
| 54990979  | Sterile subcutaneous drug delivery device 100cm tubing 2 x 10mm needle 27gauge                                |
| 55150978  | Exenatide 2mg powder and solvent for prolonged-release suspension for injection pre-filled disposable devices |
| 55151978  | Exenatide 2mg powder and solvent for prolonged-release suspension for injection pre-filled disposable devices |
| 55225978  | Gliclazide 60mg modified-release tablets                                                                      |
| 55255978  | Hypodermic insulin needles for pre-filled / reusable pen injectors screw on 4mm/32gauge                       |
| 55256978  | Hypodermic insulin needles for pre-filled / reusable pen injectors screw on 4mm/32gauge                       |
| 55534979  | Hypodermic insulin needles for pre-filled / reusable pen injectors screw on 8mm/31gauge                       |
| 55535979  | Hypodermic insulin needles for pre-filled / reusable pen injectors screw on 6mm/31gauge                       |
| 55538979  | Blood glucose biosensor testing strips                                                                        |
| 55553979  | Insulin glargine 100units/ml solution for injection 3ml pre-filled disposable devices                         |
| 55692978  | Hypodermic insulin needles for pre-filled / reusable pen injectors screw on 8mm/31gauge                       |
| 55693978  | Hypodermic insulin needles for pre-filled / reusable pen injectors screw on 5mm/31gauge                       |
| 55694978  | Blood glucose biosensor testing strips                                                                        |
| 55773978  | Gliclazide 30mg modified-release tablets                                                                      |
| 55818978  | Insulin degludec 100units/ml / Liraglutide 3.6mg/ml solution for injection 3ml pre-filled disposable devices  |
| 55819978  | Insulin degludec 100units/ml / Liraglutide 3.6mg/ml solution for injection 3ml pre-filled disposable devices  |
| 55842978  | Liraglutide 6mg/ml solution for injection 3ml pre-filled disposable devices                                   |
| 56079979  | Lancets sterile single use 0.36mm/28gauge                                                                     |
| 56080979  | Blood glucose biosensor testing strips                                                                        |
| 56220979  | Sterile subcutaneous drug delivery device 110cm tubing 6mm needle 29gauge                                     |
| 56222979  | Sterile subcutaneous drug delivery device 110cm tubing 6mm needle 27gauge                                     |
| 56860978  | Blood glucose biosensor testing strips                                                                        |
| 56861978  | Blood glucose biosensor testing strips                                                                        |
| 56930978  | Canagliflozin 50mg / Metformin 850mg tablets                                                                  |
| 56931978  | Canagliflozin 50mg / Metformin 1g tablets                                                                     |
| 56932978  | Canagliflozin 50mg / Metformin 1g tablets                                                                     |
| 57030978  | Hypodermic insulin needles for pre-filled / reusable pen injectors screw on 4mm/32gauge                       |
| 57874979  | Lancets sterile single use 0.32mm/28gauge                                                                     |
| 58748979  | Lancets sterile single use 0.34mm/28gauge                                                                     |
| 59221978  | Hypodermic insulin needles for pre-filled / reusable pen injectors screw on 8mm/31gauge                       |
| 59222978  | Hypodermic insulin needles for pre-filled / reusable pen injectors screw on 6mm/31gauge                       |
| 59223978  | Hypodermic insulin needles for pre-filled / reusable pen injectors screw on 5mm/31gauge                       |
| 59361979  | Blood glucose biosensor testing strips                                                                        |
| 59362979  | Blood glucose biosensor testing strips                                                                        |
| 59363979  | Blood glucose biosensor testing strips                                                                        |
| 59371979  | Sitagliptin 50mg tablets                                                                                      |

| <b>Drug code</b> | <b>Generic name</b>                                                                               |
|------------------|---------------------------------------------------------------------------------------------------|
| 59372979         | Sitagliptin 50mg tablets                                                                          |
| 59373979         | Sitagliptin 25mg tablets                                                                          |
| 59374979         | Sitagliptin 25mg tablets                                                                          |
| 60057979         | Hypodermic insulin needles for pre-filled / reusable pen injectors screw on 8mm/31gauge           |
| 60058979         | Hypodermic insulin needles for pre-filled / reusable pen injectors screw on 6mm/31gauge           |
| 60059979         | Hypodermic insulin needles for pre-filled / reusable pen injectors screw on 5mm/31gauge           |
| 60060979         | Hypodermic insulin needles for pre-filled / reusable pen injectors screw on 5mm/31gauge           |
| 60061979         | Hypodermic insulin needles for pre-filled / reusable pen injectors screw on 12mm/29gauge          |
| 60062979         | Lancets sterile single use 0.36mm/28gauge                                                         |
| 60064979         | Insulin aspart 100units/ml solution for injection 3ml cartridges                                  |
| 60068979         | Blood glucose biosensor testing strips                                                            |
| 60937979         | Lancets sterile single use 0.2mm/33gauge                                                          |
| 62300979         | Insulin human 100units/ml solution for injection 3.15ml cartridges                                |
| 62836979         | Gliclazide 40mg tablets                                                                           |
| 64797979         | Insulin human 100units/ml solution for injection 10ml vials                                       |
| 67235994         | Hypodermic insulin injection pen reusable for 3ml cartridge 0.5 unit dial up / range 0.5-30 units |
| 67236994         | Hypodermic insulin injection pen reusable for 3ml cartridge 0.5 unit dial up / range 0.5-30 units |
| 67237994         | Hypodermic insulin needles for pre-filled / reusable pen injectors screw on 5mm/30gauge           |
| 67238994         | Lancets sterile single use 0.36mm/28gauge                                                         |
| 67266994         | Blood glucose biosensor testing strips                                                            |
| 67276994         | Sterile subcutaneous drug delivery device 110cm tubing 17mm needle 24gauge                        |
| 67277994         | Sterile single use needle                                                                         |
| 67278994         | Sterile subcutaneous drug delivery device 110cm tubing 13mm needle 24gauge                        |
| 67283994         | Sterile subcutaneous drug delivery device 60cm tubing 13mm needle 24gauge                         |
| 67373994         | Lancets sterile single use 0.35mm/28gauge                                                         |
| 67377994         | Lancets sterile single use 0.35mm/28gauge                                                         |
| 67447994         | Hypodermic insulin needles for pre-filled / reusable pen injectors screw on 12mm/29gauge          |
| 67448994         | Hypodermic insulin needles for pre-filled / reusable pen injectors screw on 10mm/30gauge          |
| 67451994         | Hypodermic insulin needles for pre-filled / reusable pen injectors screw on 8mm/31gauge           |
| 67452994         | Hypodermic insulin needles for pre-filled / reusable pen injectors screw on 6mm/31gauge           |
| 67458994         | Lancets sterile single use 0.2mm/33gauge                                                          |
| 67734994         | Lancets sterile single use 0.3mm/30gauge                                                          |
| 67739994         | Blood glucose biosensor testing strips                                                            |
| 67742994         | Lancets sterile single use 0.3mm/30gauge                                                          |
| 67743994         | Sterile single use needle                                                                         |
| 67745994         | Blood glucose biosensor testing strips                                                            |
| 67757994         | Hypodermic insulin injection pen reusable for 3ml cartridge 1 unit dial up / range 1-60 units     |
| 67758994         | Hypodermic insulin injection pen reusable for 3ml cartridge 1 unit dial up / range 1-60 units     |
| 67789994         | Sterile dt type a lancets                                                                         |
| 67790994         | Hypodermic insulin needles for pre-filled / reusable pen injectors screw on 8mm/29gauge           |
| 67806994         | Needle free Insulin delivery system                                                               |
| 67807994         | Needle free Insulin delivery system                                                               |
| 67808994         | Needle free Insulin delivery system                                                               |
| 67809994         | Needle free Insulin delivery system                                                               |
| 67821994         | Lancets sterile single use 0.36mm/28gauge                                                         |
| 67825994         | Lancets sterile single use 2.4mm/23gauge                                                          |
| 67827994         | Lancets sterile single use 2.4mm/21gauge                                                          |
| 67828994         | Lancets sterile single use 1.8mm/28gauge                                                          |
| 67829994         | Lancets sterile single use 1.8mm/26gauge                                                          |
| 68165994         | Lancets sterile single use 0.4mm/28gauge                                                          |
| 68335994         | Sterile single use needle                                                                         |
| 68338994         | Blood glucose biosensor testing strips                                                            |
| 68575978         | Blood glucose biosensor testing strips                                                            |
| 68690978         | Gliclazide 30mg modified-release tablets                                                          |
| 68748978         | Insulin aspart 100units/ml solution for injection 1.6ml cartridges                                |
| 68749978         | Insulin aspart 100units/ml solution for injection 3ml cartridges                                  |
| 69169994         | Blood ketones testing strips                                                                      |
| 70221978         | Blood glucose biosensor testing strips                                                            |

| <b>Drug code</b> | <b>Generic name</b>                                                                           |
|------------------|-----------------------------------------------------------------------------------------------|
| 70445978         | Empagliflozin 25mg tablets                                                                    |
| 70446978         | Empagliflozin 25mg tablets                                                                    |
| 70447978         | Empagliflozin 10mg tablets                                                                    |
| 70448978         | Empagliflozin 10mg tablets                                                                    |
| 70473994         | Lancets sterile single use 0.31mm/30gauge                                                     |
| 70953994         | Urine ketones testing strips                                                                  |
| 70954994         | Urine glucose testing strips                                                                  |
| 70955994         | Blood glucose biosensor testing strips                                                        |
| 70998994         | Blood glucose biosensor testing strips                                                        |
| 71018994         | Blood glucose biosensor testing strips                                                        |
| 71039994         | Blood glucose biosensor testing strips                                                        |
| 71126994         | Lancets sterile single use 0.375mm/28gauge                                                    |
| 71254994         | Hypodermic insulin needles for pre-filled / reusable pen injectors screw on 5mm/32gauge       |
| 71255994         | Hypodermic insulin needles for pre-filled / reusable pen injectors screw on 5mm/32gauge       |
| 71403979         | GSF-Syrup oral gel 18g sachets                                                                |
| 71405979         | GSF-Syrup oral gel 18g sachets                                                                |
| 71406979         | GSF-Syrup oral gel 18g sachets                                                                |
| 71407979         | GSF-Syrup oral gel 18g sachets                                                                |
| 71799979         | Insulin lispro biphasic 50/50 100units/ml suspension for injection 3ml cartridges             |
| 72088994         | Hypodermic insulin needles for pre-filled / reusable pen injectors screw on 6mm/31gauge       |
| 72103994         | Lancets sterile single use 0.3mm/30gauge                                                      |
| 72106994         | Blood glucose biosensor testing strips                                                        |
| 72402994         | Blood glucose colorimetric testing tips                                                       |
| 72423994         | Hypodermic insulin injection pen reusable for 3ml cartridge 1 unit dial up / range 1-80 units |
| 72430994         | Hypodermic insulin injection pen reusable for 3ml cartridge 1 unit dial up / range 1-80 units |
| 72618994         | Sterile single use needle                                                                     |
| 72664994         | Blood glucose biosensor testing strips                                                        |
| 72711994         | Sterile dt type c lancets                                                                     |
| 72716994         | Blood glucose biosensor testing strips                                                        |
| 72722994         | Lancets sterile single use 0.31mm/30gauge                                                     |
| 72898978         | Urine testing strips                                                                          |
| 72899978         | Urine testing strips                                                                          |
| 73087978         | Lancets sterile single use 1.6mm/28gauge                                                      |
| 73093978         | Lancets sterile single use 1.5mm/30gauge                                                      |
| 73165978         | Lancets sterile single use 1.8mm/21gauge                                                      |
| 73166978         | Lancets sterile single use 0.2mm/33gauge                                                      |
| 73401978         | Hypodermic insulin needles for pre-filled / reusable pen injectors screw on 4mm/33gauge       |
| 73980994         | Lancets sterile single use 0.5mm/28gauge                                                      |
| 74779994         | Sterile subcutaneous drug delivery device 110cm tubing 10mm needle 29gauge                    |
| 74780994         | Sterile subcutaneous drug delivery device 110cm tubing 10mm needle 27gauge                    |
| 74782994         | Sterile subcutaneous drug delivery device 110cm tubing 8mm needle 29gauge                     |
| 74790994         | Sterile subcutaneous drug delivery device 110cm tubing 8mm needle 27gauge                     |
| 74791994         | Sterile subcutaneous drug delivery device 60cm tubing 10mm needle 29gauge                     |
| 74797994         | Sterile subcutaneous drug delivery device 60cm tubing 8mm needle 29gauge                      |
| 74817994         | Blood glucose biosensor testing strips                                                        |
| 75007994         | Lancets sterile single use 0.3mm/30gauge                                                      |
| 75771994         | Blood glucose biosensor testing strips                                                        |
| 75848994         | Lancets sterile single use 0.36mm/28gauge                                                     |
| 75997978         | Lancets sterile single use 0.2mm/33gauge                                                      |
| 76192978         | Blood glucose biosensor testing strips                                                        |
| 76193978         | Blood glucose biosensor testing strips                                                        |
| 76399978         | Canagliflozin 300mg tablets                                                                   |
| 76400978         | Canagliflozin 300mg tablets                                                                   |
| 76401978         | Canagliflozin 100mg tablets                                                                   |
| 76402978         | Canagliflozin 100mg tablets                                                                   |
| 76620994         | Lancets sterile single use 0.2mm/33gauge                                                      |
| 76624994         | Blood glucose biosensor testing strips                                                        |
| 76625994         | Blood glucose biosensor testing strips                                                        |

| <b>Drug code</b> | <b>Generic name</b>                                                                                                       |
|------------------|---------------------------------------------------------------------------------------------------------------------------|
| 76725994         | Hypodermic insulin injection pen reusable for 3ml cartridge 1 unit dial up / range 1-60 units                             |
| 76822978         | Blood glucose biosensor testing strips                                                                                    |
| 76980978         | Canagliflozin 100mg tablets                                                                                               |
| 76981978         | Canagliflozin 100mg tablets                                                                                               |
| 76990978         | Dapagliflozin 5mg / Metformin 850mg tablets                                                                               |
| 76991978         | Dapagliflozin 5mg / Metformin 850mg tablets                                                                               |
| 76992978         | Dapagliflozin 5mg / Metformin 1g tablets                                                                                  |
| 76993978         | Dapagliflozin 5mg / Metformin 1g tablets                                                                                  |
| 77040978         | Sterile subcutaneous drug delivery device 60cm tubing 9mm needle 27gauge                                                  |
| 77042978         | Sterile subcutaneous drug delivery device 60cm tubing 6mm needle 27gauge                                                  |
| 77044978         | Sterile subcutaneous drug delivery device 110cm tubing 9mm needle 27gauge                                                 |
| 77046978         | Sterile subcutaneous drug delivery device 110cm tubing 6mm needle 22gauge                                                 |
| 77052978         | Lancets sterile single use 1.8mm/18gauge                                                                                  |
| 77054978         | Hypodermic insulin needles for pre-filled / reusable pen injectors snap on 4mm/32gauge                                    |
| 77081978         | Lancets sterile single use 2.4mm/26gauge                                                                                  |
| 77097978         | Lancets sterile single use 1.8mm/28gauge                                                                                  |
| 77656994         | Hypodermic u100 insulin syringe sterile single use / single patient use 1ml with 12mm safety needle 0.33mm/29gauge        |
| 77660994         | Hypodermic U100 insulin syringe sterile single use / single patient use 1ml with not less than 12mm needle 0.33mm/29gauge |
| 77688994         | Blood glucose biosensor testing strips                                                                                    |
| 77711994         | Sterile dt type b lancets                                                                                                 |
| 78065994         | Neuropathy sweat detection pads                                                                                           |
| 78070978         | Lancets sterile single use 2.4mm/21gauge                                                                                  |
| 78071978         | Lancets sterile single use 1.8mm/26gauge                                                                                  |
| 78072978         | Lancets sterile single use 1.8mm/21gauge                                                                                  |
| 78150994         | Blood glucose biosensor testing strips                                                                                    |
| 78321994         | Lancets sterile single use 0.2mm/33gauge                                                                                  |
| 78324994         | Lancets sterile single use 0.35mm/28gauge                                                                                 |
| 78340994         | Lancets sterile single use 0.315mm/30gauge                                                                                |
| 78443978         | Hypodermic insulin needles for pre-filled / reusable pen injectors screw on 4mm/32gauge                                   |
| 78457978         | Lancets sterile single use 0.31mm/30gauge                                                                                 |
| 78541979         | Lancets sterile single use 0.2mm/33gauge                                                                                  |
| 78723978         | Alogliptin 6.25mg tablets                                                                                                 |
| 78724978         | Alogliptin 6.25mg tablets                                                                                                 |
| 78725978         | Alogliptin 25mg tablets                                                                                                   |
| 78726978         | Alogliptin 25mg tablets                                                                                                   |
| 78727978         | Alogliptin 12.5mg tablets                                                                                                 |
| 78728978         | Alogliptin 12.5mg tablets                                                                                                 |
| 78729978         | Alogliptin 12.5mg / Metformin 1g tablets                                                                                  |
| 78730978         | Alogliptin 12.5mg / Metformin 1g tablets                                                                                  |
| 78813994         | Hypodermic insulin injection pen reusable for 3ml cartridge 1 unit dial up / range 1-60 units                             |
| 78814994         | Hypodermic insulin injection pen reusable for 3ml cartridge 1 unit dial up / range 1-60 units                             |
| 78878994         | Blood glucose biosensor testing strips                                                                                    |
| 78942994         | Blood glucose biosensor testing strips                                                                                    |
| 79389978         | Hypodermic u100 insulin syringe sterile single use / single patient use 0.3ml with 8mm safety needle 0.25mm/31gauge       |
| 79407978         | Urine testing strips                                                                                                      |
| 79408978         | Hypodermic u100 insulin syringe sterile single use / single patient use 0.5ml with 8mm safety needle 0.3mm/30gauge        |
| 79409978         | Hypodermic u100 insulin syringe sterile single use / single patient use 0.5ml with 12mm safety needle 0.33mm/29gauge      |
| 79410978         | Hypodermic insulin needles for pre-filled / reusable pen injectors screw on 6mm/32gauge                                   |
| 79413978         | Hypodermic insulin needles for pre-filled / reusable pen injectors screw on 4mm/32gauge                                   |
| 79414978         | Hypodermic u100 insulin syringe sterile single use / single patient use 1ml with 12mm safety needle 0.33mm/29gauge        |
| 79645994         | Blood glucose biosensor testing strips                                                                                    |
| 79699978         | Hypodermic insulin needles for pre-filled / reusable pen injectors screw on 8mm/31gauge                                   |

| <b>Drug code</b> | <b>Generic name</b>                                                                                          |
|------------------|--------------------------------------------------------------------------------------------------------------|
| 79992978         | Hypodermic insulin needles for pre-filled / reusable pen injectors screw on 10mm/29gauge                     |
| 79994978         | Hypodermic insulin needles for pre-filled / reusable pen injectors screw on 4mm/31gauge                      |
| 80085994         | Hypodermic insulin injection pen reusable for 3ml cartridge 0.5 unit dial up / range 1-30 units              |
| 80959998         | GSF-Syrup oral gel 18g sachets                                                                               |
| 81132994         | Blood glucose colorimetric testing strips                                                                    |
| 81139994         | Blood glucose biosensor testing strips                                                                       |
| 81145994         | Blood glucose biosensor testing discs                                                                        |
| 81159998         | Linagliptin 5mg tablets                                                                                      |
| 81160998         | Linagliptin 5mg tablets                                                                                      |
| 81164998         | Insulin aspart 100units/ml solution for injection 3ml pre-filled disposable devices                          |
| 81305998         | Exenatide 2mg injection                                                                                      |
| 81307994         | Needle free Insulin delivery system                                                                          |
| 81307998         | Exenatide 2mg powder and solvent for prolonged-release suspension for injection vials                        |
| 81423994         | Hypodermic insulin injection pen reusable for 3ml cartridge 1 unit dial up / range 1-80 units                |
| 81426998         | Insulin isophane human 100units/ml suspension for injection 3ml pre-filled disposable devices                |
| 81468994         | Hypodermic insulin injection pen reusable for 3ml cartridge 1 unit dial up / range 1-80 units                |
| 81513998         | Saxagliptin 2.5mg tablets                                                                                    |
| 81514998         | Saxagliptin 2.5mg tablets                                                                                    |
| 81687998         | Insulin isophane biphasic human 15/85 100units/ml suspension for injection 3ml cartridges                    |
| 81781994         | Sterile single use needle                                                                                    |
| 81790998         | Insulin isophane biphasic human 25/75 100units/ml suspension for injection 3ml pre-filled disposable devices |
| 81962998         | Insulin isophane human 100units/ml suspension for injection 3ml pre-filled disposable devices                |
| 81963998         | Insulin isophane biphasic human 30/70 100units/ml suspension for injection 3ml pre-filled disposable devices |
| 82068998         | Metformin 1g / Sitagliptin 50mg tablets                                                                      |
| 82096979         | Insulin detemir 100units/ml solution for injection 3ml pre-filled disposable devices                         |
| 82136998         | Gliclazide 40mg tablets                                                                                      |
| 82137998         | Gliclazide 40mg tablets                                                                                      |
| 82151978         | Hypodermic insulin needles for pre-filled / reusable pen injectors screw on 8mm/31gauge                      |
| 82152978         | Hypodermic insulin needles for pre-filled / reusable pen injectors screw on 6mm/31gauge                      |
| 82153978         | Hypodermic insulin needles for pre-filled / reusable pen injectors screw on 5mm/31gauge                      |
| 82159978         | Hypodermic insulin needles for pre-filled / reusable pen injectors screw on 12mm/29gauge                     |
| 82164978         | Blood glucose biosensor testing strips                                                                       |
| 82196978         | Pioglitazone 30mg tablets                                                                                    |
| 82236994         | Blood glucose biosensor testing strips                                                                       |
| 82273978         | Hypodermic insulin needles for pre-filled / reusable pen injectors screw on 8mm/32.5gauge                    |
| 82275978         | Hypodermic insulin needles for pre-filled / reusable pen injectors screw on 4mm/32.5gauge                    |
| 82289978         | Lancets sterile single use 0.195mm/33gauge                                                                   |
| 82304998         | Gliclazide 30mg modified-release tablets                                                                     |
| 82343994         | Sterile single use needle                                                                                    |
| 82344994         | Sterile single use needle                                                                                    |
| 82419978         | Lancets sterile single use 0.32mm/30gauge                                                                    |
| 82431978         | Hypodermic insulin needles for pre-filled / reusable pen injectors screw on 4mm/32gauge                      |
| 82463994         | Hypodermic insulin injection pen reusable for 3ml cartridge 1 unit dial up / range 1-60 units                |
| 82464994         | Hypodermic insulin injection pen reusable for 3ml cartridge 1 unit dial up / range 1-60 units                |
| 82465994         | Hypodermic insulin injection pen reusable for 3ml cartridge 1 unit dial up / range 1-60 units                |
| 82531994         | Blood glucose biosensor testing strips                                                                       |
| 82534994         | Lancets sterile single use 1.8mm/28gauge                                                                     |
| 82573998         | Saxagliptin 5mg tablets                                                                                      |
| 82575998         | Saxagliptin 5mg tablets                                                                                      |
| 82720978         | Lancets sterile single use 0.32mm/30gauge                                                                    |
| 82722978         | Hypodermic insulin needles for pre-filled / reusable pen injectors screw on 4mm/31gauge                      |
| 82793998         | Liraglutide 6mg/ml solution for injection 3ml pre-filled disposable devices                                  |
| 82794998         | Liraglutide 6mg/ml solution for injection 3ml pre-filled disposable devices                                  |
| 82847994         | Lancets sterile single use 1.8mm/23gauge                                                                     |
| 82858998         | Glucose 40% oral gel                                                                                         |
| 82916998         | Metformin 1g oral powder sachets sugar free                                                                  |

| <b>Drug code</b> | <b>Generic name</b>                                                                                  |
|------------------|------------------------------------------------------------------------------------------------------|
| 82917998         | Metformin hydrochloride 500mg sachets                                                                |
| 82918998         | Metformin 1g oral powder sachets sugar free                                                          |
| 82919998         | Metformin 500mg oral powder sachets sugar free                                                       |
| 82928994         | Blood ketones testing strips                                                                         |
| 82940994         | Lancets sterile single use 1.8mm/21gauge                                                             |
| 82989998         | Gliclazide 30mg modified-release tablets                                                             |
| 82991994         | Insufflator                                                                                          |
| 82992994         | Insufflator                                                                                          |
| 82994994         | Insufflator                                                                                          |
| 83099994         | Lancets sterile single use 2mm/21gauge                                                               |
| 83401998         | Metformin 1g / Sitagliptin 50mg tablets                                                              |
| 83403998         | Insulin lispro 100units/ml solution for injection 3ml pre-filled disposable devices                  |
| 83404998         | Insulin lispro biphasic 25/75 100units/ml suspension for injection 3ml pre-filled disposable devices |
| 83405998         | Insulin lispro biphasic 50/50 100units/ml suspension for injection 3ml pre-filled disposable devices |
| 83534994         | Blood glucose biosensor testing strips                                                               |
| 83541994         | Blood glucose biosensor testing strips                                                               |
| 83542994         | Needle free Insulin delivery system                                                                  |
| 83543994         | Needle free Insulin delivery system                                                                  |
| 83544994         | Needle free Insulin delivery system                                                                  |
| 83545994         | Sterile single use needle                                                                            |
| 83546994         | Sterile single use needle                                                                            |
| 83547994         | Sterile single use needle                                                                            |
| 83548994         | Needle free Insulin delivery system                                                                  |
| 83549994         | Needle free Insulin delivery system                                                                  |
| 83551994         | Needle free Insulin delivery system                                                                  |
| 83566994         | Hypodermic insulin needles for pre-filled / reusable pen injectors screw on 8mm/31gauge              |
| 83567994         | Hypodermic insulin needles for pre-filled / reusable pen injectors screw on 6mm/31gauge              |
| 83579994         | International normalised ratio testing strips                                                        |
| 83659998         | GSF-Syrup oral gel 18g sachets                                                                       |
| 83662998         | Sucrose with glucose & fructose oral solution                                                        |
| 83726994         | Multi reagent - 5 tests - urine test strips                                                          |
| 83916998         | Gliclazide 30mg modified-release tablets                                                             |
| 83949998         | Gliclazide 30mg modified-release tablets                                                             |
| 83993994         | Hypodermic insulin injection pen reusable for 3ml cartridge 1 unit dial up / range 1-60 units        |
| 84008998         | Vildagliptin 50mg / Metformin 1g tablets                                                             |
| 84009998         | Vildagliptin 50mg / Metformin 850mg tablets                                                          |
| 84010998         | Vildagliptin 50mg / Metformin 1g tablets                                                             |
| 84011998         | Vildagliptin 50mg / Metformin 850mg tablets                                                          |
| 84082994         | Blood glucose biosensor testing strips                                                               |
| 84092994         | Lancets sterile single use 0.3mm/30gauge                                                             |
| 84165979         | Needle free Insulin delivery system                                                                  |
| 84166979         | Needle free Insulin delivery system                                                                  |
| 84167979         | Needle free Insulin delivery system                                                                  |
| 84177994         | Sterile dt type a lancets                                                                            |
| 84181994         | Lancets sterile single use 2.4mm/21gauge                                                             |
| 84185994         | Lancets sterile single use 1.8mm/21gauge                                                             |
| 84187994         | Lancets sterile single use 1.8mm/26gauge                                                             |
| 84255978         | Hypodermic insulin injection pen reusable for 3ml cartridge 1 unit dial up / range 1-60 units        |
| 84256978         | Hypodermic insulin injection pen reusable for 3ml cartridge 1 unit dial up / range 1-60 units        |
| 84257978         | Hypodermic insulin injection pen reusable for 3ml cartridge 1 unit dial up / range 1-60 units        |
| 84258978         | Hypodermic insulin injection pen reusable for 3ml cartridge 1 unit dial up / range 1-60 units        |
| 84259978         | Hypodermic insulin injection pen reusable for 3ml cartridge 1 unit dial up / range 1-60 units        |
| 84260978         | Hypodermic insulin injection pen reusable for 3ml cartridge 1 unit dial up / range 1-60 units        |
| 84263978         | Lancets sterile single use 0.3mm/30gauge                                                             |
| 84273994         | Lancets sterile single use 0.2mm/33gauge                                                             |
| 84338998         | Vildagliptin 50mg tablets                                                                            |
| 84341998         | Vildagliptin 50mg tablets                                                                            |
| 84400994         | Blood glucose biosensor testing strips                                                               |

| <b>Drug code</b> | <b>Generic name</b>                                                                                                  |
|------------------|----------------------------------------------------------------------------------------------------------------------|
| 84415994         | Blood glucose biosensor testing strips                                                                               |
| 84421998         | Insulin glulisine 100units/ml solution for injection 3ml pre-filled disposable devices                               |
| 84422998         | Insulin glargine 100units/ml solution for injection 3ml pre-filled disposable devices                                |
| 84493978         | Gliclazide 60mg modified-release tablets                                                                             |
| 84494978         | Gliclazide 60mg modified-release tablets                                                                             |
| 84553978         | Hypodermic U100 insulin syringe sterile single use / single patient use 1ml with 8mm safety needle 0.3mm/30gauge     |
| 84559978         | Hypodermic U100 insulin syringe sterile single use / single patient use 0.5ml with 8mm safety needle 0.3mm/30gauge   |
| 84563978         | Hypodermic U100 insulin syringe sterile single use / single patient use 0.5ml with 12mm safety needle 0.33mm/29gauge |
| 84567978         | Hypodermic U100 insulin syringe sterile single use / single patient use 0.3ml with 8mm safety needle 0.3mm/30gauge   |
| 84573978         | Hypodermic U100 insulin syringe sterile single use / single patient use 0.3ml with 12mm safety needle 0.33mm/29gauge |
| 84639998         | Sitagliptin 100mg tablets                                                                                            |
| 84640998         | Sitagliptin 100mg tablets                                                                                            |
| 84693998         | Exenatide 10micrograms/0.04ml solution for injection 2.4ml pre-filled disposable devices                             |
| 84694998         | Exenatide 5micrograms/0.02ml solution for injection 1.2ml pre-filled disposable devices                              |
| 84696998         | Exenatide 10micrograms/0.04ml solution for injection 2.4ml pre-filled disposable devices                             |
| 84697998         | Exenatide 5micrograms/0.02ml solution for injection 1.2ml pre-filled disposable devices                              |
| 84719994         | Hypodermic U100 insulin syringe sterile single use / single patient use 1ml with 8mm needle 0.3mm/30gauge            |
| 84779998         | Insulin detemir 100units/ml solution for injection 3ml pre-filled disposable devices                                 |
| 84816994         | International normalised ratio testing strips                                                                        |
| 85148978         | Glucose 40% oral gel                                                                                                 |
| 85266998         | Repaglinide 2mg tablets                                                                                              |
| 85267998         | Repaglinide 1mg tablets                                                                                              |
| 85268998         | Repaglinide 500microgram tablets                                                                                     |
| 85394978         | Blood glucose biosensor testing strips                                                                               |
| 85412998         | Diazoxide 50mg/5ml oral suspension                                                                                   |
| 85496994         | Hypodermic U100 insulin syringe sterile single use / single patient use 1ml with 12mm needle 0.3mm/30gauge           |
| 85497994         | Hypodermic U100 insulin syringe sterile single use / single patient use 0.5ml with 12mm needle 0.3mm/30gauge         |
| 85498994         | Hypodermic U100 insulin syringe sterile single use / single patient use 0.5ml with 8mm needle 0.3mm/30gauge          |
| 85499994         | Hypodermic U100 insulin syringe sterile single use / single patient use 1ml with 8mm needle 0.3mm/30gauge            |
| 85546994         | Blood ketones testing strips                                                                                         |
| 85547978         | Gliclazide 30mg modified-release tablets                                                                             |
| 85557994         | Needle free Insulin delivery system                                                                                  |
| 85558994         | Needle free Insulin delivery system                                                                                  |
| 85559994         | Needle free Insulin delivery system                                                                                  |
| 85560994         | Needle free Insulin delivery system                                                                                  |
| 85591998         | Insulin glulisine 100units/ml solution for injection 3ml cartridges                                                  |
| 85622998         | Pioglitazone 15mg / Metformin 850mg tablets                                                                          |
| 85624998         | Pioglitazone 15mg / Metformin 850mg tablets                                                                          |
| 85625998         | Pioglitazone 15mg / Metformin 850mg tablets                                                                          |
| 85851994         | Blood glucose biosensor testing strips                                                                               |
| 85888994         | Hypodermic U100 insulin syringe sterile single use / single patient use 1ml with 8mm needle 0.3mm/30gauge            |
| 85889994         | Hypodermic U100 insulin syringe sterile single use / single patient use 1ml with 8mm needle 0.3mm/30gauge            |
| 85890994         | Hypodermic needle sterile single use 0.5mm/25gauge 16mm                                                              |
| 85891994         | Hypodermic needle sterile single use 0.5mm/25gauge 16mm                                                              |
| 85901998         | Glibenclamide 5mg/5ml oral suspension                                                                                |
| 86018998         | Gliclazide 40mg/5ml oral suspension                                                                                  |



| <b>Drug code</b> | <b>Generic name</b>                                                                                  |
|------------------|------------------------------------------------------------------------------------------------------|
| 86020994         | Sterile dt type a lancets                                                                            |
| 86028998         | Insulin lispro biphasic 50/50 100units/ml suspension for injection 3ml cartridges                    |
| 86029998         | Insulin lispro biphasic 50/50 100units/ml suspension for injection 3ml cartridges                    |
| 86044998         | Human insulin 3mg unit dose blisters                                                                 |
| 86045998         | Human insulin 1mg unit dose blisters                                                                 |
| 86046998         | Insulin human 3mg inhalation powder blisters                                                         |
| 86047998         | Insulin human 1mg inhalation powder blisters                                                         |
| 86074994         | Sterile single use needle                                                                            |
| 86075994         | Sterile single use needle                                                                            |
| 86076994         | Sterile single use needle                                                                            |
| 86077998         | Insulin lispro 100units/ml solution for injection 3ml pre-filled disposable devices                  |
| 86078998         | Insulin isophane biphasic human 30/70 100units/ml suspension for injection 10ml vials                |
| 86080998         | Insulin isophane human 100units/ml suspension for injection 3ml pre-filled disposable devices        |
| 86081998         | Insulin isophane human 100units/ml suspension for injection 10ml vials                               |
| 86086994         | Blood glucose biosensor testing strips                                                               |
| 86168998         | Insulin isophane human 100units/ml suspension for injection 3ml cartridges                           |
| 86169998         | Insulin isophane biphasic human 50/50 100units/ml suspension for injection 3ml cartridges            |
| 86173998         | Insulin soluble bovine 100units/ml solution for injection 10ml vials                                 |
| 86174998         | Insulin soluble bovine 100units/ml solution for injection 3ml cartridges                             |
| 86175998         | Insulin soluble bovine cartridge 100unit/ml solution for injection                                   |
| 86176998         | Insulin soluble bovine 100units/ml solution for injection 10ml vials 1 10ml vial(s)                  |
| 86177998         | Human isophane insulin 100iu/ml injection cartridges                                                 |
| 86178998         | Insulin isophane bovine 100units/ml suspension for injection 10ml vials                              |
| 86179998         | Insulin isophane bovine 100units/ml suspension for injection 3ml cartridges                          |
| 86180998         | Insulin isophane bovine 100units/ml suspension for injection 10ml vials                              |
| 86182998         | Insulin soluble porcine 100units/ml solution for injection 3ml cartridges                            |
| 86183998         | Insulin soluble porcine 100units/ml solution for injection 10ml vials                                |
| 86184998         | Insulin soluble porcine 100units/ml solution for injection 3ml cartridges 5 3ml cartridge(s)         |
| 86185998         | Insulin soluble porcine 100units/ml solution for injection 10ml vials 1 vial                         |
| 86186998         | Insulin isophane biphasic porcine 30/70 100units/ml suspension for injection 3ml cartridges          |
| 86187998         | Insulin isophane biphasic porcine 30/70 100units/ml suspension for injection 10ml vials              |
| 86188998         | Insulin isophane biphasic porcine 30/70 100units/ml suspension for injection 3ml cartridges          |
| 86189998         | Insulin isophane biphasic porcine 30/70 100units/ml suspension for injection 10ml vials              |
| 86190998         | Insulin isophane porcine 100units/ml suspension for injection 3ml cartridges                         |
| 86191998         | Insulin isophane porcine 100units/ml suspension for injection 10ml vials                             |
| 86193998         | Insulin isophane porcine 100units/ml suspension for injection 3ml cartridges                         |
| 86194998         | Insulin isophane porcine 100units/ml suspension for injection 10ml vials                             |
| 86214998         | Insulin glulisine 100units/ml solution for injection 3ml pre-filled disposable devices               |
| 86215998         | Insulin glulisine 100units/ml solution for injection 3ml pre-filled disposable devices               |
| 86236998         | Insulin glulisine 100units/ml solution for injection 3ml cartridges                                  |
| 86237998         | Insulin glulisine 100units/ml solution for injection 10ml vials                                      |
| 86238998         | Insulin glargine 100units/ml solution for injection 3ml cartridges                                   |
| 86239998         | Insulin glargine 100units/ml solution for injection 3ml pre-filled disposable devices                |
| 86240998         | Insulin glargine 100units/ml solution for injection 10ml vials                                       |
| 86241998         | Insulin glargine 100units/ml solution for injection 3ml cartridges                                   |
| 86242998         | Insulin glargine 100units/ml solution for injection 3ml pre-filled disposable devices                |
| 86243998         | Insulin glargine 100units/ml solution for injection 10ml vials                                       |
| 86245998         | Insulin detemir 100units/ml solution for injection 3ml pre-filled disposable devices                 |
| 86246998         | Insulin detemir 100units/ml solution for injection 3ml cartridges                                    |
| 86247998         | Insulin lispro biphasic 25/75 100units/ml suspension for injection 3ml pre-filled disposable devices |
| 86248998         | Insulin lispro biphasic 25/75 100units/ml suspension for injection 3ml cartridges                    |
| 86249998         | Insulin lispro 100units/ml solution for injection 3ml pre-filled disposable devices                  |
| 86250998         | Insulin lispro biphasic 25/75 100units/ml suspension for injection 3ml cartridges                    |
| 86251998         | Insulin lispro 100units/ml solution for injection 3ml pre-filled disposable devices                  |
| 86252998         | Insulin lispro 100units/ml solution for injection 3ml cartridges                                     |
| 86253998         | Insulin lispro 100units/ml solution for injection 10ml vials                                         |
| 86254998         | Insulin lispro 100units/ml solution for injection 3ml pre-filled disposable devices                  |
| 86255998         | Insulin lispro 100units/ml solution for injection 3ml cartridges                                     |

| <b>Drug code</b> | <b>Generic name</b>                                                                                          |
|------------------|--------------------------------------------------------------------------------------------------------------|
| 86256998         | Insulin lispro 100units/ml solution for injection 10ml vials                                                 |
| 86259998         | Insulin aspart biphasic 30/70 100units/ml suspension for injection 3ml pre-filled disposable devices         |
| 86260998         | Insulin aspart biphasic 30/70 100units/ml suspension for injection 3ml cartridges                            |
| 86261998         | Insulin aspart biphasic 30/70 100units/ml suspension for injection 3ml pre-filled disposable devices         |
| 86262998         | Insulin aspart biphasic 30/70 100units/ml suspension for injection 3ml cartridges                            |
| 86263998         | Insulin aspart 100units/ml solution for injection 3ml pre-filled disposable devices                          |
| 86264998         | Insulin aspart 100units/ml solution for injection 3ml cartridges                                             |
| 86265998         | Insulin aspart 100units/ml solution for injection 10ml vials                                                 |
| 86266998         | Insulin isophane human 100units/ml suspension for injection 3ml pre-filled disposable devices                |
| 86267998         | Insulin isophane human 100units/ml suspension for injection 5ml vials                                        |
| 86268998         | Insulin isophane human 100units/ml suspension for injection 3ml cartridges                                   |
| 86269998         | Insulin isophane human 100units/ml suspension for injection 3ml pre-filled disposable devices                |
| 86270998         | Insulin isophane human 100units/ml suspension for injection 3ml cartridges                                   |
| 86271998         | Insulin isophane human 100units/ml suspension for injection 10ml vials                                       |
| 86272998         | Insulin glargine 100units/ml solution for injection 3ml cartridges                                           |
| 86274998         | Insulin isophane human 100units/ml suspension for injection 3ml pre-filled disposable devices                |
| 86275998         | Insulin isophane human 100units/ml suspension for injection 3ml cartridges                                   |
| 86276998         | Insulin isophane human vial 100unit/ml sterile suspension injection                                          |
| 86278998         | Insulin isophane biphasic human 25/75 100units/ml suspension for injection 3ml pre-filled disposable devices |
| 86279998         | Insulin isophane biphasic human 25/75 100units/ml suspension for injection 3ml cartridges                    |
| 86280998         | Insulin isophane biphasic human 25/75 100units/ml suspension for injection 5ml vials                         |
| 86281998         | Insulin isophane biphasic human 25/75 100units/ml suspension for injection 3ml pre-filled disposable devices |
| 86282998         | Insulin isophane biphasic human 25/75 100units/ml suspension for injection 3ml cartridges                    |
| 86283998         | Insulin isophane biphasic human 25/75 100units/ml suspension for injection 5ml vials                         |
| 86284998         | Insulin isophane biphasic human 15/85 100units/ml suspension for injection 3ml pre-filled disposable devices |
| 86285998         | Insulin isophane biphasic human 15/85 100units/ml suspension for injection 3ml pre-filled disposable devices |
| 86286998         | Insulin isophane biphasic human 50/50 100units/ml suspension for injection 3ml pre-filled disposable devices |
| 86287998         | Insulin isophane biphasic human 50/50 100units/ml suspension for injection 3ml cartridges                    |
| 86288998         | Insulin isophane biphasic human 50/50 100units/ml suspension for injection 3ml pre-filled disposable devices |
| 86291998         | Insulin isophane biphasic human 50/50 100units/ml suspension for injection 3ml cartridges                    |
| 86294998         | Insulin isophane biphasic human 40/60 100units/ml suspension for injection 3ml cartridges                    |
| 86295998         | Insulin isophane biphasic human 40/60 100units/ml suspension for injection 3ml cartridges                    |
| 86298998         | Insulin isophane biphasic human 30/70 100units/ml suspension for injection 3ml pre-filled disposable devices |
| 86300998         | Insulin isophane biphasic human 30/70 100units/ml suspension for injection 10ml vials                        |
| 86301998         | Insulin isophane biphasic human 30/70 100units/ml suspension for injection 3ml cartridges                    |
| 86303998         | Insulin isophane biphasic human 30/70 100units/ml suspension for injection 3ml cartridges                    |
| 86304998         | Insulin isophane biphasic human 30/70 100units/ml suspension for injection 3ml pre-filled disposable devices |
| 86305998         | Insulin isophane biphasic human 30/70 100units/ml suspension for injection 10ml vials                        |
| 86306998         | Insulin isophane biphasic human 30/70 100units/ml suspension for injection 3ml cartridges                    |
| 86308998         | Insulin isophane biphasic human 20/80 100units/ml suspension for injection 3ml cartridges                    |
| 86309998         | Insulin isophane biphasic human 20/80 100units/ml suspension for injection 3ml cartridges                    |
| 86310998         | Insulin isophane biphasic human 10/90 100units/ml suspension for injection 3ml cartridges                    |
| 86311998         | Insulin isophane biphasic human 10/90 100units/ml suspension for injection 3ml cartridges                    |
| 86312998         | Insulin soluble human 100units/ml solution for injection 10ml vials                                          |
| 86313998         | Human insulin 100iu/ml preloaded injection pen                                                               |
| 86314998         | Insulin soluble human 100units/ml solution for injection 3ml cartridges                                      |
| 86315998         | Insulin soluble human 100units/ml solution for injection 3ml cartridges                                      |
| 86316998         | Insulin soluble human 100units/ml solution for injection 10ml vials                                          |
| 86317998         | Insulin soluble human 100units/ml solution for injection 3ml cartridges                                      |
| 86318998         | Insulin soluble human 100units/ml solution for injection 3ml pre-filled disposable devices                   |

| <b>Drug code</b> | <b>Generic name</b>                                                                                           |
|------------------|---------------------------------------------------------------------------------------------------------------|
| 86319998         | Insulin human 100units/ml solution for injection 10ml vials                                                   |
| 86369994         | Lancets sterile single use 0.36mm/28gauge                                                                     |
| 86549998         | Insulin glulisine 100units/ml solution for injection 3ml cartridges                                           |
| 86551998         | Insulin glulisine 100units/ml solution for injection 10ml vials                                               |
| 86553998         | Insulin glulisine 100units/ml solution for injection 10ml vials                                               |
| 86574994         | Hypodermic U100 insulin syringe sterile single use / single patient use 0.5ml with 12mm needle 0.36mm/28gauge |
| 86585998         | Glucose 40% oral gel                                                                                          |
| 86764994         | Lancets sterile single use 0.36mm/28gauge                                                                     |
| 86765994         | Lancets sterile single use 0.66mm/23gauge                                                                     |
| 86766994         | Sterile dt type a lancets                                                                                     |
| 86862994         | Blood glucose biosensor testing discs                                                                         |
| 86969994         | Needle free Insulin delivery system                                                                           |
| 86971994         | Needle free Insulin delivery system                                                                           |
| 86973994         | Needle free Insulin delivery system                                                                           |
| 86974994         | Needle free Insulin delivery system                                                                           |
| 86976994         | Lancets sterile single use 0.36mm/28gauge                                                                     |
| 87008994         | Hypodermic insulin injection pen reusable for 3ml cartridge 1 unit dial up / range 1-60 units                 |
| 87165998         | Metformin with rosiglitazone 1000mg + 4mg tablet                                                              |
| 87166998         | Metformin with rosiglitazone 1000mg + 2mg tablet                                                              |
| 87179998         | Metformin & rosiglitazone 1g+4mg tablets                                                                      |
| 87180998         | Metformin & rosiglitazone 1g+2mg tablets                                                                      |
| 87181998         | Rosiglitazone 4mg / metformin 1g tablets                                                                      |
| 87182998         | Rosiglitazone 2mg / metformin 1g tablets                                                                      |
| 87184998         | Diazoxide 250mg/5ml oral suspension                                                                           |
| 87234979         | Re-usable hypodermic bs3522 needle                                                                            |
| 87306979         | Hypodermic insulin injection pen reusable for 3ml cartridge 1 unit dial up / range 1-21 units                 |
| 87317994         | Hypodermic insulin injection pen reusable for 3ml cartridge 2 unit dial up / range 2-42 units                 |
| 87319994         | Hypodermic insulin injection pen reusable for 3ml cartridge 1 unit dial up / range 1-21 units                 |
| 87320994         | Needle free Insulin delivery system                                                                           |
| 87321994         | Needle free Insulin delivery system                                                                           |
| 87322994         | Needle free Insulin delivery system                                                                           |
| 87363979         | Insulin lispro biphasic 25/75 100units/ml suspension for injection 3ml cartridges                             |
| 87364979         | Insulin lispro biphasic 25/75 100units/ml suspension for injection 3ml cartridges                             |
| 87365979         | Insulin lispro biphasic 50/50 100units/ml suspension for injection 3ml pre-filled disposable devices          |
| 87367979         | Insulin lispro biphasic 50/50 100units/ml suspension for injection 3ml pre-filled disposable devices          |
| 87372979         | Insulin lispro biphasic 25/75 100units/ml suspension for injection 3ml pre-filled disposable devices          |
| 87373979         | Insulin lispro biphasic 25/75 100units/ml suspension for injection 3ml pre-filled disposable devices          |
| 87376979         | Insulin lispro biphasic 25/75 100units/ml suspension for injection 3ml pre-filled disposable devices          |
| 87378979         | Insulin isophane porcine 100units/ml suspension for injection 10ml vials                                      |
| 87379979         | Insulin isophane human 100units/ml suspension for injection 5ml vials                                         |
| 87383979         | Insulin isophane human 100units/ml suspension for injection 10ml vials                                        |
| 87384979         | Insulin isophane human 100units/ml suspension for injection 10ml vials                                        |
| 87385979         | Insulin isophane human 100units/ml suspension for injection 10ml vials                                        |
| 87387979         | Insulin isophane bovine 100units/ml suspension for injection 10ml vials                                       |
| 87390979         | Insulin isophane biphasic porcine 30/70 100units/ml suspension for injection 10ml vials                       |
| 87392979         | Insulin isophane biphasic human 50/50 100units/ml suspension for injection 3ml cartridges                     |
| 87401979         | Insulin isophane biphasic human 30/70 100units/ml suspension for injection 3ml pre-filled disposable devices  |
| 87402979         | Insulin isophane biphasic human 30/70 100units/ml suspension for injection 3ml cartridges                     |
| 87403979         | Insulin isophane biphasic human 30/70 100units/ml suspension for injection 3ml cartridges                     |
| 87405979         | Insulin isophane biphasic human 30/70 100units/ml suspension for injection 3ml cartridges                     |
| 87406979         | Insulin isophane biphasic human 30/70 100units/ml suspension for injection 3ml cartridges                     |
| 87407979         | Insulin isophane biphasic human 30/70 100units/ml suspension for injection 3ml cartridges                     |
| 87408979         | Insulin isophane biphasic human 30/70 100units/ml suspension for injection 10ml vials                         |
| 87409979         | Insulin isophane biphasic human 30/70 100units/ml suspension for injection 10ml vials                         |
| 87410979         | Insulin isophane biphasic human 30/70 100units/ml suspension for injection 10ml vials                         |
| 87410994         | Needle free Insulin delivery system                                                                           |

| Drug code | Generic name                                                                                         |
|-----------|------------------------------------------------------------------------------------------------------|
| 87411979  | Insulin isophane biphasic human 30/70 100units/ml suspension for injection 1.5ml cartridges          |
| 87411994  | Needle free Insulin delivery system                                                                  |
| 87412994  | Needle free Insulin delivery system                                                                  |
| 87415994  | Hypodermic insulin injection pen reusable for 3ml cartridge 1 unit dial up / range 1-60 units        |
| 87416979  | Insulin isophane biphasic human 20/80 100units/ml suspension for injection 1.5ml cartridges          |
| 87416994  | Hypodermic insulin injection pen reusable for 3ml cartridge 1 unit dial up / range 1-60 units        |
| 87426979  | Insulin aspart biphasic 30/70 100units/ml suspension for injection 3ml pre-filled disposable devices |
| 87428979  | Insulin aspart biphasic 30/70 100units/ml suspension for injection 3ml pre-filled disposable devices |
| 87429979  | Insulin aspart biphasic 30/70 100units/ml suspension for injection 3ml cartridges                    |
| 87431979  | Insulin aspart biphasic 30/70 100units/ml suspension for injection 3ml cartridges                    |
| 87433979  | Insulin aspart biphasic 30/70 100units/ml suspension for injection 3ml cartridges                    |
| 87434979  | Insulin aspart 100units/ml solution for injection 3ml pre-filled disposable devices                  |
| 87435979  | Insulin aspart 100units/ml solution for injection 3ml pre-filled disposable devices                  |
| 87436979  | Insulin aspart 100units/ml solution for injection 3ml pre-filled disposable devices                  |
| 87437979  | Insulin aspart 100units/ml solution for injection 3ml pre-filled disposable devices                  |
| 87438979  | Insulin aspart 100units/ml solution for injection 3ml pre-filled disposable devices                  |
| 87440979  | Insulin aspart 100units/ml solution for injection 3ml cartridges                                     |
| 87442979  | Insulin aspart 100units/ml solution for injection 3ml cartridges                                     |
| 87471998  | Insulin detemir 100units/ml solution for injection 3ml pre-filled disposable devices                 |
| 87472998  | Insulin detemir 100units/ml solution for injection 3ml cartridges                                    |
| 87473998  | Insulin detemir 100units/ml solution for injection 3ml pre-filled disposable devices                 |
| 87494994  | Sterile dt type b lancets                                                                            |
| 87512994  | Blood glucose biosensor testing strips                                                               |
| 87598979  | Blood ketones testing strips                                                                         |
| 87770998  | Metformin & rosiglitazone 500mg+2mg tablets                                                          |
| 87771998  | Metformin & rosiglitazone 500mg+1mg tablets                                                          |
| 87772998  | Metformin with rosiglitazone 500mg + 2mg tablet                                                      |
| 87773998  | Rosiglitazone 2mg / metformin 500mg tablets                                                          |
| 87774998  | Metformin with rosiglitazone 500mg + 1mg tablet                                                      |
| 87775998  | Rosiglitazone 1mg / metformin 500mg tablets                                                          |
| 87884998  | Pioglitazone 45mg tablets                                                                            |
| 87885998  | Pioglitazone 45mg tablets                                                                            |
| 87909994  | Lancets sterile single use 0.375mm/28gauge                                                           |
| 87967998  | Insulin biphasic isophane human prb 25:75; 100 units/ml injection                                    |
| 88003998  | Insulin soluble human crb 100iu/ml injection                                                         |
| 88012994  | Blood glucose colorimetric testing strips                                                            |
| 88131996  | Nateglinide 180mg tablets                                                                            |
| 88131997  | Nateglinide 120mg tablets                                                                            |
| 88131998  | Nateglinide 60mg tablets                                                                             |
| 88132996  | Nateglinide 180mg tablets                                                                            |
| 88132997  | Nateglinide 120mg tablets                                                                            |
| 88132998  | Nateglinide 60mg tablets                                                                             |
| 88135998  | Gliclazide 80mg tablets                                                                              |
| 88210994  | Hypodermic insulin injection pen reusable for 3ml cartridge 2 unit dial up / range 2-42 units        |
| 88211994  | Hypodermic insulin injection pen reusable for 3ml cartridge 1 unit dial up / range 1-21 units        |
| 88218994  | Lancets sterile single use 0.4mm/28gauge                                                             |
| 88219994  | Blood glucose biosensor testing strips                                                               |
| 88225994  | International normalised ratio testing strips                                                        |
| 88226994  | International normalised ratio testing strips                                                        |
| 88227994  | Sterile dt type a lancets                                                                            |
| 88278994  | Blood glucose colorimetric testing strips                                                            |
| 88297994  | Blood glucose biosensor testing strips                                                               |
| 88305994  | Lancets sterile single use 0.36mm/28gauge                                                            |
| 88310994  | Blood glucose colorimetric testing strips                                                            |
| 88334998  | Glimepiride 4mg tablets                                                                              |
| 88355998  | Glimepiride 4mg tablets                                                                              |
| 88370994  | Syringe syringe                                                                                      |
| 88371994  | Syringe syringe                                                                                      |

| <b>Drug code</b> | <b>Generic name</b>                                                                                                      |
|------------------|--------------------------------------------------------------------------------------------------------------------------|
| 88413998         | Insulin soluble porcine 100units/ml solution for injection 10ml vials                                                    |
| 88447996         | Glimepiride 3mg tablets                                                                                                  |
| 88447997         | Glimepiride 1mg tablets                                                                                                  |
| 88447998         | Glimepiride 2mg tablets                                                                                                  |
| 88449996         | Glimepiride 3mg tablets                                                                                                  |
| 88449997         | Glimepiride 1mg tablets                                                                                                  |
| 88449998         | Glimepiride 2mg tablets                                                                                                  |
| 88473994         | Hypodermic U100 insulin syringe sterile single use / single patient use 0.5ml with not less than 12mm needle 0.33mm/29ga |
| 88523996         | Troglitazone 400mg tablets                                                                                               |
| 88523998         | Troglitazone 200mg tablets                                                                                               |
| 88528996         | Troglitazone 400mg tablet                                                                                                |
| 88528998         | Troglitazone 200mg tablet                                                                                                |
| 88851998         | Human insulin 100iu/ml preloaded injection pen                                                                           |
| 88972994         | Hypodermic insulin needles for pre-filled / reusable pen injectors screw on 6mm/30gauge                                  |
| 88973994         | Hypodermic insulin injection pen reusable for 3ml cartridge 1 unit dial up / range 1-21 units                            |
| 88974994         | Hypodermic insulin injection pen reusable for 3ml cartridge 2 unit dial up / range 2-42 units                            |
| 88978998         | Insulin isophane biphasic Porcine 30/70 Mix 100units/ml suspension for injection 1.5ml cartridges                        |
| 88995998         | Insulin isophane biphasic Porcine Isophane 100units/ml suspension for injection 1.5ml cartridges                         |
| 88999998         | Insulin soluble porcine 100units/ml solution for injection 10ml vials                                                    |
| 89081994         | Hypodermic insulin injection pen reusable for 3ml cartridge 0.5 unit dial up / range 1-35 units                          |
| 89082994         | Hypodermic insulin injection pen reusable for 3ml cartridge 0.5 unit dial up / range 1-35 units                          |
| 89094994         | Blood glucose colorimetric testing strips                                                                                |
| 89398994         | Sterile single use needle                                                                                                |
| 89399994         | Sterile single use needle                                                                                                |
| 89400994         | Sterile single use needle                                                                                                |
| 89401994         | Sterile single use needle                                                                                                |
| 89554998         | Insulin aspart biphasic 30/70 100units/ml suspension for injection 3ml pre-filled disposable devices                     |
| 89555998         | Insulin biphasic aspart human pyr 30:70; 100 units/ml injection 5 3ml disposable pen(s)                                  |
| 89639979         | Insulin glargine 100units/ml solution for injection 3ml pre-filled disposable devices                                    |
| 89640979         | Insulin glargine 100units/ml solution for injection 3ml pre-filled disposable devices                                    |
| 89643979         | Insulin glargine 100units/ml solution for injection 3ml pre-filled disposable devices                                    |
| 89659979         | Insulin glargine 100units/ml solution for injection 10ml vials                                                           |
| 89661979         | Insulin glargine 100units/ml solution for injection 10ml vials                                                           |
| 89661994         | Lancets sterile single use 0.5mm/28gauge                                                                                 |
| 89662994         | Hypodermic insulin injection pen reusable for 3ml cartridge 1 unit dial up / range 1-70 units                            |
| 89663994         | Hypodermic insulin injection pen reusable for 3ml cartridge 1 unit dial up / range 1-70 units                            |
| 89668979         | Insulin glargine 100units/ml solution for injection 3ml cartridges                                                       |
| 89673979         | Insulin glargine 100units/ml solution for injection 3ml cartridges                                                       |
| 89684994         | Syringe syringe                                                                                                          |
| 89685994         | Hypodermic u100 insulin (0.5ml) syringe                                                                                  |
| 89759994         | U100 insulin syringe 0.5ml                                                                                               |
| 89760994         | U100 insulin syringe 0.3ml                                                                                               |
| 89763996         | Rosiglitazone 8mg tablets                                                                                                |
| 89763997         | Rosiglitazone 4mg tablets                                                                                                |
| 89763998         | Rosiglitazone 2mg tablet                                                                                                 |
| 89799994         | Sterile dt type a lancets                                                                                                |
| 89800994         | Sterile dt type b lancets                                                                                                |
| 89801994         | Lancets sterile single use 0.66mm/23gauge                                                                                |
| 89842994         | Blood glucose colorimetric testing strips                                                                                |
| 89888998         | Insulin biphasic isophane human emp 30:70; 100 units/ml injection                                                        |
| 89897994         | Sterile dt type a lancets                                                                                                |
| 89909994         | Blood glucose biosensor testing strips                                                                                   |
| 89990997         | Insulin biphasic lispro human prb 50:50; 100 units/ml injection 5 3ml disposable pen(s)                                  |
| 89990998         | Insulin biphasic lispro human prb 25:75; 100 units/ml injection                                                          |
| 90012998         | Insulin lispro 100units/ml solution for injection 1.5ml cartridges                                                       |
| 90015998         | Insulin lispro 100units/ml solution for injection 1.5ml pre-filled disposable devices                                    |
| 90048996         | Rosiglitazone 8mg tablets                                                                                                |

| <b>Drug code</b> | <b>Generic name</b>                                                                                                       |
|------------------|---------------------------------------------------------------------------------------------------------------------------|
| 90048997         | Rosiglitazone 4mg tablets                                                                                                 |
| 90048998         | Rosiglitazone 2mg tablet                                                                                                  |
| 90098994         | Hypodermic insulin injection pen reusable for 3ml cartridge 1 unit dial up / range 1-21 units                             |
| 90109994         | Blood glucose test strips                                                                                                 |
| 90119994         | Blood glucose biosensor testing strips                                                                                    |
| 90146994         | Hypodermic U100 insulin syringe sterile single use / single patient use 1ml with not less than 12mm needle 0.33mm/29gauge |
| 90147994         | Hypodermic U100 insulin syringe sterile single use / single patient use 0.5ml with not less than 12mm needle 0.33mm/29ga  |
| 90148994         | Insulin u100 syringe plus needle                                                                                          |
| 90161994         | Generic medisense optium biosensor strips biosensor strips (abbott laboratories ltd)                                      |
| 90163994         | Hypodermic U100 insulin syringe sterile single use / single patient use 1ml with not less than 12mm needle 0.33mm/29gauge |
| 90164994         | Hypodermic U100 insulin syringe sterile single use / single patient use 1ml with 12mm needle 0.4mm/27gauge                |
| 90165994         | Hypodermic U100 insulin syringe sterile single use / single patient use 0.5ml with 12mm needle 0.4mm/27gauge              |
| 90166994         | Hypodermic U100 insulin syringe sterile single use / single patient use 0.5ml with 12mm needle 0.3mm/30gauge              |
| 90167994         | Hypodermic U100 insulin syringe sterile single use / single patient use 1ml with 12mm needle 0.3mm/30gauge                |
| 90168994         | Hypodermic U100 insulin syringe sterile single use / single patient use 1ml with 12mm needle 0.3mm/28gauge                |
| 90168998         | Insulin isophane human 100units/ml suspension for injection 3ml pre-filled disposable devices                             |
| 90169994         | Hypodermic U100 insulin syringe sterile single use / single patient use 0.5ml with 12mm needle 28gauge                    |
| 90169998         | Insulin isophane biphasic human 30/70 100units/ml suspension for injection 3ml pre-filled disposable devices              |
| 90202979         | Insulin soluble human 100units/ml solution for injection 3ml cartridges                                                   |
| 90207979         | Insulin soluble porcine 100units/ml solution for injection 10ml vials                                                     |
| 90232994         | Sterile dt type b lancets                                                                                                 |
| 90270994         | hypodermic U100 insulin syringe sterile single use / single patient use 1ml with 12.7mm needle 0.33mm/29                  |
| 90271979         | Insulin isophane human 100units/ml suspension for injection 3ml pre-filled disposable devices                             |
| 90271994         | hypodermic U100 insulin syringe sterile single use / single patient use 0.5ml with 12.7mm needle 0.33mm/                  |
| 90272979         | Insulin isophane human 100units/ml suspension for injection 3ml pre-filled disposable devices                             |
| 90272994         | Hypodermic U100 insulin syringe sterile single use / single patient use 0.5ml with 8mm needle 0.3mm/30gauge               |
| 90273994         | Insulin u100 syringe plus needle                                                                                          |
| 90274994         | Hypodermic U100 insulin syringe sterile single use / single patient use 0.3ml with 8mm needle 0.3mm/30gauge               |
| 90282994         | Multi reagent - 5 tests - urine test strips                                                                               |
| 90332994         | Blood glucose colorimetric testing strips                                                                                 |
| 90379998         | Insulin aspart human pyr 100 iu/ml injection 5 3ml disposable pen(s)                                                      |
| 90411994         | Lancets sterile single use 0.36mm/28gauge                                                                                 |
| 90412994         | Lancets sterile single use 0.65mm/23gauge                                                                                 |
| 90428994         | Hypodermic U100 insulin syringe sterile single use / single patient use 1ml with not less than 12mm needle 0.33mm/29gauge |
| 90429994         | Hypodermic U100 insulin syringe sterile single use / single patient use 1ml with 12mm needle 0.4mm/27gauge                |
| 90430994         | Hypodermic U100 insulin syringe sterile single use / single patient use 1ml with 12mm needle 0.4mm/27gauge                |
| 90431994         | Hypodermic U100 insulin syringe sterile single use / single patient use 0.5ml with not less than 12mm needle 0.33mm/29ga  |
| 90432994         | Hypodermic u100 insulin syringe sterile single use / single patient use 0.5ml with 12mm needle 0.36mm/28gauge             |
| 90433994         | Hypodermic U100 insulin syringe sterile single use / single patient use 0.5ml with 12mm needle 0.4mm/27gauge              |
| 90434994         | Hypodermic u100 insulin syringe sterile single use / single patient use 0.3ml with 12mm needle 0.33mm/29gauge             |

| Drug code | Generic name                                                                                                 |
|-----------|--------------------------------------------------------------------------------------------------------------|
| 90435994  | U100 insulin syringe 0.3ml                                                                                   |
| 90444994  | U100 insulin syringe 0.3ml                                                                                   |
| 90508994  | Hypodermic insulin injection pen reusable for 3ml cartridge 0.5 unit dial up / range 1-35 units              |
| 90622994  | Sterile dt type b lancets                                                                                    |
| 90681996  | Insulin biphasic isophane human emp 25:75; 100 units/ml injection                                            |
| 90682997  | Insulin biphasic isophane human prb 50:50; 100 units/ml injection                                            |
| 90682998  | Insulin biphasic isophane human prb 40:60; 100 units/ml injection                                            |
| 90683997  | Insulin isophane biphasic human 50/50 100units/ml suspension for injection 1.5ml cartridges                  |
| 90683998  | Insulin biphasic isophane human pyr 40:60; 100 units/ml injection                                            |
| 90684996  | Insulin isophane biphasic human 30/70 100units/ml suspension for injection 3ml pre-filled disposable devices |
| 90684997  | Insulin biphasic isophane human pyr 20:80; 100 units/ml injection                                            |
| 90684998  | Insulin biphasic isophane human pyr 10:90; 100 units/ml injection                                            |
| 90685998  | Insulin zinc mixed human 100units/ml suspension for injection 10ml vials                                     |
| 90686998  | Insulin isophane human 100units/ml suspension for injection 3ml pre-filled disposable devices                |
| 90687998  | Insulin isophane human prb 100iu/ml injection                                                                |
| 90688998  | Insulin isophane human 100units/ml suspension for injection 1.5ml cartridges                                 |
| 90689998  | Insulin soluble human prb 100unit/ml injection                                                               |
| 90690998  | Insulin human 100units/ml solution for injection 10ml vials                                                  |
| 90691998  | Insulin soluble human pyr 100unit/ml injection                                                               |
| 90697996  | Insulin isophane biphasic human 30/70 100units/ml suspension for injection 3ml pre-filled disposable devices |
| 90697997  | Insulin biphasic isophane human prb 20:80; 100 units/ml injection                                            |
| 90697998  | Insulin biphasic isophane human prb 10:90; 100 units/ml injection                                            |
| 90698998  | Insulin zinc suspension mixed bovine and porcine 100unit/ml injection                                        |
| 90767994  | Sterile single use needle                                                                                    |
| 90817994  | Generic bd ultra pen 1.5ml insulin pen (becton, dickinson uk ltd)                                            |
| 90818994  | Generic bd ultra pen 3ml insulin pen (becton, dickinson uk ltd)                                              |
| 90819994  | Hypodermic insulin injection pen reusable for 3ml cartridge 2 unit dial up / range 2-42 units                |
| 90820994  | Hypodermic insulin injection pen reusable for 1.5ml cartridge 2 unit dial up / range 2-32 units              |
| 90821994  | Hypodermic insulin injection pen reusable for 1.5ml cartridge 1 unit dial up / range 1-16 units              |
| 90822994  | Hypodermic insulin needles for pre-filled / reusable pen injectors screw on 12mm/29gauge                     |
| 90823994  | Hypodermic insulin needles for pre-filled / reusable pen injectors screw on 8mm/30gauge                      |
| 90828994  | Hypodermic insulin injection pen reusable for 3ml cartridge 1 unit dial up / range 2-70 units                |
| 90829994  | Hypodermic insulin injection pen reusable for 3ml cartridge 1 unit dial up / range 2-70 units                |
| 90830994  | Hypodermic insulin injection pen reusable for 3ml cartridge 1 unit dial up / range 2-70 units                |
| 90874994  | Lancets sterile single use 0.36mm/28gauge                                                                    |
| 90978994  | Hypodermic insulin needles for pre-filled / reusable pen injectors screw on 6mm/31gauge                      |
| 91010994  | Lancets sterile single use 0.4mm/28gauge                                                                     |
| 91160998  | Insulin zinc suspension mixed porcine 100unit/ml injection                                                   |
| 91179994  | Blood glucose biosensor testing strips                                                                       |
| 91273997  | Insulin biphasic isophane human prb 50:50; 100 units/ml injection                                            |
| 91273998  | Insulin biphasic isophane human prb 40:60; 100 units/ml injection                                            |
| 91274998  | Human insulin 100iu/ml preloaded injection pen                                                               |
| 91275996  | Insulin isophane biphasic human 30/70 100units/ml suspension for injection 3ml pre-filled disposable devices |
| 91275997  | Insulin biphasic isophane human prb 20:80; 100 units/ml injection                                            |
| 91275998  | Insulin biphasic isophane human prb 10:90; 100 units/ml injection                                            |
| 91276998  | Human isophane insulin 100iu/ml preloaded injection pen                                                      |
| 91289998  | Insulin isophane biphasic human 15/85 100units/ml suspension for injection 5ml vials                         |
| 91290996  | Insulin isophane biphasic human 50/50 100units/ml suspension for injection 10ml vials                        |
| 91290997  | Insulin isophane biphasic human 50/50 100units/ml suspension for injection 3ml pre-filled disposable devices |
| 91290998  | Insulin isophane biphasic human 50/50 100units/ml suspension for injection 1.5ml cartridges                  |
| 91291997  | Insulin isophane biphasic human 40/60 100units/ml suspension for injection 3ml pre-filled disposable devices |
| 91291998  | Insulin biphasic isophane human pyr 40:60; 100 units/ml injection                                            |
| 91292996  | Insulin isophane biphasic human 30/70 100units/ml suspension for injection 10ml vials                        |

| Drug code | Generic name                                                                                                 |
|-----------|--------------------------------------------------------------------------------------------------------------|
| 91292997  | Insulin isophane biphasic human 30/70 100units/ml suspension for injection 3ml pre-filled disposable devices |
| 91292998  | Insulin isophane biphasic human 30/70 100units/ml suspension for injection 3ml cartridges                    |
| 91293997  | Insulin isophane biphasic human 20/80 100units/ml suspension for injection 3ml pre-filled disposable devices |
| 91293998  | Insulin biphasic isophane human pyr 20:80; 100 units/ml injection                                            |
| 91294997  | Insulin isophane biphasic human 10/90 100units/ml suspension for injection 3ml pre-filled disposable devices |
| 91294998  | Insulin biphasic isophane human pyr 10:90; 100 units/ml injection                                            |
| 91295998  | Insulin isophane human 100units/ml suspension for injection 3ml pre-filled disposable devices                |
| 91307994  | Generic penject 100unit/ml injection device (hypoguard ltd)                                                  |
| 91326994  | Sterile dt type c lancets                                                                                    |
| 91394994  | Multi reagent - 5 tests - urine test strips                                                                  |
| 91407998  | Gliclazide 30mg modified-release tablets                                                                     |
| 91505998  | Insulin isophane human 100units/ml suspension for injection 3ml pre-filled disposable devices                |
| 91509998  | Insulin aspart 100units/ml solution for injection 3ml pre-filled disposable devices                          |
| 91559998  | Glibornuride 25mg tablet                                                                                     |
| 91577994  | Urine protein testing strips                                                                                 |
| 91612998  | Insulin aspart 100units/ml solution for injection 3ml pre-filled disposable devices                          |
| 91641994  | Hypodermic insulin injection pen reusable for 3ml cartridge 1 unit dial up / range 1-60 units                |
| 91700998  | Insulin isophane biphasic human 50/50 100units/ml suspension for injection 5ml vials                         |
| 91701998  | Insuman comb 25 100iu/ml Injection                                                                           |
| 91758998  | Insulin glargine 100units/ml solution for injection 3ml cartridges                                           |
| 91767994  | Generic novopen fun inj device injection device (novo nordisk ltd)                                           |
| 91777994  | Generic novopen classic inj device injection device (novo nordisk ltd)                                       |
| 91880990  | Pioglitazone 15mg tablets                                                                                    |
| 91908990  | Repaglinide 500microgram tablets                                                                             |
| 91923996  | Repaglinide 2mg tablets                                                                                      |
| 91923997  | Repaglinide 1mg tablets                                                                                      |
| 91923998  | Repaglinide 500microgram tablets                                                                             |
| 91924996  | Repaglinide 2mg tablets                                                                                      |
| 91924997  | Repaglinide 1mg tablets                                                                                      |
| 91924998  | Repaglinide 500microgram tablets                                                                             |
| 91933994  | Generic novopen inj device injection device (novo nordisk ltd)                                               |
| 91942994  | Hypodermic U100 insulin syringe sterile single use / single patient use 0.5ml with 8mm needle 0.3mm/30gauge  |
| 91943994  | Hypodermic U100 insulin syringe sterile single use / single patient use 0.3ml with 8mm needle 0.3mm/30gauge  |
| 92012994  | Lancets sterile single use 0.66mm/23gauge                                                                    |
| 92013994  | Lancets sterile single use 0.66mm/23gauge                                                                    |
| 92061998  | Glucagon 1mg(1iu) injection (powder plus diluent)                                                            |
| 92120994  | Lancets sterile single use 0.3mm/30gauge                                                                     |
| 92237997  | Pioglitazone 30mg tablets                                                                                    |
| 92237998  | Pioglitazone 15mg tablets                                                                                    |
| 92238997  | Pioglitazone 30mg tablets                                                                                    |
| 92238998  | Pioglitazone 15mg tablets                                                                                    |
| 92323998  | Insulin lispro biphasic 50/50 100units/ml suspension for injection 3ml pre-filled disposable devices         |
| 92376996  | Insulin isophane biphasic human 50/50 100units/ml suspension for injection 5ml vials                         |
| 92376997  | Insulin biphasic isophane human crb 25:75; 100 units/ml injection                                            |
| 92456994  | Sterile single use needle                                                                                    |
| 92458994  | Hypodermic insulin needles for pre-filled / reusable pen injectors screw on 5mm/31gauge                      |
| 92460994  | Hypodermic insulin needles for pre-filled / reusable pen injectors screw on 8mm/31gauge                      |
| 92482994  | Lancets sterile single use 0.36mm/28gauge                                                                    |
| 92555998  | Insulin glargine 100units/ml solution for injection 3ml cartridges                                           |
| 92590994  | Sterile dt type a lancets                                                                                    |
| 92621994  | Lancets sterile single use 0.4mm/28gauge                                                                     |
| 92627994  | Blood glucose test strips                                                                                    |
| 92647994  | Hypodermic insulin needles for pre-filled / reusable pen injectors screw on 8mm/30gauge                      |



| <b>Drug code</b> | <b>Generic name</b>                                                                                                       |
|------------------|---------------------------------------------------------------------------------------------------------------------------|
| 92648994         | Sterile single use needle                                                                                                 |
| 92649994         | Sterile single use needle                                                                                                 |
| 92813994         | Blood glucose biosensor testing discs                                                                                     |
| 92831990         | Gliclazide 30mg modified-release tablets                                                                                  |
| 92906998         | Insulin isophane biphasic human 50/50 100units/ml suspension for injection 1.5ml cartridges                               |
| 92907998         | Insulin biphasic isophane human pyr 40:60; 100 units/ml injection                                                         |
| 92908998         | Insulin biphasic isophane human pyr 20:80; 100 units/ml injection                                                         |
| 92909998         | Insulin biphasic isophane human pyr 10:90; 100 units/ml injection                                                         |
| 92924994         | Hypodermic U100 insulin syringe sterile single use / single patient use 1ml with 12mm needle 0.36mm/28gauge               |
| 92925994         | Hypodermic U100 insulin syringe sterile single use / single patient use 0.5ml with 12mm needle 0.36mm/28gauge             |
| 92932998         | Insulin biphasic isophane human pyr 30:70; 100 units/ml injection                                                         |
| 92940994         | Hypodermic U100 insulin syringe sterile single use / single patient use 1ml with not less than 12mm needle 0.33mm/29gauge |
| 92941994         | Hypodermic U100 insulin syringe sterile single use / single patient use 0.5ml with 8mm needle 0.3mm/30gauge               |
| 92948994         | Hypodermic U100 insulin syringe sterile single use / single patient use 0.5ml with 8mm needle 0.3mm/30gauge               |
| 92949994         | Hypodermic U100 insulin syringe sterile single use / single patient use 0.3ml with 8mm needle 0.3mm/30gauge               |
| 92950994         | Hypodermic U100 insulin syringe sterile single use / single patient use 0.3ml with 8mm needle 0.3mm/30gauge               |
| 92981979         | Repaglinide 2mg tablets                                                                                                   |
| 92983994         | Multi reagent - 4 tests - urine test strips                                                                               |
| 92988994         | Needle clipping / chopping device                                                                                         |
| 92996979         | Repaglinide 1mg tablets                                                                                                   |
| 93009979         | Repaglinide 500microgram tablets                                                                                          |
| 93067992         | Easistix ug urine glucose strips                                                                                          |
| 93070992         | Blood lancets                                                                                                             |
| 93078992         | Easistix bg blood glucose strips                                                                                          |
| 93137992         | Insulin isophane (human) 100 i/u inj                                                                                      |
| 93139992         | Insulin isophane 100 i/u                                                                                                  |
| 93430994         | Sterile dt type a lancets                                                                                                 |
| 93448979         | Guar gum 5g/sachet granules                                                                                               |
| 93467992         | Insulin soluble inj i/u <sup>2</sup>                                                                                      |
| 93476994         | Sterile dt type a lancets                                                                                                 |
| 93477994         | Sterile dt type a lancets                                                                                                 |
| 93483979         | Glimepiride 4mg tablets                                                                                                   |
| 93489994         | Sterile dt type a lancets                                                                                                 |
| 93509979         | Glimepiride 1mg tablets                                                                                                   |
| 93528979         | Glimepiride 2mg tablets                                                                                                   |
| 93543992         | Lancets (lifescan)                                                                                                        |
| 93545979         | Gliclazide 80mg tablets                                                                                                   |
| 93546979         | Gliclazide 80mg tablets                                                                                                   |
| 93556979         | Glibenclamide 5mg tablets                                                                                                 |
| 93564990         | Glimepiride 1mg tablets                                                                                                   |
| 93566979         | Insulin isophane human 100units/ml suspension for injection 3ml cartridges                                                |
| 93567979         | Insulin isophane human 100units/ml suspension for injection 3ml cartridges                                                |
| 93568979         | Insulin isophane human 100units/ml suspension for injection 3ml cartridges                                                |
| 93569979         | Insulin isophane human 100units/ml suspension for injection 3ml cartridges                                                |
| 93570979         | Insulin aspart 100units/ml solution for injection 10ml vials                                                              |
| 93572979         | Insulin lispro 100units/ml solution for injection 3ml pre-filled disposable devices                                       |
| 93574979         | Insulin lispro 100units/ml solution for injection 3ml pre-filled disposable devices                                       |
| 93582979         | Insulin lispro 100units/ml solution for injection 10ml vials                                                              |
| 93585979         | Insulin lispro 100units/ml solution for injection 10ml vials                                                              |
| 93586979         | Insulin lispro 100units/ml solution for injection 10ml vials                                                              |
| 93587979         | Insulin lispro 100units/ml solution for injection 10ml vials                                                              |

| <b>Drug code</b> | <b>Generic name</b>                                                                                          |
|------------------|--------------------------------------------------------------------------------------------------------------|
| 93589979         | Insulin soluble human 100units/ml solution for injection 10ml vials                                          |
| 93590979         | Insulin soluble human 100units/ml solution for injection 10ml vials                                          |
| 93592979         | Insulin soluble human 100units/ml solution for injection 3ml cartridges                                      |
| 93594979         | Neutral insulin 100iu/ml injection cartridges                                                                |
| 93712998         | Insulin u100 preset (1ml) syringe                                                                            |
| 93713996         | Insulin 1ml pre-set syringe                                                                                  |
| 93713997         | Insulin 2ml syringe                                                                                          |
| 93713998         | Insulin 1ml disposable syringe                                                                               |
| 93714996         | Insulin 1 ml syringe                                                                                         |
| 93714997         | Insulin 0.5ml disposable syringe                                                                             |
| 93714998         | Insulin 0.5 0.5ml syringe                                                                                    |
| 93715998         | Syringe                                                                                                      |
| 93716996         | Syringe 2ml                                                                                                  |
| 93716997         | Syringe 1ml                                                                                                  |
| 93716998         | Syringe 0.5ml                                                                                                |
| 93800998         | Glucose 40% oral gel                                                                                         |
| 93836998         | Glucose 40% oral gel                                                                                         |
| 94063994         | Sterile dt type a lancets                                                                                    |
| 94064994         | Sterile dt type b lancets                                                                                    |
| 94065994         | Sterile dt type a lancets                                                                                    |
| 94190994         | Lancets sterile single use 0.66mm/23gauge                                                                    |
| 94191994         | Lancets sterile single use 0.66mm/23gauge                                                                    |
| 94192994         | Lancets sterile single use 0.66mm/23gauge                                                                    |
| 94193994         | Lancets sterile single use 0.66mm/23gauge                                                                    |
| 94201992         | Insulin zinc lente 100iu/ml injection                                                                        |
| 94202992         | Insulin neusulin (neutral)(purified) 100 i/u inj                                                             |
| 94225994         | Sterile dt type a lancets                                                                                    |
| 94226994         | Sterile dt type a lancets                                                                                    |
| 94292998         | Insulin soluble human emp 100unit/ml injection                                                               |
| 94298998         | Insulin biphasic isophane human emp 25:75; 100 units/ml injection                                            |
| 94319998         | Insulin biphasic isophane human pyr 10:90; 100 units/ml injection                                            |
| 94322998         | Insulin isophane human crb 100iu/ml injection                                                                |
| 94328998         | Insulin biphasic isophane human pyr 20:80; 100 units/ml injection                                            |
| 94337998         | Insulin isophane biphasic human 30/70 100units/ml suspension for injection 3ml pre-filled disposable devices |
| 94341994         | Urine albumin test strips                                                                                    |
| 94342994         | Urine albumin test strips                                                                                    |
| 94371992         | Tolbutamide 100 mg tab                                                                                       |
| 94413998         | Insulin biphasic isophane human pyr 40:60; 100 units/ml injection                                            |
| 94436998         | Insulin isophane biphasic human 50/50 100units/ml suspension for injection 1.5ml cartridges                  |
| 94470992         | Glymidine 500mg tablets                                                                                      |
| 94477992         | Neutral insulin 100iu/ml injection                                                                           |
| 94581997         | Glucagon 10mg injection                                                                                      |
| 94581998         | Glucagon 1mg powder and solvent for solution for injection vials                                             |
| 94582997         | Glucagon 10mg(10iu) injection (powder plus diluent)                                                          |
| 94582998         | Glucagon 1mg(1iu) injection (powder, diluent and syringe)                                                    |
| 94948998         | Insulin soluble porcine 100units/ml solution for injection 1.5ml cartridges                                  |
| 95025990         | Gliclazide 80mg tablets                                                                                      |
| 95124994         | Lancets sterile single use 0.66mm/23gauge                                                                    |
| 95125994         | Lancets sterile single use 0.66mm/23gauge                                                                    |
| 95130994         | Blood glucose colorimetric testing strips                                                                    |
| 95148998         | Tolbutamide 50mg/ml injection                                                                                |
| 95149997         | Tolazamide 250mg tablets                                                                                     |
| 95149998         | Tolazamide 100mg tablets                                                                                     |
| 95150997         | Tolazamide 250mg tablets                                                                                     |
| 95150998         | Tolazamide 100mg tablet                                                                                      |
| 95158992         | INSULIN HUMAN (NEUTRAL) 40 I/U INJ                                                                           |
| 95162992         | Insulin soluble human 100units/ml solution for injection 10ml vials                                          |

| <b>Drug code</b> | <b>Generic name</b>                                                                           |
|------------------|-----------------------------------------------------------------------------------------------|
| 95163992         | Isophane insulin 100iu/ml injection                                                           |
| 95164992         | Insulin zinc lente 100iu/ml injection                                                         |
| 95168992         | Insulin semitard 40 i/u inj                                                                   |
| 95175994         | Litmus 6cm x 10mm red papers                                                                  |
| 95185994         | Blood glucose colorimetric testing strips                                                     |
| 95186994         | Urine glucose testing strips                                                                  |
| 95194994         | Sterile dt type b lancets                                                                     |
| 95200994         | Blood glucose biosensor testing strips                                                        |
| 95217994         | Generic glucose vt colorimetric strips colorimetric strips (biocare ltd)                      |
| 95244994         | Hypodermic needle sterile single use 0.45mm/26gauge 12mm                                      |
| 95246994         | Hypodermic needle sterile single use 0.4mm/27gauge 12mm                                       |
| 95247994         | Hypodermic needle sterile single use 0.5mm/25gauge 16mm                                       |
| 95305994         | Urine glucose testing strips                                                                  |
| 95377994         | Sterile dt type a lancets                                                                     |
| 95386994         | Litmus 6cm x 10mm blue papers                                                                 |
| 95653992         | Urine glucose test strips                                                                     |
| 95672992         | Tolbutamide 1 gm tab                                                                          |
| 95674992         | Tolbutamide 250 mg tab                                                                        |
| 95693994         | Blood glucose colorimetric testing strips                                                     |
| 95781992         | Syringe                                                                                       |
| 95846992         | Insulin zinc lente 100iu/ml injection                                                         |
| 95870992         | Butamide cap                                                                                  |
| 95898990         | Gliclazide 80mg tablets                                                                       |
| 96044992         | Insulin bp 100 i/u                                                                            |
| 96045998         | Isophane insulin 100iu/ml injection                                                           |
| 96046992         | Insulin humulin m4 cartridge 100 i/u                                                          |
| 96046998         | Insulin zinc mixed bovine 100units/ml suspension for injection 10ml vials                     |
| 96047998         | Insulin neutral human 100unit/ml injection                                                    |
| 96048998         | Insulin neutral human 100unit/ml injection                                                    |
| 96049998         | Insulin soluble porcine 100units/ml solution for injection 1.5ml cartridges                   |
| 96050998         | Neutral insulin bovine 100unit/ml injection                                                   |
| 96051992         | Guar gum 5g/sachet                                                                            |
| 96051998         | Insulin protamine zinc bovine 100units/ml suspension for injection 10ml vials                 |
| 96052998         | Insulin isophane mixed human 100unit/ml injection                                             |
| 96053997         | Insulin isophane biphasic porcine 30/70 100units/ml suspension for injection 1.5ml cartridges |
| 96055998         | Insulin isophane porcine 100units/ml suspension for injection 1.5ml cartridges                |
| 96056998         | Insulin isophane bovine 100units/ml suspension for injection 1.5ml cartridges                 |
| 96057998         | Insulin zinc crystalline human 100units/ml suspension for injection 10ml vials                |
| 96058998         | Insulin zinc suspension crystalline human pyr 100unit/ml long acting injection                |
| 96060998         | Insulin zinc suspension mixed human pyr 100unit/ml injection                                  |
| 96061998         | Insulin zinc mixed bovine vial 100unit/ml sterile suspension injection                        |
| 96062998         | Insulin biphasic 100 units/ml injection                                                       |
| 96064992         | Insulin semitard 100 i/u inj                                                                  |
| 96065998         | Insulin soluble bovine 100units/ml solution for injection 3ml cartridges                      |
| 96076992         | Insulin bovine protamine zinc 100 i/u inj                                                     |
| 96220990         | Glibenclamide 5mg tablets                                                                     |
| 96252998         | Guar gum 5g/sachet granules                                                                   |
| 96253996         | Guar gum 90% granules                                                                         |
| 96253997         | Guar gum 5g granules sachets sugar free                                                       |
| 96253998         | Guar gum mini tablets                                                                         |
| 96264998         | Glymidine sodium 500mg tablet                                                                 |
| 96280998         | Gliquidone 30mg tablets                                                                       |
| 96281998         | Glipizide 2.5mg tablets                                                                       |
| 96282992         | Isophane insulin 100iu/ml injection                                                           |
| 96282997         | Glipizide 5mg tablets                                                                         |
| 96282998         | Glipizide 2.5mg tablets                                                                       |
| 96283992         | Insulin isophane (nph) 100 i/u inj                                                            |
| 96283997         | Gliclazide 30mg modified-release tablets                                                      |

| <b>Drug code</b> | <b>Generic name</b>                                                                                           |
|------------------|---------------------------------------------------------------------------------------------------------------|
| 96283998         | Gliclazide 80mg tablets                                                                                       |
| 96284992         | Insulin humulin m4 100 i/u inj                                                                                |
| 96285992         | Insulin hypurin protamine zinc 100 i/u inj                                                                    |
| 96286992         | Insulin human velosulin 100 i/u inj 0                                                                         |
| 96287992         | Insulin isophane human 100units/ml suspension for injection 10ml vials                                        |
| 96289992         | Insulin novo ultratard mc 100 i/u inj                                                                         |
| 96290992         | Insulin human 100units/ml solution for injection 10ml vials                                                   |
| 96291992         | Isophane insulin 100iu/ml injection                                                                           |
| 96292992         | Insulin isophane (highly purified) 100 i/u inj                                                                |
| 96294992         | Insulin zinc bovine susp 100 i/u inj                                                                          |
| 96295992         | Insulin quicksol (soluble neutral) 100 i/u inj                                                                |
| 96406998         | Diazoxide 50mg tablets                                                                                        |
| 96427990         | Gliclazide 80mg tablets                                                                                       |
| 96495990         | Gliclazide 80mg tablets                                                                                       |
| 96548992         | Insulin humulin m cartridge 100 i/u                                                                           |
| 96561992         | Hypodermic U100 insulin syringe sterile single use / single patient use 0.5ml with 12mm needle 0.36mm/28gauge |
| 96686992         | Hypoguard ga reagent strip                                                                                    |
| 96687998         | Chlorpropamide 250mg tablets                                                                                  |
| 96688992         | Insulin human 100units/ml solution for injection 10ml vials                                                   |
| 96689992         | Insulin zinc crystalline susp 100 i/u inj                                                                     |
| 96755997         | Chlorpropamide 250mg tablets                                                                                  |
| 96755998         | Chlorpropamide 100mg tablets                                                                                  |
| 96787992         | Insulin soluble human 100units/ml solution for injection 3ml cartridges                                       |
| 96792992         | Insulin pur-in mix 50/50 100 i/u inj                                                                          |
| 96794992         | Insulin pur-in mix 15/85 100 i/u inj                                                                          |
| 96795992         | Insulin pur-in isophane 100 i/u inj                                                                           |
| 96893990         | Glipizide 5mg tablets                                                                                         |
| 96920992         | Multi reagent - 4 tests - urine test strips                                                                   |
| 96921992         | Multi reagent - 4 tests - urine test strips                                                                   |
| 96981998         | Acetohexamide 500mg tablets                                                                                   |
| 97023994         | Sterile dt type c lancets                                                                                     |
| 97026990         | Gliclazide 80mg tablets                                                                                       |
| 97027994         | Generic clinitest urine sugar analysis set (bayer diagnostics manufacturing ltd)                              |
| 97032990         | Gliclazide 80mg tablets                                                                                       |
| 97051997         | Insulin isophane biphasic human 50/50 100units/ml suspension for injection 10ml vials                         |
| 97051998         | Insulin biphasic isophane human prb 40:60; 100 units/ml injection                                             |
| 97052996         | Insulin isophane biphasic human 30/70 100units/ml suspension for injection 10ml vials                         |
| 97052997         | Insulin isophane biphasic human 20/80 100units/ml suspension for injection 3ml cartridges                     |
| 97052998         | Insulin biphasic isophane human prb 10:90; 100 units/ml injection                                             |
| 97053998         | Insulin zinc lente 100iu/ml injection                                                                         |
| 97057997         | Glibenclamide 2.5mg tablets                                                                                   |
| 97057998         | Glibenclamide 5mg tablets                                                                                     |
| 97089998         | Tolbutamide 500mg tablets                                                                                     |
| 97092994         | Hypodermic needle sterile single use 0.45mm/26gauge 12mm                                                      |
| 97097997         | Glibenclamide 5mg tablets                                                                                     |
| 97109998         | Tolbutamide 500mg tablets                                                                                     |
| 97127997         | Glibenclamide 5mg tablets                                                                                     |
| 97127998         | Glibenclamide 2.5mg tablets                                                                                   |
| 97133992         | Chlorpropamide 500 mg tab                                                                                     |
| 97146990         | Glipizide 5mg tablets                                                                                         |
| 97154990         | Gliclazide 80mg tablets                                                                                       |
| 97166990         | Gliclazide 80mg tablets                                                                                       |
| 97202990         | Glipizide 5mg tablets                                                                                         |
| 97236992         | Daonil 10 mg tab                                                                                              |
| 97244992         | Insulin depo s.c.s. 5 400 i/u inj                                                                             |
| 97268994         | Hypodermic u100 insulin syringe glass reusable 1ml                                                            |
| 97281992         | Diagnostic solution-tablets of copper (r                                                                      |

| <b>Drug code</b> | <b>Generic name</b>                                                                           |
|------------------|-----------------------------------------------------------------------------------------------|
| 97303998         | Gliclazide 80mg tablets                                                                       |
| 97322994         | Blood glucose colorimetric testing strips                                                     |
| 97322997         | Insulin soluble human 100units/ml solution for injection 3ml cartridges                       |
| 97322998         | Neutral insulin 100iu/ml injection cartridges                                                 |
| 97323994         | Urine glucose testing strips                                                                  |
| 97323998         | Isophane insulin 100iu/ml injection                                                           |
| 97325994         | Generic clinitest replacement test tube (bayer diagnostics manufacturing ltd)                 |
| 97524998         | Insulin 100iu/ml injection                                                                    |
| 97525998         | Insulin soluble bovine 100units/ml solution for injection 3ml cartridges                      |
| 97526998         | Human isophane insulin 100iu/ml injection cartridges                                          |
| 97527998         | Insulin zinc mixed bovine 100units/ml suspension for injection 10ml vials                     |
| 97528998         | Insulin protamine zinc bovine 100units/ml suspension for injection 10ml vials                 |
| 97537997         | Glibenclamide 5mg tablets                                                                     |
| 97537998         | Glibenclamide 2.5mg tablets                                                                   |
| 97538990         | Gliclazide 80mg tablets                                                                       |
| 97552990         | Glibenclamide 2.5mg tablets                                                                   |
| 97583997         | Glibenclamide 5mg tablets                                                                     |
| 97583998         | Glibenclamide 2.5mg tablets                                                                   |
| 97590990         | Gliclazide 80mg tablets                                                                       |
| 97598992         | Insulin isophane (nph) 40 i/u                                                                 |
| 97599992         | Isophane insulin 100iu/ml injection                                                           |
| 97600992         | Insulin bovine protamine zinc 40 i/u inj                                                      |
| 97602992         | Insulin soluble 40 i/u inj                                                                    |
| 97722994         | Sterile dt type b lancets                                                                     |
| 97723994         | Sterile dt type a lancets                                                                     |
| 97778994         | Generic albym test strips (boehringer mannheim uk ltd)                                        |
| 97800994         | Generic dextrostix colorimetric strips                                                        |
| 97834990         | Glipizide 5mg tablets                                                                         |
| 97854998         | Insulin isophane human 100units/ml suspension for injection 3ml pre-filled disposable devices |
| 97889990         | Gliclazide 80mg tablets                                                                       |
| 97938990         | Gliclazide 80mg tablets                                                                       |
| 98036992         | Sterile single use needle                                                                     |
| 98048990         | Insulin isophane bovine 100units/ml suspension for injection 1.5ml cartridges                 |
| 98053990         | Tolbutamide 500mg tablets                                                                     |
| 98133990         | Gliclazide 80mg tablets                                                                       |
| 98188989         | Chlorpropamide 250mg tablets                                                                  |
| 98188994         | Carrying case spec 17a hypodermic syringe                                                     |
| 98189994         | Hypodermic syringe ordinary purpose glass reusable 2ml                                        |
| 98198998         | Insulin aspart 100units/ml solution for injection 3ml cartridges                              |
| 98218994         | U100 insulin syringe 1ml                                                                      |
| 98219994         | U100 insulin syringe 0.5ml                                                                    |
| 98225994         | Hypodermic needle sterile single use 0.4mm/27gauge 12mm                                       |
| 98225998         | Insulin biphasic isophane human emp 50:50; 100 units/ml injection                             |
| 98226994         | Hypodermic needle sterile single use 0.5mm/25gauge 16mm                                       |
| 98226998         | Insulin biphasic isophane human emp 30:70; 100 units/ml injection                             |
| 98227994         | Sterile dt type b lancets                                                                     |
| 98227998         | Neutral insulin 100iu/ml injection                                                            |
| 98228994         | Sterile dt type b lancets                                                                     |
| 98228996         | Insulin isophane human 100units/ml suspension for injection 3ml cartridges                    |
| 98228997         | Insulin isophane human 100units/ml suspension for injection 10ml vials                        |
| 98228998         | Insulin isophane human 100units/ml suspension for injection 3ml pre-filled disposable devices |
| 98229994         | Sterile dt type a lancets                                                                     |
| 98230994         | Sterile dt type c lancets                                                                     |
| 98231994         | Sterile dt type a lancets                                                                     |
| 98232994         | Needle clipping / chopping device                                                             |
| 98237994         | Glass u100 hypodermic syringe                                                                 |
| 98238994         | U100 insulin syringe sp.36 1ml                                                                |
| 98239994         | U100 insulin syringe 0.5ml                                                                    |

| <b>Drug code</b> | <b>Generic name</b>                                                                                  |
|------------------|------------------------------------------------------------------------------------------------------|
| 98240994         | Luer mount hypodermic needle sp15                                                                    |
| 98268998         | Insulin zinc crystalline human 100units/ml suspension for injection 10ml vials                       |
| 98312994         | Blood glucose biosensor testing strips                                                               |
| 98313994         | Generic ga colorimetric strips (hypoguard ltd)                                                       |
| 98329994         | Urine ketones testing strips                                                                         |
| 98330994         | Urine ketones testing strips                                                                         |
| 98331994         | Urine ketones testing tablets                                                                        |
| 98332994         | Urine glucose testing strips                                                                         |
| 98333994         | Urine glucose testing tablets                                                                        |
| 98334994         | Urine protein testing strips                                                                         |
| 98335994         | Generic clinitest replacement dropper (bayer diagnostics manufacturing ltd)                          |
| 98337994         | Test tube 12.5cm x 16mm                                                                              |
| 98474990         | Insulin human 100units/ml solution for injection 10ml vials                                          |
| 98475997         | Acarbose 100mg tablets                                                                               |
| 98475998         | Acarbose 50mg tablets                                                                                |
| 98480998         | Insulin soluble porcine 100units/ml solution for injection 1.5ml cartridges                          |
| 98481997         | Human isophane insulin 100iu/ml injection cartridges                                                 |
| 98481998         | Isophane insulin 100iu/ml injection                                                                  |
| 98503992         | Syringe ordinary purpose 2ml                                                                         |
| 98504992         | Needle hypodermic                                                                                    |
| 98505998         | Insulin zinc lente 100iu/ml injection                                                                |
| 98525990         | Insulin zinc mixed bovine 100units/ml suspension for injection 10ml vials                            |
| 98664989         | Glibenclamide 2.5mg tablets                                                                          |
| 98664990         | Glibenclamide 5mg tablets                                                                            |
| 98803998         | Guar gum 5g/sachet granules                                                                          |
| 98817998         | Insulin zinc crystalline human 100units/ml suspension for injection 10ml vials                       |
| 98861992         | Hypodermic needle sterile single use 0.4mm/27gauge 12mm                                              |
| 98875992         | Needle clipper holder                                                                                |
| 98877992         | Autoclax lancet                                                                                      |
| 98878992         | Hypodermic see syringe or needle                                                                     |
| 98895998         | Insulin lispro biphasic 25/75 100units/ml suspension for injection 3ml pre-filled disposable devices |
| 98896998         | Glucagon 1mg powder and solvent for solution for injection vials                                     |
| 98915997         | Acarbose 100mg tablets                                                                               |
| 98915998         | Acarbose 50mg tablets                                                                                |
| 98982998         | Insulin soluble human 100units/ml solution for injection 10ml vials                                  |
| 99045992         | Needle clipping / chopping device                                                                    |
| 99046992         | Syringe ordinary purpose 1ml                                                                         |
| 99047992         | Syringe pre-set insulin for blind 2ml                                                                |
| 99048992         | Syringe insulin (bs1619/1) 2ml                                                                       |
| 99144998         | Insulin zinc suspension amorphous porcine 100unit/ml injection                                       |
| 99145998         | Glibenclamide 2.5mg tablets                                                                          |
| 99195998         | Tolbutamide 500mg tablets                                                                            |
| 99196998         | Insulin biphasic 100 units/ml injection                                                              |
| 99246990         | Chlorpropamide 100mg tablets                                                                         |
| 99247989         | Chlorpropamide 250mg tablets                                                                         |
| 99268994         | Blood glucose colorimetric testing strips                                                            |
| 99336994         | Blood glucose colorimetric testing strips                                                            |
| 99347990         | Tolbutamide 500mg tablets                                                                            |
| 99349990         | Tolbutamide 500mg tablets                                                                            |
| 99359998         | Isophane insulin 100iu/ml injection                                                                  |
| 99391994         | U100 insulin syringe 0.3ml                                                                           |
| 99401998         | Insulin zinc lente 100iu/ml injection                                                                |
| 99402998         | Insulin aspart 100units/ml solution for injection 10ml vials                                         |
| 99415998         | Insulin isophane biphasic porcine 30/70 100units/ml suspension for injection 10ml vials              |
| 99419998         | Glipizide 5mg tablets                                                                                |
| 99480998         | Insulin zinc lente 100iu/ml injection                                                                |
| 99532998         | Isophane insulin 100iu/ml injection                                                                  |
| 99533998         | Isophane insulin 100iu/ml injection                                                                  |

| <b>Drug code</b> | <b>Generic name</b>                                                     |
|------------------|-------------------------------------------------------------------------|
| 99553998         | Insulin soluble human 100units/ml solution for injection 3ml cartridges |
| 99554998         | Insulin isophane human 100units/ml suspension for injection 10ml vials  |
| 99556998         | Insulin zinc lente 100iu/ml injection                                   |
| 99557998         | Insulin soluble human 100units/ml solution for injection 3ml cartridges |
| 99580989         | Glibenclamide 2.5mg tablets                                             |
| 99580990         | Glibenclamide 5mg tablets                                               |
| 99582989         | Glibenclamide 2.5mg tablets                                             |
| 99582990         | Glibenclamide 5mg tablets                                               |
| 99588998         | Glibornuride 25mg tablets                                               |
| 99589998         | Gliquidone 30mg tablets                                                 |
| 99591998         | Glipizide 5mg tablets                                                   |
| 99592994         | Blood glucose colorimetric testing strips                               |
| 99668997         | Glibenclamide 5mg tablets                                               |
| 99668998         | Glibenclamide 2.5mg tablets                                             |
| 99670998         | Diazoxide 50mg tablets                                                  |
| 99733994         | Hypodermic syringe ordinary purpose glass reusable 1ml                  |
| 99754998         | Acetohexamide 500mg tablets                                             |
| 99764997         | Chlorpropamide 250mg tablets                                            |
| 99764998         | Chlorpropamide 100mg tablets                                            |
| 99787998         | Glibenclamide 5mg tablets                                               |
| 99976992         | Insulin soluble 100 i/u inj                                             |
| 99977992         | Insulin isophane 50%/neutral 50% 100 i/u inj                            |
| 99978992         | Insulin isophane (purified) 100 i/u inj                                 |

#### **Appendix table XXIII.5: Drug codes for metformin**

| <b>Drug code</b> | <b>Generic name</b>                          |
|------------------|----------------------------------------------|
| 54496979         | Metformin 1g modified-release tablets        |
| 54786979         | Metformin 500mg modified-release tablets     |
| 58558979         | Metformin 500mg modified-release tablets     |
| 71281979         | Metformin 500mg/5ml oral solution            |
| 74441978         | Metformin 1g modified-release tablets        |
| 74453978         | Metformin 500mg modified-release tablets     |
| 74454978         | Metformin 500mg modified-release tablets     |
| 76199978         | Metformin 1g modified-release tablets        |
| 79512979         | Metformin 500mg/5ml oral solution            |
| 81158998         | Metformin 500mg modified-release tablets     |
| 81344998         | Metformin 1g modified-release tablets        |
| 81701998         | Metformin 500mg modified-release tablets     |
| 83031998         | Metformin 1g modified-release tablets        |
| 83032998         | Metformin 1g modified-release tablets        |
| 83619998         | Metformin 500mg modified-release tablets     |
| 83732998         | Metformin 750mg modified-release tablets     |
| 83733998         | Metformin 750mg modified-release tablets     |
| 85673998         | Metformin 500mg/5ml oral solution sugar free |
| 85674998         | Metformin 500mg/5ml oral solution            |
| 87053998         | Metformin 500mg modified-release tablets     |
| 87054998         | Metformin 500mg modified-release tablets     |
| 87536998         | Metformin 500mg/5ml oral solution            |
| 87883998         | Metformin 500mg tablets                      |
| 89128979         | Metformin 1g modified-release tablets        |
| 89129979         | Metformin 1g modified-release tablets        |
| 89188979         | Metformin 500mg/5ml oral solution            |
| 89868979         | Metformin 500mg modified-release tablets     |
| 89870979         | Metformin 500mg modified-release tablets     |
| 89871979         | Metformin 500mg modified-release tablets     |
| 91221997         | Metformin hydrochloride 850mg tablets        |
| 91221998         | Metformin hydrochloride 500mg tablets        |

| Drug code | Generic name                      |
|-----------|-----------------------------------|
| 91686990  | Metformin 500mg/5ml oral solution |
| 92983990  | Metformin 500mg/5ml oral solution |
| 93167990  | Metformin 500mg/5ml oral solution |
| 93459979  | Metformin 850mg tablets           |
| 93462979  | Metformin 500mg tablets           |
| 93469979  | Metformin 500mg tablets           |
| 94235992  | Metformin 500mg tablets           |
| 94248990  | Metformin 500mg tablets           |
| 95270992  | Metformin 800 mg tab              |
| 95271992  | Metformin 850mg tablets           |
| 95272992  | Metformin 250 mg tab              |
| 95600990  | Metformin 500mg tablets           |
| 95880998  | Metformin 500mg tablets           |
| 96111990  | Metformin 500mg tablets           |
| 96270990  | Metformin 500mg tablets           |
| 96850990  | Metformin 500mg tablets           |
| 97087997  | Metformin 850mg tablets           |
| 97087998  | Metformin 500mg tablets           |
| 97110989  | Metformin 850mg tablets           |
| 97110990  | Metformin 500mg tablets           |
| 98125989  | Metformin 850mg tablets           |
| 98125990  | Metformin 500mg tablets           |
| 98493989  | Metformin 500mg tablets           |
| 98493990  | Metformin 850mg tablets           |
| 98654989  | Metformin 500mg tablets           |
| 98654990  | Metformin 850mg tablets           |
| 99149990  | Metformin 500mg tablets           |
| 99513989  | Metformin 850mg tablets           |
| 99513990  | Metformin 500mg tablets           |
| 99514989  | Metformin 850mg tablets           |
| 99514990  | Metformin 500mg tablets           |
| 99590997  | Metformin 850mg tablets           |
| 99590998  | Metformin 500mg tablets           |

#### Appendix table XXIII.6: Read codes for polycystic ovary syndrome

| Read code | Description                          |
|-----------|--------------------------------------|
| C165.00   | Polycystic ovarian syndrome          |
| C164.00   | Polycystic ovaries                   |
| C164.11   | Isosexual virilisation               |
| C164.12   | Stein - Leventhal syndrome           |
| C164.13   | Multicystic ovaries                  |
| 7E25300   | Endoscopic drilling of ovary         |
| 7E25200   | Endoscopic drainage of cyst of ovary |
| 7E25211   | Laparoscopic drainage ovarian cyst   |



**Appendix table XXIII.7: Read codes for obesity**

| Read code | Description                                                    |
|-----------|----------------------------------------------------------------|
| 222A.00   | O/E - obese                                                    |
| 22A5.00   | O/E - weight > 20% over ideal                                  |
| 22A5.11   | O/E - obese                                                    |
| 22K5.00   | Body mass index 30+ - obesity                                  |
| 22K7.00   | Body mass index 40+ - severely obese                           |
| 22KC.00   | Obese class I (body mass index 30.0 - 34.9)                    |
| 22KD.00   | Obese class II (body mass index 35.0 - 39.9)                   |
| 22KE.00   | Obese class III (BMI equal to or greater than 40.0)            |
| 38B2.00   | Bariatric risk assessment                                      |
| 38F..00   | Assessment for bariatric surgery                               |
| 66C..00   | Obesity monitoring                                             |
| 66C1.00   | Initial obesity assessment                                     |
| 66C2.00   | Follow-up obesity assessment                                   |
| 66C4.00   | Has seen dietician - obesity                                   |
| 66C5.00   | Treatment of obesity changed                                   |
| 66C6.00   | Treatment of obesity started                                   |
| 66C7.00   | Treatment of obesity stopped                                   |
| 66CE.00   | Reason for obesity therapy - occupational                      |
| 66CS.00   | Inter risk hlth overweight obesity adv diet phys act cons drug |
| 66CT.00   | Inter risk hlth owt ob adv diet phy ac cons dgs cons surgery   |
| 66CX.00   | Obesity multidisciplinary case review                          |
| 66CZ.00   | Obesity monitoring NOS                                         |
| 66Cb.00   | Intensive weight management programme commenced                |
| 66Cc.00   | Intensive weight management programme ended                    |
| 66Cd.00   | Intensive weight management programme declined                 |
| 66Ce.00   | Telehealth obesity monitoring                                  |
| 7611.00   | Partial excision of stomach                                    |
| 7611100   | Partial gastrectomy & anastomosis stomach to transp jejunum    |
| 7611200   | Partial gastrectomy and anastomosis stomach to jejunum NEC     |
| 7611400   | Sleeve gastrectomy and duodenal switch                         |
| 7611500   | Sleeve gastrectomy NEC                                         |
| 7611600   | Laparoscopic sleeve gastrectomy                                |
| 7611y00   | Other specified partial excision of stomach                    |
| 7611z00   | Partial excision of stomach NOC                                |
| 7613000   | Gastroplasty NEC                                               |
| 7613100   | Partitioning of stomach                                        |
| 7613111   | Mason vertical banded gastroplasty                             |
| 7613200   | Laparoscopic adjustable gastric banding                        |
| 7613300   | Partitioning of stomach using band                             |
| 7613400   | Partitioning of stomach using staples                          |
| 7613500   | Partitioning of stomach NEC                                    |
| 7613600   | Maintenance of gastric band                                    |
| 7615.00   | Connection of stomach to transposed jejunum                    |
| 7615000   | Bypass stomach by anastomosis stomach to transposed jejunum    |
| 7615y00   | Other specified connection of stomach to transposed jejunum    |
| 7615z00   | Connection of stomach to transposed jejunum NOS                |
| 7616.00   | Other connection of stomach to jejunum                         |
| 7616000   | Bypass of stomach by anastomosis of stomach to jejunum NEC     |
| 7616013   | Mason high gastric bypass                                      |
| 7616600   | Laparoscopic gastric bypass                                    |
| 7616y00   | Other specified other connection of stomach to jejunum         |
| 7616z00   | Other connection of stomach to jejunum NOS                     |
| 761H000   | Insertion of gastric bubble                                    |
| 761H011   | Insertion of gastric balloon                                   |
| 761H100   | Attention to gastric bubble                                    |

| Read code | Description                                             |
|-----------|---------------------------------------------------------|
| 761H400   | Removal of gastric balloon                              |
| 761H411   | Removal of gastric bubble                               |
| 761H500   | Insertion of gastric balloon                            |
| 761H600   | Attention to gastric balloon                            |
| 7622.00   | Bypass of duodenum                                      |
| 7622000   | Bypass of duodenum by anastomosis of stomach to jejunum |
| 7622z00   | Bypass of duodenum NOS                                  |
| 7633.00   | Bypass of jejunum                                       |
| 7633y00   | Other specified bypass of jejunum                       |
| 7633z00   | Bypass of jejunum NOS                                   |
| 7642500   | Duodenal switch                                         |
| 8CP4.00   | Discussion about bariatric operative procedure          |
| 8CV7.00   | Anti-obesity drug therapy commenced                     |
| 8H5N.00   | Referral to bariatric surgeon                           |
| 8Hlv.00   | Referral for pre-bariatric surgery assessment           |
| 8T11.00   | Referral to multidisciplinary obesity clinic            |
| 9N1yF00   | Seen in bariatric surgery clinic                        |
| 9Nt4000   | Seen by consultant bariatric physician                  |
| 9OK..00   | Obesity monitoring admin.                               |
| 9OK..11   | Obesity clinic administration                           |
| 9OK1.00   | Attends obesity monitoring                              |
| 9OK2.00   | Refuses obesity monitoring                              |
| 9OK3.00   | Obesity monitoring default                              |
| 9OK4.00   | Obesity monitoring 1st letter                           |
| 9OK5.00   | Obesity monitoring 2nd letter                           |
| 9OK6.00   | Obesity monitoring 3rd letter                           |
| 9OK7.00   | Obesity monitoring verbal inv.                          |
| 9OK8.00   | Obesity monitor phone invite                            |
| 9OKA.00   | Obesity monitoring check done                           |
| 9OKZ.00   | Obesity monitoring admin.NOS                            |
| C38..00   | Obesity and other hyperalimentation                     |
| C380.00   | Obesity                                                 |
| C380000   | Obesity due to excess calories                          |
| C380100   | Drug-induced obesity                                    |
| C380200   | Extreme obesity with alveolar hypoventilation           |
| C380300   | Morbid obesity                                          |
| C380400   | Central obesity                                         |
| C380500   | Generalised obesity                                     |
| C380600   | Adult-onset obesity                                     |
| C380700   | Lifelong obesity                                        |
| C38y011   | Obesity hypoventilation syndrome                        |
| C38z.00   | Obesity and other hyperalimentation NOS                 |
| C38z000   | Simple obesity NOS                                      |
| Cyu7.00   | [X]Obesity and other hyperalimentation                  |
| Cyu7000   | [X]Other obesity                                        |
| ZC2CM00   | Dietary advice for obesity                              |
| ZV65319   | [V]Dietary counselling in obesity                       |

**Appendix table XXIII.8: Read codes for current smoking**

| Read code | Description                    |
|-----------|--------------------------------|
| 137..00   | Tobacco consumption            |
| 137..11   | Smoker - amount smoked         |
| 1372.00   | Trivial smoker - < 1 cig/day   |
| 1372.11   | Occasional smoker              |
| 1373.00   | Light smoker - 1-9 cigs/day    |
| 1374.00   | Moderate smoker - 10-19 cigs/d |
| 1375.00   | Heavy smoker - 20-39 cigs/day  |

| Read code | Description                                                   |
|-----------|---------------------------------------------------------------|
| 1376.00   | Very heavy smoker - 40+cigs/d                                 |
| 137C.00   | Keeps trying to stop smoking                                  |
| 137G.00   | Trying to give up smoking                                     |
| 137H.00   | Pipe smoker                                                   |
| 137J.00   | Cigar smoker                                                  |
| 137M.00   | Rolls own cigarettes                                          |
| 137P.00   | Cigarette smoker                                              |
| 137P.11   | Smoker                                                        |
| 137Q.00   | Smoking started                                               |
| 137Q.11   | Smoking restarted                                             |
| 137R.00   | Current smoker                                                |
| 137V.00   | Smoking reduced                                               |
| 137W.00   | Chews tobacco                                                 |
| 137X.00   | Cigarette consumption                                         |
| 137Y.00   | Cigar consumption                                             |
| 137Z.00   | Tobacco consumption NOS                                       |
| 137a.00   | Pipe tobacco consumption                                      |
| 137b.00   | Ready to stop smoking                                         |
| 137c.00   | Thinking about stopping smoking                               |
| 137d.00   | Not interested in stopping smoking                            |
| 137e.00   | Smoking restarted                                             |
| 137f.00   | Reason for restarting smoking                                 |
| 137g.00   | Cigarette pack-years                                          |
| 137h.00   | Minutes from waking to first tobacco consumption              |
| 137m.00   | Failed attempt to stop smoking                                |
| 137n.00   | Total time smoked                                             |
| 137o.00   | Waterpipe tobacco consumption                                 |
| 13p.00    | Smoking cessation milestones                                  |
| 13p0.00   | Negotiated date for cessation of smoking                      |
| 13p1.00   | Smoking status at 4 weeks                                     |
| 13p2.00   | Smoking status between 4 and 52 weeks                         |
| 13p3.00   | Smoking status at 52 weeks                                    |
| 13p5.00   | Smoking cessation programme start date                        |
| 13p5000   | Practice based smoking cessation programme start date         |
| 13p6.00   | Carbon monoxide reading at 4 weeks                            |
| 13p7.00   | Smoking status at 12 weeks                                    |
| 13p8.00   | Lost to smoking cessation follow-up                           |
| 1V08.00   | Smokes drugs in cigarette form                                |
| 38DH.00   | Fagerstr test for nicotine dep                                |
| 6791.00   | Health ed. - smoking                                          |
| 6791000   | Health education - parental smoking                           |
| 67A3.00   | Pregnancy smoking advice                                      |
| 67H1.00   | Lifestyle advice regarding smoking                            |
| 67H6.00   | Brief intervention for smoking cessation                      |
| 745H.00   | Smoking cessation therapy                                     |
| 745H000   | Nicotine replacement therapy using nicotine patches           |
| 745H100   | Nicotine replacement therapy using nicotine gum               |
| 745H200   | Nicotine replacement therapy using nicotine inhalator         |
| 745H300   | Nicotine replacement therapy using nicotine lozenges          |
| 745H400   | Smoking cessation drug therapy                                |
| 745Hy00   | Other specified smoking cessation therapy                     |
| 745Hz00   | Smoking cessation therapy NOS                                 |
| 8B2B.00   | Nicotine replacement therapy                                  |
| 8B31G00   | Varenicline smoking cessation therapy offered                 |
| 8B3Y.00   | Over the counter nicotine replacement therapy                 |
| 8B3f.00   | Nicotine replacement therapy provided free                    |
| 8BP3.00   | Nicotine replacement therapy provided by community pharmacist |
| 8CAL.00   | Smoking cessation advice                                      |
| 8CAg.00   | Smoking cessation advice provided by community pharmacist     |

| Read code | Description                                                  |
|-----------|--------------------------------------------------------------|
| 8CdB.00   | Stop smoking service opportunity signposted                  |
| 8H7i.00   | Referral to smoking cessation advisor                        |
| 8HBM.00   | Stop smoking face to face follow-up                          |
| 8HBP.00   | Smoking cessation 12 week follow-up                          |
| 8HTK.00   | Referral to stop-smoking clinic                              |
| 8HkQ.00   | Referral to NHS stop smoking service                         |
| 8I2I.00   | Nicotine replacement therapy contraindicated                 |
| 8I39.00   | Nicotine replacement therapy refused                         |
| 8IAj.00   | Smoking cessation advice declined                            |
| 8IEK.00   | Smoking cessation programme declined                         |
| 8IEM.00   | Smoking cessation drug therapy declined                      |
| 8IEM000   | Varenicline smoking cessation therapy declined               |
| 8IEo.00   | Referral to smoking cessation service declined               |
| 8T08.00   | Referral to smoking cessation service                        |
| 9N2k.00   | Seen by smoking cessation advisor                            |
| 9N4M.00   | DNA - Did not attend smoking cessation clinic                |
| 9NS0200   | Referral for smoking cessation service offered               |
| 9NdW.00   | Consent given for smoking cessation data sharing             |
| 9NdZ.00   | Declined consent for smoking cessation data sharing          |
| 9Ndf.00   | Consent given for follow-up by smoking cessation team        |
| 9Ndg.00   | Declined consent for follow-up by smoking cessation team     |
| 9OO..00   | Anti-smoking monitoring admin.                               |
| 9OO..11   | Stop smoking clinic admin.                                   |
| 9OO..12   | Stop smoking monitoring admin.                               |
| 9OO1.00   | Attends stop smoking monitor.                                |
| 9OO2.00   | Refuses stop smoking monitor                                 |
| 9OO3.00   | Stop smoking monitor default                                 |
| 9OO4.00   | Stop smoking monitor 1st lettr                               |
| 9OO5.00   | Stop smoking monitor 2nd lettr                               |
| 9OO6.00   | Stop smoking monitor 3rd lettr                               |
| 9OO7.00   | Stop smoking monitor verb.inv.                               |
| 9OO8.00   | Stop smoking monitor phone inv                               |
| 9OO9.00   | Stop smoking monitoring delete                               |
| 9OOA.00   | Stop smoking monitor.chk done                                |
| 9OOB.00   | Stop smoking invitation short message service text message   |
| 9OOB000   | Stop smoking invitation first SMS text message               |
| 9OOB100   | Stop smoking invitation second SMS text message              |
| 9OOB200   | Stop smoking invitation third SMS text message               |
| 9OOZ.00   | Stop smoking monitor admin.NOS                               |
| 9hG..00   | Exception reporting: smoking quality indicators              |
| 9hG0.00   | Excepted from smoking quality indicators: Patient unsuitable |
| 9hG1.00   | Excepted from smoking quality indicators: Informed dissent   |
| 9kc..00   | Smoking cessation - enhanced services administration         |
| 9kc0.00   | Smoking cessatn monitor template complet - enhanc serv admin |
| 9kc0.11   | Smoking cessation ESA monitoring template completed          |
| 9kf1.00   | Refer COPD structured smoking assessment - enhanc serv admin |
| 9kf1.11   | Referred for COPD structured smoking assessment              |
| 9kf2.00   | COPD structured smoking assessment declined - enh serv admin |
| 9kf2.11   | COPD structured smoking assessment declined                  |
| 9ko..00   | Current smoker annual review - enhanced services admin       |
| 9ko..11   | Current smoker annual review                                 |
| E023.00   | Nicotine withdrawal                                          |
| E251.00   | Tobacco dependence                                           |
| E251000   | Tobacco dependence, unspecified                              |
| E251100   | Tobacco dependence, continuous                               |
| E251200   | Tobacco dependence, episodic                                 |
| E251300   | Tobacco dependence in remission                              |
| E251z00   | Tobacco dependence NOS                                       |
| Eu17.00   | [X]Mental and behavioural disorder due to use of tobacco     |

| Read code | Description                                                  |
|-----------|--------------------------------------------------------------|
| Eu17000   | [X]Mental & behav dis due to use tobacco: acute intoxication |
| Eu17100   | [X]Mental and behav dis due to use of tobacco: harmful use   |
| Eu17200   | [X]Mental and behav dis due to use tobacco: dependence syndr |
| Eu17300   | [X]Mental and behav dis due to use tobacco: withdrawal state |
| Eu17400   | [X]Men & behav dis due tobacco: withdrawl state wth delirium |
| Eu17500   | [X]Mental & behav dis due to use tobacco: psychotic disorder |
| Eu17600   | [X]Mental and behav dis due to use tobacco: amnesic syndrome |
| Eu17700   | [X]Men & beh dis due tobacco: resid & late-onset psychot dis |
| Eu17y00   | [X]Men & behav dis due to use tobacco: oth men & behav dis   |
| Eu17z00   | [X]Ment & behav dis due use tobacco: unsp ment & behav dis   |
| H310100   | Smokers' cough                                               |
| J036400   | Tobacco deposit on teeth                                     |
| ZG23300   | Advice on smoking                                            |
| ZRBm200   | Fagerstrom test for nicotine dependence                      |
| ZRBm211   | FTND - Fagerstrom test for nicotine dependence               |
| ZRaM.00   | Motives for smoking scale                                    |
| ZRaM.11   | MFS - Motives for smoking scale                              |
| ZRao.00   | Occasions for smoking scale                                  |
| ZRao.11   | OFS - Occasions for smoking scale                            |
| ZRh4.00   | Reasons for smoking scale                                    |
| ZRh4.11   | RFS - Reasons for smoking scale                              |
| ZV4K000   | [V]Tobacco use                                               |
| ZV6D800   | [V]Tobacco abuse counselling                                 |

#### Appendix table XXIII.9: Read codes for ex-smoking

| Read code | Description                                                  |
|-----------|--------------------------------------------------------------|
| 1377.00   | Ex-trivial smoker (<1/day)                                   |
| 1378.00   | Ex-light smoker (1-9/day)                                    |
| 1379.00   | Ex-moderate smoker (10-19/day)                               |
| 137A.00   | Ex-heavy smoker (20-39/day)                                  |
| 137B.00   | Ex-very heavy smoker (40+/day)                               |
| 137F.00   | Ex-smoker - amount unknown                                   |
| 137K.00   | Stopped smoking                                              |
| 137K000   | Recently stopped smoking                                     |
| 137L.00   | Current non-smoker                                           |
| 137N.00   | Ex pipe smoker                                               |
| 137O.00   | Ex cigar smoker                                              |
| 137S.00   | Ex smoker                                                    |
| 137T.00   | Date ceased smoking                                          |
| 137j.00   | Ex-cigarette smoker                                          |
| 137l.00   | Ex roll-up cigarette smoker                                  |
| 13p4.00   | Smoking free weeks                                           |
| 8l6H.00   | Smoking review not indicated                                 |
| 9NdV.00   | Consent given follow-up after smoking cessation intervention |
| 9NdY.00   | Declin cons follow-up evaluation after smoking cess interven |
| 9km..00   | Ex-smoker annual review - enhanced services administration   |
| 9km..11   | Ex-smoker annual review                                      |
| ZV11600   | [V]Personal history of tobacco abuse                         |

#### Appendix table XXIII.10: Read codes for non-smoking

| Read code | Description                                                 |
|-----------|-------------------------------------------------------------|
| 1371.00   | Never smoked tobacco                                        |
| 1371.11   | Non-smoker                                                  |
| 9kn..00   | Non-smoker annual review - enhanced services administration |
| 9kn..11   | Non-smoker annual review                                    |

**Appendix table XXIII.11: Read codes for human immunodeficiency virus used in calculation of Charlson index**

| Read code | Description                                                  |
|-----------|--------------------------------------------------------------|
| A788W00   | HIV disease resulting in unspecified malignant neoplasm      |
| A788V00   | HIV disease resulting in multiple diseases CE                |
| AyuC.00   | [X]Human immunodeficiency virus disease                      |
| A789000   | HIV disease resulting in mycobacterial infection             |
| A788400   | Human immunodeficiency virus with neurological disease       |
| AyuC600   | [X]HIV disease resulting in other non-Hodgkin's lymphoma     |
| A788X00   | HIV disease resulting/unspsc infectious disease              |
| A788z00   | Acquired human immunodeficiency virus infection syndrome NOS |
| AyuC900   | [X]HIV disease resulting in unspecified malignant neoplasm   |
| AyuC300   | [X]HIV disease resulting in multiple infections              |
| A789200   | HIV disease resulting in candidiasis                         |
| A788500   | Human immunodeficiency virus with secondary infection        |
| AyuC000   | [X]HIV disease resulting in other bacterial infections       |
| AyuCD00   | [X]Unspecified human immunodeficiency virus [HIV] disease    |
| AyuCC00   | [X]HIV disease resulting in other specified conditions       |
| A789600   | HIV disease resulting in Burkitt's lymphoma                  |
| AyuC200   | [X]HIV disease resulting in other mycoses                    |
| A789900   | HIV disease resulting in lymphoid interstitial pneumonitis   |
| A789.00   | Human immunodef virus resulting in other disease             |
| A789A00   | HIV disease resulting in wasting syndrome                    |
| AyuC100   | [X]HIV disease resulting in other viral infections           |
| A788300   | Human immunodeficiency virus with constitutional disease     |
| A788.00   | Acquired immune deficiency syndrome                          |
| AyuCB00   | [X]HIV disease result/haematological???? abnorms,NEC         |
| A789100   | HIV disease resulting in cytomegaloviral disease             |
| A789500   | HIV disease resulting in Kaposi's sarcoma                    |
| A788200   | HIV infection with persistent generalised lymphadenopathy    |
| A788U00   | HIV disease result/haematological???? abnorms,NEC            |
| A788y00   | Human immunodeficiency virus with other clinical findings    |
| A788600   | Human immunodeficiency virus with secondary cancers          |
| L7990A    | ACQUIRED IMMUNE DEFICIENCY SYNDROME                          |
| A789300   | HIV disease resulting in Pneumocystis carinii pneumonia      |
| AyuC500   | [X]HIV disease resulting/unspsc infectious??? disease        |
| A789X00   | HIV dis reslt/oth mal neopl/lymph,h'matopoetc? tissu         |
| AyuC700   | [X]HIV dis reslt/oth mal neopl/lymph,h'matopoetc? tissu      |
| A788100   | Asymptomatic human immunodeficiency virus infection          |
| AyuC800   | [X]HIV disease resulting in other malignant neoplasms        |
| AyuC400   | [X]HIV disease resulting/other infectious??? diseases        |
| A789400   | HIV disease resulting in multiple infections                 |
| A789800   | HIV disease resulting in multiple malignant neoplasms        |
| AyuCA00   | [X]HIV disease resulting in multiple diseases CE             |

**Appendix table XXIII.12: Read codes for cancer used in calculation of Charlson index**

| Read code | Description                                        |
|-----------|----------------------------------------------------|
| B....00   | Neoplasms                                          |
| B....11   | Cancers                                            |
| B0...00   | Malignant neoplasm of lip, oral cavity and pharynx |
| B0...11   | Carcinoma of lip, oral cavity and pharynx          |
| B00..00   | Malignant neoplasm of lip                          |
| B00..11   | Carcinoma of lip                                   |

| <b>Read code</b> | <b>Description</b>                                           |
|------------------|--------------------------------------------------------------|
| B000.00          | Malignant neoplasm of upper lip, vermilion border            |
| B000000          | Malignant neoplasm of upper lip, external                    |
| B000100          | Malignant neoplasm of upper lip, lipstick area               |
| B000z00          | Malignant neoplasm of upper lip, vermilion border NOS        |
| B001.00          | Malignant neoplasm of lower lip, vermilion border            |
| B001000          | Malignant neoplasm of lower lip, external                    |
| B001100          | Malignant neoplasm of lower lip, lipstick area               |
| B001z00          | Malignant neoplasm of lower lip, vermilion border NOS        |
| B002.00          | Malignant neoplasm of upper lip, inner aspect                |
| B002000          | Malignant neoplasm of upper lip, buccal aspect               |
| B002100          | Malignant neoplasm of upper lip, frenulum                    |
| B002200          | Malignant neoplasm of upper lip, mucosa                      |
| B002300          | Malignant neoplasm of upper lip, oral aspect                 |
| B002z00          | Malignant neoplasm of upper lip, inner aspect NOS            |
| B003.00          | Malignant neoplasm of lower lip, inner aspect                |
| B003000          | Malignant neoplasm of lower lip, buccal aspect               |
| B003100          | Malignant neoplasm of lower lip, frenulum                    |
| B003200          | Malignant neoplasm of lower lip, mucosa                      |
| B003300          | Malignant neoplasm of lower lip, oral aspect                 |
| B003z00          | Malignant neoplasm of lower lip, inner aspect NOS            |
| B004.00          | Malignant neoplasm of lip unspecified, inner aspect          |
| B004000          | Malignant neoplasm of lip unspecified, buccal aspect         |
| B004100          | Malignant neoplasm of lip unspecified, frenulum              |
| B004200          | Malignant neoplasm of lip unspecified, mucosa                |
| B004300          | Malignant neoplasm of lip, oral aspect                       |
| B004z00          | Malignant neoplasm of lip, inner aspect NOS                  |
| B005.00          | Malignant neoplasm of commissure of lip                      |
| B006.00          | Malignant neoplasm of overlapping lesion of lip              |
| B007.00          | Malignant neoplasm of lip, unspecified                       |
| B00y.00          | Malignant neoplasm of other sites of lip                     |
| B00z.00          | Malignant neoplasm of vermilion border of lip unspecified    |
| B00z000          | Malignant neoplasm of lip, unspecified, external             |
| B00z100          | Malignant neoplasm of lip, unspecified, lipstick area        |
| B00zz00          | Malignant neoplasm of lip, vermilion border NOS              |
| B01..00          | Malignant neoplasm of tongue                                 |
| B010.00          | Malignant neoplasm of base of tongue                         |
| B010.11          | Malignant neoplasm of posterior third of tongue              |
| B010000          | Malignant neoplasm of base of tongue dorsal surface          |
| B010z00          | Malignant neoplasm of fixed part of tongue NOS               |
| B011.00          | Malignant neoplasm of dorsal surface of tongue               |
| B011000          | Malignant neoplasm of anterior 2/3 of tongue dorsal surface  |
| B011100          | Malignant neoplasm of midline of tongue                      |
| B011z00          | Malignant neoplasm of dorsum of tongue NOS                   |
| B012.00          | Malignant neoplasm of tongue, tip and lateral border         |
| B013.00          | Malignant neoplasm of ventral surface of tongue              |
| B013000          | Malignant neoplasm of anterior 2/3 of tongue ventral surface |
| B013100          | Malignant neoplasm of frenulum linguae                       |
| B013z00          | Malignant neoplasm of ventral tongue surface NOS             |
| B014.00          | Malignant neoplasm of anterior 2/3 of tongue unspecified     |
| B015.00          | Malignant neoplasm of tongue, junctional zone                |
| B016.00          | Malignant neoplasm of lingual tonsil                         |
| B017.00          | Malignant overlapping lesion of tongue                       |
| B01y.00          | Malignant neoplasm of other sites of tongue                  |
| B01z.00          | Malignant neoplasm of tongue NOS                             |
| B02..00          | Malignant neoplasm of major salivary glands                  |
| B020.00          | Malignant neoplasm of parotid gland                          |
| B021.00          | Malignant neoplasm of submandibular gland                    |
| B022.00          | Malignant neoplasm of sublingual gland                       |

| Read code | Description                                                 |
|-----------|-------------------------------------------------------------|
| B023.00   | Malignant neoplasm, overlapping lesion of major saliv gland |
| B02y.00   | Malignant neoplasm of other major salivary glands           |
| B02z.00   | Malignant neoplasm of major salivary gland NOS              |
| B03..00   | Malignant neoplasm of gum                                   |
| B030.00   | Malignant neoplasm of upper gum                             |
| B031.00   | Malignant neoplasm of lower gum                             |
| B03y.00   | Malignant neoplasm of other sites of gum                    |
| B03z.00   | Malignant neoplasm of gum NOS                               |
| B04..00   | Malignant neoplasm of floor of mouth                        |
| B040.00   | Malignant neoplasm of anterior portion of floor of mouth    |
| B041.00   | Malignant neoplasm of lateral portion of floor of mouth     |
| B042.00   | Malignant neoplasm, overlapping lesion of floor of mouth    |
| B04y.00   | Malignant neoplasm of other sites of floor of mouth         |
| B04z.00   | Malignant neoplasm of floor of mouth NOS                    |
| B05..00   | Malignant neoplasm of other and unspecified parts of mouth  |
| B050.00   | Malignant neoplasm of cheek mucosa                          |
| B050.11   | Malignant neoplasm of buccal mucosa                         |
| B051.00   | Malignant neoplasm of vestibule of mouth                    |
| B051000   | Malignant neoplasm of upper buccal sulcus                   |
| B051100   | Malignant neoplasm of lower buccal sulcus                   |
| B051200   | Malignant neoplasm of upper labial sulcus                   |
| B051300   | Malignant neoplasm of lower labial sulcus                   |
| B051z00   | Malignant neoplasm of vestibule of mouth NOS                |
| B052.00   | Malignant neoplasm of hard palate                           |
| B053.00   | Malignant neoplasm of soft palate                           |
| B054.00   | Malignant neoplasm of uvula                                 |
| B055.00   | Malignant neoplasm of palate unspecified                    |
| B055000   | Malignant neoplasm of junction of hard and soft palate      |
| B055100   | Malignant neoplasm of roof of mouth                         |
| B055z00   | Malignant neoplasm of palate NOS                            |
| B056.00   | Malignant neoplasm of retromolar area                       |
| B057.00   | Overlapping lesion of other and unspecified parts of mouth  |
| B05y.00   | Malignant neoplasm of other specified mouth parts           |
| B05z.00   | Malignant neoplasm of mouth NOS                             |
| B05z000   | Kaposi's sarcoma of palate                                  |
| B06..00   | Malignant neoplasm of oropharynx                            |
| B060.00   | Malignant neoplasm of tonsil                                |
| B060000   | Malignant neoplasm of faucial tonsil                        |
| B060100   | Malignant neoplasm of palatine tonsil                       |
| B060200   | Malignant neoplasm of overlapping lesion of tonsil          |
| B060z00   | Malignant neoplasm tonsil NOS                               |
| B061.00   | Malignant neoplasm of tonsillar fossa                       |
| B062.00   | Malignant neoplasm of tonsillar pillar                      |
| B062000   | Malignant neoplasm of faucial pillar                        |
| B062100   | Malignant neoplasm of glossopalatine fold                   |
| B062200   | Malignant neoplasm of palatoglossal arch                    |
| B062300   | Malignant neoplasm of palatopharyngeal arch                 |
| B062z00   | Malignant neoplasm of tonsillar fossa NOS                   |
| B063.00   | Malignant neoplasm of vallecula                             |
| B064.00   | Malignant neoplasm of anterior epiglottis                   |
| B064000   | Malignant neoplasm of epiglottis, free border               |
| B064100   | Malignant neoplasm of glossoepiglottic fold                 |
| B064z00   | Malignant neoplasm of anterior epiglottis NOS               |
| B065.00   | Malignant neoplasm of junctional region of epiglottis       |
| B066.00   | Malignant neoplasm of lateral wall of oropharynx            |
| B067.00   | Malignant neoplasm of posterior wall of oropharynx          |
| B06y.00   | Malignant neoplasm of oropharynx, other specified sites     |
| B06y000   | Malignant neoplasm of branchial cleft                       |



| Read code | Description                                                  |
|-----------|--------------------------------------------------------------|
| B06yz00   | Malignant neoplasm of other specified site of oropharynx NOS |
| B06z.00   | Malignant neoplasm of oropharynx NOS                         |
| B07..00   | Malignant neoplasm of nasopharynx                            |
| B070.00   | Malignant neoplasm of roof of nasopharynx                    |
| B071.00   | Malignant neoplasm of posterior wall of nasopharynx          |
| B071000   | Malignant neoplasm of adenoid                                |
| B071100   | Malignant neoplasm of pharyngeal tonsil                      |
| B071z00   | Malignant neoplasm of posterior wall of nasopharynx NOS      |
| B072.00   | Malignant neoplasm of lateral wall of nasopharynx            |
| B072000   | Malignant neoplasm of pharyngeal recess                      |
| B072100   | Malignant neoplasm of opening of auditory tube               |
| B072z00   | Malignant neoplasm of lateral wall of nasopharynx NOS        |
| B073.00   | Malignant neoplasm of anterior wall of nasopharynx           |
| B073000   | Malignant neoplasm of floor of nasopharynx                   |
| B073100   | Malignant neoplasm of nasopharyngeal soft palate surface     |
| B073200   | Malignant neoplasm posterior margin nasal septum and choanae |
| B073z00   | Malignant neoplasm of anterior wall of nasopharynx NOS       |
| B074.00   | Malignant neoplasm, overlapping lesion of nasopharynx        |
| B07y.00   | Malignant neoplasm of other specified site of nasopharynx    |
| B07z.00   | Malignant neoplasm of nasopharynx NOS                        |
| B08..00   | Malignant neoplasm of hypopharynx                            |
| B080.00   | Malignant neoplasm of postcricoid region                     |
| B081.00   | Malignant neoplasm of pyriform sinus                         |
| B082.00   | Malignant neoplasm aryepiglottic fold, hypopharyngeal aspect |
| B083.00   | Malignant neoplasm of posterior pharynx                      |
| B084.00   | Malignant neoplasm, overlapping lesion of hypopharynx        |
| B08y.00   | Malignant neoplasm of other specified hypopharyngeal site    |
| B08z.00   | Malignant neoplasm of hypopharynx NOS                        |
| B0z..00   | Malig neop other/ill-defined sites lip, oral cavity, pharynx |
| B0z0.00   | Malignant neoplasm of pharynx unspecified                    |
| B0z1.00   | Malignant neoplasm of Waldeyer's ring                        |
| B0z2.00   | Malignant neoplasm of laryngopharynx                         |
| B0zy.00   | Malignant neoplasm of other sites lip, oral cavity, pharynx  |
| B0zz.00   | Malignant neoplasm of lip, oral cavity and pharynx NOS       |
| B1...00   | Malignant neoplasm of digestive organs and peritoneum        |
| B1...11   | Carcinoma of digestive organs and peritoneum                 |
| B10..00   | Malignant neoplasm of oesophagus                             |
| B100.00   | Malignant neoplasm of cervical oesophagus                    |
| B101.00   | Malignant neoplasm of thoracic oesophagus                    |
| B102.00   | Malignant neoplasm of abdominal oesophagus                   |
| B103.00   | Malignant neoplasm of upper third of oesophagus              |
| B104.00   | Malignant neoplasm of middle third of oesophagus             |
| B105.00   | Malignant neoplasm of lower third of oesophagus              |
| B106.00   | Malignant neoplasm, overlapping lesion of oesophagus         |
| B10y.00   | Malignant neoplasm of other specified part of oesophagus     |
| B10z.00   | Malignant neoplasm of oesophagus NOS                         |
| B10z.11   | Oesophageal cancer                                           |
| B11..00   | Malignant neoplasm of stomach                                |
| B11..11   | Gastric neoplasm                                             |
| B110.00   | Malignant neoplasm of cardia of stomach                      |
| B110000   | Malignant neoplasm of cardiac orifice of stomach             |
| B110100   | Malignant neoplasm of cardio-oesophageal junction of stomach |
| B110111   | Malignant neoplasm of gastro-oesophageal junction            |
| B110z00   | Malignant neoplasm of cardia of stomach NOS                  |
| B111.00   | Malignant neoplasm of pylorus of stomach                     |
| B111000   | Malignant neoplasm of prepylorus of stomach                  |
| B111100   | Malignant neoplasm of pyloric canal of stomach               |
| B111z00   | Malignant neoplasm of pylorus of stomach NOS                 |

| <b>Read code</b> | <b>Description</b>                                           |
|------------------|--------------------------------------------------------------|
| B112.00          | Malignant neoplasm of pyloric antrum of stomach              |
| B113.00          | Malignant neoplasm of fundus of stomach                      |
| B114.00          | Malignant neoplasm of body of stomach                        |
| B115.00          | Malignant neoplasm of lesser curve of stomach unspecified    |
| B116.00          | Malignant neoplasm of greater curve of stomach unspecified   |
| B117.00          | Malignant neoplasm, overlapping lesion of stomach            |
| B11y.00          | Malignant neoplasm of other specified site of stomach        |
| B11y000          | Malignant neoplasm of anterior wall of stomach NEC           |
| B11y100          | Malignant neoplasm of posterior wall of stomach NEC          |
| B11yz00          | Malignant neoplasm of other specified site of stomach NOS    |
| B11z.00          | Malignant neoplasm of stomach NOS                            |
| B12..00          | Malignant neoplasm of small intestine and duodenum           |
| B120.00          | Malignant neoplasm of duodenum                               |
| B121.00          | Malignant neoplasm of jejunum                                |
| B122.00          | Malignant neoplasm of ileum                                  |
| B123.00          | Malignant neoplasm of Meckel's diverticulum                  |
| B124.00          | Malignant neoplasm, overlapping lesion of small intestine    |
| B12y.00          | Malignant neoplasm of other specified site small intestine   |
| B12z.00          | Malignant neoplasm of small intestine NOS                    |
| B13..00          | Malignant neoplasm of colon                                  |
| B130.00          | Malignant neoplasm of hepatic flexure of colon               |
| B131.00          | Malignant neoplasm of transverse colon                       |
| B132.00          | Malignant neoplasm of descending colon                       |
| B133.00          | Malignant neoplasm of sigmoid colon                          |
| B134.00          | Malignant neoplasm of caecum                                 |
| B134.11          | Carcinoma of caecum                                          |
| B135.00          | Malignant neoplasm of appendix                               |
| B136.00          | Malignant neoplasm of ascending colon                        |
| B137.00          | Malignant neoplasm of splenic flexure of colon               |
| B138.00          | Malignant neoplasm, overlapping lesion of colon              |
| B13y.00          | Malignant neoplasm of other specified sites of colon         |
| B13z.00          | Malignant neoplasm of colon NOS                              |
| B13z.11          | Colonic cancer                                               |
| B14..00          | Malignant neoplasm of rectum, rectosigmoid junction and anus |
| B140.00          | Malignant neoplasm of rectosigmoid junction                  |
| B141.00          | Malignant neoplasm of rectum                                 |
| B141.11          | Carcinoma of rectum                                          |
| B141.12          | Rectal carcinoma                                             |
| B142.00          | Malignant neoplasm of anal canal                             |
| B142.11          | Anal carcinoma                                               |
| B142000          | Malignant neoplasm of cloacogenic zone                       |
| B143.00          | Malignant neoplasm of anus unspecified                       |
| B14y.00          | Malig neop other site rectum, rectosigmoid junction and anus |
| B14z.00          | Malignant neoplasm rectum,rectosigmoid junction and anus NOS |
| B15..00          | Malignant neoplasm of liver and intrahepatic bile ducts      |
| B150.00          | Primary malignant neoplasm of liver                          |
| B150000          | Primary carcinoma of liver                                   |
| B150100          | Hepatoblastoma of liver                                      |
| B150200          | Primary angiosarcoma of liver                                |
| B150300          | Hepatocellular carcinoma                                     |
| B150z00          | Primary malignant neoplasm of liver NOS                      |
| B151.00          | Malignant neoplasm of intrahepatic bile ducts                |
| B151000          | Malignant neoplasm of interlobular bile ducts                |
| B151100          | Malignant neoplasm of interlobular biliary canals            |
| B151200          | Malignant neoplasm of intrahepatic biliary passages          |
| B151300          | Malignant neoplasm of intrahepatic canaliculi                |
| B151400          | Malignant neoplasm of intrahepatic gall duct                 |
| B151z00          | Malignant neoplasm of intrahepatic bile ducts NOS            |

| <b>Read code</b> | <b>Description</b>                                           |
|------------------|--------------------------------------------------------------|
| B152.00          | Malignant neoplasm of liver unspecified                      |
| B15z.00          | Malignant neoplasm of liver and intrahepatic bile ducts NOS  |
| B16..00          | Malignant neoplasm gallbladder and extrahepatic bile ducts   |
| B160.00          | Malignant neoplasm of gallbladder                            |
| B160.11          | Carcinoma gallbladder                                        |
| B161.00          | Malignant neoplasm of extrahepatic bile ducts                |
| B161000          | Malignant neoplasm of cystic duct                            |
| B161100          | Malignant neoplasm of hepatic duct                           |
| B161200          | Malignant neoplasm of common bile duct                       |
| B161211          | Carcinoma common bile duct                                   |
| B161300          | Malignant neoplasm of sphincter of Oddi                      |
| B161z00          | Malignant neoplasm of extrahepatic bile ducts NOS            |
| B162.00          | Malignant neoplasm of ampulla of Vater                       |
| B163.00          | Malignant neoplasm, overlapping lesion of biliary tract      |
| B16y.00          | Malignant neoplasm other gallbladder/extrahepatic bile duct  |
| B16z.00          | Malignant neoplasm gallbladder/extrahepatic bile ducts NOS   |
| B17..00          | Malignant neoplasm of pancreas                               |
| B170.00          | Malignant neoplasm of head of pancreas                       |
| B171.00          | Malignant neoplasm of body of pancreas                       |
| B172.00          | Malignant neoplasm of tail of pancreas                       |
| B173.00          | Malignant neoplasm of pancreatic duct                        |
| B174.00          | Malignant neoplasm of Islets of Langerhans                   |
| B175.00          | Malignant neoplasm, overlapping lesion of pancreas           |
| B17y.00          | Malignant neoplasm of other specified sites of pancreas      |
| B17y000          | Malignant neoplasm of ectopic pancreatic tissue              |
| B17yz00          | Malignant neoplasm of specified site of pancreas NOS         |
| B17z.00          | Malignant neoplasm of pancreas NOS                           |
| B18..00          | Malignant neoplasm of retroperitoneum and peritoneum         |
| B180.00          | Malignant neoplasm of retroperitoneum                        |
| B180000          | Malignant neoplasm of peria renal tissue                     |
| B180100          | Malignant neoplasm of perinephric tissue                     |
| B180200          | Malignant neoplasm of retrocaecal tissue                     |
| B180z00          | Malignant neoplasm of retroperitoneum NOS                    |
| B181.00          | Mesothelioma of peritoneum                                   |
| B182.00          | Overlapping malign lesion of retroperitoneum and peritoneum  |
| B18y.00          | Malignant neoplasm of specified parts of peritoneum          |
| B18y000          | Malignant neoplasm of mesocolon                              |
| B18y100          | Malignant neoplasm of mesocaecum                             |
| B18y200          | Malignant neoplasm of mesorectum                             |
| B18y300          | Malignant neoplasm of omentum                                |
| B18y400          | Malignant neoplasm of parietal peritoneum                    |
| B18y500          | Malignant neoplasm of pelvic peritoneum                      |
| B18y600          | Malignant neoplasm of the pouch of Douglas                   |
| B18y700          | Malignant neoplasm of mesentery                              |
| B18yz00          | Malignant neoplasm of specified parts of peritoneum NOS      |
| B18z.00          | Malignant neoplasm of retroperitoneum and peritoneum NOS     |
| B1z..00          | Malig neop oth/ill-defined sites digestive tract/peritoneum  |
| B1z0.00          | Malignant neoplasm of intestinal tract, part unspecified     |
| B1z0.11          | Cancer of bowel                                              |
| B1z1.00          | Malignant neoplasm of spleen NEC                             |
| B1z1000          | Angiosarcoma of spleen                                       |
| B1z1100          | Fibrosarcoma of spleen                                       |
| B1z1z00          | Malignant neoplasm of spleen NOS                             |
| B1z2.00          | Malignant neoplasm, overlapping lesion of digestive system   |
| B1zy.00          | Malignant neoplasm other spec digestive tract and peritoneum |
| B1zz.00          | Malignant neoplasm of digestive tract and peritoneum NOS     |
| B2...00          | Malig neop of respiratory tract and intrathoracic organs     |
| B2...11          | Carcinoma of respiratory tract and intrathoracic organs      |

| <b>Read code</b> | <b>Description</b>                                          |
|------------------|-------------------------------------------------------------|
| B20..00          | Malig neop nasal cavities, middle ear and accessory sinuses |
| B200.00          | Malignant neoplasm of nasal cavities                        |
| B200000          | Malignant neoplasm of cartilage of nose                     |
| B200100          | Malignant neoplasm of nasal conchae                         |
| B200200          | Malignant neoplasm of septum of nose                        |
| B200300          | Malignant neoplasm of vestibule of nose                     |
| B200z00          | Malignant neoplasm of nasal cavities NOS                    |
| B201.00          | Malig neop auditory tube, middle ear and mastoid air cells  |
| B201000          | Malignant neoplasm of auditory (Eustachian) tube            |
| B201100          | Malignant neoplasm of tympanic cavity                       |
| B201200          | Malignant neoplasm of tympanic antrum                       |
| B201300          | Malignant neoplasm of mastoid air cells                     |
| B201z00          | Malig neop auditory tube, middle ear, mastoid air cells NOS |
| B202.00          | Malignant neoplasm of maxillary sinus                       |
| B203.00          | Malignant neoplasm of ethmoid sinus                         |
| B204.00          | Malignant neoplasm of frontal sinus                         |
| B205.00          | Malignant neoplasm of sphenoidal sinus                      |
| B206.00          | Malignant neoplasm, overlapping lesion of accessory sinuses |
| B20y.00          | Malig neop other site nasal cavity, middle ear and sinuses  |
| B20z.00          | Malignant neoplasm of accessory sinus NOS                   |
| B21..00          | Malignant neoplasm of larynx                                |
| B210.00          | Malignant neoplasm of glottis                               |
| B211.00          | Malignant neoplasm of supraglottis                          |
| B212.00          | Malignant neoplasm of subglottis                            |
| B213.00          | Malignant neoplasm of laryngeal cartilage                   |
| B213000          | Malignant neoplasm of arytenoid cartilage                   |
| B213100          | Malignant neoplasm of cricoid cartilage                     |
| B213200          | Malignant neoplasm of cuneiform cartilage                   |
| B213300          | Malignant neoplasm of thyroid cartilage                     |
| B213z00          | Malignant neoplasm of laryngeal cartilage NOS               |
| B214.00          | Malignant neoplasm, overlapping lesion of larynx            |
| B215.00          | Malignant neoplasm of epiglottis NOS                        |
| B21y.00          | Malignant neoplasm of larynx, other specified site          |
| B21z.00          | Malignant neoplasm of larynx NOS                            |
| B22..00          | Malignant neoplasm of trachea, bronchus and lung            |
| B220.00          | Malignant neoplasm of trachea                               |
| B220000          | Malignant neoplasm of cartilage of trachea                  |
| B220100          | Malignant neoplasm of mucosa of trachea                     |
| B220z00          | Malignant neoplasm of trachea NOS                           |
| B221.00          | Malignant neoplasm of main bronchus                         |
| B221000          | Malignant neoplasm of carina of bronchus                    |
| B221100          | Malignant neoplasm of hilus of lung                         |
| B221z00          | Malignant neoplasm of main bronchus NOS                     |
| B222.00          | Malignant neoplasm of upper lobe, bronchus or lung          |
| B222.11          | Pancoast's syndrome                                         |
| B222000          | Malignant neoplasm of upper lobe bronchus                   |
| B222100          | Malignant neoplasm of upper lobe of lung                    |
| B222z00          | Malignant neoplasm of upper lobe, bronchus or lung NOS      |
| B223.00          | Malignant neoplasm of middle lobe, bronchus or lung         |
| B223000          | Malignant neoplasm of middle lobe bronchus                  |
| B223100          | Malignant neoplasm of middle lobe of lung                   |
| B223z00          | Malignant neoplasm of middle lobe, bronchus or lung NOS     |
| B224.00          | Malignant neoplasm of lower lobe, bronchus or lung          |
| B224000          | Malignant neoplasm of lower lobe bronchus                   |
| B224100          | Malignant neoplasm of lower lobe of lung                    |
| B224z00          | Malignant neoplasm of lower lobe, bronchus or lung NOS      |
| B225.00          | Malignant neoplasm of overlapping lesion of bronchus & lung |
| B226.00          | Mesothelioma                                                |

| <b>Read code</b> | <b>Description</b>                                            |
|------------------|---------------------------------------------------------------|
| B22y.00          | Malignant neoplasm of other sites of bronchus or lung         |
| B22z.00          | Malignant neoplasm of bronchus or lung NOS                    |
| B22z.11          | Lung cancer                                                   |
| B23..00          | Malignant neoplasm of pleura                                  |
| B230.00          | Malignant neoplasm of parietal pleura                         |
| B231.00          | Malignant neoplasm of visceral pleura                         |
| B232.00          | Mesothelioma of pleura                                        |
| B23y.00          | Malignant neoplasm of other specified pleura                  |
| B23z.00          | Malignant neoplasm of pleura NOS                              |
| B24..00          | Malignant neoplasm of thymus, heart and mediastinum           |
| B240.00          | Malignant neoplasm of thymus                                  |
| B241.00          | Malignant neoplasm of heart                                   |
| B241000          | Malignant neoplasm of endocardium                             |
| B241100          | Malignant neoplasm of epicardium                              |
| B241200          | Malignant neoplasm of myocardium                              |
| B241300          | Malignant neoplasm of pericardium                             |
| B241400          | Mesothelioma of pericardium                                   |
| B241z00          | Malignant neoplasm of heart NOS                               |
| B242.00          | Malignant neoplasm of anterior mediastinum                    |
| B243.00          | Malignant neoplasm of posterior mediastinum                   |
| B24X.00          | Malignant neoplasm of mediastinum, part unspecified           |
| B24y.00          | Malig neop of other site of heart, thymus and mediastinum     |
| B24z.00          | Malignant neoplasm of heart, thymus and mediastinum NOS       |
| B25..00          | Malig neo, overlapping lesion of heart, mediastinum & pleura  |
| B26..00          | Malignant neoplasm, overlap lesion of resp & intrathor organs |
| B2z..00          | Malig neop other/ill-defined sites resp/intrathoracic organs  |
| B2z0.00          | Malig neop of upper respiratory tract, part unspecified       |
| B2zy.00          | Malignant neoplasm of other site of respiratory tract         |
| B2zz.00          | Malignant neoplasm of respiratory tract NOS                   |
| B3...00          | Malig neop of bone, connective tissue, skin and breast        |
| B3...11          | Carcinoma of bone, connective tissue, skin and breast         |
| B3...12          | Sarcoma of bone and connective tissue                         |
| B30..00          | Malignant neoplasm of bone and articular cartilage            |
| B30..11          | Chondroma                                                     |
| B30..12          | Osteoma                                                       |
| B300.00          | Malignant neoplasm of bones of skull and face                 |
| B300000          | Malignant neoplasm of ethmoid bone                            |
| B300100          | Malignant neoplasm of frontal bone                            |
| B300200          | Malignant neoplasm of malar bone                              |
| B300300          | Malignant neoplasm of nasal bone                              |
| B300400          | Malignant neoplasm of occipital bone                          |
| B300500          | Malignant neoplasm of orbital bone                            |
| B300600          | Malignant neoplasm of parietal bone                           |
| B300700          | Malignant neoplasm of sphenoid bone                           |
| B300800          | Malignant neoplasm of temporal bone                           |
| B300900          | Malignant neoplasm of zygomatic bone                          |
| B300A00          | Malignant neoplasm of maxilla                                 |
| B300C00          | Malignant neoplasm of vomer                                   |
| B300z00          | Malignant neoplasm of bones of skull and face NOS             |
| B301.00          | Malignant neoplasm of mandible                                |
| B302.00          | Malignant neoplasm of vertebral column                        |
| B302000          | Malignant neoplasm of cervical vertebra                       |
| B302100          | Malignant neoplasm of thoracic vertebra                       |
| B302200          | Malignant neoplasm of lumbar vertebra                         |
| B302z00          | Malignant neoplasm of vertebral column NOS                    |
| B303.00          | Malignant neoplasm of ribs, sternum and clavicle              |
| B303000          | Malignant neoplasm of rib                                     |
| B303100          | Malignant neoplasm of sternum                                 |

| <b>Read code</b> | <b>Description</b>                                        |
|------------------|-----------------------------------------------------------|
| B303200          | Malignant neoplasm of clavicle                            |
| B303300          | Malignant neoplasm of costal cartilage                    |
| B303400          | Malignant neoplasm of costo-vertebral joint               |
| B303500          | Malignant neoplasm of xiphoid process                     |
| B303z00          | Malignant neoplasm of rib, sternum and clavicle NOS       |
| B304.00          | Malignant neoplasm of scapula and long bones of upper arm |
| B304000          | Malignant neoplasm of scapula                             |
| B304100          | Malignant neoplasm of acromion                            |
| B304200          | Malignant neoplasm of humerus                             |
| B304300          | Malignant neoplasm of radius                              |
| B304400          | Malignant neoplasm of ulna                                |
| B304z00          | Malig neop of scapula and long bones of upper arm NOS     |
| B305.00          | Malignant neoplasm of hand bones                          |
| B305.11          | Malignant neoplasm of carpal bones                        |
| B305.12          | Malignant neoplasm of metacarpal bones                    |
| B305000          | Malignant neoplasm of carpal bone - scaphoid              |
| B305100          | Malignant neoplasm of carpal bone - lunate                |
| B305200          | Malignant neoplasm of carpal bone - triquetrum            |
| B305300          | Malignant neoplasm of carpal bone - pisiform              |
| B305400          | Malignant neoplasm of carpal bone - trapezium             |
| B305500          | Malignant neoplasm of carpal bone - trapezoid             |
| B305600          | Malignant neoplasm of carpal bone - capitate              |
| B305700          | Malignant neoplasm of carpal bone - hamate                |
| B305800          | Malignant neoplasm of first metacarpal bone               |
| B305900          | Malignant neoplasm of second metacarpal bone              |
| B305A00          | Malignant neoplasm of third metacarpal bone               |
| B305C00          | Malignant neoplasm of fifth metacarpal bone               |
| B305D00          | Malignant neoplasm of phalanges of hand                   |
| B305z00          | Malignant neoplasm of hand bones NOS                      |
| B306.00          | Malignant neoplasm of pelvic bones, sacrum and coccyx     |
| B306000          | Malignant neoplasm of ilium                               |
| B306100          | Malignant neoplasm of ischium                             |
| B306200          | Malignant neoplasm of pubis                               |
| B306300          | Malignant neoplasm of sacral vertebra                     |
| B306400          | Malignant neoplasm of coccygeal vertebra                  |
| B306500          | Malignant sacral teratoma                                 |
| B306z00          | Malignant neoplasm of pelvis, sacrum or coccyx NOS        |
| B307.00          | Malignant neoplasm of long bones of leg                   |
| B307000          | Malignant neoplasm of femur                               |
| B307100          | Malignant neoplasm of fibula                              |
| B307200          | Malignant neoplasm of tibia                               |
| B307z00          | Malignant neoplasm of long bones of leg NOS               |
| B308.00          | Malignant neoplasm of short bones of leg                  |
| B308.11          | Malignant neoplasm of metatarsal bones of foot            |
| B308000          | Malignant neoplasm of patella                             |
| B308100          | Malignant neoplasm of talus                               |
| B308200          | Malignant neoplasm of calcaneum                           |
| B308300          | Malignant neoplasm of medial cuneiform                    |
| B308400          | Malignant neoplasm of intermediate cuneiform              |
| B308500          | Malignant neoplasm of lateral cuneiform                   |
| B308600          | Malignant neoplasm of cuboid                              |
| B308700          | Malignant neoplasm of navicular                           |
| B308800          | Malignant neoplasm of first metatarsal bone               |
| B308900          | Malignant neoplasm of second metatarsal bone              |
| B308A00          | Malignant neoplasm of third metatarsal bone               |
| B308C00          | Malignant neoplasm of fifth metatarsal bone               |
| B308D00          | Malignant neoplasm of phalanges of foot                   |
| B308z00          | Malignant neoplasm of short bones of leg NOS              |

| Read code | Description                                                  |
|-----------|--------------------------------------------------------------|
| B309.00   | Malignant neoplasm, overlap les bone and artic cart of limbs |
| B30W.00   | Malignant neoplasm/overlap lesion/bone??? cartilage          |
| B30X.00   | Malignant neoplasm/bones??? cartilage/limb,unspfd            |
| B30z.00   | Malignant neoplasm of bone and articular cartilage NOS       |
| B30z000   | Osteosarcoma                                                 |
| B31..00   | Malignant neoplasm of connective and other soft tissue       |
| B310.00   | Malig neop of connective and soft tissue head, face and neck |
| B310000   | Malignant neoplasm of soft tissue of head                    |
| B310100   | Malignant neoplasm of soft tissue of face                    |
| B310200   | Malignant neoplasm of soft tissue of neck                    |
| B310300   | Malignant neoplasm of cartilage of ear                       |
| B310400   | Malignant neoplasm of tarsus of eyelid                       |
| B310500   | Malignant neoplasm soft tissues of cervical spine            |
| B310z00   | Malig neop connective and soft tissue head, face, neck NOS   |
| B311.00   | Malig neop connective and soft tissue upper limb/shoulder    |
| B311000   | Malignant neoplasm of connective and soft tissue of shoulder |
| B311100   | Malignant neoplasm of connective and soft tissue, upper arm  |
| B311200   | Malignant neoplasm of connective and soft tissue of fore-arm |
| B311300   | Malignant neoplasm of connective and soft tissue of hand     |
| B311400   | Malignant neoplasm of connective and soft tissue of finger   |
| B311500   | Malignant neoplasm of connective and soft tissue of thumb    |
| B311z00   | Malig neop connective soft tissue upper limb/shoulder NOS    |
| B312.00   | Malig neop of connective and soft tissue of hip and leg      |
| B312000   | Malignant neoplasm of connective and soft tissue of hip      |
| B312100   | Malig neop of connective and soft tissue thigh and upper leg |
| B312200   | Malig neop connective and soft tissue of popliteal space     |
| B312300   | Malig neop of connective and soft tissue of lower leg        |
| B312400   | Malignant neoplasm of connective and soft tissue of foot     |
| B312500   | Malignant neoplasm of connective and soft tissue of toe      |
| B312600   | Malig neop of connective and soft tissue of great toe        |
| B312z00   | Malig neop connective and soft tissue hip and leg NOS        |
| B313.00   | Malignant neoplasm of connective and soft tissue of thorax   |
| B313000   | Malignant neoplasm of connective and soft tissue of axilla   |
| B313100   | Malignant neoplasm of diaphragm                              |
| B313200   | Malignant neoplasm of great vessels                          |
| B313300   | Malig neoplasm of connective and soft tissues of thor spine  |
| B313z00   | Malig neop of connective and soft tissue of thorax NOS       |
| B314.00   | Malignant neoplasm of connective and soft tissue of abdomen  |
| B314000   | Malig neop of connective and soft tissue of abdominal wall   |
| B314100   | Malig neoplasm of connective and soft tissues of lumb spine  |
| B314z00   | Malig neop of connective and soft tissue of abdomen NOS      |
| B315.00   | Malignant neoplasm of connective and soft tissue of pelvis   |
| B315000   | Malignant neoplasm of connective and soft tissue of buttock  |
| B315100   | Malig neop of connective and soft tissue of inguinal region  |
| B315200   | Malignant neoplasm of connective and soft tissue of perineum |
| B315300   | Malig neopl of connective and soft tissue - sacrum or coccyx |
| B315z00   | Malig neop of connective and soft tissue of pelvis NOS       |
| B316.00   | Malig neop of connective and soft tissue trunk unspecified   |
| B317.00   | Malignant neoplasm, overlap lesion connective & soft tissue  |
| B31y.00   | Malig neop connective and soft tissue other specified site   |
| B31z.00   | Malignant neoplasm of connective and soft tissue, site NOS   |
| B31z000   | Kaposi's sarcoma of soft tissue                              |
| B32..00   | Malignant melanoma of skin                                   |
| B320.00   | Malignant melanoma of lip                                    |
| B321.00   | Malignant melanoma of eyelid including canthus               |
| B322.00   | Malignant melanoma of ear and external auricular canal       |
| B322000   | Malignant melanoma of auricle (ear)                          |
| B322100   | Malignant melanoma of external auditory meatus               |

| Read code | Description                                                 |
|-----------|-------------------------------------------------------------|
| B322z00   | Malignant melanoma of ear and external auricular canal NOS  |
| B323.00   | Malignant melanoma of other and unspecified parts of face   |
| B323000   | Malignant melanoma of external surface of cheek             |
| B323100   | Malignant melanoma of chin                                  |
| B323200   | Malignant melanoma of eyebrow                               |
| B323300   | Malignant melanoma of forehead                              |
| B323400   | Malignant melanoma of external surface of nose              |
| B323500   | Malignant melanoma of temple                                |
| B323z00   | Malignant melanoma of face NOS                              |
| B324.00   | Malignant melanoma of scalp and neck                        |
| B324000   | Malignant melanoma of scalp                                 |
| B324100   | Malignant melanoma of neck                                  |
| B324z00   | Malignant melanoma of scalp and neck NOS                    |
| B325.00   | Malignant melanoma of trunk (excluding scrotum)             |
| B325000   | Malignant melanoma of axilla                                |
| B325100   | Malignant melanoma of breast                                |
| B325200   | Malignant melanoma of buttock                               |
| B325300   | Malignant melanoma of groin                                 |
| B325400   | Malignant melanoma of perianal skin                         |
| B325500   | Malignant melanoma of perineum                              |
| B325600   | Malignant melanoma of umbilicus                             |
| B325700   | Malignant melanoma of back                                  |
| B325800   | Malignant melanoma of chest wall                            |
| B325z00   | Malignant melanoma of trunk, excluding scrotum, NOS         |
| B326.00   | Malignant melanoma of upper limb and shoulder               |
| B326000   | Malignant melanoma of shoulder                              |
| B326100   | Malignant melanoma of upper arm                             |
| B326200   | Malignant melanoma of fore-arm                              |
| B326300   | Malignant melanoma of hand                                  |
| B326400   | Malignant melanoma of finger                                |
| B326500   | Malignant melanoma of thumb                                 |
| B326z00   | Malignant melanoma of upper limb or shoulder NOS            |
| B327.00   | Malignant melanoma of lower limb and hip                    |
| B327000   | Malignant melanoma of hip                                   |
| B327100   | Malignant melanoma of thigh                                 |
| B327200   | Malignant melanoma of knee                                  |
| B327300   | Malignant melanoma of popliteal fossa area                  |
| B327400   | Malignant melanoma of lower leg                             |
| B327500   | Malignant melanoma of ankle                                 |
| B327600   | Malignant melanoma of heel                                  |
| B327700   | Malignant melanoma of foot                                  |
| B327800   | Malignant melanoma of toe                                   |
| B327900   | Malignant melanoma of great toe                             |
| B327z00   | Malignant melanoma of lower limb or hip NOS                 |
| B32y.00   | Malignant melanoma of other specified skin site             |
| B32y000   | Overlapping malignant melanoma of skin                      |
| B32z.00   | Malignant melanoma of skin NOS                              |
| B33..00   | Other malignant neoplasm of skin                            |
| B33..12   | Epithelioma                                                 |
| B33..14   | Malignant neoplasm of sebaceous gland                       |
| B33..15   | Malignant neoplasm of sweat gland                           |
| B330.00   | Malignant neoplasm of skin of lip                           |
| B331.00   | Malignant neoplasm of eyelid including canthus              |
| B331000   | Malignant neoplasm of canthus                               |
| B331100   | Malignant neoplasm of upper eyelid                          |
| B331200   | Malignant neoplasm of lower eyelid                          |
| B332.00   | Malignant neoplasm skin of ear and external auricular canal |
| B332000   | Malignant neoplasm of skin of auricle (ear)                 |



| <b>Read code</b> | <b>Description</b>                                          |
|------------------|-------------------------------------------------------------|
| B332100          | Malignant neoplasm of skin of external auditory meatus      |
| B332200          | Malignant neoplasm of pinna NEC                             |
| B332z00          | Malig neop skin of ear and external auricular canal NOS     |
| B333.00          | Malignant neoplasm skin of other and unspecified parts face |
| B333000          | Malignant neoplasm of skin of cheek, external               |
| B333100          | Malignant neoplasm of skin of chin                          |
| B333200          | Malignant neoplasm of skin of eyebrow                       |
| B333300          | Malignant neoplasm of skin of forehead                      |
| B333400          | Malignant neoplasm of skin of nose (external)               |
| B333500          | Malignant neoplasm of skin of temple                        |
| B333z00          | Malignant neoplasm skin other and unspec part of face NOS   |
| B334.00          | Malignant neoplasm of scalp and skin of neck                |
| B334000          | Malignant neoplasm of scalp                                 |
| B334100          | Malignant neoplasm of skin of neck                          |
| B334z00          | Malignant neoplasm of scalp or skin of neck NOS             |
| B335.00          | Malignant neoplasm of skin of trunk, excluding scrotum      |
| B335000          | Malignant neoplasm of skin of axillary fold                 |
| B335100          | Malignant neoplasm of skin of chest, excluding breast       |
| B335200          | Malignant neoplasm of skin of breast                        |
| B335300          | Malignant neoplasm of skin of abdominal wall                |
| B335400          | Malignant neoplasm of skin of umbilicus                     |
| B335500          | Malignant neoplasm of skin of groin                         |
| B335600          | Malignant neoplasm of skin of perineum                      |
| B335700          | Malignant neoplasm of skin of back                          |
| B335800          | Malignant neoplasm of skin of buttock                       |
| B335900          | Malignant neoplasm of perianal skin                         |
| B335A00          | Malignant neoplasm of skin of scapular region               |
| B335z00          | Malignant neoplasm of skin of trunk, excluding scrotum, NOS |
| B336.00          | Malignant neoplasm of skin of upper limb and shoulder       |
| B336000          | Malignant neoplasm of skin of shoulder                      |
| B336100          | Malignant neoplasm of skin of upper arm                     |
| B336200          | Malignant neoplasm of skin of fore-arm                      |
| B336300          | Malignant neoplasm of skin of hand                          |
| B336400          | Malignant neoplasm of skin of finger                        |
| B336500          | Malignant neoplasm of skin of thumb                         |
| B336z00          | Malignant neoplasm of skin of upper limb or shoulder NOS    |
| B337.00          | Malignant neoplasm of skin of lower limb and hip            |
| B337000          | Malignant neoplasm of skin of hip                           |
| B337100          | Malignant neoplasm of skin of thigh                         |
| B337200          | Malignant neoplasm of skin of knee                          |
| B337300          | Malignant neoplasm of skin of popliteal fossa area          |
| B337400          | Malignant neoplasm of skin of lower leg                     |
| B337500          | Malignant neoplasm of skin of ankle                         |
| B337600          | Malignant neoplasm of skin of heel                          |
| B337700          | Malignant neoplasm of skin of foot                          |
| B337800          | Malignant neoplasm of skin of toe                           |
| B337900          | Malignant neoplasm of skin of great toe                     |
| B337z00          | Malignant neoplasm of skin of lower limb or hip NOS         |
| B339.00          | Dermatofibrosarcoma protuberans                             |
| B33X.00          | Malignant neoplasm overlapping lesion of skin               |
| B33y.00          | Malignant neoplasm of other specified skin sites            |
| B33z.00          | Malignant neoplasm of skin NOS                              |
| B33z000          | Kaposi's sarcoma of skin                                    |
| B34..00          | Malignant neoplasm of female breast                         |
| B34..11          | Ca female breast                                            |
| B340.00          | Malignant neoplasm of nipple and areola of female breast    |
| B340000          | Malignant neoplasm of nipple of female breast               |
| B340100          | Malignant neoplasm of areola of female breast               |

| Read code | Description                                                 |
|-----------|-------------------------------------------------------------|
| B340z00   | Malignant neoplasm of nipple or areola of female breast NOS |
| B341.00   | Malignant neoplasm of central part of female breast         |
| B342.00   | Malignant neoplasm of upper-inner quadrant of female breast |
| B343.00   | Malignant neoplasm of lower-inner quadrant of female breast |
| B344.00   | Malignant neoplasm of upper-outer quadrant of female breast |
| B345.00   | Malignant neoplasm of lower-outer quadrant of female breast |
| B346.00   | Malignant neoplasm of axillary tail of female breast        |
| B347.00   | Malignant neoplasm, overlapping lesion of breast            |
| B34y.00   | Malignant neoplasm of other site of female breast           |
| B34y000   | Malignant neoplasm of ectopic site of female breast         |
| B34yz00   | Malignant neoplasm of other site of female breast NOS       |
| B34z.00   | Malignant neoplasm of female breast NOS                     |
| B35..00   | Malignant neoplasm of male breast                           |
| B350.00   | Malignant neoplasm of nipple and areola of male breast      |
| B350000   | Malignant neoplasm of nipple of male breast                 |
| B350100   | Malignant neoplasm of areola of male breast                 |
| B350z00   | Malignant neoplasm of nipple or areola of male breast NOS   |
| B35z.00   | Malignant neoplasm of other site of male breast             |
| B35z000   | Malignant neoplasm of ectopic site of male breast           |
| B35zz00   | Malignant neoplasm of male breast NOS                       |
| B3y..00   | Malig neop of bone, connective tissue, skin and breast OS   |
| B3z..00   | Malig neop of bone, connective tissue, skin and breast NOS  |
| B4...00   | Malignant neoplasm of genitourinary organ                   |
| B4...11   | Carcinoma of genitourinary organ                            |
| B40..00   | Malignant neoplasm of uterus, part unspecified              |
| B41..00   | Malignant neoplasm of cervix uteri                          |
| B41..11   | Cervical carcinoma (uterus)                                 |
| B410.00   | Malignant neoplasm of endocervix                            |
| B410000   | Malignant neoplasm of endocervical canal                    |
| B410100   | Malignant neoplasm of endocervical gland                    |
| B410z00   | Malignant neoplasm of endocervix NOS                        |
| B411.00   | Malignant neoplasm of exocervix                             |
| B412.00   | Malignant neoplasm, overlapping lesion of cervix uteri      |
| B41y.00   | Malignant neoplasm of other site of cervix                  |
| B41y000   | Malignant neoplasm of cervical stump                        |
| B41y100   | Malignant neoplasm of squamocolumnar junction of cervix     |
| B41yz00   | Malignant neoplasm of other site of cervix NOS              |
| B41z.00   | Malignant neoplasm of cervix uteri NOS                      |
| B42..00   | Malignant neoplasm of placenta                              |
| B420.00   | Choriocarcinoma                                             |
| B43..00   | Malignant neoplasm of body of uterus                        |
| B430.00   | Malignant neoplasm of corpus uteri, excluding isthmus       |
| B430000   | Malignant neoplasm of cornu of corpus uteri                 |
| B430100   | Malignant neoplasm of fundus of corpus uteri                |
| B430200   | Malignant neoplasm of endometrium of corpus uteri           |
| B430211   | Malignant neoplasm of endometrium                           |
| B430300   | Malignant neoplasm of myometrium of corpus uteri            |
| B430z00   | Malignant neoplasm of corpus uteri NOS                      |
| B431.00   | Malignant neoplasm of isthmus of uterine body               |
| B431000   | Malignant neoplasm of lower uterine segment                 |
| B431z00   | Malignant neoplasm of isthmus of uterine body NOS           |
| B432.00   | Malignant neoplasm of overlapping lesion of corpus uteri    |
| B43y.00   | Malignant neoplasm of other site of uterine body            |
| B43z.00   | Malignant neoplasm of body of uterus NOS                    |
| B44..00   | Malignant neoplasm of ovary and other uterine adnexa        |
| B440.00   | Malignant neoplasm of ovary                                 |
| B440.11   | Cancer of ovary                                             |
| B441.00   | Malignant neoplasm of fallopian tube                        |

| <b>Read code</b> | <b>Description</b>                                           |
|------------------|--------------------------------------------------------------|
| B442.00          | Malignant neoplasm of broad ligament                         |
| B443.00          | Malignant neoplasm of parametrium                            |
| B444.00          | Malignant neoplasm of round ligament                         |
| B44y.00          | Malignant neoplasm of other site of uterine adnexa           |
| B44z.00          | Malignant neoplasm of uterine adnexa NOS                     |
| B45..00          | Malig neop of other and unspecified female genital organs    |
| B450.00          | Malignant neoplasm of vagina                                 |
| B450000          | Malignant neoplasm of Gartner's duct                         |
| B450100          | Malignant neoplasm of vaginal vault                          |
| B450z00          | Malignant neoplasm of vagina NOS                             |
| B451.00          | Malignant neoplasm of labia majora                           |
| B451000          | Malignant neoplasm of greater vestibular (Bartholin's) gland |
| B451z00          | Malignant neoplasm of labia majora NOS                       |
| B452.00          | Malignant neoplasm of labia minora                           |
| B453.00          | Malignant neoplasm of clitoris                               |
| B454.00          | Malignant neoplasm of vulva unspecified                      |
| B454.11          | Primary vulval cancer                                        |
| B45X.00          | Malignant neoplasm/overlapping lesion/feml genital organs    |
| B45y.00          | Malignant neoplasm of other specified female genital organ   |
| B45y000          | Malignant neoplasm of overlapping lesion of vulva            |
| B45z.00          | Malignant neoplasm of female genital organ NOS               |
| B46..00          | Malignant neoplasm of prostate                               |
| B47..00          | Malignant neoplasm of testis                                 |
| B470.00          | Malignant neoplasm of undescended testis                     |
| B470000          | Malignant neoplasm of ectopic testis                         |
| B470100          | Malignant neoplasm of retained testis                        |
| B470200          | Seminoma of undescended testis                               |
| B470300          | Teratoma of undescended testis                               |
| B470z00          | Malignant neoplasm of undescended testis NOS                 |
| B471.00          | Malignant neoplasm of descended testis                       |
| B471000          | Seminoma of descended testis                                 |
| B471100          | Teratoma of descended testis                                 |
| B47z.00          | Malignant neoplasm of testis NOS                             |
| B47z.11          | Seminoma of testis                                           |
| B47z.12          | Teratoma of testis                                           |
| B48..00          | Malignant neoplasm of penis and other male genital organs    |
| B480.00          | Malignant neoplasm of prepuce (foreskin)                     |
| B481.00          | Malignant neoplasm of glans penis                            |
| B482.00          | Malignant neoplasm of body of penis                          |
| B483.00          | Malignant neoplasm of penis, part unspecified                |
| B484.00          | Malignant neoplasm of epididymis                             |
| B485.00          | Malignant neoplasm of spermatic cord                         |
| B486.00          | Malignant neoplasm of scrotum                                |
| B487.00          | Malignant neoplasm, overlapping lesion of penis              |
| B48y.00          | Malignant neoplasm of other male genital organ               |
| B48y000          | Malignant neoplasm of seminal vesicle                        |
| B48y100          | Malignant neoplasm of tunica vaginalis                       |
| B48y200          | Malignant neoplasm, overlapping lesion male genital orgs     |
| B48yz00          | Malignant neoplasm of other male genital organ NOS           |
| B48z.00          | Malignant neoplasm of penis and other male genital organ NOS |
| B49..00          | Malignant neoplasm of urinary bladder                        |
| B490.00          | Malignant neoplasm of trigone of urinary bladder             |
| B491.00          | Malignant neoplasm of dome of urinary bladder                |
| B492.00          | Malignant neoplasm of lateral wall of urinary bladder        |
| B493.00          | Malignant neoplasm of anterior wall of urinary bladder       |
| B494.00          | Malignant neoplasm of posterior wall of urinary bladder      |
| B495.00          | Malignant neoplasm of bladder neck                           |
| B496.00          | Malignant neoplasm of ureteric orifice                       |

| <b>Read code</b> | <b>Description</b>                                           |
|------------------|--------------------------------------------------------------|
| B497.00          | Malignant neoplasm of urachus                                |
| B49y.00          | Malignant neoplasm of other site of urinary bladder          |
| B49y000          | Malignant neoplasm, overlapping lesion of bladder            |
| B49z.00          | Malignant neoplasm of urinary bladder NOS                    |
| B4A..00          | Malig neop of kidney and other unspecified urinary organs    |
| B4A..11          | Renal malignant neoplasm                                     |
| B4A0.00          | Malignant neoplasm of kidney parenchyma                      |
| B4A0000          | Hypernephroma                                                |
| B4A1.00          | Malignant neoplasm of renal pelvis                           |
| B4A1000          | Malignant neoplasm of renal calyces                          |
| B4A1100          | Malignant neoplasm of ureteropelvic junction                 |
| B4A1z00          | Malignant neoplasm of renal pelvis NOS                       |
| B4A2.00          | Malignant neoplasm of ureter                                 |
| B4A3.00          | Malignant neoplasm of urethra                                |
| B4A4.00          | Malignant neoplasm of paraurethral glands                    |
| B4Ay.00          | Malignant neoplasm of other urinary organs                   |
| B4Ay000          | Malignant neoplasm of overlapping lesion of urinary organs   |
| B4Az.00          | Malignant neoplasm of kidney or urinary organs NOS           |
| B4y..00          | Malignant neoplasm of genitourinary organ OS                 |
| B4z..00          | Malignant neoplasm of genitourinary organ NOS                |
| B5...00          | Malignant neoplasm of other and unspecified sites            |
| B5...11          | Carcinoma of other and unspecified sites                     |
| B50..00          | Malignant neoplasm of eye                                    |
| B500.00          | Malig neop eyeball excl conjunctiva, cornea, retina, choroid |
| B500000          | Malignant neoplasm of ciliary body                           |
| B500100          | Malignant neoplasm of iris                                   |
| B500200          | Malignant neoplasm of crystalline lens                       |
| B500300          | Malignant neoplasm of sclera                                 |
| B500z00          | Malignant neoplasm of eyeball NOS                            |
| B501.00          | Malignant neoplasm of orbit                                  |
| B501000          | Malignant neoplasm of connective tissue of orbit             |
| B501100          | Malignant neoplasm of extraocular muscle of orbit            |
| B501z00          | Malignant neoplasm of orbit NOS                              |
| B502.00          | Malignant neoplasm of lacrimal gland                         |
| B503.00          | Malignant neoplasm of conjunctiva                            |
| B504.00          | Malignant neoplasm of cornea                                 |
| B505.00          | Malignant neoplasm of retina                                 |
| B506.00          | Malignant neoplasm of choroid                                |
| B507.00          | Malignant neoplasm of lacrimal duct                          |
| B507000          | Malignant neoplasm of lacrimal sac                           |
| B507100          | Malignant neoplasm of nasolacrimal duct                      |
| B507z00          | Malignant neoplasm of lacrimal duct NOS                      |
| B508.00          | Malignant neoplasm, overlapping lesion of eye and adnexa     |
| B50y.00          | Malignant neoplasm of other specified site of eye            |
| B50z.00          | Malignant neoplasm of eye NOS                                |
| B51..00          | Malignant neoplasm of brain                                  |
| B51..11          | Cerebral tumour - malignant                                  |
| B510.00          | Malignant neoplasm cerebrum (excluding lobes and ventricles) |
| B510000          | Malignant neoplasm of basal ganglia                          |
| B510100          | Malignant neoplasm of cerebral cortex                        |
| B510200          | Malignant neoplasm of corpus striatum                        |
| B510300          | Malignant neoplasm of globus pallidus                        |
| B510400          | Malignant neoplasm of hypothalamus                           |
| B510500          | Malignant neoplasm of thalamus                               |
| B510z00          | Malignant neoplasm of cerebrum NOS                           |
| B511.00          | Malignant neoplasm of frontal lobe                           |
| B512.00          | Malignant neoplasm of temporal lobe                          |
| B512000          | Malignant neoplasm of hippocampus                            |

| <b>Read code</b> | <b>Description</b>                                           |
|------------------|--------------------------------------------------------------|
| B512100          | Malignant neoplasm of uncus                                  |
| B512z00          | Malignant neoplasm of temporal lobe NOS                      |
| B513.00          | Malignant neoplasm of parietal lobe                          |
| B514.00          | Malignant neoplasm of occipital lobe                         |
| B515.00          | Malignant neoplasm of cerebral ventricles                    |
| B515000          | Malignant neoplasm of choroid plexus                         |
| B515100          | Malignant neoplasm of floor of cerebral ventricle            |
| B515z00          | Malignant neoplasm of cerebral ventricle NOS                 |
| B516.00          | Malignant neoplasm of cerebellum                             |
| B517.00          | Malignant neoplasm of brain stem                             |
| B517000          | Malignant neoplasm of cerebral peduncle                      |
| B517100          | Malignant neoplasm of medulla oblongata                      |
| B517200          | Malignant neoplasm of midbrain                               |
| B517300          | Malignant neoplasm of pons                                   |
| B517z00          | Malignant neoplasm of brain stem NOS                         |
| B51y.00          | Malignant neoplasm of other parts of brain                   |
| B51y000          | Malignant neoplasm of corpus callosum                        |
| B51y100          | Malignant neoplasm of tapetum                                |
| B51y200          | Malignant neoplasm, overlapping lesion of brain              |
| B51yz00          | Malignant neoplasm of other part of brain NOS                |
| B51z.00          | Malignant neoplasm of brain NOS                              |
| B52..00          | Malig neop of other and unspecified parts of nervous system  |
| B520.00          | Malignant neoplasm of cranial nerves                         |
| B520000          | Malignant neoplasm of olfactory bulb                         |
| B520100          | Malignant neoplasm of optic nerve                            |
| B520200          | Malignant neoplasm of acoustic nerve                         |
| B520z00          | Malignant neoplasm of cranial nerves NOS                     |
| B521.00          | Malignant neoplasm of cerebral meninges                      |
| B521000          | Malignant neoplasm of cerebral dura mater                    |
| B521100          | Malignant neoplasm of cerebral arachnoid mater               |
| B521200          | Malignant neoplasm of cerebral pia mater                     |
| B521z00          | Malignant neoplasm of cerebral meninges NOS                  |
| B522.00          | Malignant neoplasm of spinal cord                            |
| B523.00          | Malignant neoplasm of spinal meninges                        |
| B523000          | Malignant neoplasm of spinal dura mater                      |
| B523100          | Malignant neoplasm of spinal arachnoid mater                 |
| B523200          | Malignant neoplasm of spinal pia mater                       |
| B523z00          | Malignant neoplasm of spinal meninges NOS                    |
| B524.00          | Malig neopl peripheral nerves and autonomic nervous system   |
| B524000          | Malignant neoplasm of peripheral nerves of head, face & neck |
| B524100          | Malignant neoplasm of peripheral nerve,upp limb,incl should  |
| B524200          | Malignant neoplasm of peripheral nerve of low limb, incl hip |
| B524300          | Malignant neoplasm of peripheral nerve of thorax             |
| B524400          | Malignant neoplasm of peripheral nerve of abdomen            |
| B524500          | Malignant neoplasm of peripheral nerve of pelvis             |
| B524600          | Malignant neoplasm,overlap lesion periph nerve & auton ns    |
| B524W00          | Mal neoplasm/periph nerves??? nervous system,unspc           |
| B524X00          | Malignant neoplasm/peripheral nerves of trunk,unspecified    |
| B525.00          | Malignant neoplasm of cauda equina                           |
| B52W.00          | Malig neopl, overlap lesion brain & other part of CNS        |
| B52X.00          | Malignant neoplasm of meninges, unspecified                  |
| B52y.00          | Malignant neoplasm of other specified part of nervous system |
| B52z.00          | Malignant neoplasm of nervous system NOS                     |
| B53..00          | Malignant neoplasm of thyroid gland                          |
| B54..00          | Malig neop of other endocrine glands and related structures  |
| B540.00          | Malignant neoplasm of adrenal gland                          |
| B540.11          | Phaeochromocytoma                                            |
| B540000          | Malignant neoplasm of adrenal cortex                         |

| <b>Read code</b> | <b>Description</b>                                           |
|------------------|--------------------------------------------------------------|
| B540100          | Malignant neoplasm of adrenal medulla                        |
| B540z00          | Malignant neoplasm of adrenal gland NOS                      |
| B541.00          | Malignant neoplasm of parathyroid gland                      |
| B542.00          | Malignant neoplasm pituitary gland and craniopharyngeal duct |
| B542000          | Malignant neoplasm of pituitary gland                        |
| B542100          | Malignant neoplasm of craniopharyngeal duct                  |
| B542z00          | Malig neop pituitary gland or craniopharyngeal duct NOS      |
| B543.00          | Malignant neoplasm of pineal gland                           |
| B544.00          | Malignant neoplasm of carotid body                           |
| B545.00          | Malignant neoplasm of aortic body and other paraganglia      |
| B545000          | Malignant neoplasm of glomus jugulare                        |
| B545100          | Malignant neoplasm of aortic body                            |
| B545200          | Malignant neoplasm of coccygeal body                         |
| B545z00          | Malignant neoplasm of aortic body or paraganglia NOS         |
| B54X.00          | Malignant neoplasm-pluriglandular involvement,unspecified    |
| B54y.00          | Malignant neoplasm of other specified endocrine gland        |
| B54z.00          | Malig neop of endocrine gland or related structure NOS       |
| B55..00          | Malignant neoplasm of other and ill-defined sites            |
| B550.00          | Malignant neoplasm of head, neck and face                    |
| B550000          | Malignant neoplasm of head NOS                               |
| B550100          | Malignant neoplasm of cheek NOS                              |
| B550200          | Malignant neoplasm of nose NOS                               |
| B550300          | Malignant neoplasm of jaw NOS                                |
| B550400          | Malignant neoplasm of neck NOS                               |
| B550500          | Malignant neoplasm of supraclavicular fossa NOS              |
| B550z00          | Malignant neoplasm of head, neck and face NOS                |
| B551.00          | Malignant neoplasm of thorax                                 |
| B551000          | Malignant neoplasm of axilla NOS                             |
| B551100          | Malignant neoplasm of chest wall NOS                         |
| B551200          | Malignant neoplasm of intrathoracic site NOS                 |
| B551z00          | Malignant neoplasm of thorax NOS                             |
| B552.00          | Malignant neoplasm of abdomen                                |
| B553.00          | Malignant neoplasm of pelvis                                 |
| B553000          | Malignant neoplasm of inguinal region NOS                    |
| B553100          | Malignant neoplasm of presacral region                       |
| B553200          | Malignant neoplasm of sacrococcygeal region                  |
| B553z00          | Malignant neoplasm of pelvis NOS                             |
| B554.00          | Malignant neoplasm of upper limb NOS                         |
| B555.00          | Malignant neoplasm of lower limb NOS                         |
| B55y.00          | Malignant neoplasm of other specified sites                  |
| B55y000          | Malignant neoplasm of back NOS                               |
| B55y100          | Malignant neoplasm of trunk NOS                              |
| B55y200          | Malignant neoplasm of flank NOS                              |
| B55yz00          | Malignant neoplasm of specified site NOS                     |
| B55z.00          | Malignant neoplasm of other and ill defined site NOS         |
| B59zX00          | Kaposi's sarcoma, unspecified                                |
| B6...00          | Malignant neoplasm of lymphatic and haemopoietic tissue      |
| B6...11          | Malignant neoplasm of histiocytic tissue                     |
| B60..00          | Lymphosarcoma and reticulosarcoma                            |
| B600.00          | Reticulosarcoma                                              |
| B600000          | Reticulosarcoma of unspecified site                          |
| B600100          | Reticulosarcoma of lymph nodes of head, face and neck        |
| B600200          | Reticulosarcoma of intrathoracic lymph nodes                 |
| B600300          | Reticulosarcoma of intra-abdominal lymph nodes               |
| B600400          | Reticulosarcoma of lymph nodes of axilla and upper limb      |
| B600500          | Reticulosarcoma of lymph nodes of inguinal region and leg    |
| B600600          | Reticulosarcoma of intrapelvic lymph nodes                   |
| B600700          | Reticulosarcoma of spleen                                    |

| <b>Read code</b> | <b>Description</b>                                           |
|------------------|--------------------------------------------------------------|
| B600800          | Reticulosarcoma of lymph nodes of multiple sites             |
| B600z00          | Reticulosarcoma NOS                                          |
| B601.00          | Lymphosarcoma                                                |
| B601000          | Lymphosarcoma of unspecified site                            |
| B601100          | Lymphosarcoma of lymph nodes of head, face and neck          |
| B601200          | Lymphosarcoma of intrathoracic lymph nodes                   |
| B601300          | Lymphosarcoma of intra-abdominal lymph nodes                 |
| B601400          | Lymphosarcoma of lymph nodes of axilla and upper limb        |
| B601500          | Lymphosarcoma of lymph nodes of inguinal region and leg      |
| B601600          | Lymphosarcoma of intrapelvic lymph nodes                     |
| B601700          | Lymphosarcoma of spleen                                      |
| B601800          | Lymphosarcoma of lymph nodes of multiple sites               |
| B601z00          | Lymphosarcoma NOS                                            |
| B602.00          | Burkitt's lymphoma                                           |
| B602000          | Burkitt's lymphoma of unspecified site                       |
| B602100          | Burkitt's lymphoma of lymph nodes of head, face and neck     |
| B602200          | Burkitt's lymphoma of intrathoracic lymph nodes              |
| B602300          | Burkitt's lymphoma of intra-abdominal lymph nodes            |
| B602400          | Burkitt's lymphoma of lymph nodes of axilla and upper limb   |
| B602500          | Burkitt's lymphoma of lymph nodes of inguinal region and leg |
| B602600          | Burkitt's lymphoma of intrapelvic lymph nodes                |
| B602700          | Burkitt's lymphoma of spleen                                 |
| B602800          | Burkitt's lymphoma of lymph nodes of multiple sites          |
| B602z00          | Burkitt's lymphoma NOS                                       |
| B60y.00          | Other specified reticulosarcoma or lymphosarcoma             |
| B60z.00          | Reticulosarcoma or lymphosarcoma NOS                         |
| B61..00          | Hodgkin's disease                                            |
| B610.00          | Hodgkin's paraganuloma                                       |
| B610000          | Hodgkin's paraganuloma of unspecified site                   |
| B610100          | Hodgkin's paraganuloma of lymph nodes of head, face, neck    |
| B610200          | Hodgkin's paraganuloma of intrathoracic lymph nodes          |
| B610300          | Hodgkin's paraganuloma of intra-abdominal lymph nodes        |
| B610400          | Hodgkin's paraganuloma of lymph nodes of axilla and arm      |
| B610500          | Hodgkin's paraganuloma lymph nodes inguinal region and leg   |
| B610600          | Hodgkin's paraganuloma of intrapelvic lymph nodes            |
| B610700          | Hodgkin's paraganuloma of spleen                             |
| B610800          | Hodgkin's paraganuloma of lymph nodes of multiple sites      |
| B610z00          | Hodgkin's paraganuloma NOS                                   |
| B611.00          | Hodgkin's granuloma                                          |
| B611000          | Hodgkin's granuloma of unspecified site                      |
| B611100          | Hodgkin's granuloma of lymph nodes of head, face and neck    |
| B611200          | Hodgkin's granuloma of intrathoracic lymph nodes             |
| B611300          | Hodgkin's granuloma of intra-abdominal lymph nodes           |
| B611400          | Hodgkin's granuloma of lymph nodes of axilla and upper limb  |
| B611500          | Hodgkin's granuloma lymph nodes of inguinal region and leg   |
| B611600          | Hodgkin's granuloma of intrapelvic lymph nodes               |
| B611700          | Hodgkin's granuloma of spleen                                |
| B611800          | Hodgkin's granuloma of lymph nodes of multiple sites         |
| B611z00          | Hodgkin's granuloma NOS                                      |
| B612.00          | Hodgkin's sarcoma                                            |
| B612000          | Hodgkin's sarcoma of unspecified site                        |
| B612100          | Hodgkin's sarcoma of lymph nodes of head, face and neck      |
| B612200          | Hodgkin's sarcoma of intrathoracic lymph nodes               |
| B612300          | Hodgkin's sarcoma of intra-abdominal lymph nodes             |
| B612400          | Hodgkin's sarcoma of lymph nodes of axilla and upper limb    |
| B612500          | Hodgkin's sarcoma of lymph nodes of inguinal region and leg  |
| B612600          | Hodgkin's sarcoma of intrapelvic lymph nodes                 |
| B612700          | Hodgkin's sarcoma of spleen                                  |

| Read code | Description                                                  |
|-----------|--------------------------------------------------------------|
| B612800   | Hodgkin's sarcoma of lymph nodes of multiple sites           |
| B612z00   | Hodgkin's sarcoma NOS                                        |
| B613.00   | Hodgkin's disease, lymphocytic-histiocytic predominance      |
| B613000   | Hodgkin's, lymphocytic-histiocytic predominance unspec site  |
| B613100   | Hodgkin's, lymphocytic-histiocytic pred of head, face, neck  |
| B613200   | Hodgkin's, lymphocytic-histiocytic pred intrathoracic nodes  |
| B613300   | Hodgkin's, lymphocytic-histiocytic pred intra-abdominal node |
| B613400   | Hodgkin's, lymphocytic-histiocytic pred axilla and arm       |
| B613500   | Hodgkin's, lymphocytic-histiocytic pred inguinal and leg     |
| B613600   | Hodgkin's, lymphocytic-histiocytic pred intrapelvic nodes    |
| B613700   | Hodgkin's, lymphocytic-histiocytic predominance of spleen    |
| B613800   | Hodgkin's, lymphocytic-histiocytic pred of multiple sites    |
| B613z00   | Hodgkin's, lymphocytic-histiocytic predominance NOS          |
| B614.00   | Hodgkin's disease, nodular sclerosis                         |
| B614000   | Hodgkin's disease, nodular sclerosis of unspecified site     |
| B614100   | Hodgkin's nodular sclerosis of head, face and neck           |
| B614200   | Hodgkin's nodular sclerosis of intrathoracic lymph nodes     |
| B614300   | Hodgkin's nodular sclerosis of intra-abdominal lymph nodes   |
| B614400   | Hodgkin's nodular sclerosis of lymph nodes of axilla and arm |
| B614500   | Hodgkin's nodular sclerosis of inguinal region and leg       |
| B614600   | Hodgkin's nodular sclerosis of intrapelvic lymph nodes       |
| B614700   | Hodgkin's disease, nodular sclerosis of spleen               |
| B614800   | Hodgkin's nodular sclerosis of lymph nodes of multiple sites |
| B614z00   | Hodgkin's disease, nodular sclerosis NOS                     |
| B615.00   | Hodgkin's disease, mixed cellularity                         |
| B615000   | Hodgkin's disease, mixed cellularity of unspecified site     |
| B615100   | Hodgkin's mixed cellularity of lymph nodes head, face, neck  |
| B615200   | Hodgkin's mixed cellularity of intrathoracic lymph nodes     |
| B615300   | Hodgkin's mixed cellularity of intra-abdominal lymph nodes   |
| B615400   | Hodgkin's mixed cellularity of lymph nodes of axilla and arm |
| B615500   | Hodgkin's mixed cellularity of lymph nodes inguinal and leg  |
| B615600   | Hodgkin's mixed cellularity of intrapelvic lymph nodes       |
| B615700   | Hodgkin's disease, mixed cellularity of spleen               |
| B615800   | Hodgkin's mixed cellularity of lymph nodes of multiple sites |
| B615z00   | Hodgkin's disease, mixed cellularity NOS                     |
| B616.00   | Hodgkin's disease, lymphocytic depletion                     |
| B616000   | Hodgkin's lymphocytic depletion of unspecified site          |
| B616100   | Hodgkin's lymphocytic depletion of head, face and neck       |
| B616200   | Hodgkin's lymphocytic depletion of intrathoracic lymph nodes |
| B616300   | Hodgkin's lymphocytic depletion intra-abdominal lymph nodes  |
| B616400   | Hodgkin's lymphocytic depletion lymph nodes axilla and arm   |
| B616500   | Hodgkin's lymphocytic depletion lymph nodes inguinal and leg |
| B616600   | Hodgkin's lymphocytic depletion of intrapelvic lymph nodes   |
| B616700   | Hodgkin's disease, lymphocytic depletion of spleen           |
| B616800   | Hodgkin's lymphocytic depletion lymph nodes multiple sites   |
| B616z00   | Hodgkin's disease, lymphocytic depletion NOS                 |
| B61z.00   | Hodgkin's disease NOS                                        |
| B61z000   | Hodgkin's disease NOS, unspecified site                      |
| B61z100   | Hodgkin's disease NOS of lymph nodes of head, face and neck  |
| B61z200   | Hodgkin's disease NOS of intrathoracic lymph nodes           |
| B61z300   | Hodgkin's disease NOS of intra-abdominal lymph nodes         |
| B61z400   | Hodgkin's disease NOS of lymph nodes of axilla and arm       |
| B61z500   | Hodgkin's disease NOS of lymph nodes inguinal region and leg |
| B61z600   | Hodgkin's disease NOS of intrapelvic lymph nodes             |
| B61z700   | Hodgkin's disease NOS of spleen                              |
| B61z800   | Hodgkin's disease NOS of lymph nodes of multiple sites       |
| B61zz00   | Hodgkin's disease NOS                                        |
| B62..00   | Other malignant neoplasm of lymphoid and histiocytic tissue  |



| <b>Read code</b> | <b>Description</b>                                           |
|------------------|--------------------------------------------------------------|
| B620.00          | Nodular lymphoma (Brill - Symmers disease)                   |
| B620.11          | Reticulosarcoma - follicular or nodular                      |
| B620000          | Nodular lymphoma of unspecified site                         |
| B620100          | Nodular lymphoma of lymph nodes of head, face and neck       |
| B620200          | Nodular lymphoma of intrathoracic lymph nodes                |
| B620300          | Nodular lymphoma of intra-abdominal lymph nodes              |
| B620400          | Nodular lymphoma of lymph nodes of axilla and upper limb     |
| B620500          | Nodular lymphoma of lymph nodes of inguinal region and leg   |
| B620600          | Nodular lymphoma of intrapelvic lymph nodes                  |
| B620700          | Nodular lymphoma of spleen                                   |
| B620800          | Nodular lymphoma of lymph nodes of multiple sites            |
| B620z00          | Nodular lymphoma NOS                                         |
| B621.00          | Mycosis fungoides                                            |
| B621000          | Mycosis fungoides of unspecified site                        |
| B621100          | Mycosis fungoides of the lymph nodes of head, face and neck  |
| B621200          | Mycosis fungoides of intrathoracic lymph nodes               |
| B621300          | Mycosis fungoides of intra-abdominal lymph nodes             |
| B621400          | Mycosis fungoides of lymph nodes of axilla and upper limb    |
| B621500          | Mycosis fungoides of lymph nodes of inguinal region and leg  |
| B621600          | Mycosis fungoides of intrapelvic lymph nodes                 |
| B621700          | Mycosis fungoides of spleen                                  |
| B621800          | Mycosis fungoides of lymph nodes of multiple sites           |
| B621z00          | Mycosis fungoides NOS                                        |
| B622.00          | Sezary's disease                                             |
| B622000          | Sezary's disease of unspecified site                         |
| B622100          | Sezary's disease of lymph nodes of head, face and neck       |
| B622200          | Sezary's disease of intrathoracic lymph nodes                |
| B622300          | Sezary's disease of intra-abdominal lymph nodes              |
| B622400          | Sezary's disease of lymph nodes of axilla and upper limb     |
| B622500          | Sezary's disease of lymph nodes of inguinal region and leg   |
| B622600          | Sezary's disease of intrapelvic lymph nodes                  |
| B622700          | Sezary's disease of spleen                                   |
| B622800          | Sezary's disease of lymph nodes of multiple sites            |
| B622z00          | Sezary's disease NOS                                         |
| B623.00          | Malignant histiocytosis                                      |
| B623000          | Malignant histiocytosis of unspecified site                  |
| B623100          | Malignant histiocytosis of lymph nodes head, face and neck   |
| B623200          | Malignant histiocytosis of intrathoracic lymph nodes         |
| B623300          | Malignant histiocytosis of intra-abdominal lymph nodes       |
| B623400          | Malignant histiocytosis of lymph nodes of axilla and arm     |
| B623500          | Malignant histiocytosis of lymph nodes inguinal and leg      |
| B623600          | Malignant histiocytosis of intrapelvic lymph nodes           |
| B623700          | Malignant histiocytosis of spleen                            |
| B623800          | Malignant histiocytosis of lymph nodes of multiple sites     |
| B623z00          | Malignant histiocytosis NOS                                  |
| B624.00          | Leukaemic reticuloendotheliosis                              |
| B624.11          | Leukaemic reticuloendotheliosis                              |
| B624000          | Leukaemic reticuloendotheliosis of unspecified sites         |
| B624100          | Leukaemic reticuloend of lymph nodes of head, face and neck  |
| B624200          | Leukaemic reticuloendotheliosis of intrathoracic lymph nodes |
| B624300          | Leukaemic reticuloend of intra-abdominal lymph nodes         |
| B624400          | Leukaemic reticuloend of lymph nodes of axilla and arm       |
| B624500          | Leukaemic reticuloend of lymph nodes inguinal region and leg |
| B624600          | Leukaemic reticuloendotheliosis of intrapelvic lymph nodes   |
| B624700          | Leukaemic reticuloendotheliosis of spleen                    |
| B624800          | Leukaemic reticuloend of lymph nodes of multiple sites       |
| B624z00          | Leukaemic reticuloendotheliosis NOS                          |
| B625.00          | Letterer-Siwe disease                                        |

| Read code | Description                                                  |
|-----------|--------------------------------------------------------------|
| B625.11   | Histiocytosis X (acute, progressive)                         |
| B625000   | Letterer-Siwe disease of unspecified sites                   |
| B625100   | Letterer-Siwe disease of lymph nodes of head, face and neck  |
| B625200   | Letterer-Siwe disease of intrathoracic lymph nodes           |
| B625300   | Letterer-Siwe disease of intra-abdominal lymph nodes         |
| B625400   | Letterer-Siwe disease of lymph nodes of axilla and arm       |
| B625500   | Letterer-Siwe disease of lymph nodes inguinal region and leg |
| B625600   | Letterer-Siwe disease of intrapelvic lymph nodes             |
| B625700   | Letterer-Siwe disease of spleen                              |
| B625800   | Letterer-Siwe disease of lymph nodes of multiple sites       |
| B625z00   | Letterer-Siwe disease NOS                                    |
| B626.00   | Malignant mast cell tumours                                  |
| B626000   | Mast cell malignancy of unspecified site                     |
| B626100   | Mast cell malignancy of lymph nodes of head, face and neck   |
| B626200   | Mast cell malignancy of intrathoracic lymph nodes            |
| B626300   | Mast cell malignancy of intra-abdominal lymph nodes          |
| B626400   | Mast cell malignancy of lymph nodes of axilla and upper limb |
| B626500   | Mast cell malignancy of lymph nodes inguinal region and leg  |
| B626600   | Mast cell malignancy of intrapelvic lymph nodes              |
| B626700   | Mast cell malignancy of spleen                               |
| B626800   | Mast cell malignancy of lymph nodes of multiple sites        |
| B626z00   | Malignant mast cell tumour NOS                               |
| B627.00   | Non - Hodgkin's lymphoma                                     |
| B627000   | Follicular non-Hodgkin's small cleaved cell lymphoma         |
| B627100   | Follicular non-Hodg mixed sml cleavd & lge cell lymphoma     |
| B627200   | Follicular non-Hodgkin's large cell lymphoma                 |
| B627300   | Diffuse non-Hodgkin's small cell (diffuse) lymphoma          |
| B627400   | Diffuse non-Hodgkin's small cleaved cell (diffuse) lymphoma  |
| B627500   | Diffuse non-Hodgkin mixed sml & lge cell (diffuse) lymphoma  |
| B627600   | Diffuse non-Hodgkin's immunoblastic (diffuse) lymphoma       |
| B627700   | Diffuse non-Hodgkin's lymphoblastic (diffuse) lymphoma       |
| B627800   | Diffuse non-Hodgkin's lymphoma undifferentiated (diffuse)    |
| B627C00   | Follicular non-Hodgkin's lymphoma                            |
| B627C11   | Follicular lymphoma NOS                                      |
| B627D00   | Diffuse non-Hodgkin's centroblastic lymphoma                 |
| B627W00   | Unspecified B-cell non-Hodgkin's lymphoma                    |
| B627X00   | Diffuse non-Hodgkin's lymphoma, unspecified                  |
| B62x.00   | Malignant lymphoma otherwise specified                       |
| B62x000   | T-zone lymphoma                                              |
| B62x100   | Lymphoepithelioid lymphoma                                   |
| B62x200   | Peripheral T-cell lymphoma                                   |
| B62x300   | Malignant reticuloendotheliosis                              |
| B62x400   | Malignant reticulosis                                        |
| B62x500   | Malignant immunoproliferative small intestinal disease       |
| B62x600   | True histiocytic lymphoma                                    |
| B62xX00   | Oth and unspecif peripheral & cutaneous T-cell lymphomas     |
| B62y.00   | Malignant lymphoma NOS                                       |
| B62y000   | Malignant lymphoma NOS of unspecified site                   |
| B62y100   | Malignant lymphoma NOS of lymph nodes of head, face and neck |
| B62y200   | Malignant lymphoma NOS of intrathoracic lymph nodes          |
| B62y300   | Malignant lymphoma NOS of intra-abdominal lymph nodes        |
| B62y400   | Malignant lymphoma NOS of lymph nodes of axilla and arm      |
| B62y500   | Malignant lymphoma NOS of lymph node inguinal region and leg |
| B62y600   | Malignant lymphoma NOS of intrapelvic lymph nodes            |
| B62y700   | Malignant lymphoma NOS of spleen                             |
| B62y800   | Malignant lymphoma NOS of lymph nodes of multiple sites      |
| B62yz00   | Malignant lymphoma NOS                                       |
| B62z.00   | Malignant neoplasms of lymphoid and histiocytic tissue NOS   |

| Read code | Description                                                  |
|-----------|--------------------------------------------------------------|
| B62z000   | Unspec malig neop lymphoid/histiocytic of unspecified site   |
| B62z100   | Unspec malig neop lymphoid/histiocytic lymph node head/neck  |
| B62z200   | Unspec malig neop lymphoid/histiocytic of intrathoracic node |
| B62z300   | Unspec malig neop lymphoid/histiocytic intra-abdominal nodes |
| B62z400   | Unspec malig neop lymphoid/histiocytic lymph node axilla/arm |
| B62z500   | Unspec malig neop lymphoid/histiocytic nodes inguinal/leg    |
| B62z600   | Unspec malig neop lymphoid/histiocytic of intrapelvic nodes  |
| B62z700   | Unspec malig neop lymphoid/histiocytic of spleen             |
| B62z800   | Unspec malig neop lymphoid/histiocytic of multiple sites     |
| B62zz00   | Lymphoid and histiocytic malignancy NOS                      |
| B62zz11   | Immunoproliferative neoplasm                                 |
| B63..00   | Multiple myeloma and immunoproliferative neoplasms           |
| B630.00   | Multiple myeloma                                             |
| B630.11   | Kahler's disease                                             |
| B630.12   | Myelomatosis                                                 |
| B630000   | Malignant plasma cell neoplasm, extramedullary plasmacytoma  |
| B630100   | Solitary myeloma                                             |
| B630200   | Plasmacytoma NOS                                             |
| B630300   | Lambda light chain myeloma                                   |
| B631.00   | Plasma cell leukaemia                                        |
| B63y.00   | Other immunoproliferative neoplasms                          |
| B63z.00   | Immunoproliferative neoplasm or myeloma NOS                  |
| B64..00   | Lymphoid leukaemia                                           |
| B64..11   | Lymphatic leukaemia                                          |
| B640.00   | Acute lymphoid leukaemia                                     |
| B641.00   | Chronic lymphoid leukaemia                                   |
| B641.11   | Chronic lymphatic leukaemia                                  |
| B642.00   | Subacute lymphoid leukaemia                                  |
| B64y.00   | Other lymphoid leukaemia                                     |
| B64y000   | Aleukaemic lymphoid leukaemia                                |
| B64y100   | Prolymphocytic leukaemia                                     |
| B64y200   | Adult T-cell leukaemia                                       |
| B64yz00   | Other lymphoid leukaemia NOS                                 |
| B64z.00   | Lymphoid leukaemia NOS                                       |
| B65..00   | Myeloid leukaemia                                            |
| B650.00   | Acute myeloid leukaemia                                      |
| B651.00   | Chronic myeloid leukaemia                                    |
| B651.11   | Chronic granulocytic leukaemia                               |
| B651000   | Chronic eosinophilic leukaemia                               |
| B651200   | Chronic neutrophilic leukaemia                               |
| B651z00   | Chronic myeloid leukaemia NOS                                |
| B652.00   | Subacute myeloid leukaemia                                   |
| B653.00   | Myeloid sarcoma                                              |
| B653000   | Chloroma                                                     |
| B653100   | Granulocytic sarcoma                                         |
| B653z00   | Myeloid sarcoma NOS                                          |
| B65y.00   | Other myeloid leukaemia                                      |
| B65y000   | Aleukaemic myeloid leukaemia                                 |
| B65y100   | Acute promyelocytic leukaemia                                |
| B65yz00   | Other myeloid leukaemia NOS                                  |
| B65z.00   | Myeloid leukaemia NOS                                        |
| B66..00   | Monocytic leukaemia                                          |
| B66..11   | Histiocytic leukaemia                                        |
| B66..12   | Monoblastic leukaemia                                        |
| B660.00   | Acute monocytic leukaemia                                    |
| B661.00   | Chronic monocytic leukaemia                                  |
| B662.00   | Subacute monocytic leukaemia                                 |
| B66y.00   | Other monocytic leukaemia                                    |

| Read code | Description                                                   |
|-----------|---------------------------------------------------------------|
| B66y000   | Aleukaemic monocytic leukaemia                                |
| B66yz00   | Other monocytic leukaemia NOS                                 |
| B66z.00   | Monocytic leukaemia NOS                                       |
| B67..00   | Other specified leukaemia                                     |
| B670.00   | Acute erythraemia and erythroleukaemia                        |
| B670.11   | Di Guglielmo's disease                                        |
| B671.00   | Chronic erythraemia                                           |
| B671.11   | Heilmeyer - Schoner disease                                   |
| B672.00   | Megakaryocytic leukaemia                                      |
| B672.11   | Thrombocytic leukaemia                                        |
| B673.00   | Mast cell leukaemia                                           |
| B674.00   | Acute panmyelosis                                             |
| B675.00   | Acute myelofibrosis                                           |
| B67y.00   | Other and unspecified leukaemia                               |
| B67y000   | Lymphosarcoma cell leukaemia                                  |
| B67yz00   | Other and unspecified leukaemia NOS                           |
| B67z.00   | Other specified leukaemia NOS                                 |
| B68..00   | Leukaemia of unspecified cell type                            |
| B680.00   | Acute leukaemia NOS                                           |
| B681.00   | Chronic leukaemia NOS                                         |
| B682.00   | Subacute leukaemia NOS                                        |
| B68y.00   | Other leukaemia of unspecified cell type                      |
| B68z.00   | Leukaemia NOS                                                 |
| B69..00   | Myelomonocytic leukaemia                                      |
| B690.00   | Acute myelomonocytic leukaemia                                |
| B691.00   | Chronic myelomonocytic leukaemia                              |
| B692.00   | Subacute myelomonocytic leukaemia                             |
| B6y..00   | Malignant neoplasm lymphatic or haematopoietic tissue OS      |
| B6y0.00   | Myeloproliferative disorder                                   |
| B6y0.11   | Myeloproliferative disease                                    |
| B6y1.00   | Myelosclerosis with myeloid metaplasia                        |
| B6y1.11   | Megakaryocytic myelosclerosis                                 |
| B6z..00   | Malignant neoplasm lymphatic or haematopoietic tissue NOS     |
| B6z0.00   | Kaposi's sarcoma of lymph nodes                               |
| By...00   | Neoplasms otherwise specified                                 |
| Byu..00   | [X]Additional neoplasm classification terms                   |
| Byu0.00   | [X]Malignant neoplasm of lip, oral cavity and pharynx         |
| Byu1.00   | [X]Malignant neoplasm of digestive organs                     |
| Byu1000   | [X]Other sarcomas of the liver                                |
| Byu1100   | [X]Other specified carcinomas of liver                        |
| Byu1200   | [X]Malignant neoplasm of intestinal tract, part unspecified   |
| Byu1300   | [X]Malignant neoplasm/ill-defin sites within digestive system |
| Byu2.00   | [X]Malignant neoplasm of respiratory and intrathoracic organ  |
| Byu2000   | [X]Malignant neoplasm of bronchus or lung, unspecified        |
| Byu2100   | [X]Malignant neoplasm/overlap lesion/heart,mediastinum??      |
| Byu2200   | [X]Malignant neoplasm/upper resp tract, part unspecified      |
| Byu2300   | [X]Malignant neoplasm/overlapping les/resp???? organs         |
| Byu2400   | [X]Malignant neoplasm/ill-defined sites within resp system    |
| Byu2500   | [X]Malignant neoplasm of mediastinum, part unspecified        |
| Byu3.00   | [X]Malignant neoplasm of bone and articular cartilage         |
| Byu3000   | [X]Malignant neoplasm/overlap lesion/bone??? cartilage/limb   |
| Byu3100   | [X]Malignant neoplasm/bones??? cartilage/limb,unspfd          |
| Byu3200   | [X]Malignant neoplasm/overlap lesion/bone??? cartilage        |
| Byu3300   | [X]Malignant neoplasm/bone??? cartilage, unspecified          |
| Byu4.00   | [X]Melanoma and other malignant neoplasms of skin             |
| Byu4000   | [X]Malignant melanoma of other???? parts of face              |
| Byu4100   | [X]Malignant melanoma of skin, unspecified                    |
| Byu4200   | [X]Other malignant neoplasm/skin of other??? parts of face    |

| Read code | Description                                                  |
|-----------|--------------------------------------------------------------|
| Byu4300   | [X]Malignant neoplasm of skin, unspecified                   |
| Byu5.00   | [X]Malignant neoplasm of mesothelial and soft tissue         |
| Byu5000   | [X]Mesothelioma of other sites                               |
| Byu5011   | [X]Mesothelioma of lung                                      |
| Byu5100   | [X]Mesothelioma, unspecified                                 |
| Byu5200   | [X]Kaposi's sarcoma of multiple organs                       |
| Byu5300   | [X]Kaposi's sarcoma, unspecified                             |
| Byu5400   | [X]Malignant neoplasm/peripheral nerves of trunk,unspecified |
| Byu5500   | [X]Mal neoplasm/overlap les/periph nerv??? nerv systm        |
| Byu5600   | [X]Mal neoplasm/periph nerves??? nervous system,unspc        |
| Byu5700   | [X]Malignant neoplasm of peritoneum, unspecified             |
| Byu5800   | [X]Mal neoplasm/connective? tissue of trunk,unspecified      |
| Byu5900   | [X]Malignant neoplasm/connective soft tissue,unspecified     |
| Byu5A00   | [X]Malignant neoplasm overlapping lesion of skin             |
| Byu6.00   | [X]Malignant neoplasm of breast                              |
| Byu7.00   | [X]Malignant neoplasm of female genital organs               |
| Byu7000   | [X]Malignant neoplasm of uterine adnexa, unspecified         |
| Byu7100   | [X]Malignant neoplasm/other specified female genital organs  |
| Byu7200   | [X]Malignant neoplasm/overlapping lesion/feml genital organs |
| Byu7300   | [X]Malignant neoplasm of female genital organ, unspecified   |
| Byu8.00   | [X]Malignant neoplasm of male genital organs                 |
| Byu8000   | [X]Malignant neoplasm/other specified male genital organs    |
| Byu8100   | [X]Malignant neoplasm/overlapping lesion/male genital organs |
| Byu8200   | [X]Malignant neoplasm of male genital organ, unspecified     |
| Byu9.00   | [X]Malignant neoplasm of urinary tract                       |
| Byu9000   | [X]Malignant neoplasm of urinary organ, unspecified          |
| ByuA.00   | [X]Malignant neoplasm of eye, brain and other parts of cent  |
| ByuA000   | [X]Malignant neoplasm/other and unspecified cranial nerves   |
| ByuA100   | [X]Malignant neoplasm/central nervous system, unspecified    |
| ByuA200   | [X]Malignant neoplasm of meninges, unspecified               |
| ByuA300   | [X]Malig neopl, overlap lesion brain & other part of CNS     |
| ByuC000   | [X]Malignant neoplasm of other specified sites               |
| ByuD.00   | [X]Malignant neoplasms of lymphoid, haematopoietic and rela  |
| ByuD000   | [X]Other Hodgkin's disease                                   |
| ByuD100   | [X]Other types of follicular non-Hodgkin's lymphoma          |
| ByuD200   | [X]Other types of diffuse non-Hodgkin's lymphoma             |
| ByuD300   | [X]Other specified types of non-Hodgkin's lymphoma           |
| ByuD400   | [X]Other malignant immunoproliferative diseases              |
| ByuD500   | [X]Other lymphoid leukaemia                                  |
| ByuD600   | [X]Other myeloid leukaemia                                   |
| ByuD700   | [X]Other monocytic leukaemia                                 |
| ByuD800   | [X]Other specified leukaemias                                |
| ByuD900   | [X]Other leukaemia of unspecified cell type                  |
| ByuDA00   | [X]Oth spcf mal neoplsm/lymphoid,haematopoietic? tissue      |
| ByuDC00   | [X]Diffuse non-Hodgkin's lymphoma, unspecified               |
| ByuDD00   | [X]Oth and unspecif peripheral & cutaneous T-cell lymphomas  |
| ByuDE00   | [X]Unspecified B-cell non-Hodgkin's lymphoma                 |
| ByuDF00   | [X]Non-Hodgkin's lymphoma, unspecified type                  |
| ByuDF11   | [X]Non-Hodgkin's lymphoma NOS                                |
| ByuE.00   | [X]Malignant neoplasms/independent (primary) multiple sites  |
| ByuE000   | [X]Malignant neoplasms/independent(primary)multiple sites    |
| Bz...00   | Neoplasms NOS                                                |
| ZV10.00   | [V]Personal history of malignant neoplasm                    |
| ZV10000   | [V]Personal history of malig neop of gastrointestinal tract  |
| ZV10011   | [V]Personal history of malignant neoplasm of anus            |
| ZV10012   | [V]Personal history of malig neop of gastrointestinal tract  |
| ZV10013   | [V]Personal history of malignant neoplasm of intestine       |
| ZV10014   | [V]Personal history of malignant neoplasm of large intestine |

| Read code | Description                                                 |
|-----------|-------------------------------------------------------------|
| ZV10015   | [V]Personal history of malignant neoplasm of liver          |
| ZV10016   | [V]Personal history of malignant neoplasm of oesophagus     |
| ZV10017   | [V]Personal history of malignant neoplasm of rectum         |
| ZV10018   | [V]Personal history of malignant neoplasm of stomach        |
| ZV10019   | [V]Personal history of malignant neoplasm of tongue         |
| ZV10100   | [V]Personal history of malig neop of trachea/bronchus/lung  |
| ZV10111   | [V]Personal history of malignant neoplasm of bronchus       |
| ZV10112   | [V]Personal history of malignant neoplasm of lung           |
| ZV10113   | [V]Personal history of malignant neoplasm of trachea        |
| ZV10200   | [V]Personal history of malig neop other intrathoracic organ |
| ZV10211   | [V]Personal history of malignant neoplasm - accessory sinus |
| ZV10212   | [V]Personal history of malignant neoplasm of larynx         |
| ZV10213   | [V]Personal history of malignant neoplasm of middle ear     |
| ZV10214   | [V]Personal history of malignant neoplasm of nose           |
| ZV10300   | [V]Personal history of malignant neoplasm of breast         |
| ZV10400   | [V]Personal history of malignant neoplasm of genital organ  |
| ZV10411   | [V]Personal history of malignant neoplasm of cervix uteri   |
| ZV10412   | [V]Personal history of malignant neoplasm of genital organ  |
| ZV10413   | [V]Personal history malignant neoplasm - male genital organ |
| ZV10414   | [V]Personal history of malignant neoplasm of ovary          |
| ZV10415   | [V]Personal history of malignant neoplasm of prostate       |
| ZV10416   | [V]Personal history of malignant neoplasm of testis         |
| ZV10417   | [V]Personal history of malignant neoplasm of uterine body   |
| ZV10500   | [V]Personal history of malignant neoplasm of urinary organ  |
| ZV10511   | [V]Personal history of malignant neoplasm of bladder        |
| ZV10512   | [V]Personal history of malignant neoplasm of kidney         |
| ZV10513   | [V]Personal history of malignant neoplasm of kidney         |
| ZV10600   | [V]Personal history of leukaemia                            |
| ZV10611   | [V]Personal history of lymphoid leukaemia                   |
| ZV10612   | [V]Personal history of monocytic leukaemia                  |
| ZV10613   | [V]Personal history of myeloid leukaemia                    |
| ZV10700   | [V]Personal history other lymphatic/haematopoietic neoplasm |
| ZV10711   | [V]Personal history of Hodgkin's disease                    |
| ZV10712   | [V]Personal history of lymphosarcoma                        |
| ZV10713   | [V]Personal history of other haematopoietic neoplasm        |
| ZV10714   | [V]Personal history of reticulosarcoma                      |
| ZV10y00   | [V]Personal history of other specified malignant neoplasm   |
| ZV10y11   | [V]Personal history of malignant neoplasm of bone           |
| ZV10y12   | [V]Personal history of malignant neoplasm of brain          |
| ZV10y13   | [V]Personal history of malignant neoplasm of eye            |
| ZV10y14   | [V]Personal history of malignant neoplasm of skin           |
| ZV10y15   | [V]Personal history of malignant neoplasm of thyroid        |
| ZV10y16   | [V]Personal history of malignant neoplasm of tongue         |
| ZV10z00   | [V]Personal history of unspecified malignant neoplasm       |

**Appendix table XXIII.13: Read codes for metastatic cancer used in calculation of Charlson index**

| Read code | Description                                                 |
|-----------|-------------------------------------------------------------|
| B153.00   | Secondary malignant neoplasm of liver                       |
| B56..00   | Secondary and unspecified malignant neoplasm of lymph nodes |
| B56..11   | Lymph node metastases                                       |
| B560.00   | Secondary and unspec malig neop lymph nodes head/face/neck  |
| B560000   | Secondary and unspec malig neop of superficial parotid LN   |
| B560100   | Secondary and unspec malignant neoplasm mastoid lymph nodes |
| B560200   | Secondary and unspec malig neop superficial cervical LN     |

| <b>Read code</b> | <b>Description</b>                                           |
|------------------|--------------------------------------------------------------|
| B560300          | Secondary and unspec malignant neoplasm occipital lymph node |
| B560400          | Secondary and unspec malig neop deep parotid lymph nodes     |
| B560500          | Secondary and unspec malig neop submandibular lymph nodes    |
| B560600          | Secondary and unspec malig neop of facial lymph nodes        |
| B560700          | Secondary and unspec malig neop submental lymph nodes        |
| B560800          | Secondary and unspec malig neop anterior cervical LN         |
| B560900          | Secondary and unspec malig neop deep cervical LN             |
| B560z00          | Secondary unspec malig neop lymph nodes head/face/neck NOS   |
| B561.00          | Secondary and unspec malig neop intrathoracic lymph nodes    |
| B561000          | Secondary and unspec malig neop internal mammary lymph nodes |
| B561100          | Secondary and unspec malig neop intercostal lymph nodes      |
| B561200          | Secondary and unspec malig neop diaphragmatic lymph nodes    |
| B561300          | Secondary and unspec malig neop ant mediastinal lymph nodes  |
| B561400          | Secondary and unspec malig neop post mediastinal lymph nodes |
| B561500          | Secondary and unspec malig neop paratracheal lymph nodes     |
| B561600          | Secondary and unspec malig neop superfic tracheobronchial LN |
| B561700          | Secondary and unspec malig neop inferior tracheobronchial LN |
| B561800          | Secondary and unspec malig neop bronchopulmonary lymph nodes |
| B561900          | Secondary and unspec malig neop pulmonary lymph nodes        |
| B561z00          | Secondary and unspec malig neop intrathoracic LN NOS         |
| B562.00          | Secondary and unspec malig neop intra-abdominal lymph nodes  |
| B562000          | Secondary and unspec malig neop coeliac lymph nodes          |
| B562100          | Secondary and unspec malig neop superficial mesenteric LN    |
| B562200          | Secondary and unspec malig neop inferior mesenteric LN       |
| B562300          | Secondary and unspec malig neop common iliac lymph nodes     |
| B562400          | Secondary and unspec malig neop external iliac lymph nodes   |
| B562z00          | Secondary and unspec malig neop intra-abdominal LN NOS       |
| B563.00          | Secondary and unspec malig neop axilla and upper limb LN     |
| B563000          | Secondary and unspec malig neop axillary lymph nodes         |
| B563100          | Secondary and unspec malig neop supratrochlear lymph nodes   |
| B563200          | Secondary and unspec malig neop infraclavicular lymph nodes  |
| B563300          | Secondary and unspec malig neop pectoral lymph nodes         |
| B563z00          | Secondary and unspec malig neop axilla and upper limb LN NOS |
| B564.00          | Secondary and unspec malig neop inguinal and lower limb LN   |
| B564000          | Secondary and unspec malig neop superficial inguinal LN      |
| B564100          | Secondary and unspec malig neop deep inguinal lymph nodes    |
| B564200          | Secondary and unspec malig neop popliteal lymph nodes        |
| B564z00          | Secondary and unspec malig neop of inguinal and leg LN NOS   |
| B565.00          | Secondary and unspec malig neop intrapelvic lymph nodes      |
| B565000          | Secondary and unspec malig neop internal iliac lymph nodes   |
| B565100          | Secondary and unspec malig neop inferior epigastric LN       |
| B565200          | Secondary and unspec malig neop circumflex iliac LN          |
| B565300          | Secondary and unspec malig neop sacral lymph nodes           |
| B565400          | Secondary and unspec malig neop obturator lymph nodes        |
| B565z00          | Secondary and unspec malig neop intrapelvic LN NOS           |
| B56y.00          | Secondary and unspec malig neop lymph nodes multiple sites   |
| B56z.00          | Secondary and unspec malig neop lymph nodes NOS              |
| B57..00          | Secondary malig neop of respiratory and digestive systems    |
| B57..11          | Metastases of respiratory and/or digestive systems           |
| B57..12          | Secondary carcinoma of respiratory and/or digestive systems  |
| B570.00          | Secondary malignant neoplasm of lung                         |
| B571.00          | Secondary malignant neoplasm of mediastinum                  |
| B572.00          | Secondary malignant neoplasm of pleura                       |
| B573.00          | Secondary malignant neoplasm of other respiratory organs     |
| B574.00          | Secondary malignant neoplasm of small intestine and duodenum |
| B574000          | Secondary malignant neoplasm of duodenum                     |
| B574100          | Secondary malignant neoplasm of jejunum                      |
| B574200          | Secondary malignant neoplasm of ileum                        |

| <b>Read code</b> | <b>Description</b>                                           |
|------------------|--------------------------------------------------------------|
| B574z00          | Secondary malig neop of small intestine or duodenum NOS      |
| B575.00          | Secondary malignant neoplasm of large intestine and rectum   |
| B575000          | Secondary malignant neoplasm of colon                        |
| B575100          | Secondary malignant neoplasm of rectum                       |
| B575z00          | Secondary malig neop of large intestine or rectum NOS        |
| B576.00          | Secondary malig neop of retroperitoneum and peritoneum       |
| B576000          | Secondary malignant neoplasm of retroperitoneum              |
| B576100          | Secondary malignant neoplasm of peritoneum                   |
| B576200          | Malignant ascites                                            |
| B576z00          | Secondary malig neop of retroperitoneum or peritoneum NOS    |
| B577.00          | Secondary malignant neoplasm of liver                        |
| B577.11          | Liver metastases                                             |
| B57y.00          | Secondary malignant neoplasm of other digestive organ        |
| B57z.00          | Secondary malig neop of respiratory or digestive system NOS  |
| B58..00          | Secondary malignant neoplasm of other specified sites        |
| B58..11          | Secondary carcinoma of other specified sites                 |
| B580.00          | Secondary malignant neoplasm of kidney                       |
| B581.00          | Secondary malignant neoplasm of other urinary organs         |
| B581000          | Secondary malignant neoplasm of ureter                       |
| B581100          | Secondary malignant neoplasm of bladder                      |
| B581200          | Secondary malignant neoplasm of urethra                      |
| B581z00          | Secondary malignant neoplasm of other urinary organ NOS      |
| B582.00          | Secondary malignant neoplasm of skin                         |
| B582000          | Secondary malignant neoplasm of skin of head                 |
| B582100          | Secondary malignant neoplasm of skin of face                 |
| B582200          | Secondary malignant neoplasm of skin of neck                 |
| B582300          | Secondary malignant neoplasm of skin of trunk                |
| B582400          | Secondary malignant neoplasm of skin of shoulder and arm     |
| B582500          | Secondary malignant neoplasm of skin of hip and leg          |
| B582600          | Secondary malignant neoplasm of skin of breast               |
| B582z00          | Secondary malignant neoplasm of skin NOS                     |
| B583.00          | Secondary malignant neoplasm of brain and spinal cord        |
| B583000          | Secondary malignant neoplasm of brain                        |
| B583100          | Secondary malignant neoplasm of spinal cord                  |
| B583200          | Cerebral metastasis                                          |
| B583z00          | Secondary malignant neoplasm of brain or spinal cord NOS     |
| B584.00          | Secondary malignant neoplasm of other part of nervous system |
| B585.00          | Secondary malignant neoplasm of bone and bone marrow         |
| B585000          | Pathological fracture due to metastatic bone disease         |
| B586.00          | Secondary malignant neoplasm of ovary                        |
| B587.00          | Secondary malignant neoplasm of adrenal gland                |
| B58y.00          | Secondary malignant neoplasm of other specified sites        |
| B58y000          | Secondary malignant neoplasm of breast                       |
| B58y100          | Secondary malignant neoplasm of uterus                       |
| B58y200          | Secondary malignant neoplasm of cervix uteri                 |
| B58y211          | Secondary cancer of the cervix                               |
| B58y300          | Secondary malignant neoplasm of vagina                       |
| B58y400          | Secondary malignant neoplasm of vulva                        |
| B58y411          | Secondary cancer of the vulva                                |
| B58y500          | Secondary malignant neoplasm of prostate                     |
| B58y600          | Secondary malignant neoplasm of testis                       |
| B58y700          | Secondary malignant neoplasm of penis                        |
| B58y800          | Secondary malignant neoplasm of epididymis and vas deferens  |
| B58y900          | Secondary malignant neoplasm of tongue                       |
| B58yz00          | Secondary malignant neoplasm of other specified site NOS     |
| B58z.00          | Secondary malignant neoplasm of other specified site NOS     |
| B59..00          | Malignant neoplasm of unspecified site                       |
| B590.00          | Disseminated malignancy NOS                                  |



| Read code | Description                                                 |
|-----------|-------------------------------------------------------------|
| B590.11   | Carcinomatosis                                              |
| B591.00   | Other malignant neoplasm NOS                                |
| B592.00   | Malignant neoplasms of independent (primary) multiple sites |
| B592X00   | Kaposi's sarcoma of multiple organs                         |
| B593.00   | Primary malignant neoplasm of unknown site                  |
| B594.00   | Secondary malignant neoplasm of unknown site                |
| B59z.00   | Malignant neoplasm of unspecified site NOS                  |
| B5y..00   | Malignant neoplasm of other and unspecified site OS         |
| B5z..00   | Malignant neoplasm of other and unspecified site NOS        |
| ByuC.00   | [X]Malignant neoplasm of ill-defined, secondary and unspeci |
| ByuC100   | [X]Malignant neoplasm/overlap lesion/other?defined sites    |
| ByuC200   | [X]2ndry?? malignant neoplasm lymph nodes/multi regions     |
| ByuC300   | [X]Secondary malignant neoplasm/oth? respiratory organs     |
| ByuC400   | [X]Secondary malignant neoplasm/oth?? digestive organs      |
| ByuC500   | [X]2ndry malignant neoplasm/bladder??? urinary organs       |
| ByuC600   | [X]2ndry malignant neoplasm/oth?? parts/nervous system      |
| ByuC700   | [X]Secondary malignant neoplasm of other specified sites    |
| ByuC800   | [X]Malignant neoplasm without specification of site         |

**Appendix table XXIII.14: Read codes for chronic pulmonary disease used in calculation of Charlson index**

| Read code | Description                                           |
|-----------|-------------------------------------------------------|
| 14B4.00   | H/O: asthma                                           |
| 173A.00   | Exercise induced asthma                               |
| 173c.00   | Occupational asthma                                   |
| 1761      | C/O bronchial catarrh                                 |
| 1780      | Aspirin induced asthma                                |
| 102..00   | Asthma confirmed                                      |
| 663       | Asthma sometimes restricts exercise                   |
| 663       | Asthma severely restricts exercise                    |
| 663e.00   | Asthma restricts exercise                             |
| 663f.00   | Asthma never restricts exercise                       |
| 663h.00   | Asthma - currently dormant                            |
| 663N.00   | Asthma disturbing sleep                               |
| 663N000   | Asthma causing night waking                           |
| 663N100   | Asthma disturbs sleep weekly                          |
| 663P.00   | Asthma limiting activities                            |
| 663p.00   | Asthma treatment compliance unsatisfactory            |
| 663q.00   | Asthma daytime symptoms                               |
| 663r.00   | Asthma causes night symptoms 1 to 2 times per month   |
| 663s.00   | Asthma never causes daytime symptoms                  |
| 663t.00   | Asthma causes daytime symptoms 1 to 2 times per month |
| 663u.00   | Asthma causes daytime symptoms 1 to 2 times per week  |
| 663v.00   | Asthma causes daytime symptoms most days              |
| 663V000   | Occasional asthma                                     |
| 663V100   | Mild asthma                                           |
| 663V200   | Moderate asthma                                       |
| 663V300   | Severe asthma                                         |
| 663w.00   | Asthma limits walking up hills or stairs              |
| 663W.00   | Asthma prophylactic medication used                   |
| 66YC.00   | Absent from work or school due to asthma              |
| 66YP.00   | Asthma night-time symptoms                            |
| 8H2P.00   | Emergency admission, asthma                           |
| 90J1.00   | Attends asthma monitoring                             |
| 90JA.11   | Asthma monitored                                      |

| <b>Read code</b> | <b>Description</b>                               |
|------------------|--------------------------------------------------|
| H30..00          | Bronchitis unspecified                           |
| H30..11          | Chest infection - unspecified bronchitis         |
| H300.00          | Tracheobronchitis NOS                            |
| H30z.00          | Bronchitis NOS                                   |
| H31..00          | Chronic bronchitis                               |
| H310.00          | Simple chronic bronchitis                        |
| H310000          | Chronic catarrhal bronchitis                     |
| H310100          | Smokers' cough                                   |
| H310z00          | Simple chronic bronchitis NOS                    |
| H311.00          | Mucopurulent chronic bronchitis                  |
| H311000          | Purulent chronic bronchitis                      |
| H311100          | Fetid chronic bronchitis                         |
| H311z00          | Mucopurulent chronic bronchitis NOS              |
| H312.00          | Obstructive chronic bronchitis                   |
| H312000          | Chronic asthmatic bronchitis                     |
| H312011          | Chronic wheezy bronchitis                        |
| H312100          | Emphysematous bronchitis                         |
| H312z00          | Obstructive chronic bronchitis NOS               |
| H313.00          | Mixed simple and mucopurulent chronic bronchitis |
| H31y.00          | Other chronic bronchitis                         |
| H31y100          | Chronic tracheobronchitis                        |
| H31yz00          | Other chronic bronchitis NOS                     |
| H31z.00          | Chronic bronchitis NOS                           |
| H32..00          | Emphysema                                        |
| H320.00          | Chronic bullous emphysema                        |
| H320000          | Segmental bullous emphysema                      |
| H320200          | Giant bullous emphysema                          |
| H320z00          | Chronic bullous emphysema NOS                    |
| H321.00          | Panlobular emphysema                             |
| H322.00          | Centrilobular emphysema                          |
| H32y.00          | Other emphysema                                  |
| H32y000          | Acute vesicular emphysema                        |
| H32y100          | Atrophic (senile) emphysema                      |
| H32y200          | MacLeod's unilateral emphysema                   |
| H32yz00          | Other emphysema NOS                              |
| H32z.00          | Emphysema NOS                                    |
| H33..00          | Asthma                                           |
| H33..11          | Bronchial asthma                                 |
| H330.00          | Extrinsic (atopic) asthma                        |
| H330.12          | Childhood asthma                                 |
| H330.13          | Hay fever with asthma                            |
| H330.14          | Pollen asthma                                    |
| H330000          | Extrinsic asthma without status asthmaticus      |
| H330011          | Hay fever with asthma                            |
| H330111          | Extrinsic asthma with asthma attack              |
| H330z00          | Extrinsic asthma NOS                             |
| H331.00          | Intrinsic asthma                                 |
| H331.11          | Late onset asthma                                |
| H331000          | Intrinsic asthma without status asthmaticus      |
| H331100          | Intrinsic asthma with status asthmaticus         |
| H331111          | Intrinsic asthma with asthma attack              |
| H331z00          | Intrinsic asthma NOS                             |
| H332.00          | Mixed asthma                                     |
| H333.00          | Acute exacerbation of asthma                     |
| H334.00          | Brittle asthma                                   |
| H33z.00          | Asthma unspecified                               |
| H33z000          | Status asthmaticus NOS                           |
| H33z011          | Severe asthma attack                             |

| <b>Read code</b> | <b>Description</b>                                   |
|------------------|------------------------------------------------------|
| h33z100          | Asthma attack                                        |
| H33z111          | Asthma attack NOS                                    |
| H33z200          | Late-onset asthma                                    |
| H33zz11          | Exercise induced asthma                              |
| H33zz12          | Allergic asthma NEC                                  |
| H33zz13          | Allergic bronchitis NEC                              |
| H34..00          | Bronchiectasis                                       |
| H340.00          | Recurrent bronchiectasis                             |
| H341.00          | Post-infective bronchiectasis                        |
| H34z.00          | Bronchiectasis NOS                                   |
| H35..00          | Extrinsic allergic alveolitis                        |
| H350.00          | Farmers' lung                                        |
| H351.00          | Bagassosis                                           |
| H352.00          | Bird-fancier's lung                                  |
| H352000          | Budgerigar-fanciers' lung                            |
| H352100          | Pigeon-fanciers' lung                                |
| H352z00          | Bird-fancier's lung NOS                              |
| H353.00          | Suberosis ( cork-handlers' lung )                    |
| H354.00          | Malt workers' lung                                   |
| H355.00          | Mushroom workers' lung                               |
| H356.00          | Maple bark strippers' lung                           |
| H35y.00          | Other allergic alveolitis                            |
| H35y300          | Furriers' lung                                       |
| H35y500          | Pituitary snuff-takers' disease                      |
| H35y600          | Sequoiosis (red-cedar asthma)                        |
| H35y700          | Wood asthma                                          |
| H35yz00          | Other allergic alveolitis NOS                        |
| H35z.00          | Allergic alveolitis and pneumonitis NOS              |
| H35z100          | Hypersensitivity pneumonitis NOS                     |
| H35zz00          | Allergic alveolitis and pneumonitis NOS              |
| H3z..11          | Chronic obstructive pulmonary disease NOS            |
| H40..00          | Coal workers' pneumoconiosis                         |
| H41..00          | Asbestosis                                           |
| H410.00          | Pleural plaque disease due to asbestosis             |
| H41z.00          | Asbestosis NOS                                       |
| H42..00          | Silica and silicate pneumoconiosis                   |
| H420.00          | Talc pneumoconiosis                                  |
| H423.00          | Massive silicotic fibrosis                           |
| H42z.00          | Silica pneumoconiosis NOS                            |
| H43..00          | Pneumoconiosis due to other inorganic dust           |
| H430.00          | Aluminosis of lung                                   |
| H431.00          | Bauxite fibrosis of lung                             |
| H432.00          | Berylliosis                                          |
| H434.00          | Siderosis                                            |
| H435.00          | Stannosis                                            |
| H43z.00          | Pneumoconiosis due to inorganic dust NOS             |
| H440.00          | Byssinosis                                           |
| H441.00          | Cannabinosis                                         |
| H442.00          | Flax-dressers' disease                               |
| H45..00          | Pneumoconiosis NOS                                   |
| H460.00          | Bronchitis and pneumonitis due to chemical fumes     |
| H460z00          | Bronchitis and pneumonitis due to chemical fumes NOS |
| H464000          | Chronic emphysema due to chemical fumes              |
| H464100          | Obliterative bronchiolitis due to chemical fumes     |
| H464200          | Chronic pulmonary fibrosis due to chemical fumes     |
| H47y000          | Detergent asthma                                     |
| H4y1000          | Chronic pulmonary fibrosis following radiation       |
| H4z..00          | Lung disease due to external agents NOS              |

| <b>Read code</b> | <b>Description</b>                                         |
|------------------|------------------------------------------------------------|
| H57y.00          | Lung disease with diseases EC                              |
| H57yz00          | Lung disease with diseases EC NOS                          |
| H581.00          | Interstitial emphysema                                     |
| H582.00          | Compensatory emphysema                                     |
| Hyu3000          | [X]Other emphysema                                         |
| Hyu4000          | [X]Pneumoconiosis due to other dust containing silica      |
| Hyu4100          | [X]Pneumoconiosis due to other specified inorganic dusts   |
| Hyu4300          | [X]Hypersensitivity pneumonitis due to other organic dusts |
| SK07.00          | Subcutaneous emphysema                                     |

**Appendix table XXIII.15: Read codes for congestive heart failure used in calculation of Charlson index**

| <b>Read code</b> | <b>Description</b>                                          |
|------------------|-------------------------------------------------------------|
| 14A6.00          | H/O: heart failure                                          |
| 14AM.00          | H/O: Heart failure in last year                             |
| 101..00          | Heart failure confirmed                                     |
| 662W.00          | Heart failure annual review                                 |
| 8B29.00          | Cardiac failure therapy                                     |
| 8CL3.00          | Heart failure care plan discussed with patient              |
| 8H2S.00          | Admit heart failure emergency                               |
| G232.00          | Hypertensive heart&renal dis wth (congestive) heart failure |
| G554000          | Congestive cardiomyopathy                                   |
| G58..00          | Heart failure                                               |
| G58..11          | Cardiac failure                                             |
| G580.00          | Congestive heart failure                                    |
| G580.11          | Congestive cardiac failure                                  |
| G580.12          | Right heart failure                                         |
| G580000          | Acute congestive heart failure                              |
| G580100          | Chronic congestive heart failure                            |
| G580200          | Decompensated cardiac failure                               |
| G580300          | Compensated cardiac failure                                 |
| G581.00          | Left ventricular failure                                    |
| G581000          | Acute left ventricular failure                              |
| G582.00          | Acute heart failure                                         |
| G58z.00          | Heart failure NOS                                           |
| G58z.11          | Weak heart                                                  |
| G58z.12          | Cardiac failure NOS                                         |
| SP11111          | Heart failure as a complication of care                     |

**Appendix table XXIII.16: Read codes for dementia used in calculation of Charlson index**

| <b>Read code</b> | <b>Description</b>               |
|------------------|----------------------------------|
| 1461             | H/O: dementia                    |
| E00..11          | Senile dementia                  |
| E00..12          | Senile/presenile dementia        |
| E000.00          | Uncomplicated senile dementia    |
| e000.00          | Uncomplicated senile dementia    |
| E001.00          | Presenile dementia               |
| E001000          | Uncomplicated presenile dementia |
| E001z00          | Presenile dementia NOS           |
| E004.00          | Arteriosclerotic dementia        |
| E004.11          | Multi infarct dementia           |

| <b>Read code</b> | <b>Description</b>                                           |
|------------------|--------------------------------------------------------------|
| E004000          | Uncomplicated arteriosclerotic dementia                      |
| E004100          | Arteriosclerotic dementia with delirium                      |
| E004200          | Arteriosclerotic dementia with paranoia                      |
| E004300          | Arteriosclerotic dementia with depression                    |
| E004z00          | Arteriosclerotic dementia NOS                                |
| E041.00          | Dementia in conditions EC                                    |
| Eu00.00          | [X]Dementia in Alzheimer's disease                           |
| Eu00000          | [X]Dementia in Alzheimer's disease with early onset          |
| Eu00011          | [X]Presenile dementia,Alzheimer's type                       |
| Eu00012          | [X]Primary degen dementia, Alzheimer's type, presenile onset |
| Eu00100          | [X]Dementia in Alzheimer's disease with late onset           |
| Eu00112          | [X]Senile dementia,Alzheimer's type                          |
| Eu00113          | [X]Primary degen dementia of Alzheimer's type, senile onset  |
| Eu00200          | [X]Dementia in Alzheimer's dis, atypical or mixed type       |
| Eu00z00          | [X]Dementia in Alzheimer's disease, unspecified              |
| Eu00z11          | [X]Alzheimer's dementia unspec                               |
| Eu01.00          | [X]Vascular dementia                                         |
| Eu01.11          | [X]Arteriosclerotic dementia                                 |
| Eu01000          | [X]Vascular dementia of acute onset                          |
| Eu01100          | [X]Multi-infarct dementia                                    |
| Eu01111          | [X]Predominantly cortical dementia                           |
| Eu01200          | [X]Subcortical vascular dementia                             |
| Eu01300          | [X]Mixed cortical and subcortical vascular dementia          |
| Eu01y00          | [X]Other vascular dementia                                   |
| Eu01z00          | [X]Vascular dementia, unspecified                            |
| Eu02.00          | [X]Dementia in other diseases classified elsewhere           |
| Eu02500          | [X]Lewy body dementia                                        |
| Eu02y00          | [X]Dementia in other specified diseases classif elsewhere    |
| Eu02z00          | [X] Unspecified dementia                                     |
| Eu02z13          | [X] Primary degenerative dementia NOS                        |
| Eu02z14          | [X] Senile dementia NOS                                      |
| Eu02z16          | [X] Senile dementia, depressed or paranoid type              |

**Appendix table XXIII.17: Read codes for hemiplegia and paraplegia used in calculation of Charlson index**

| <b>Read code</b> | <b>Description</b>            |
|------------------|-------------------------------|
| F230000          | Congenital paraplegia         |
| F220.00          | Flaccid hemiplegia            |
| F241000          | Flaccid paraplegia            |
| F22..00          | Hemiplegia                    |
| F22z.00          | Hemiplegia NOS                |
| F141.00          | Hereditary spastic paraplegia |
| F222.00          | Left hemiplegia               |
| 2833             | O/E - hemiplegia              |
| 2835             | O/E - paraplegia              |
| F241.00          | Paraplegia                    |
| F230.11          | Paraplegia - congenital       |
| F223.00          | Right hemiplegia              |
| F221.00          | Spastic hemiplegia            |
| F241100          | Spastic paraplegia            |

**Appendix table XXIII.18: Read codes for mild liver disease used in calculation of Charlson index**

| Read code | Description                                              |
|-----------|----------------------------------------------------------|
| C310400   | Glycogenosis with hepatic cirrhosis                      |
| C350012   | Pigmentary cirrhosis of liver                            |
| J600200   | Acute yellow atrophy                                     |
| J601200   | Subacute yellow atrophy                                  |
| J61...00  | Cirrhosis and chronic liver disease                      |
| J612.00   | Alcoholic cirrhosis of liver                             |
| J612.11   | Florid cirrhosis                                         |
| J614.00   | Chronic hepatitis                                        |
| J614000   | Chronic persistent hepatitis                             |
| J614100   | Chronic active hepatitis                                 |
| J614200   | Chronic aggressive hepatitis                             |
| J614300   | Recurrent hepatitis                                      |
| J614y00   | Chronic hepatitis unspecified                            |
| J614z00   | Chronic hepatitis NOS                                    |
| J615.00   | Cirrhosis - non alcoholic                                |
| J615.11   | Portal cirrhosis                                         |
| J615000   | Unilobular portal cirrhosis                              |
| J615100   | Multilobular portal cirrhosis                            |
| J615111   | Postnecrotic cirrhosis of liver                          |
| J615300   | Diffuse nodular cirrhosis                                |
| J615400   | Fatty portal cirrhosis                                   |
| J615700   | Cardiac portal cirrhosis                                 |
| J615A00   | Pipe-stem portal cirrhosis                               |
| J615B00   | Toxic portal cirrhosis                                   |
| J615C00   | Xanthomatous portal cirrhosis                            |
| J615F00   | Syphilitic portal cirrhosis                              |
| J615y00   | Portal cirrhosis unspecified                             |
| J615z00   | Non-alcoholic cirrhosis NOS                              |
| J615z11   | Macronodular cirrhosis of liver                          |
| J615z12   | Cryptogenic cirrhosis of liver                           |
| J615z13   | Cirrhosis of liver NOS                                   |
| J615z14   | Laennec's cirrhosis, non-alcoholic                       |
| J616.00   | Biliary cirrhosis                                        |
| J616000   | Primary biliary cirrhosis                                |
| J616100   | Secondary biliary cirrhosis                              |
| J616z00   | Biliary cirrhosis NOS                                    |
| J617000   | Chronic alcoholic hepatitis                              |
| J61y300   | Portal fibrosis without cirrhosis                        |
| J633.00   | Hepatitis unspecified                                    |
| J635600   | Toxic liver disease with fibrosis and cirrhosis of liver |
| Jyu7100   | [X]Other and unspecified cirrhosis of liver              |

**Appendix table XXIII.19: Read codes for moderate or severe liver disease used in calculation of Charlson index**

| Read code | Description                                                 |
|-----------|-------------------------------------------------------------|
| 760F300   | Rigid oesophagoscopy injection sclerotherapy oesoph varices |
| A704z00   | Other specified viral hepatitis with hepatic coma NOS       |
| G85...11  | Oesophageal varices                                         |
| G850.00   | Oesophageal varices with bleeding                           |
| G851.00   | Oesophageal varices without bleeding                        |
| G852.00   | Oesophageal varices in diseases EC                          |
| G852000   | Oesophageal varices with bleeding in diseases EC            |

| Read code | Description                                                  |
|-----------|--------------------------------------------------------------|
| G852100   | Oesophageal varices without bleeding in diseases EC          |
| G852200   | Oesophageal varices in cirrhosis of the liver                |
| G852300   | Oesophageal varices in alcoholic cirrhosis of the liver      |
| G852z00   | Oesophageal varices in diseases EC NOS                       |
| G858.00   | Oesophageal varices NOS                                      |
| Gyu9400   | [X]Oesophageal varices in diseases classified elsewhere      |
| J622.00   | Hepatic coma                                                 |
| J623.00   | Portal hypertension                                          |
| J624.00   | Hepatorenal syndrome                                         |
| J62y.00   | Other sequelae of chronic liver disease                      |
| J62z.00   | Liver abscess and chronic liver disease causing sequelae NOS |

**Appendix table XXIII.20: Read codes for peptic ulcer disease used in calculation of Charlson index**

| Read code | Description                                               |
|-----------|-----------------------------------------------------------|
| 1956      | Peptic ulcer symptoms                                     |
| 7612111   | Balfour excision of gastric ulcer                         |
| 7612500   | Resection of gastric ulcer by cautery                     |
| 761D600   | Endoscopic injection haemostasis of gastric ulcer         |
| 761J.00   | Operations on gastric ulcer                               |
| 761J.11   | Stomach ulcer operations                                  |
| 761J000   | Closure of perforated gastric ulcer                       |
| 761J100   | Closure of gastric ulcer NEC                              |
| 761J111   | Suture of ulcer of stomach NEC                            |
| 761Jy00   | Other specified operation on gastric ulcer                |
| 761Jz00   | Operation on gastric ulcer NOS                            |
| 7627      | Operations on duodenal ulcer                              |
| 7627000   | Closure of perforated duodenal ulcer                      |
| J102000   | Peptic ulcer of oesophagus                                |
| J11..00   | Gastric ulcer - (GU)                                      |
| J11..11   | Prepyloric ulcer                                          |
| J11..12   | Pyloric ulcer                                             |
| J110.00   | Acute gastric ulcer                                       |
| J110000   | Acute gastric ulcer without mention of complication       |
| J110100   | Acute gastric ulcer with haemorrhage                      |
| J110111   | Bleeding acute gastric ulcer                              |
| J110200   | Acute gastric ulcer with perforation                      |
| J110300   | Acute gastric ulcer with haemorrhage and perforation      |
| J110400   | Acute gastric ulcer with obstruction                      |
| J110y00   | Acute gastric ulcer unspecified                           |
| J110z00   | Acute gastric ulcer NOS                                   |
| J111.00   | Chronic gastric ulcer                                     |
| J111000   | Chronic gastric ulcer without mention of complication     |
| J111100   | Chronic gastric ulcer with haemorrhage                    |
| J111111   | Bleeding chronic gastric ulcer                            |
| J111200   | Chronic gastric ulcer with perforation                    |
| J111211   | Perforated chronic gastric ulcer                          |
| J111300   | Chronic gastric ulcer with haemorrhage and perforation    |
| J111400   | Chronic gastric ulcer with obstruction                    |
| J111y00   | Chronic gastric ulcer unspecified                         |
| J111z00   | Chronic gastric ulcer NOS                                 |
| J112.00   | Anti-platelet induced gastric ulcer                       |
| J11y.00   | Unspecified gastric ulcer                                 |
| J11y000   | Unspecified gastric ulcer without mention of complication |
| J11y100   | Unspecified gastric ulcer with haemorrhage                |

| <b>Read code</b> | <b>Description</b>                                           |
|------------------|--------------------------------------------------------------|
| J11y200          | Unspecified gastric ulcer with perforation                   |
| J11y300          | Unspecified gastric ulcer with haemorrhage and perforation   |
| J11y400          | Unspecified gastric ulcer with obstruction                   |
| J11yy00          | Unspec gastric ulcer; unspec haemorrhage and/or perforation  |
| J11yz00          | Unspecified gastric ulcer NOS                                |
| J11z.00          | Gastric ulcer NOS                                            |
| J11z.12          | Multiple gastric ulcers                                      |
| J12..00          | Duodenal ulcer - (DU)                                        |
| J120.00          | Acute duodenal ulcer                                         |
| J120000          | Acute duodenal ulcer without mention of complication         |
| J120100          | Acute duodenal ulcer with haemorrhage                        |
| J120200          | Acute duodenal ulcer with perforation                        |
| J120300          | Acute duodenal ulcer with haemorrhage and perforation        |
| J120400          | Acute duodenal ulcer with obstruction                        |
| J120y00          | Acute duodenal ulcer unspecified                             |
| J120z00          | Acute duodenal ulcer NOS                                     |
| J121.00          | Chronic duodenal ulcer                                       |
| J121000          | Chronic duodenal ulcer without mention of complication       |
| J121111          | Bleeding chronic duodenal ulcer                              |
| J121300          | Chronic duodenal ulcer with haemorrhage and perforation      |
| J121400          | Chronic duodenal ulcer with obstruction                      |
| J121y00          | Chronic duodenal ulcer unspecified                           |
| J121z00          | Chronic duodenal ulcer NOS                                   |
| J122.00          | Duodenal ulcer disease                                       |
| J123.00          | Duodenal erosion                                             |
| J124.00          | Recurrent duodenal ulcer                                     |
| J12y.00          | Unspecified duodenal ulcer                                   |
| J12y000          | Unspecified duodenal ulcer without mention of complication   |
| J12y200          | Unspecified duodenal ulcer with perforation                  |
| J12y300          | Unspecified duodenal ulcer with haemorrhage and perforation  |
| J12y400          | Unspecified duodenal ulcer with obstruction                  |
| J12yy00          | Unspec duodenal ulcer; unspec haemorrhage and/or perforation |
| J12yz00          | Unspecified duodenal ulcer NOS                               |
| J12z.00          | Duodenal ulcer NOS                                           |
| J13..00          | Peptic ulcer - (PU) site unspecified                         |
| J13..11          | Stress ulcer NOS                                             |
| J130.00          | Acute peptic ulcer                                           |
| J130000          | Acute peptic ulcer without mention of complication           |
| J130100          | Acute peptic ulcer with haemorrhage                          |
| J130200          | Acute peptic ulcer with perforation                          |
| J130300          | Acute peptic ulcer with haemorrhage and perforation          |
| J130400          | Acute peptic ulcer with obstruction                          |
| J130y00          | Acute peptic ulcer unspecified                               |
| J130z00          | Acute peptic ulcer NOS                                       |
| J131.00          | Chronic peptic ulcer                                         |
| J131000          | Chronic peptic ulcer without mention of complication         |
| J131100          | Chronic peptic ulcer with haemorrhage                        |
| J131200          | Chronic peptic ulcer with perforation                        |
| J131300          | Chronic peptic ulcer with haemorrhage and perforation        |
| J131400          | Chronic peptic ulcer with obstruction                        |
| J131y00          | Chronic peptic ulcer unspecified                             |
| J131z00          | Chronic peptic ulcer NOS                                     |
| J13y.00          | Unspecified peptic ulcer                                     |
| J13y000          | Unspecified peptic ulcer without mention of complication     |
| J13y100          | Unspecified peptic ulcer with haemorrhage                    |
| J13y200          | Unspecified peptic ulcer with perforation                    |
| J13y300          | Unspecified peptic ulcer with haemorrhage and perforation    |
| J13y400          | Unspecified peptic ulcer with obstruction                    |



| Read code | Description                                                  |
|-----------|--------------------------------------------------------------|
| J13yy00   | Unspec peptic ulcer; unspec haemorrhage and/or perforation   |
| J13yz00   | Unspecified peptic ulcer NOS                                 |
| J13z.00   | Peptic ulcer NOS                                             |
| J14..00   | Gastrojejunal ulcer (GJU)                                    |
| J14..12   | Gastrocolic ulcer                                            |
| J14..15   | Stomal ulcer                                                 |
| J140.00   | Acute gastrojejunal ulcer                                    |
| J140000   | Acute gastrojejunal ulcer without mention of complication    |
| J140100   | Acute gastrojejunal ulcer with haemorrhage                   |
| J140200   | Acute gastrojejunal ulcer with perforation                   |
| J140300   | Acute gastrojejunal ulcer with haemorrhage and perforation   |
| J140400   | Acute gastrojejunal ulcer with obstruction                   |
| J140y00   | Acute gastrojejunal ulcer unspecified                        |
| J140z00   | Acute gastrojejunal ulcer NOS                                |
| J141.00   | Chronic gastrojejunal ulcer                                  |
| J141000   | Chronic gastrojejunal ulcer without mention of complication  |
| J141100   | Chronic gastrojejunal ulcer with haemorrhage                 |
| J141200   | Chronic gastrojejunal ulcer with perforation                 |
| J141300   | Chronic gastrojejunal ulcer with haemorrhage and perforation |
| J141400   | Chronic gastrojejunal ulcer with obstruction                 |
| J141y00   | Chronic gastrojejunal ulcer unspecified                      |
| J141z00   | Chronic gastrojejunal ulcer NOS                              |
| J14y.00   | Unspecified gastrojejunal ulcer                              |
| J14y000   | Unspecified gastrojejunal ulcer without mention complication |
| J14y100   | Unspecified gastrojejunal ulcer with haemorrhage             |
| J14y200   | Unspecified gastrojejunal ulcer with perforation             |
| J14y300   | Unspec gastrojejunal ulcer with haemorrhage and perforation  |
| J14y400   | Unspecified gastrojejunal ulcer with obstruction             |
| J14yy00   | Unspec gastrojejunal ulcer; unspec haemorrhage/perforation   |
| J14yz00   | Unspecified gastrojejunal ulcer NOS                          |
| J14z.00   | Gastrojejunal ulcer NOS                                      |
| ZV12711   | [V]Personal history of peptic ulcer                          |
| ZV12C00   | [V] Personal history of gastric ulcer                        |

**Appendix table XXIII.21: Read codes for renal disease used in calculation of Charlson index**

| Read code | Description                                                |
|-----------|------------------------------------------------------------|
| 14D1.00   | H/O: nephritis                                             |
| 1Z10.00   | Chronic kidney disease stage 1                             |
| 1Z11.00   | Chronic kidney disease stage 2                             |
| 1Z12.00   | Chronic kidney disease stage 3                             |
| 1Z13.00   | Chronic kidney disease stage 4                             |
| 1Z14.00   | Chronic kidney disease stage 5                             |
| K0...00   | Nephritis, nephrosis and nephrotic syndrome                |
| K001.00   | Acute nephritis with lesions of necrotising glomerulitis   |
| K012.00   | Nephrotic syndrome?????? glomerulonephritis                |
| K019.00   | Nephrotic syn,diffuse mesangiocapillary glomerulonephritis |
| K02..00   | Chronic glomerulonephritis                                 |
| K02..11   | Nephritis - chronic                                        |
| K02..12   | Nephropathy - chronic                                      |
| K021.00   | Chronic membranous glomerulonephritis                      |
| K022.00   | Chronic membranoproliferative glomerulonephritis           |
| K023.00   | Chronic rapidly progressive glomerulonephritis             |
| K02y000   | Chronic glomerulonephritis diseases EC                     |
| K02y200   | Chronic focal glomerulonephritis                           |
| K02y300   | Chronic diffuse glomerulonephritis                         |

| Read code | Description                                                  |
|-----------|--------------------------------------------------------------|
| K02yz00   | Other chronic glomerulonephritis NOS                         |
| K02z.00   | Chronic glomerulonephritis NOS                               |
| K03..00   | Nephritis and nephropathy unspecified                        |
| K03..11   | Nephritis and nephropathy unspecified                        |
| K032.00   | Membranoproliferative nephritis unspecified                  |
| K032000   | Focal membranoproliferative glomerulonephritis               |
| K032y00   | Nephritis unsp membranoprolif glomerulonephritis lesion      |
| K032y13   | Mesangioproliferative glomerulonephritis NEC                 |
| K032y14   | Mesangiocapillary glomerulonephritis NEC                     |
| K032z00   | Nephritis unsp???? glomerulonephritis lesion NOS             |
| K034.00   | Renal cortical necrosis unspecified                          |
| K035.00   | Renal medullary necrosis unspecified                         |
| K041.00   | Acute renal cortical necrosis                                |
| K042.00   | Acute renal medullary necrosis                               |
| K04y.00   | Other acute renal failure                                    |
| K04z.00   | Acute renal failure NOS                                      |
| K05..00   | Chronic renal failure                                        |
| K050.00   | End stage renal failure                                      |
| K06..00   | Renal failure unspecified                                    |
| K060.11   | Impaired renal function                                      |
| K080.00   | Renal osteodystrophy                                         |
| K080000   | Phosphate-losing tubular disorders                           |
| K080100   | Renal dwarfism                                               |
| K080200   | Renal infantilism                                            |
| K080300   | Renal rickets                                                |
| K080z00   | Renal osteodystrophy NOS                                     |
| K081.00   | Nephrogenic diabetes insipidus                               |
| K08y000   | Hypokalaemic nephropathy                                     |
| K08yz00   | Other impaired renal function disorder NOS                   |
| K08z.00   | Impaired renal function disorder NOS                         |
| K0A3200   | Chron nephritic syndrom difuse membranous glomerulonephritis |
| K0A3300   | Chron neph syn difus mesangial prolifrtiv glomerulonephritis |
| K0A3400   | Chron neph syn difuse endocap prolifrativ glomerulonephritis |
| K0A3500   | Chronic neph syn difus mesangiocapillary glomerulonephritis  |
| K0A3700   | Chronic nephritic syn diffuse crescentic glomerulonephritis  |
| K0A5500   | [X]Heredtry nephropthy NEC difus mesangiocapilry glomneph    |
| K100000   | Chronic pyelonephritis without medullary necrosis            |
| K100100   | Chronic pyelonephritis with medullary necrosis               |
| K101000   | Acute pyelonephritis without medullary necrosis              |
| K101100   | Acute pyelonephritis with medullary necrosis                 |
| Kyu2.00   | [X]Renal failure                                             |
| Kyu2000   | [X]Other acute renal failure                                 |
| Kyu2100   | [X]Other chronic renal failure                               |

**Appendix table XXIII.22: Read codes for rheumatological disease used in calculation of Charlson index**

| Read code | description                                      |
|-----------|--------------------------------------------------|
| F371200   | Polyneuropathy in rheumatoid arthritis           |
| F396100   | Myopathy due to disseminated lupus erythematosus |
| F396400   | Myopathy due to rheumatoid arthritis             |
| F396600   | Myopathy due to scleroderma                      |
| G5yA.00   | Rheumatoid carditis                              |
| H570.00   | Rheumatoid lung                                  |
| H572.00   | Lung disease with systemic sclerosis             |
| H57y100   | Lung disease with polymyositis                   |

| <b>Read code</b> | <b>description</b>                                          |
|------------------|-------------------------------------------------------------|
| H57y400          | Lung disease with systemic lupus erythematosus              |
| K01x400          | Nephrotic syndrome in systemic lupus erythematosus          |
| K01x411          | Lupus nephritis                                             |
| N000.00          | Systemic lupus erythematosus                                |
| N000000          | Disseminated lupus erythematosus                            |
| N000100          | Libman-Sacks disease                                        |
| N000200          | Drug-induced systemic lupus erythematosus                   |
| N000300          | Systemic lupus erythematosus with organ or sys involv       |
| N000400          | Systemic lupus erythematosus with pericarditis              |
| N000z00          | Systemic lupus erythematosus NOS                            |
| N001.00          | Scleroderma                                                 |
| N001.11          | Acrosclerosis                                               |
| N001.12          | Systemic sclerosis                                          |
| N001000          | Progressive systemic sclerosis                              |
| N001200          | Systemic sclerosis induced by drugs and chemicals           |
| N004.00          | Polymyositis                                                |
| N04..00          | Rheumatoid arthritis and other inflammatory polyarthropathy |
| N040.00          | Rheumatoid arthritis                                        |
| N040200          | Rheumatoid arthritis of shoulder                            |
| N040300          | Rheumatoid arthritis of sternoclavicular joint              |
| N040400          | Rheumatoid arthritis of acromioclavicular joint             |
| N040500          | Rheumatoid arthritis of elbow                               |
| N040600          | Rheumatoid arthritis of distal radio-ulnar joint            |
| N040700          | Rheumatoid arthritis of wrist                               |
| N040800          | Rheumatoid arthritis of MCP joint                           |
| N040900          | Rheumatoid arthritis of PIP joint of finger                 |
| N040A00          | Rheumatoid arthritis of DIP joint of finger                 |
| N040B00          | Rheumatoid arthritis of hip                                 |
| N040C00          | Rheumatoid arthritis of sacro-iliac joint                   |
| N040D00          | Rheumatoid arthritis of knee                                |
| N040E00          | Rheumatoid arthritis of tibio-fibular joint                 |
| N040F00          | Rheumatoid arthritis of ankle                               |
| N040G00          | Rheumatoid arthritis of subtalar joint                      |
| N040H00          | Rheumatoid arthritis of talonavicular joint                 |
| N040J00          | Rheumatoid arthritis of other tarsal joint                  |
| N040K00          | Rheumatoid arthritis of 1st MTP joint                       |
| N040L00          | Rheumatoid arthritis of lesser MTP joint                    |
| N040M00          | Rheumatoid arthritis of IP joint of toe                     |
| N040P00          | Seronegative rheumatoid arthritis                           |
| N040T00          | Flare of rheumatoid arthritis                               |
| N041.00          | Felty's syndrome                                            |
| N042100          | Rheumatoid lung disease                                     |
| N047.00          | Seropositive erosive rheumatoid arthritis                   |
| N04X.00          | Seropositive rheumatoid arthritis, unspecified              |
| N04y000          | Rheumatoid lung                                             |
| N04y011          | Caplan's syndrome                                           |
| N04y012          | Fibrosing alveolitis associated with rheumatoid arthritis   |
| N04y111          | Sero negative polyarthrititis                               |
| N060.11          | Endemic polyarthrititis                                     |
| N20..00          | Polymyalgia rheumatica                                      |
| N200.00          | Giant cell arteritis with polymyalgia rheumatica            |
| N231400          | Polymyositis ossificans                                     |
| N240.00          | Rheumatism and fibrositis unspecified                       |
| N240000          | Rheumatism unspecified                                      |
| N240200          | Muscular rheumatism                                         |
| N240700          | Hand rheumatism                                             |
| N240z00          | Rheumatism or fibrositis NOS                                |
| N2y..00          | Other specified nonarticular rheumatism                     |

| <b>Read code</b> | <b>description</b>                                |
|------------------|---------------------------------------------------|
| N2z.00           | Nonarticular rheumatism NOS                       |
| Nyu1000          | [X]Rheumatoid arthritis????? organs or systems    |
| Nyu1100          | [X]Other seropositive rheumatoid arthritis        |
| Nyu1200          | [X]Other specified rheumatoid arthritis           |
| Nyu1G00          | [X]Seropositive rheumatoid arthritis, unspecified |
| Nyu4300          | [X]Other forms of systemic lupus erythematosus    |
| Nyu4500          | [X]Other forms of systemic sclerosis              |

**Appendix table XXIII.23: Read codes for ethnicity**

| <b>Read code</b> | <b>Description</b>        | <b>Ethnicity (5 categories)</b> | <b>Ethnicity (10 categories)</b> |
|------------------|---------------------------|---------------------------------|----------------------------------|
| 1341.00          | European origin           | White                           | White                            |
| 1342.00          | African origin            | Black                           | Black African                    |
| 1343.00          | Asian origin              | Asian                           | Other Asian                      |
| 1345.00          | South American origin     | Other                           | Other                            |
| 1347.00          | Indian origin             | Asian                           | Indian                           |
| 1348.00          | Middle Eastern origin     | Other                           | Other                            |
| 1349.00          | Far Eastern origin        | Other                           | Other                            |
| 134A.00          | West Indian origin        | Black                           | Black Caribbean                  |
| 134B.00          | RACE: CauAsian            | White                           | White                            |
| 134C.00          | RACE: Arab                | Other                           | Other                            |
| 134D.00          | RACE: Chinese             | Chinese                         | Chinese                          |
| 134E.00          | RACE: Japanese            | Other                           | Other                            |
| 134F.00          | RACE: Korean              | Other                           | Other                            |
| 134G.00          | RACE: Oriental            | Other                           | Other                            |
| 134H.00          | RACE: Afro-caribbean      | Black                           | Black Caribbean                  |
| 134I.00          | RACE: Bangladeshi         | Asian                           | Bangladeshi                      |
| 134J.00          | RACE: Mixed               | mixed                           | Other                            |
| 134K.00          | RACE: West indian         | Black                           | Black Caribbean                  |
| 134L.00          | RACE: Afro-caucAsian      | mixed                           | Other                            |
| 134M.00          | RACE: Pakistani           | Asian                           | Pakistani                        |
| 134N.00          | RACE: White               | White                           | White                            |
| 1358.00          | Hindu                     | Asian                           | Indian                           |
| 135B.00          | Sikh                      | Asian                           | Indian                           |
| 135V.00          | Jainism                   | Asian                           | Indian                           |
| 135g.00          | Jain                      | Asian                           | Indian                           |
| 135v.00          | Radha Soami               | Asian                           | Indian                           |
| 13Z6100          | Language Bengali          | Asian                           | Bangladeshi                      |
| 13Z6200          | Language Gujurati         | Asian                           | Indian                           |
| 13Z6300          | Language Hindi            | Asian                           | Indian                           |
| 13Z6400          | Language Pashtu           | Asian                           | Pakistani                        |
| 13Z6500          | Language Punjabi          | Asian                           | Indian                           |
| 13Z6600          | Language Urdu             | Asian                           | Pakistani                        |
| 13b0.00          | Vietnamese language       | Other                           | Other                            |
| 13b1.00          | Cantonese Chinese dialect | Chinese                         | Chinese                          |
| 13b2.00          | Sylhety                   | Asian                           | Bangladeshi                      |
| 13b4.00          | Mirpuri language          | Asian                           | Pakistani                        |
| 13d3.00          | Born in Azerbaijan        | Other                           | Other                            |
| 13e0.00          | Born in Afghanistan       | Other                           | Other                            |
| 13e1.00          | Born in Armenia           | Other                           | Other                            |
| 13e2.00          | Born in Bahrain           | Other                           | Other                            |
| 13e3.00          | Born in Bangladesh        | Asian                           | Bangladeshi                      |
| 13e4.00          | Born in Bhutan            | Asian                           | Other Asian                      |
| 13e5.00          | Born in Brunei            | Other                           | Other                            |
| 13e6.00          | Born in Burma             | Other                           | Other                            |

| <b>Read code</b> | <b>Description</b>                            | <b>Ethnicity (5 categories)</b> | <b>Ethnicity (10 categories)</b> |
|------------------|-----------------------------------------------|---------------------------------|----------------------------------|
| 13e8.00          | Born in China                                 | Chinese                         | Chinese                          |
| 13e9.00          | Born in Democratic People's Republic of Korea | Other                           | Other                            |
| 13eA.00          | Born in East Timor                            | Other                           | Other                            |
| 13eC.00          | Born in Hong Kong                             | Chinese                         | Chinese                          |
| 13eD.00          | Born in India                                 | Asian                           | Indian                           |
| 13eE.00          | Born in Indonesia                             | Other                           | Other                            |
| 13eF.00          | Born in Iran                                  | Other                           | Other                            |
| 13eG.00          | Born in Iraq                                  | Other                           | Other                            |
| 13eH.00          | Born in Israel                                | Other                           | Other                            |
| 13eI.00          | Born in Japan                                 | Other                           | Other                            |
| 13eJ.00          | Born in Jordan                                | Other                           | Other                            |
| 13eK.00          | Born in Kazakhstan                            | Other                           | Other                            |
| 13eL.00          | Born in Kuwait                                | Other                           | Other                            |
| 13eM.00          | Born in Kyrgyzstan                            | Other                           | Other                            |
| 13eN.00          | Born in Laos                                  | Other                           | Other                            |
| 13eO.00          | Born in Lebanon                               | Other                           | Other                            |
| 13eP.00          | Born in Malaysia                              | Other                           | Other                            |
| 13eQ.00          | Born in Maldives                              | Asian                           | Other Asian                      |
| 13eR.00          | Born in Mali                                  | Black                           | Black African                    |
| 13eS.00          | Born in Mongolia                              | Other                           | Other                            |
| 13eT.00          | Born in Nepal                                 | Asian                           | Other Asian                      |
| 13eV.00          | Born in Oman                                  | Other                           | Other                            |
| 13eW.00          | Born in Pakistan                              | Asian                           | Pakistani                        |
| 13eX.00          | Born in Palestine                             | Other                           | Other                            |
| 13eY.00          | Born in Philippines                           | Other                           | Other                            |
| 13eZ.00          | Born in Qatar                                 | Other                           | Other                            |
| 13ea.00          | Born in Republic of Korea                     | Other                           | Other                            |
| 13ec.00          | Born in Saudi Arabia                          | Other                           | Other                            |
| 13ed.00          | Born in Singapore                             | Chinese                         | Chinese                          |
| 13ee.00          | Born in South Korea                           | Other                           | Other                            |
| 13ef.00          | Born in Sri Lanka                             | Asian                           | Other Asian                      |
| 13eg.00          | Born in Syria                                 | Other                           | Other                            |
| 13eh.00          | Born in Taiwan                                | Chinese                         | Chinese                          |
| 13ei.00          | Born in Tajikistan                            | Other                           | Other                            |
| 13ej.00          | Born in Thailand                              | Other                           | Other                            |
| 13el.00          | Born in Turkmenistan                          | Other                           | Other                            |
| 13em.00          | Born in United Arab Emirates                  | Other                           | Other                            |
| 13en.00          | Born in Uzbekistan                            | Other                           | Other                            |
| 13eo.00          | Born in Vietnam                               | Other                           | Other                            |
| 13ep.00          | Born in Yemen                                 | Other                           | Other                            |
| 13es.00          |                                               | Other                           | Other                            |
| 13f0.00          | Born in Argentina                             | Other                           | Other                            |
| 13f1.00          | Born in Belize                                | Other                           | Other                            |
| 13f2.00          | Born in Bolivia                               | Other                           | Other                            |
| 13f3.00          | Born in Brazil                                | Other                           | Other                            |
| 13f4.00          | Born in British Guyana                        | Black                           | Black Caribbean                  |
| 13f6.00          | Born in Chile                                 | Other                           | Other                            |
| 13f7.00          | Born in Columbia                              | Other                           | Other                            |
| 13f8.00          | Born in Costa Rica                            | Other                           | Other                            |
| 13f9.00          | Born in Ecuador                               | Other                           | Other                            |
| 13fA.00          | Born in El Salvador                           | Other                           | Other                            |
| 13fB.00          | Born in Grenada                               | Black                           | Black Caribbean                  |
| 13fC.00          | Born in Guatemala                             | Other                           | Other                            |
| 13fD.00          | Born in Guyana                                | Other                           | Other                            |
| 13fE.00          | Born in Honduras                              | Other                           | Other                            |
| 13fF.00          | Born in Mexico                                | Other                           | Other                            |
| 13fH.00          | Born in Panama                                | Other                           | Other                            |

| <b>Read<br/>code</b> | <b>Description</b>                   | <b>Ethnicity<br/>(5<br/>categories)</b> | <b>Ethnicity (10<br/>categories)</b> |
|----------------------|--------------------------------------|-----------------------------------------|--------------------------------------|
| 13fl.00              | Born in Paraguay                     | Other                                   | Other                                |
| 13fj.00              | Born in Peru                         | Other                                   | Other                                |
| 13fk.00              | Born in Suriname                     | Other                                   | Other                                |
| 13fm.00              | Born in Uruguay                      | Other                                   | Other                                |
| 13fN.00              | Born in Venezuela                    | Other                                   | Other                                |
| 13g0.00              | Born in Algeria                      | Other                                   | Other                                |
| 13g1.00              | Born in Angola                       | Black                                   | Black African                        |
| 13g2.00              | Born in Benin                        | Black                                   | Black African                        |
| 13g3.00              | Born in Botswana                     | Black                                   | Black African                        |
| 13g4.00              | Born in Burkina Faso                 | Black                                   | Black African                        |
| 13g5.00              | Born in Burundi                      | Black                                   | Black African                        |
| 13g6.00              | Born in Cambodia                     | Other                                   | Other                                |
| 13g7.00              | Born in Cameroon                     | Black                                   | Black African                        |
| 13g9.00              | Born in Central African Republic     | Black                                   | Black African                        |
| 13gA.00              | Born in Chad                         | Black                                   | Black African                        |
| 13gB.00              | Born in Comoros Islands              | Black                                   | Black African                        |
| 13gC.00              | Born in Congo                        | Black                                   | Black African                        |
| 13gD.00              | Born in Djibouti                     | Black                                   | Black African                        |
| 13gE.00              | Born in Egypt                        | Other                                   | Other                                |
| 13gF.00              | Born in Equatorial Guinea            | Black                                   | Black African                        |
| 13gG.00              | Born in Ethiopia                     | Black                                   | Black African                        |
| 13gH.00              | Born in Gabon                        | Black                                   | Black African                        |
| 13gI.00              | Born in Gambia                       | Black                                   | Black African                        |
| 13gJ.00              | Born in Ghana                        | Black                                   | Black African                        |
| 13gK.00              | Born in Guinea Bissau                | Black                                   | Black African                        |
| 13gL.00              | Born in Guinea Republic              | Black                                   | Black African                        |
| 13gM.00              | Born in Ivory Coast                  | Black                                   | Black African                        |
| 13gN.00              | Born in Kenya                        | Black                                   | Black African                        |
| 13gO.00              | Born in Lesotho                      | Black                                   | Black African                        |
| 13gP.00              | Born in Liberia                      | Black                                   | Black African                        |
| 13gQ.00              | Born in Libya                        | Other                                   | Other                                |
| 13gR.00              | Born in Madagascar                   | Black                                   | Black African                        |
| 13gS.00              | Born in Malawi                       | Black                                   | Black African                        |
| 13gV.00              | Born in Morocco                      | Other                                   | Other                                |
| 13gW.00              | Born in Mozambique                   | Black                                   | Black African                        |
| 13gX.00              | Born in Namibia                      | Black                                   | Black African                        |
| 13gY.00              | Born in Niger                        | Black                                   | Black African                        |
| 13gZ.00              | Born in Nigeria                      | Black                                   | Black African                        |
| 13ga.00              | Born in Rwanda                       | Black                                   | Black African                        |
| 13gb.00              | Born in Sao Tome and Principe        | Black                                   | Black African                        |
| 13gc.00              | Born in Senegal                      | Black                                   | Black African                        |
| 13gd.00              | Born in Sierra Leone                 | Black                                   | Black African                        |
| 13ge.00              | Born in Somalia                      | Black                                   | Black African                        |
| 13gg.00              | Born in Sudan                        | Black                                   | Black African                        |
| 13gh.00              | Born in Swaziland                    | Black                                   | Black African                        |
| 13gi.00              | Born in Tanzania                     | Black                                   | Black African                        |
| 13gj.00              | Born in The Gambia                   | Black                                   | Black African                        |
| 13gk.00              | Born in Tunisia                      | Other                                   | Other                                |
| 13gl.00              | Born in Uganda                       | Black                                   | Black African                        |
| 13gm.00              | Born in Zaire                        | Black                                   | Black African                        |
| 13gn.00              | Born in Zambia                       | Black                                   | Black African                        |
| 13go.00              | Born in Zimbabwe                     | Black                                   | Black African                        |
| 13gp.00              | Born in Eritrea                      | Black                                   | Black African                        |
| 13gq.00              | Born in Democratic Republic of Congo | Black                                   | Black African                        |
| 13gr.00              |                                      | Black                                   | Black Caribbean                      |
| 13j0.00              | Born in Antigua and Barbuda          | Black                                   | Black Caribbean                      |
| 13j1.00              | Born in Bahamas                      | Black                                   | Black Caribbean                      |

| Read code | Description                              | Ethnicity (5 categories) | Ethnicity (10 categories) |
|-----------|------------------------------------------|--------------------------|---------------------------|
| 13j2.00   | Born in Barbados                         | Black                    | Black Caribbean           |
| 13j3.00   | Born in Cuba                             | Other                    | Other                     |
| 13j4.00   | Born in Dominican Republic               | mixed                    | Other                     |
| 13j5.00   | Born in Haiti                            | Black                    | Black Caribbean           |
| 13j6.00   | Born in Jamaica                          | Black                    | Black Caribbean           |
| 13j7.00   | Born in Puerto Rico                      | Other                    | Other                     |
| 13j8.00   | Born in St. Kitts and Nevis              | Black                    | Black Caribbean           |
| 13j9.00   | Born in St. Lucia                        | Black                    | Black Caribbean           |
| 13jA.00   | Born in St. Vincent                      | Black                    | Black Caribbean           |
| 13jB.00   | Born in Togo                             | Black                    | Black African             |
| 13jC.00   | Born in Trinidad and Tobago              | Black                    | Black Caribbean           |
| 13jD.00   | Born in Dominica                         | Black                    | Black Caribbean           |
| 13jE.00   | Born in Aruba                            | Black                    | Black Caribbean           |
| 13jF.00   |                                          | Black                    | Black Caribbean           |
| 13jG.00   | Born in Saint Vincent and the Grenadines | Black                    | Black Caribbean           |
| 13jH.00   |                                          | Black                    | Black Caribbean           |
| 13jJ.00   |                                          | Black                    | Black Caribbean           |
| 13jK.00   |                                          | Black                    | Black Caribbean           |
| 13jL.00   |                                          | Black                    | Black Caribbean           |
| 13k0.00   | Born in Fiji                             | Other                    | Other                     |
| 13k1.00   |                                          | Other                    | Other                     |
| 13k2.00   |                                          | Other                    | Other                     |
| 13k3.00   | Born in Papua New Guinea                 | Other                    | Other                     |
| 13k4.00   | Born in Seychelles                       | Other                    | Other                     |
| 13k5.00   | Born in Solomon Islands                  | Other                    | Other                     |
| 13k6.00   | Born in Tonga                            | Other                    | Other                     |
| 13k7.00   | Born in Tuvalu                           | Other                    | Other                     |
| 13k8.00   | Born in Vanuatu                          | Other                    | Other                     |
| 13k9.00   | Born in Western Samoa                    | Other                    | Other                     |
| 13kA.00   |                                          | Other                    | Other                     |
| 13kB.00   |                                          | Other                    | Other                     |
| 13kC.00   |                                          | Other                    | Other                     |
| 13kD.00   |                                          | Other                    | Other                     |
| 13kE.00   |                                          | Other                    | Other                     |
| 13kF.00   |                                          | Other                    | Other                     |
| 13kG.00   |                                          | Other                    | Other                     |
| 13kH.00   |                                          | Other                    | Other                     |
| 13kJ.00   |                                          | Other                    | Other                     |
| 13kK.00   |                                          | Other                    | Other                     |
| 13kL.00   | Born in Northern Mariana Islands         | Other                    | Other                     |
| 13kM.00   |                                          | Other                    | Other                     |
| 13kN.00   |                                          | Other                    | Other                     |
| 13l1.00   | Main spoken language Bengali             | Asian                    | Bangladeshi               |
| 13l2.00   | Main spoken language Cantonese           | Chinese                  | Chinese                   |
| 13l6.00   | Main spoken language Gujarati            | Asian                    | Indian                    |
| 13l6.11   | Main spoken language Gujarati            | Asian                    | Indian                    |
| 13l7.00   | Main spoken language Hausa               | Black                    | Black African             |
| 13l8.00   | Main spoken language Hindi               | Asian                    | Indian                    |
| 13lA.00   | Main spoken language Kutchi              | Asian                    | Indian                    |
| 13lB.00   | Main spoken language Mandarin            | Chinese                  | Chinese                   |
| 13lE.00   | Main spoken language Punjabi             | Asian                    | Indian                    |
| 13lE.11   | Main spoken language Panjabi             | Asian                    | Indian                    |
| 13lG.00   | Main spoken language Somali              | Black                    | Black African             |
| 13lI.00   | Main spoken language Swahili             | Black                    | Black African             |
| 13lJ.00   | Main spoken language Sylheti             | Asian                    | Bangladeshi               |
| 13lK.00   | Main spoken language Tamil               | Asian                    | Indian                    |
| 13lL.00   | Main spoken language Urdu                | Asian                    | Pakistani                 |

| Read code | Description                                          | Ethnicity (5 categories) | Ethnicity (10 categories) |
|-----------|------------------------------------------------------|--------------------------|---------------------------|
| 13IM.00   | Main spoken language Yoruba                          | Black                    | Black African             |
| 13IO.00   | Main spoken language Farsi                           | Other                    | Other                     |
| 13IP.00   | Main spoken language Shona                           | Black                    | Black African             |
| 13IW.00   | Main spoken language Japanese                        | Other                    | Other                     |
| 13IX.00   | Main spoken language Korean                          | Other                    | Other                     |
| 13Ib.00   | Main spoken language Vietnamese                      | Other                    | Other                     |
| 13Ic.00   | Main spoken language Akan                            | Black                    | Black African             |
| 13Id.00   | Main spoken language Amharic                         | Black                    | Black African             |
| 13Ie.00   | Main spoken language Brawa                           | Black                    | Black African             |
| 13Ig.00   | Main spoken language Ethiopian                       | Black                    | Black African             |
| 13Ik.00   | Main spoken language Hakka                           | Chinese                  | Chinese                   |
| 13Im.00   | Main spoken language Igbo                            | Black                    | Black African             |
| 13In.00   | Main spoken language Lingala                         | Black                    | Black African             |
| 13Io.00   | Main spoken language Luganda                         | Black                    | Black African             |
| 13Ip.00   | Main spoken language Malayalam                       | Asian                    | Indian                    |
| 13Ir.00   | Main spoken language Pashto                          | Asian                    | Pakistani                 |
| 13Is.00   | Main spoken language Patois                          | Black                    | Black Caribbean           |
| 13Iu.00   | Main spoken language Sinhala                         | Asian                    | Other Asian               |
| 13Iu.11   | Main spoken language Sinhalese                       | Asian                    | Other Asian               |
| 13Iw.00   | Main spoken language Tagalog                         | Other                    | Other                     |
| 13Ix.00   | Main spoken language Thai                            | Other                    | Other                     |
| 13Iy.00   | Main spoken language Tigrinya                        | Black                    | Black African             |
| 13n2.00   | Reads Punjabi                                        | Asian                    | Indian                    |
| 13n4.00   | Reads Somali                                         | Black                    | Black African             |
| 13n6.00   | Reads Tamil                                          | Asian                    | Indian                    |
| 13n7.00   | Reads Urdu                                           | Asian                    | Pakistani                 |
| 13n8.00   | Reads Bengali                                        | Asian                    | Bangladeshi               |
| 13nD.00   | Reads Hindi                                          | Asian                    | Indian                    |
| 13nK.00   | Reads Gujarati                                       | Asian                    | Indian                    |
| 13nL.00   |                                                      | Black                    | Black Caribbean           |
| 13nN.00   | Reads Swahili                                        | Black                    | Black African             |
| 13nP.00   | Reads Yoruba                                         | Black                    | Black African             |
| 13na.00   | Reads Amharic                                        | Black                    | Black African             |
| 13nb.00   | Reads Lingala                                        | Black                    | Black African             |
| 13nc.00   | Reads Pashto                                         | Asian                    | Pakistani                 |
| 13ne.00   | Reads Sinhala                                        | Asian                    | Other Asian               |
| 13nf.00   | Reads Tigrinya                                       | Black                    | Black African             |
| 13nk.00   |                                                      | Black                    | Black Caribbean           |
| 13nI.00   |                                                      | Black                    | Black Caribbean           |
| 13no.00   | Reads Ndebele                                        | Black                    | Black African             |
| 13t0.00   | Born in Montserrat                                   | Black                    | Black Caribbean           |
| 13t1.00   | Born in Bermuda                                      | Black                    | Black Caribbean           |
| 13t2.00   | Born in Anguilla                                     | Black                    | Black Caribbean           |
| 13t3.00   | Born in British Virgin Islands                       | Black                    | Black Caribbean           |
| 13t4.00   |                                                      | Other                    | Other                     |
| 13t5.00   | Born in Saint Helena, Ascension and Tristan da Cunha | Black                    | Black African             |
| 13t6.00   |                                                      | Black                    | Black Caribbean           |
| 13u2.00   | Main spoken language Oromo                           | Black                    | Black African             |
| 13u4.00   | Main spoken language Afar                            | Black                    | Black African             |
| 13u6.00   | Main spoken language Armenian                        | Other                    | Other                     |
| 13u8.00   | Main spoken language Aymara                          | Other                    | Other                     |
| 13u9.00   | Main spoken language Azerbaijani                     | Other                    | Other                     |
| 13uA.00   | Main spoken language Bashkir                         | Other                    | Other                     |
| 13uB.00   | Main spoken language Basque                          | White                    | White                     |
| 13uE.00   | Main spoken language Bislama                         | Other                    | Other                     |
| 13uG.00   | Main spoken language Burmese                         | Other                    | Other                     |
| 13uJ.00   | Main spoken language Central Khmer                   | Other                    | Other                     |



| Read code | Description                                                  | Ethnicity (5 categories) | Ethnicity (10 categories) |
|-----------|--------------------------------------------------------------|--------------------------|---------------------------|
| 13uP.00   | Main spoken language Esperanto                               | Other                    | Other                     |
| 13uS.00   | Main spoken language Fijian                                  | Other                    | Other                     |
| 13uW.00   | Main spoken language Galician                                | White                    | White                     |
| 13uY.00   | Main spoken language Kalaallisut                             | Other                    | Other                     |
| 13uc.00   | Main spoken language Indonesian                              | Other                    | Other                     |
| 13uf.00   |                                                              | Other                    | Other                     |
| 13ug.00   | Main spoken language Inuktitut                               | Other                    | Other                     |
| 13ui.00   | Main spoken language Javanese                                | Other                    | Other                     |
| 13ul.00   | Main spoken language Kazakh                                  | Other                    | Other                     |
| 13um.00   | Main spoken language Kinyarwanda                             | Black                    | Black African             |
| 13un.00   |                                                              | Other                    | Other                     |
| 13up.00   | Main spoken language Lao                                     | Other                    | Other                     |
| 13uq.00   | Main spoken language Bamun                                   | Other                    | Other                     |
| 13uq.11   | Main spoken language Bamoun                                  | Black                    | Black African             |
| 13ut.00   | Main spoken language Malagasy                                | Black                    | Black African             |
| 13uu.00   | Main spoken language Malay                                   | Other                    | Other                     |
| 13uv.00   | Main spoken language Maltese                                 | Other                    | Other                     |
| 13uw.00   | Main spoken language Maori                                   | Other                    | Other                     |
| 13uz.00   | Main spoken language Mongolian                               | Other                    | Other                     |
| 13v0.00   | Born in Martinique                                           | Black                    | Black Caribbean           |
| 13v1.00   |                                                              | Black                    | Black Caribbean           |
| 13v2.00   |                                                              | Black                    | Black Caribbean           |
| 13v4.00   |                                                              | Other                    | Other                     |
| 13v5.00   |                                                              | Other                    | Other                     |
| 13w1.00   | Main spoken language Nepali                                  | Asian                    | Other Asian               |
| 13w4.00   | Main spoken language Filipino                                | Other                    | Other                     |
| 13w5.00   | Main spoken language Quechua                                 | Other                    | Other                     |
| 13w6.00   | Main spoken language Romansh                                 | White                    | White                     |
| 13w7.00   | Main spoken language Samoan                                  | Other                    | Other                     |
| 13w8.00   | Main spoken language Sango                                   | Other                    | Other                     |
| 13wA.00   | Main spoken language Dari                                    | Other                    | Other                     |
| 13wB.00   | Main spoken language Southern Sotho                          | Black                    | Black African             |
| 13wC.00   | Main spoken language Tswana                                  | Black                    | Black African             |
| 13wH.00   | Main spoken language Sundanese                               | Black                    | Black African             |
| 13wJ.00   | Main spoken language Tajik                                   | Other                    | Other                     |
| 13wK.00   | Main spoken language Tatar                                   | Other                    | Other                     |
| 13wN.00   | Main spoken language Tongan                                  | Other                    | Other                     |
| 13wP.00   | Main spoken language Tsonga                                  | Black                    | Black African             |
| 13wQ.00   | Main spoken language Turkmen                                 | Other                    | Other                     |
| 13wR.00   | Main spoken language Twi                                     | Black                    | Black African             |
| 13wS.00   | Main spoken language Uighur                                  | Other                    | Other                     |
| 13wT.00   | Main spoken language Uzbek                                   | Other                    | Other                     |
| 13wV.00   | Main spoken language Tetum                                   | Other                    | Other                     |
| 13wZ.00   | Main spoken language Zhuang                                  | Chinese                  | Chinese                   |
| 13wa.00   | Main spoken language Zulu                                    | Black                    | Black African             |
| 13zZ.00   |                                                              | Asian                    | Indian                    |
| 13za.00   |                                                              | Asian                    | Indian                    |
| 13zb.00   |                                                              | Asian                    | Indian                    |
| 13zc.00   |                                                              | Asian                    | Indian                    |
| 13zd.00   |                                                              | Asian                    | Indian                    |
| 13ze.00   | Smarta Hindu                                                 | Asian                    | Indian                    |
| 13zf.00   | Advaitin Hindu                                               | Asian                    | Indian                    |
| 13zg.00   | Arya Samaj Hindu                                             | Asian                    | Indian                    |
| 1X0..00   | Sick Cell Thalaz Scr Prog fam orig African or African-Carib  | Black                    | Black African             |
| 1X00.00   | NHS Sick Cell Thal Scr Prog Caribbean Islands family origin  | Black                    | Black Caribbean           |
| 1X01.00   | NHS Sick Cell Thalassaemia Screen Prog African family origin | Black                    | Black African             |
| 1X1..00   | Sick Cell Thalaz Scr Prog fam orig South Asia (Asian)        | Asian                    | Other Asian               |

| Read code | Description                                                  | Ethnicity (5 categories) | Ethnicity (10 categories) |
|-----------|--------------------------------------------------------------|--------------------------|---------------------------|
| 1X10.00   |                                                              | Asian                    | Indian                    |
| 1X11.00   |                                                              | Asian                    | Indian                    |
| 1X12.00   | NHS Sickle Cell Thal Screening Prog Bangladesh family origin | Asian                    | Bangladeshi               |
| 1X2..00   | NHS Sick Cell Thal Scr Prog fam orig South East Asia (Asian) | Asian                    | Other Asian               |
| 1X20.00   |                                                              | Other                    | Other                     |
| 1X21.00   | N Sic Cell Th Scr P Thailand, Indonesia, Burma family origin | Other                    | Other                     |
| 1X22.00   | NSCTSP Malaysia, Vietnam, Philippin, Cambodia, Laos fam orig | Other                    | Other                     |
| 1X3..00   | NHS Sickle Cell Thal Scr Prog fam origin other non-European  | Other                    | Other                     |
| 1X30.00   | NHS Sickle Cell Thalass Scr Prog North Africa family origin  | Other                    | Other                     |
| 1X31.00   | NHS Sickle Cell Thal Scr Program South America family origin | Other                    | Other                     |
| 1X32.00   |                                                              | Other                    | Other                     |
| 1X4..00   | NHS Sic Cel Th Scr Prog fam orig Southern and other European | White                    | White                     |
| 1X40.00   |                                                              | White                    | White                     |
| 1X41.00   | NSCTSP Greece, Turkey, Cyprus family origin                  | White                    | White                     |
| 1X42.00   | NSCTSP Italy, Portugal, Spain family origin                  | White                    | White                     |
| 1X5..00   | NHS Sick Cel Thal Scr Prog fam origin United Kingdom (White) | White                    | White                     |
| 1X6..00   | NHS Sic Cel Thal Scr Prog fam orig Northern European (White) | White                    | White                     |
| 1X60.00   | NSCTSP Austr, Belg, Ire, Fr, Germ, Netherland family origin  | White                    | White                     |
| 1X61.00   | NSCTSP Scandinavia, Switzerland family origin                | White                    | White                     |
| 2261.00   | O/E - Europeanoid                                            | White                    | White                     |
| 2262.00   | O/E - Negroid                                                | Black                    | Black African             |
| 2263.00   | O/E - Mongoloid origin                                       | Other                    | Other                     |
| 9S1..00   | White                                                        | White                    | White                     |
| 9S10.00   | White British                                                | White                    | White                     |
| 9S11.00   | White Irish                                                  | White                    | White                     |
| 9S12.00   | Other White ethnic group                                     | White                    | White                     |
| 9S13.00   | White Scottish                                               | White                    | White                     |
| 9S14.00   | Other White British ethnic group                             | White                    | White                     |
| 9S2..00   | Black Caribbean                                              | Black                    | Black Caribbean           |
| 9S3..00   | Black African                                                | Black                    | Black African             |
| 9S4..00   | Black; other; non-mixed origin                               | Black                    | Black African             |
| 9S41.00   | Black British                                                | Black                    | Black African             |
| 9S42.00   | Black Caribbean/W.I./Guyana                                  | Black                    | Black Caribbean           |
| 9S42.11   | Black Caribbean                                              | Black                    | Black Caribbean           |
| 9S42.12   | Black West Indian                                            | Black                    | Black Caribbean           |
| 9S42.13   | Black Guyana                                                 | Black                    | Black Caribbean           |
| 9S43.00   | Black N African/Arab/Iranian                                 | Other                    | Other                     |
| 9S43.11   | Black North African                                          | Other                    | Other                     |
| 9S43.12   | Black Arab                                                   | Other                    | Other                     |
| 9S43.13   | Black Iranian                                                | Other                    | Other                     |
| 9S44.00   | Black - other African country                                | Black                    | Black African             |
| 9S45.00   | Black E Afric Asia/Indo-Caribb                               | Asian                    | Other Asian               |
| 9S45.11   | Black East African Asian                                     | Asian                    | Other Asian               |
| 9S45.12   | Black Indo-Caribbean                                         | Asian                    | Other Asian               |
| 9S46.00   | Black Indian sub-continent                                   | Asian                    | Other Asian               |
| 9S47.00   | Black - other Asian                                          | Asian                    | Other Asian               |
| 9S48.00   | Black Black - other                                          | Black                    | Black African             |
| 9S5..00   | Black - other, mixed                                         | Black                    | Black African             |
| 9S51.00   | Other Black - Black/White orig                               | mixed                    | Other                     |
| 9S52.00   | Other Black - Black/Asian orig                               | mixed                    | Other                     |
| 9S6..00   | Indian                                                       | Asian                    | Indian                    |
| 9S7..00   | Pakistani                                                    | Asian                    | Pakistani                 |
| 9S8..00   | Bangladeshi                                                  | Asian                    | Bangladeshi               |
| 9S9..00   | Chinese                                                      | Chinese                  | Chinese                   |
| 9SA..00   | Other ethnic non-mixed (NMO)                                 | Other                    | Other                     |
| 9SA1.00   | Brit. ethnic minor. spec.(NMO)                               | Other                    | Other                     |
| 9SA2.00   | Brit. ethnic minor. unsp (NMO)                               | Other                    | Other                     |

| <b>Read code</b> | <b>Description</b>             | <b>Ethnicity (5 categories)</b> | <b>Ethnicity (10 categories)</b> |
|------------------|--------------------------------|---------------------------------|----------------------------------|
| 9SA3.00          | Caribbean I./W.I./Guyana (NMO) | Black                           | Black Caribbean                  |
| 9SA3.11          | Caribbean Island (NMO)         | Black                           | Black Caribbean                  |
| 9SA3.12          | West Indian (NMO)              | Black                           | Black Caribbean                  |
| 9SA3.13          | Guyana (NMO)                   | Black                           | Black Caribbean                  |
| 9SA4.00          | N African Arab/Iranian (NMO)   | Other                           | Other                            |
| 9SA4.11          | North African Arab (NMO)       | Other                           | Other                            |
| 9SA4.12          | Iranian (NMO)                  | Other                           | Other                            |
| 9SA5.00          | Other African countries (NMO)  | Black                           | Black African                    |
| 9SA6.00          | E Afric Asian/Indo-Carib (NMO) | Asian                           | Other Asian                      |
| 9SA6.11          | East African Asian (NMO)       | Asian                           | Other Asian                      |
| 9SA6.12          | Indo-Caribbean (NMO)           | Asian                           | Other Asian                      |
| 9SA7.00          | Indian sub-continent (NMO)     | Asian                           | Other Asian                      |
| 9SA8.00          | Other Asian (NMO)              | Asian                           | Other Asian                      |
| 9SA9.00          | Irish (NMO)                    | White                           | White                            |
| 9SAA.00          | Greek/Greek Cypriot (NMO)      | White                           | White                            |
| 9SAA.11          | Greek (NMO)                    | White                           | White                            |
| 9SAA.12          | Greek Cypriot (NMO)            | White                           | White                            |
| 9SAB.00          | Turkish/Turkish Cypriot (NMO)  | White                           | White                            |
| 9SAB.11          | Turkish (NMO)                  | White                           | White                            |
| 9SAB.12          | Turkish Cypriot (NMO)          | White                           | White                            |
| 9SAC.00          | Other European (NMO)           | White                           | White                            |
| 9SAD.00          | Other ethnic NEC (NMO)         | Other                           | Other                            |
| 9SB..00          | Other ethnic; mixed origin     | mixed                           | Other                            |
| 9SB1.00          | Other ethnic, Black/White orig | mixed                           | Other                            |
| 9SB2.00          | Other ethnic; Asian/White orig | mixed                           | Other                            |
| 9SB3.00          | Other ethnic, mixed White orig | White                           | White                            |
| 9SB4.00          | Other ethnic; other mixed orig | mixed                           | Other                            |
| 9SB5.00          | Black Caribbean and White      | mixed                           | Other                            |
| 9SB6.00          | Black African and White        | mixed                           | Other                            |
| 9SC..00          | Vietnamese                     | Other                           | Other                            |
| 9SG..00          | Other Black ethnic group       | Black                           | Black African                    |
| 9SH..00          | Other Asian ethnic group       | Asian                           | Other Asian                      |
| 9SI..00          | Irish traveller                | White                           | White                            |
| 9SJ..00          | Other ethnic group             | Other                           | Other                            |
| 9T1..00          | New Zealand ethnic groups      | Other                           | Other                            |
| 9T11.00          | New Zealand European           | White                           | White                            |
| 9T11.11          | Pakeha                         | White                           | White                            |
| 9T12.00          | Other European in New Zealand  | White                           | White                            |
| 9T13.00          | New Zealand Maori              | Other                           | Other                            |
| 9T14.00          | Samoan                         | Other                           | Other                            |
| 9T15.00          | Cook Island Maori              | Other                           | Other                            |
| 9T16.00          | Tongan                         | Other                           | Other                            |
| 9T17.00          |                                | Other                           | Other                            |
| 9T18.00          | Tokelauan                      | Other                           | Other                            |
| 9T19.00          | Fijian                         | Other                           | Other                            |
| 9T1A.00          | Other Pacific ethnic group     | Other                           | Other                            |
| 9T1B.00          | South East Asian               | Asian                           | Other Asian                      |
| 9T1C.00          | Chinese                        | Chinese                         | Chinese                          |
| 9T1D.00          | Indian                         | Asian                           | Indian                           |
| 9T1E.00          | Other Asian                    | Asian                           | Other Asian                      |
| 9T1Y.00          | Other New Zealand ethnic group | Other                           | Other                            |
| 9T1Z.00          | New Zealand ethnic group NOS   | Other                           | Other                            |
| 9T2..00          | Traveller - gypsy              | White                           | White                            |
| 9T3..00          | Yemeni                         | Other                           | Other                            |
| 9T4..00          | Romanian                       | White                           | White                            |
| 9T5..00          | Bulgarian                      | White                           | White                            |
| 9T6..00          | Czech                          | White                           | White                            |

| Read code | Description                                                  | Ethnicity (5 categories) | Ethnicity (10 categories) |
|-----------|--------------------------------------------------------------|--------------------------|---------------------------|
| 9T7..00   | Slovak                                                       | White                    | White                     |
| 9T8..00   | Portuguese                                                   | White                    | White                     |
| 9T9..00   | Nepali                                                       | Asian                    | Other Asian               |
| 9TC..00   | Roma ethnic group                                            | White                    | White                     |
| 9TC0.00   | Bulgarian Roma                                               | White                    | White                     |
| 9TC1.00   | Czech Roma                                                   | White                    | White                     |
| 9TC2.00   | Polish Roma                                                  | White                    | White                     |
| 9TC3.00   | Romanian Roma                                                | White                    | White                     |
| 9TC4.00   | Slovak Roma                                                  | White                    | White                     |
| 9TC5.00   | Hungarian Roma                                               | White                    | White                     |
| 9i0..00   | British or mixed British - ethnic category 2001 census       | White                    | White                     |
| 9i00.00   | White British - ethnic category 2001 census                  | White                    | White                     |
| 9i1..00   | Irish - ethnic category 2001 census                          | White                    | White                     |
| 9i10.00   | White Irish - ethnic category 2001 census                    | White                    | White                     |
| 9i2..00   | Other White background - ethnic category 2001 census         | White                    | White                     |
| 9i20.00   | English - ethnic category 2001 census                        | White                    | White                     |
| 9i21.00   | Scottish - ethnic category 2001 census                       | White                    | White                     |
| 9i22.00   | Welsh - ethnic category 2001 census                          | White                    | White                     |
| 9i23.00   | Cornish - ethnic category 2001 census                        | White                    | White                     |
| 9i24.00   | Northern Irish - ethnic category 2001 census                 | White                    | White                     |
| 9i25.00   | Ulster Scots - ethnic category 2001 census                   | White                    | White                     |
| 9i26.00   | Cypriot (part not stated) - ethnic category 2001 census      | White                    | White                     |
| 9i27.00   | Greek - ethnic category 2001 census                          | White                    | White                     |
| 9i28.00   | Greek Cypriot - ethnic category 2001 census                  | White                    | White                     |
| 9i29.00   | Turkish - ethnic category 2001 census                        | White                    | White                     |
| 9i2A.00   | Turkish Cypriot - ethnic category 2001 census                | White                    | White                     |
| 9i2B.00   | Italian - ethnic category 2001 census                        | White                    | White                     |
| 9i2C.00   | Irish Traveller - ethnic category 2001 census                | White                    | White                     |
| 9i2D.00   | Traveller - ethnic category 2001 census                      | White                    | White                     |
| 9i2E.00   | Gypsy/Romany - ethnic category 2001 census                   | White                    | White                     |
| 9i2F.00   | Polish - ethnic category 2001 census                         | White                    | White                     |
| 9i2G.00   | Baltic Estonian/Latvian/Lithuanian - ethn categ 2001 census  | White                    | White                     |
| 9i2H.00   | Commonwealth (Russian) Indep States - ethn categ 2001 census | White                    | White                     |
| 9i2J.00   | Kosovan - ethnic category 2001 census                        | White                    | White                     |
| 9i2K.00   | Albanian - ethnic category 2001 census                       | White                    | White                     |
| 9i2L.00   | Bosnian - ethnic category 2001 census                        | White                    | White                     |
| 9i2M.00   | Croatian - ethnic category 2001 census                       | White                    | White                     |
| 9i2N.00   | Serbian - ethnic category 2001 census                        | White                    | White                     |
| 9i2P.00   | Other republics former Yugoslavia - ethnic categ 2001 census | White                    | White                     |
| 9i2Q.00   | Mixed Irish and other White - ethnic category 2001 census    | White                    | White                     |
| 9i2R.00   | Oth White European/European unsp/Mixed European 2001 census  | White                    | White                     |
| 9i2S.00   | Other mixed White - ethnic category 2001 census              | White                    | White                     |
| 9i2T.00   | Other White or White unspecified ethnic category 2001 census | White                    | White                     |
| 9i3..00   | White and Black Caribbean - ethnic category 2001 census      | mixed                    | Other                     |
| 9i4..00   | White and Black African - ethnic category 2001 census        | mixed                    | Other                     |
| 9i5..00   | White and Asian - ethnic category 2001 census                | mixed                    | Other                     |
| 9i6..00   | Other Mixed background - ethnic category 2001 census         | mixed                    | Other                     |
| 9i60.00   | Black and Asian - ethnic category 2001 census                | mixed                    | Other                     |
| 9i61.00   | Black and Chinese - ethnic category 2001 census              | mixed                    | Other                     |
| 9i62.00   | Black and White - ethnic category 2001 census                | mixed                    | Other                     |
| 9i63.00   | Chinese and White - ethnic category 2001 census              | mixed                    | Other                     |
| 9i64.00   | Asian and Chinese - ethnic category 2001 census              | mixed                    | Other                     |
| 9i65.00   | Other Mixed or Mixed unspecified ethnic category 2001 census | mixed                    | Other                     |
| 9i7..00   | Indian or British Indian - ethnic category 2001 census       | Asian                    | Indian                    |
| 9i8..00   | Pakistani or British Pakistani - ethnic category 2001 census | Asian                    | Pakistani                 |
| 9i9..00   | Bangladeshi or British Bangladeshi - ethn categ 2001 census  | Asian                    | Bangladeshi               |
| 9iA..00   | Other Asian background - ethnic category 2001 census         | Asian                    | Other Asian               |

| Read code | Description                                                  | Ethnicity (5 categories) | Ethnicity (10 categories) |
|-----------|--------------------------------------------------------------|--------------------------|---------------------------|
| 9iA1.00   | Punjabi - ethnic category 2001 census                        | Asian                    | Indian                    |
| 9iA2.00   | Kashmiri - ethnic category 2001 census                       | Asian                    | Pakistani                 |
| 9iA3.00   | East African Asian - ethnic category 2001 census             | Asian                    | Other Asian               |
| 9iA4.00   | Sri Lankan - ethnic category 2001 census                     | Asian                    | Other Asian               |
| 9iA5.00   | Tamil - ethnic category 2001 census                          | Asian                    | Indian                    |
| 9iA6.00   | Sinhalese - ethnic category 2001 census                      | Asian                    | Other Asian               |
| 9iA7.00   | Caribbean Asian - ethnic category 2001 census                | Asian                    | Other Asian               |
| 9iA8.00   | British Asian - ethnic category 2001 census                  | Asian                    | Indian                    |
| 9iA9.00   | Mixed Asian - ethnic category 2001 census                    | Asian                    | Other Asian               |
| 9iAA.00   | Other Asian or Asian unspecified ethnic category 2001 census | Asian                    | Other Asian               |
| 9iB..00   | Caribbean - ethnic category 2001 census                      | Black                    | Black Caribbean           |
| 9iC..00   | African - ethnic category 2001 census                        | Black                    | Black African             |
| 9iD..00   | Other Black background - ethnic category 2001 census         | Black                    | Black African             |
| 9iD0.00   | Somali - ethnic category 2001 census                         | Black                    | Black African             |
| 9iD1.00   | Nigerian - ethnic category 2001 census                       | Black                    | Black African             |
| 9iD2.00   | Black British - ethnic category 2001 census                  | Black                    | Black African             |
| 9iD3.00   | Mixed Black - ethnic category 2001 census                    | Black                    | Black African             |
| 9iD4.00   | Other Black or Black unspecified ethnic category 2001 census | Black                    | Black African             |
| 9iE..00   | Chinese - ethnic category 2001 census                        | Chinese                  | Chinese                   |
| 9iF..00   | Other - ethnic category 2001 census                          | Other                    | Other                     |
| 9iF0.00   | Vietnamese - ethnic category 2001 census                     | Other                    | Other                     |
| 9iF1.00   | Japanese - ethnic category 2001 census                       | Other                    | Other                     |
| 9iF2.00   | Filipino - ethnic category 2001 census                       | Other                    | Other                     |
| 9iF3.00   | Malaysian - ethnic category 2001 census                      | Other                    | Other                     |
| 9iF4.00   | Buddhist - ethnic category 2001 census                       | Other                    | Other                     |
| 9iF5.00   | Hindu - ethnic category 2001 census                          | Asian                    | Indian                    |
| 9iF8.00   | Sikh - ethnic category 2001 census                           | Asian                    | Indian                    |
| 9iF9.00   | Arab - ethnic category 2001 census                           | Other                    | Other                     |
| 9iFA.00   | North African - ethnic category 2001 census                  | Other                    | Other                     |
| 9iFB.00   | Mid East (excl Israeli; Iranian & Arab) - eth cat 2001 cens  | Other                    | Other                     |
| 9iFC.00   | Israeli - ethnic category 2001 census                        | Other                    | Other                     |
| 9iFD.00   | Iranian - ethnic category 2001 census                        | Other                    | Other                     |
| 9iFE.00   | Kurdish - ethnic category 2001 census                        | Other                    | Other                     |
| 9iFF.00   | Moroccan - ethnic category 2001 census                       | Other                    | Other                     |
| 9iFG.00   | Latin American - ethnic category 2001 census                 | Other                    | Other                     |
| 9iFH.00   | South and Central American - ethnic category 2001 census     | Other                    | Other                     |
| 9iFJ.00   | Mauritian/Seychellois/Maldivian/St Helena eth cat 2001census | Asian                    | Other Asian               |
| 9iFK.00   | Any other group - ethnic category 2001 census                | Other                    | Other                     |
| 9t00.00   | White:Eng/Welsh/Scot/Nl/Brit - England and Wales 2011 census | White                    | White                     |
| 9t01.00   | White: Irish - England and Wales ethnic category 2011 census | White                    | White                     |
| 9t02.00   | White: Gypsy/Irish Traveller - Eng+Wales eth cat 2011 census | White                    | White                     |
| 9t03.00   | White: other White backgrd- Eng+Wales ethnic cat 2011 census | White                    | White                     |
| 9t04.00   | Mixed: White+Black Caribbean - Eng+Wales eth cat 2011 census | mixed                    | Other                     |
| 9t05.00   | Mixed: White+Black African - Eng+Wales eth cat 2011 census   | mixed                    | Other                     |
| 9t06.00   | Mixed: White+Asian - Eng+Wales ethnic category 2011 census   | mixed                    | Other                     |
| 9t07.00   | Mixed: other Mixed/multiple backgrd - Eng+Wales 2011 census  | mixed                    | Other                     |
| 9t08.00   | Asian/Asian Brit: Indian - Eng+Wales ethnic cat 2011 census  | Asian                    | Indian                    |
| 9t09.00   | Asian/Asian British:Pakistani- Eng+Wales eth cat 2011 census | Asian                    | Pakistani                 |
| 9t0A.00   | Asian/Asian Brit: Bangladeshi- Eng+Wales eth cat 2011 census | Asian                    | Bangladeshi               |
| 9t0B.00   | Asian/Asian Brit: Chinese - Eng+Wales ethnic cat 2011 census | Chinese                  | Chinese                   |
| 9t0C.00   | Asian/Asian Brit: other Asian- Eng+Wales eth cat 2011 census | Asian                    | Other Asian               |
| 9t0D.00   | Black/African/Carib/Black Brit: African- Eng+Wales 2011 cens | Black                    | Black African             |
| 9t0E.00   | Black/African/Caribbn/Black Brit: Caribbean - Eng+Wales 2011 | Black                    | Black Caribbean           |
| 9t0F.00   | Black/Afr/Carib/Black Brit: other Black- Eng+Wales 2011 cens | Black                    | Black African             |
| 9t0G.00   | Other ethnic group: Arab - Eng+Wales ethnic cat 2011 census  | Other                    | Other                     |
| 9t0H.00   | Other ethnic: any other grp - Eng+Wales eth cat 2011 census  | Other                    | Other                     |
| 9t10.00   | White - Northern Ireland ethnic category 2011 census         | White                    | White                     |

| <b>Read<br/>code</b> | <b>Description</b>                                           | <b>Ethnicity<br/>(5<br/>categories)</b> | <b>Ethnicity (10<br/>categories)</b> |
|----------------------|--------------------------------------------------------------|-----------------------------------------|--------------------------------------|
| 9t11.00              |                                                              | White                                   | White                                |
| 9t12.00              | Mixed: White and Black Caribbean - NI ethnic cat 2011 census | mixed                                   | Other                                |
| 9t13.00              | Mixed: White and Black African - NI ethnic cat 2011 census   | mixed                                   | Other                                |
| 9t14.00              | Mixed: White and Asian - NI ethnic category 2011 census      | mixed                                   | Other                                |
| 9t15.00              | Mixed: other Mixed/multiple ethnic backgrd - NI 2011 census  | mixed                                   | Other                                |
| 9t16.00              | Asian or Asian British: Indian - NI ethnic cat 2011 census   | Asian                                   | Indian                               |
| 9t17.00              | Asian/Asian British: Pakistani - NI ethnic cat 2011 census   | Asian                                   | Pakistani                            |
| 9t18.00              | Asian/Asian British: Bangladeshi - NI ethnic cat 2011 census | Asian                                   | Bangladeshi                          |
| 9t19.00              | Asian/Asian British: Chinese - NI ethnic cat 2011 census     | Chinese                                 | Chinese                              |
| 9t1A.00              | Asian/Asian British: other Asian - NI ethnic cat 2011 census | Asian                                   | Other Asian                          |
| 9t1B.00              | Black/Afri/Carib/Black Brit: African- NI eth cat 2011 census | Black                                   | Black African                        |
| 9t1C.00              | Black/Afri/Carib/Black Brit: Caribbean- NI eth cat 2011 cens | Black                                   | Black Caribbean                      |
| 9t1D.00              | Black/Afri/Carib/Black Brit: other - NI eth cat 2011 census  | Black                                   | Black African                        |
| 9t1E.00              | Other ethnic group: Arab - NI ethnic category 2011 census    | Other                                   | Other                                |
| 9t1F.00              | Other ethnic group: any other grp- NI ethnic cat 2011 census | Other                                   | Other                                |
| 9t20.00              | White: Scottish - Scotland ethnic category 2011 census       | White                                   | White                                |
| 9t21.00              | White: other British - Scotland ethnic category 2011 census  | White                                   | White                                |
| 9t22.00              | White: Irish - Scotland ethnic category 2011 census          | White                                   | White                                |
| 9t23.00              | White: Gypsy/Irish Traveller - Scotland ethnic cat 2011 cens | White                                   | White                                |
| 9t24.00              | White: Polish - Scotland ethnic category 2011 census         | White                                   | White                                |
| 9t25.00              | White: other White ethnic grp- Scotland ethnic cat 2011 cens | White                                   | White                                |
| 9t26.00              | Mixed/multiple ethnic grps: any- Scot ethnic cat 2011 census | mixed                                   | Other                                |
| 9t27.00              | Asian: Pakistani/Pakistani Scot/Pakistani Brit- Scot 2011    | Asian                                   | Pakistani                            |
| 9t28.00              | Asian: Indian, Indian Scot/Indian Brit- Scotland 2011 census | Asian                                   | Indian                               |
| 9t29.00              | Bangladeshi, Bangladeshi Scot or Bangladeshi Brit- Scot 2011 | Asian                                   | Bangladeshi                          |
| 9t2A.00              | Asian: Chinese - Scotland ethnic category 2011 census        | Chinese                                 | Chinese                              |
| 9t2B.00              | Asian: other Asian group - Scotland ethnic cat 2011 census   | Asian                                   | Other Asian                          |
| 9t2C.00              | African: African/African Scot/African Brit - Scotland 2011   | Black                                   | Black African                        |
| 9t2D.00              | African: any other African - Scotland ethnic cat 2011 census | Black                                   | Black African                        |
| 9t2E.00              | Carib/Black: Caribbean/Carib Scot/Carib Brit- Scotland 2011  | Black                                   | Black Caribbean                      |
| 9t2F.00              |                                                              | Black                                   | Black Caribbean                      |
| 9t2G.00              | Carib/Black: any other Black/Caribbean grp - Scotland 2011   | Black                                   | Black Caribbean                      |
| 9t2H.00              |                                                              | Other                                   | Other                                |
| 9t2J.00              | Other ethnic grp: any other ethnic grp- Scotland 2011 census | Other                                   | Other                                |

## APPENDIX XXIV GROUPS OF READ CODES POTENTIALLY IDENTIFYING SEVERE MENTAL ILLNESS

Source: NHS Clinical Terminology Browser (Version 2, 2016-04-01)

| Read codes                              | Description                    |
|-----------------------------------------|--------------------------------|
| 146%                                    | H-O psychiatric disorder       |
| 1B%                                     | Nervous system symptoms        |
| 1S4%                                    | Mood observations              |
| 2126J, 212S%, 212T% 212V%, 212W%, 212X% | Mental_dis_resolved            |
| 28%                                     | Nerv sys and mental state exam |
| 8HHs%                                   | Ref to early int psych         |
| 9H%                                     | MH admin                       |
| E0%                                     | Organic psychotic disorders    |
| E1%                                     | Non-organic psychoses          |
| E10%                                    | Schizophrenic disorders        |
| E11%                                    | Affective psychoses            |
| E12%                                    | Paranoid states                |
| E13%                                    | Oth nonorganic psychoses       |
| E1y%                                    | Oth spec non-org psychoses     |
| E1z%                                    | Non-org psychosis NOS          |
| E21%                                    | Personality disorders          |
| E29%                                    | Adjustment reaction            |
| E2B%                                    | Depressive disorder NEC        |
| Eu%                                     | X Mental and behavioural dis   |
| ZV11%                                   | Personal history of mental dis |

## APPENDIX XXV READ CODES FOR SEVERE MENTAL ILLNESS CATEGORIES NOT USED IN THE FINAL ANALYSIS

**Appendix table XXV.1: Read codes for other SMI**

| Read code | Description                                                  | Incident or prevalent |
|-----------|--------------------------------------------------------------|-----------------------|
| 9H6..00   | On national service framework mental health register         | incident              |
| 9H8..00   | On severe mental illness register                            | incident              |
| 212T.00   | Psychosis, schizophrenia + bipolar affective disord resolved | prevalent             |
| 9H9..00   | Mental health annual physical examination done               | prevalent             |
| 9h9..00   | Exception reporting: mental health quality indicators        | prevalent             |
| 9h91.00   | Except from mental health quality indicators: Patient unsuit | prevalent             |
| 9h92.00   | Except from mental health quality indicators: Informed diss  | prevalent             |

**Appendix table XXV.2: Drug code list for schizophrenia-specific antipsychotic medications**

| Drug code | Generic name                                                             |
|-----------|--------------------------------------------------------------------------|
| 96360979  | Amisulpride 200mg tablets                                                |
| 94544990  | Amisulpride 200mg tablets                                                |
| 94546990  | Amisulpride 50mg tablets                                                 |
| 64989979  | Amisulpride 12.5mg/5ml oral suspension                                   |
| 94844990  | Amisulpride 200mg tablets                                                |
| 94846990  | Amisulpride 50mg tablets                                                 |
| 81131998  | Amisulpride 25mg/5ml oral solution                                       |
| 90209998  | Amisulpride 100mg/ml oral solution sugar free                            |
| 88383996  | Amisulpride 400mg tablets                                                |
| 88387998  | Amisulpride 50mg tablets                                                 |
| 91083998  | Amisulpride 100mg tablets                                                |
| 81029979  | Amisulpride 50mg/5ml oral suspension                                     |
| 94845990  | Amisulpride 100mg tablets                                                |
| 91077998  | Amisulpride 100mg tablets                                                |
| 94545990  | Amisulpride 100mg tablets                                                |
| 88383998  | Amisulpride 50mg tablets                                                 |
| 96363979  | Amisulpride 200mg tablets                                                |
| 88383997  | Amisulpride 200mg tablets                                                |
| 91785990  | Amisulpride 50mg tablets                                                 |
| 64991979  | Amisulpride 12.5mg/5ml oral solution                                     |
| 88387996  | Amisulpride 400mg tablets                                                |
| 86433998  | Amisulpride 25mg/5ml oral suspension                                     |
| 88387997  | Amisulpride 200mg tablets                                                |
| 91425998  | Amisulpride 100mg/ml oral solution sugar free                            |
| 39110978  | Aripiprazole 400mg powder and solvent for suspension for injection vials |
| 34055978  | Aripiprazole 7.5mg/ml oral solution                                      |
| 85836998  | Aripiprazole 15mg orodispersible tablets sugar free                      |
| 85833998  | Aripiprazole 15mg orodispersible tablets sugar free                      |
| 87451998  | Aripiprazole 30mg tablets                                                |
| 85834998  | Aripiprazole 10mg orodispersible tablets sugar free                      |
| 85835998  | Aripiprazole 1mg/ml oral solution                                        |
| 87449998  | Aripiprazole 15mg tablets                                                |
| 39109978  | Aripiprazole 400mg powder and solvent for suspension for injection vials |
| 89520979  | Aripiprazole 15mg tablets                                                |
| 89529979  | Aripiprazole 5mg tablets                                                 |



| Drug code | Generic name                                                             |
|-----------|--------------------------------------------------------------------------|
| 55056978  | Aripiprazole 30mg tablets                                                |
| 39301978  | Aripiprazole 5mg tablets                                                 |
| 87090998  | Aripiprazole 5mg tablets                                                 |
| 83903998  | Aripiprazole 9.75mg/1.3ml solution for injection vials                   |
| 85837998  | Aripiprazole 10mg orodispersible tablets sugar free                      |
| 87448998  | Aripiprazole 30mg tablets                                                |
| 85832998  | Aripiprazole 1mg/ml oral solution                                        |
| 87452998  | Aripiprazole 15mg tablets                                                |
| 89524979  | Aripiprazole 10mg tablets                                                |
| 78405978  | Aripiprazole 400mg powder and solvent for suspension for injection vials |
| 55724978  | Aripiprazole 15mg tablets                                                |
| 39298978  | Aripiprazole 30mg tablets                                                |
| 87453998  | Aripiprazole 10mg tablets                                                |
| 89532979  | Aripiprazole 5mg tablets                                                 |
| 87089998  | Aripiprazole 5mg tablets                                                 |
| 87450998  | Aripiprazole 10mg tablets                                                |
| 78406978  | Aripiprazole 400mg powder and solvent for suspension for injection vials |
| 82802998  | Clozapine 50mg tablets                                                   |
| 93595997  | Clozapine 100mg tablets                                                  |
| 87341998  | Clozapine 25mg tablets                                                   |
| 82801998  | Clozapine 200mg tablets                                                  |
| 87020998  | Clozapine 25mg tablets                                                   |
| 82803998  | Clozapine 50mg tablets                                                   |
| 82798998  | Clozapine 50mg/ml oral suspension sugar free                             |
| 87019998  | Clozapine 100mg tablets                                                  |
| 93596998  | Clozapine 25mg tablets                                                   |
| 93595998  | Clozapine 25mg tablets                                                   |
| 87340998  | Clozapine 100mg tablets                                                  |
| 82799998  | Clozapine 50mg/ml oral suspension sugar free                             |
| 82800998  | Clozapine 200mg tablets                                                  |
| 93596997  | Clozapine 100mg tablets                                                  |
| 97516998  | Flupentixol 200mg/1ml solution for injection ampoules                    |
| 94879998  | Flupentixol 40mg/2ml solution for injection ampoules                     |
| 98766997  | Flupentixol 40mg/2ml solution for injection ampoules                     |
| 85614998  | Flupentixol 20mg/1ml solution for injection ampoules                     |
| 86539998  | Flupentixol 20mg/1ml solution for injection ampoules                     |
| 86423998  | Flupentixol 50mg/0.5ml solution for injection ampoules                   |
| 96502997  | Flupentixol 200mg/1ml solution for injection ampoules                    |
| 85613998  | Flupentixol 20mg/1ml solution for injection ampoules                     |
| 99775998  | Flupentixol 50mg/0.5ml solution for injection ampoules                   |
| 86420998  | Flupentixol 100mg/1ml solution for injection ampoules                    |
| 86536998  | Flupentixol 100mg/1ml solution for injection ampoules                    |
| 96502998  | Flupentixol 20mg/1ml solution for injection ampoules                     |
| 86422998  | Flupentixol 100mg/1ml solution for injection ampoules                    |
| 86537998  | Flupentixol 50mg/0.5ml solution for injection ampoules                   |
| 96502996  | Flupentixol 200mg/1ml solution for injection ampoules                    |
| 86421998  | Flupentixol 50mg/0.5ml solution for injection ampoules                   |
| 98766998  | Flupentixol decanoate 20mg/1ml prefilled syringes                        |
| 96286990  | Fluphenazine decanoate 25mg/1ml solution for injection ampoules          |
| 85302998  | Fluphenazine decanoate 25mg/1ml solution for injection ampoules          |
| 85300998  | Fluphenazine decanoate 12.5mg/0.5ml oily injection                       |
| 85294998  | Fluphenazine decanoate 100mg/1ml solution for injection ampoules         |
| 98759998  | Fluphenazine decanoate 50mg/0.5ml oily injection                         |
| 96344979  | Fluphenazine decanoate 12.5mg/0.5ml solution for injection ampoules      |

| Drug code | Generic name                                                        |
|-----------|---------------------------------------------------------------------|
| 85297998  | Fluphenazine decanoate 50mg/0.5ml solution for injection ampoules   |
| 85303998  | Fluphenazine decanoate 12.5mg/0.5ml solution for injection ampoules |
| 96342992  | Fluphenazine decanoate 12.5mg/0.5ml oily injection                  |
| 96742990  | Fluphenazine decanoate 25mg/1ml solution for injection ampoules     |
| 85295998  | Fluphenazine decanoate 50mg/0.5ml oily injection                    |
| 98668990  | Fluphenazine decanoate 100mg/1ml solution for injection ampoules    |
| 85301998  | Fluphenazine decanoate 50mg/2ml solution for injection ampoules     |
| 85299998  | Fluphenazine decanoate 25mg/1ml solution for injection ampoules     |
| 96498997  | Fluphenazine decanoate 100mg/1ml solution for injection ampoules    |
| 99414998  | Fluphenazine decanoate 25mg/1ml prefilled syringes                  |
| 85298998  | Fluphenazine decanoate 50mg/2ml oily injection                      |
| 93092998  | Fluphenazine decanoate 25mg/1ml oily injection                      |
| 93032992  | Fluphenazine decanoate 12.5 mg inj                                  |
| 85296998  | Fluphenazine decanoate 100mg/1ml solution for injection ampoules    |
| 96498998  | Fluphenazine decanoate 25mg/ml injection                            |
| 99408998  | Fluphenazine enantate 25mg/1ml injection                            |
| 96500998  | Fluphenazine enanthate 25mg/ml injection                            |
| 96494998  | Fluspirilene 2mg/ml injection                                       |
| 99189998  | Fluspirilene 12mg/6ml injection                                     |
| 96245998  | Haloperidol decanoate 50mg/1ml solution for injection ampoules      |
| 96307992  | Haloperidol decanoate 100mg/1ml solution for injection ampoules     |
| 97344998  | Haloperidol decanoate 50mg/1ml solution for injection ampoules      |
| 96245997  | Haloperidol decanoate 100mg/1ml solution for injection ampoules     |
| 97344997  | Haloperidol decanoate 100mg/1ml solution for injection ampoules     |
| 87647998  | Olanzapine 10mg powder for solution for injection vials             |
| 96416979  | Olanzapine 2.5mg tablets                                            |
| 61166979  | Olanzapine 5mg orodispersible tablets                               |
| 61583979  | Olanzapine 15mg orodispersible tablets                              |
| 96421979  | Olanzapine 2.5mg tablets                                            |
| 61145979  | Olanzapine 20mg orodispersible tablets                              |
| 85377998  | Olanzapine 20mg tablets                                             |
| 97995998  | Olanzapine 15mg orodispersible tablets                              |
| 80981998  | Olanzapine 5mg orodispersible tablets                               |
| 91824990  | Olanzapine 20mg orodispersible tablets                              |
| 97433998  | Olanzapine 15mg tablets                                             |
| 89567997  | Olanzapine 7.5mg tablets                                            |
| 63461979  | Olanzapine 1.25mg/5ml oral suspension                               |
| 80973998  | Olanzapine 15mg orodispersible tablets                              |
| 96404979  | Olanzapine 10mg oral lyophilisates sugar free                       |
| 91618997  | Olanzapine 10mg oral lyophilisates sugar free                       |
| 80972998  | Olanzapine 15mg orodispersible tablets                              |
| 96450979  | Olanzapine 5mg tablets                                              |
| 90664998  | Olanzapine 2.5mg tablets                                            |
| 61579979  | Olanzapine 5mg orodispersible tablets                               |
| 89569997  | Olanzapine 7.5mg tablets                                            |
| 89569998  | Olanzapine 5mg tablets                                              |
| 80969998  | Olanzapine 20mg orodispersible tablets                              |
| 86325998  | Olanzapine 20mg orodispersible tablets                              |
| 80978998  | Olanzapine 10mg orodispersible tablets                              |
| 91364998  | Olanzapine 15mg oral lyophilisates sugar free                       |
| 91871990  | Olanzapine 7.5mg tablets                                            |
| 91866990  | Olanzapine 10mg orodispersible tablets                              |
| 91828990  | Olanzapine 20mg tablets                                             |
| 80971998  | Olanzapine 20mg orodispersible tablets                              |

| Drug code | Generic name                                                                                                             |
|-----------|--------------------------------------------------------------------------------------------------------------------------|
| 91869990  | Olanzapine 15mg tablets                                                                                                  |
| 89569996  | Olanzapine 10mg tablets                                                                                                  |
| 91864990  | Olanzapine 20mg orodispersible tablets                                                                                   |
| 64673979  | Olanzapine 2.5mg/5ml oral suspension                                                                                     |
| 80970998  | Olanzapine 20mg orodispersible tablets                                                                                   |
| 89567998  | Olanzapine 5mg tablets                                                                                                   |
| 80980998  | Olanzapine 5mg orodispersible tablets                                                                                    |
| 81040998  | Olanzapine 10mg orodispersible tablets sugar free                                                                        |
| 64675979  | Olanzapine 2.5mg/5ml oral solution                                                                                       |
| 80974998  | Olanzapine 15mg orodispersible tablets                                                                                   |
| 91825990  | Olanzapine 15mg orodispersible tablets                                                                                   |
| 61165979  | Olanzapine 10mg orodispersible tablets                                                                                   |
| 96427979  | Olanzapine 10mg tablets                                                                                                  |
| 80976998  | Olanzapine 10mg orodispersible tablets                                                                                   |
| 80979998  | Olanzapine 5mg orodispersible tablets                                                                                    |
| 91827990  | Olanzapine 5mg orodispersible tablets                                                                                    |
| 61602979  | Olanzapine 5mg orodispersible tablets                                                                                    |
| 60067979  | Olanzapine 15mg oral lyophilisates sugar free                                                                            |
| 91618998  | Olanzapine 5mg oral lyophilisates sugar free                                                                             |
| 89981979  | Olanzapine 15mg tablets                                                                                                  |
| 90659998  | Olanzapine 2.5mg tablets                                                                                                 |
| 90659997  | Olanzapine 5mg orodispersible tablets                                                                                    |
| 80977998  | Olanzapine 10mg orodispersible tablets                                                                                   |
| 89567996  | Olanzapine 10mg tablets                                                                                                  |
| 91870990  | Olanzapine 10mg tablets                                                                                                  |
| 61610979  | Olanzapine 15mg orodispersible tablets                                                                                   |
| 61131979  | Olanzapine 15mg orodispersible tablets                                                                                   |
| 97111998  | Olanzapine 15mg tablets                                                                                                  |
| 85376998  | Olanzapine 20mg oral lyophilisates sugar free                                                                            |
| 86324998  | Olanzapine 20mg oral lyophilisates sugar free                                                                            |
| 61605979  | Olanzapine 20mg orodispersible tablets sugar free                                                                        |
| 90190979  | Olanzapine 20mg tablets                                                                                                  |
| 90659996  | Olanzapine 10mg orodispersible tablets                                                                                   |
| 81043998  | Olanzapine 15mg tablets                                                                                                  |
| 61585979  | Olanzapine 10mg orodispersible tablets                                                                                   |
| 81041998  | Olanzapine 5mg orodispersible tablets sugar free                                                                         |
| 91867990  | Olanzapine 5mg orodispersible tablets                                                                                    |
| 61581979  | Olanzapine 20mg orodispersible tablets                                                                                   |
| 82199998  | Olanzapine embonate 300mg powder and solvent for suspension for injection vials                                          |
| 82198998  | Olanzapine embonate 405mg powder and solvent for suspension for injection vials                                          |
| 82202998  | Olanzapine embonate 210mg powder and solvent for suspension for injection vials                                          |
| 82201998  | Olanzapine embonate 300mg powder and solvent for suspension for injection vials                                          |
| 82200998  | Olanzapine embonate 405mg powder and solvent for suspension for injection vials                                          |
| 54953979  | Paliperidone 150mg/1.5ml suspension for injection pre-filled syringes and paliperidone 100mg/1ml suspension for injectio |
| 81423998  | Paliperidone 100mg/1ml suspension for injection pre-filled syringes                                                      |
| 30144978  | Paliperidone 525mg/2.625ml prolonged-release suspension for injection pre-filled syringes                                |
| 81422998  | Paliperidone 150mg/1.5ml suspension for injection pre-filled syringes                                                    |
| 81420998  | Paliperidone 75mg/0.75ml suspension for injection pre-filled syringes                                                    |
| 81418998  | Paliperidone 150mg/1.5ml suspension for injection pre-filled syringes                                                    |
| 30145978  | Paliperidone 525mg/2.625ml prolonged-release suspension for injection pre-filled syringes                                |
| 30151978  | Paliperidone 175mg/0.875ml prolonged-release suspension for injection pre-filled syringes                                |
| 81424998  | Paliperidone 75mg/0.75ml suspension for injection pre-filled syringes                                                    |
| 30147978  | Paliperidone 350mg/1.75ml prolonged-release suspension for injection pre-filled syringes                                 |
| 30148978  | Paliperidone 263mg/1.315ml prolonged-release suspension for injection pre-filled syringes                                |

| Drug code | Generic name                                                                              |
|-----------|-------------------------------------------------------------------------------------------|
| 81421998  | Paliperidone 50mg/0.5ml suspension for injection pre-filled syringes                      |
| 30146978  | Paliperidone 350mg/1.75ml prolonged-release suspension for injection pre-filled syringes  |
| 81419998  | Paliperidone 100mg/1ml suspension for injection pre-filled syringes                       |
| 81425998  | Paliperidone 50mg/0.5ml suspension for injection pre-filled syringes                      |
| 30150978  | Paliperidone 175mg/0.875ml prolonged-release suspension for injection pre-filled syringes |
| 30149978  | Paliperidone 263mg/1.315ml prolonged-release suspension for injection pre-filled syringes |
| 95516997  | Pimozide 4mg tablets                                                                      |
| 95516996  | Pimozide 10mg tablet                                                                      |
| 95516998  | Pimozide 2mg tablets                                                                      |
| 72658978  | Pimozide 1mg tablets                                                                      |
| 97342998  | Pimozide 2mg tablets                                                                      |
| 97342996  | Pimozide 10mg tablets                                                                     |
| 97342997  | Pimozide 4mg tablets                                                                      |
| 85413998  | Pipotiazine 50mg/1ml solution for injection ampoules                                      |
| 85411998  | Pipotiazine 100mg/2ml solution for injection ampoules                                     |
| 85409998  | Pipotiazine palmitate 100mg/2ml oily injection                                            |
| 98622998  | Pipotiazine palmitate 100mg/2ml oily injection                                            |
| 95503998  | Pipotiazine palmitate 50mg/ml depot injection                                             |
| 85410998  | Pipotiazine palmitate 50mg/1ml oily injection                                             |
| 91374998  | Risperidone 1mg orodispersible tablets sugar free                                         |
| 91968998  | Risperidone 500microgram tablets                                                          |
| 79816978  | Risperidone 2mg tablets                                                                   |
| 98585998  | Risperidone 1mg tablets                                                                   |
| 95519998  | Risperidone 50mg powder and solvent for suspension for injection vials                    |
| 55523979  | Risperidone 25mg powder and solvent for suspension for injection vials                    |
| 96554979  | Risperidone 1mg tablets                                                                   |
| 88163998  | Risperidone 37.5mg powder and solvent for suspension for injection vials                  |
| 99649997  | Risperidone 2mg tablets                                                                   |
| 63094979  | Risperidone 125micrograms/5ml oral solution                                               |
| 99649996  | Risperidone 3mg tablets                                                                   |
| 92908990  | Risperidone 1mg/ml oral solution sugar free                                               |
| 99637997  | Risperidone 1mg/ml oral solution sugar free                                               |
| 88164998  | Risperidone 25mg powder and solvent for suspension for injection vials                    |
| 52748979  | Risperidone 2mg tablets                                                                   |
| 92491990  | Risperidone 500microgram orodispersible tablets sugar free                                |
| 86983998  | Risperidone 500microgram orodispersible tablets sugar free                                |
| 92917990  | Risperidone 1mg tablets                                                                   |
| 46610978  | Risperidone 1mg/ml oral solution sugar free                                               |
| 98585996  | Risperidone 3mg tablets                                                                   |
| 92107998  | Risperidone 2mg orodispersible tablets sugar free                                         |
| 89908998  | Risperidone 50mg powder and solvent for suspension for injection vials                    |
| 96914992  | Risperidone 3mg tablets                                                                   |
| 92352990  | Risperidone 500microgram orodispersible tablets sugar free                                |
| 86984998  | Risperidone 500microgram orodispersible tablets sugar free                                |
| 90396998  | Risperidone 2mg orodispersible tablets sugar free                                         |
| 92625990  | Risperidone 500microgram orodispersible tablets sugar free                                |
| 85038998  | Risperidone 4mg orodispersible tablets sugar free                                         |
| 99637998  | Risperidone 4mg tablets                                                                   |
| 98585997  | Risperidone 2mg tablets                                                                   |
| 99637996  | Risperidone 6mg tablets                                                                   |
| 92957990  | Risperidone 500microgram tablets                                                          |
| 99649998  | Risperidone 1mg tablets                                                                   |
| 90395998  | Risperidone 1mg orodispersible tablets sugar free                                         |
| 92953990  | Risperidone 4mg tablets                                                                   |

| Drug code | Generic name                                                             |
|-----------|--------------------------------------------------------------------------|
| 92023998  | Risperidone 500microgram tablets                                         |
| 91676998  | Risperidone 25mg powder and solvent for suspension for injection vials   |
| 93240996  | Risperidone 6mg tablets                                                  |
| 85040998  | Risperidone 4mg orodispersible tablets sugar free                        |
| 93240997  | Risperidone 1mg/ml oral solution sugar free                              |
| 92089998  | Risperidone 37.5mg powder and solvent for suspension for injection vials |
| 85039998  | Risperidone 3mg orodispersible tablets sugar free                        |
| 92954990  | Risperidone 3mg tablets                                                  |
| 85042998  | Risperidone 3mg orodispersible tablets sugar free                        |
| 93240998  | Risperidone 4mg tablets                                                  |
| 92956990  | Risperidone 1mg tablets                                                  |
| 92955990  | Risperidone 2mg tablets                                                  |
| 97858990  | Sulpiride 200mg tablets                                                  |
| 98149992  | Sulpiride 500 mg tab                                                     |
| 97966990  | Sulpiride 200mg tablets                                                  |
| 95226997  | Sulpiride 200mg/5ml oral solution sugar free                             |
| 89497979  | Sulpiride 200mg/5ml oral solution                                        |
| 97163989  | Sulpiride 400mg tablets                                                  |
| 98796997  | Sulpiride 400mg tablets                                                  |
| 95226996  | Sulpiride 400mg tablets                                                  |
| 65123979  | Sulpiride 150mg/5ml oral solution                                        |
| 90158998  | Sulpiride 200mg/5ml oral solution sugar free                             |
| 97163990  | Sulpiride 200mg tablets                                                  |
| 90805998  | Sulpiride 200mg tablets                                                  |
| 95226998  | Sulpiride 200mg tablets                                                  |
| 98796998  | Sulpiride 200mg tablets                                                  |
| 97176998  | Sulpiride 200mg tablets                                                  |
| 95524990  | Sulpiride 400mg tablets                                                  |
| 99821998  | Zuclopenthixol 2mg tablets                                               |
| 96629996  | Zuclopenthixol 25mg tablets                                              |
| 96629998  | Zuclopenthixol 2mg tablets                                               |
| 99821997  | Zuclopenthixol 10mg tablets                                              |
| 99821996  | Zuclopenthixol 25mg tablets                                              |
| 96629997  | Zuclopenthixol 10mg tablets                                              |
| 86332998  | Zuclopenthixol acetate 100mg/2ml oily injection                          |
| 93519998  | Zuclopenthixol acetate 50mg/1ml solution for injection ampoules          |
| 93520998  | Zuclopenthixol acetate 50mg/1ml solution for injection ampoules          |
| 86334998  | Zuclopenthixol acetate 100mg/2ml solution for injection ampoules         |
| 86333998  | Zuclopenthixol acetate 50mg/1ml solution for injection ampoules          |
| 86335998  | Zuclopenthixol acetate 50mg/1ml solution for injection ampoules          |
| 85607998  | Zuclopenthixol decanoate 200mg/1ml solution for injection ampoules       |
| 95071998  | Zuclopenthixol decanoate 500mg/1ml solution for injection ampoules       |
| 96628998  | Zuclopenthixol decanoate 200mg/ml oily injection                         |
| 98767998  | Zuclopenthixol decanoate 500mg/1ml solution for injection ampoules       |
| 96628997  | Zuclopenthixol decanoate 500mg/1ml solution for injection ampoules       |
| 85609998  | Zuclopenthixol decanoate 200mg/1ml solution for injection ampoules       |
| 98155990  | Haloperidol 5mg/1ml solution for injection ampoules                      |
| 97944997  | Haloperidol 20mg/2ml injection                                           |
| 83786998  | Haloperidol 5mg/1ml solution for injection ampoules                      |
| 93695998  | Haloperidol 5mg/ml injection                                             |
| 93695997  | Haloperidol 20mg/2ml solution for injection ampoules                     |
| 97345997  | Haloperidol 10mg/2ml injection                                           |
| 97944998  | Haloperidol 5mg/1ml solution for injection ampoules                      |
| 83787998  | Haloperidol 5mg/1ml solution for injection ampoules                      |

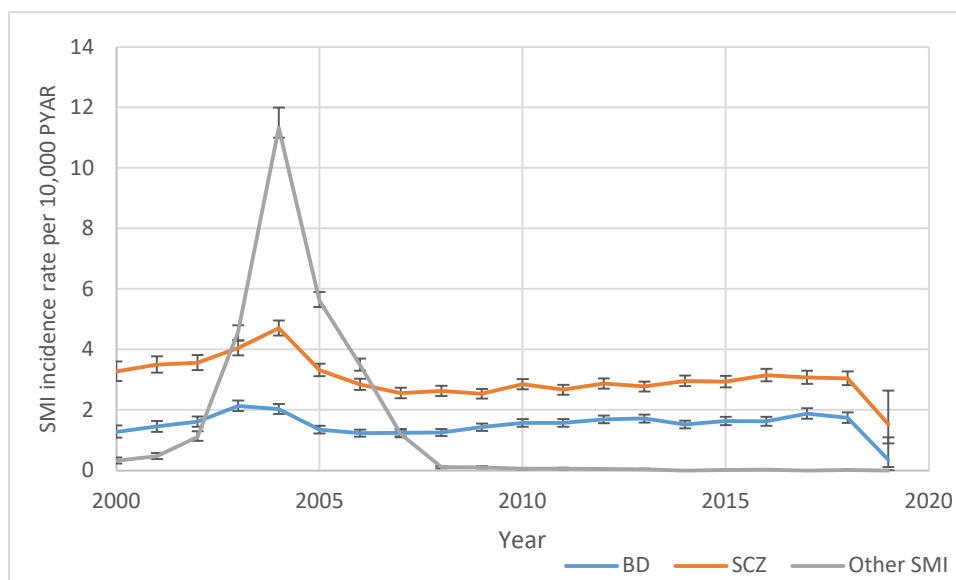
| Drug code | Generic name                   |
|-----------|--------------------------------|
| 96758992  | Haloperidol 20mg/2ml injection |

**Appendix table XXV.3: Drug code list for bipolar disorder-specific medications**

| Drug code | Generic name                                       |
|-----------|----------------------------------------------------|
| 97674992  | Lithium 250 mg cap                                 |
| 96335979  | Lithium carbonate 400mg modified-release tablets   |
| 42703978  | Lithium carbonate 250mg tablets                    |
| 42704978  | Lithium carbonate 250mg tablets                    |
| 99217997  | Lithium carbonate 400mg modified-release tablets   |
| 96003998  | Lithium carbonate 400mg modified-release tablets   |
| 99465998  | Lithium carbonate 450mg modified-release tablets   |
| 93412998  | Lithium carbonate 520mg/5ml sugar free liquid      |
| 97979990  | Lithium carbonate 400mg modified-release tablets   |
| 92542998  | Lithium carbonate 400mg modified-release tablets   |
| 39734978  | Lithium carbonate 250mg tablets                    |
| 99217998  | Lithium carbonate 200mg modified-release tablets   |
| 96001998  | Lithium carbonate 300mg modified release tablets   |
| 96004998  | Lithium carbonate 200mg modified-release tablets   |
| 99858998  | Lithium carbonate 250mg tablets                    |
| 84977998  | Lithium carbonate 200mg/5ml oral suspension        |
| 96004996  | Lithium carbonate 300mg modified-release tablet    |
| 98814998  | Lithium carbonate 400mg modified-release tablets   |
| 96002998  | Lithium carbonate 450mg modified-release tablets   |
| 96331979  | Lithium carbonate 400mg modified-release tablets   |
| 96004997  | Lithium carbonate 250mg tablets                    |
| 97673992  | Lithium chloride 400 mg sol                        |
| 97705997  | Lithium citrate 1.018g/5ml oral solution           |
| 96000996  | Lithium citrate 509mg/5ml oral solution            |
| 97716998  | Lithium citrate 1.018g/5ml oral solution           |
| 96865992  | Lithium citrate 1.018g/5ml oral solution           |
| 97534998  | Lithium citrate 564mg modified release tablets     |
| 97705998  | Lithium citrate 509mg/5ml oral solution            |
| 52732979  | Lithium citrate 509mg/5ml oral solution            |
| 96000997  | Lithium citrate 520mg/5ml oral solution sugar free |
| 96000998  | Lithium citrate 564mg modified-release tablets     |
| 97951992  | Priadel 800 mg tab                                 |
| 81170998  | Asenapine 10mg sublingual tablets sugar free       |
| 81172998  | Asenapine 5mg sublingual tablets sugar free        |

## APPENDIX XXVI INCIDENCE OF “OTHER SMI”

Early work to define SMI by Read code included a category of “other SMI”. This mainly included Read codes relating to the administration of SMI disease registers (see Appendix XXV ). A closer examination of the incidence rate for SMI patients who had a code for other SMI, but no Read code for either schizophrenia or BD revealed a large spike in incidence in 2004 (Appendix figure XXVI.1). This coincided with the development of the Quality Outcomes Framework (QOF) in England<sup>1</sup>. The large numbers of patients in the other SMI category in 2004 reduced to virtually nil after a few years, whereas the numbers with BD and schizophrenia remained much more consistent. Thus, this category was not thought to be a reliable way of identifying patients with SMI. Patients previously classed with other SMI were instead added to the non-SMI comparison group of patients.



**Appendix figure XXVI.1: SMI incidence rate per 10,000 person years at risk, by SMI type, prevalent cohort**

<sup>1</sup> Lester H, Campbell S. Developing Quality and Outcomes Framework (QOF) indicators and the concept of 'QOFability'. *Qual Prim Care*. 2010;18(2):103-9

## APPENDIX XXVII EXPLORATORY ANALYSIS OF AGE AT ONSET OF SEVERE MENTAL ILLNESS

### Introduction

Severe Mental Illness (SMI) was initially specified using a combination of Read codes and drug codes specific to SMI. However, 16% of those with a first diagnosis of SMI were aged 65-74 years. This was much higher than expected since SMI is typically diagnosed at a much younger age. Three possible explanations were tested by comparing the age distribution of SMI patients with other published work. The explanations considered were:

- The use of drug codes to specify SMI may have inflated the number of cases and included older patients without SMI
- The inclusion of all diagnoses between 60 days and one year of registration in the practice may have led to prevalent rather than incident SMI patients being counted; other authors assessing disease incidence using electronic health data (*e.g.* Hardoon, 2013) excluded individuals diagnosed within one year of registration to avoid counting prevalent rather than incident patients
- Dementia cases were not initially excluded from being in the SMI group. A proportion of those presenting with symptoms indicating SMI could be diagnosed with dementia a few months later; some of the SMI patients could be mis-diagnosed dementia

### Methods

To test the first theory, patients with SMI in the incident cohort were categorised into five groups according to SMI type and whether defined by Read code or drug prescription. Cases were allocated to categories in the following order:



1. Schizophrenia diagnosis: if ever had a Read code indicating incidence or prevalence of schizophrenia (**SCZ\_diag**)
2. Bipolar disorder diagnosis: if not in (1) and ever had a Read code indicating incidence or prevalence of BD (**BD\_diag**)
3. BD drug: if not in (1) or (2) and ever had a prescription for BD drug (lithium or asenapine) (**BD\_drug**)
4. Other SMI diagnosis: if not in (1)-(3) and ever had a Read code indicating SMI, but not able to categorise as BD or schizophrenia (**SMI\_diag**)
5. Schizophrenia drug: if not in (1)-(4) and ever had a prescription for SCZ drug (mainly olanzapine, risperidone, amisulpride, aripiprazole, sulpiride, clozapine or injectable) (**SCZ\_drug**)

Histograms showing age at onset of SMI were plotted for the five different groups.

Secondly, patients with index date within one year of registration were identified for each of the diagnosis groups and the age distributions with and without those patients were compared for each diagnosis group.

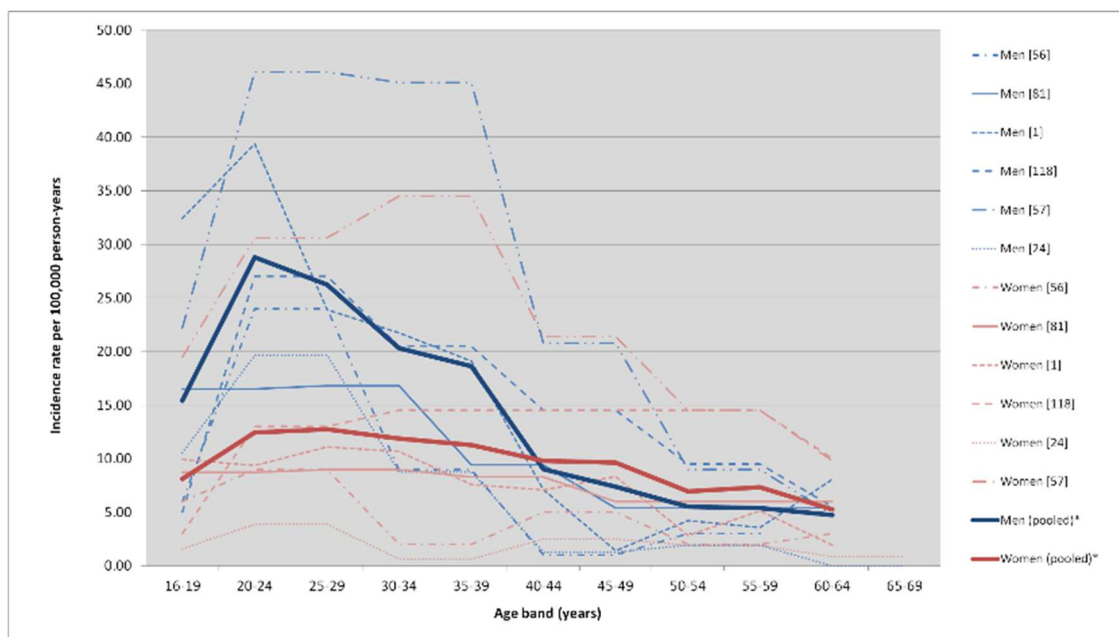
Thirdly, the date of earliest dementia Read code was added to the 1% sample of THIN data.

The numbers and percentage with SMI who also had a dementia diagnosis were calculated and age distributions compared with histograms.

## Results

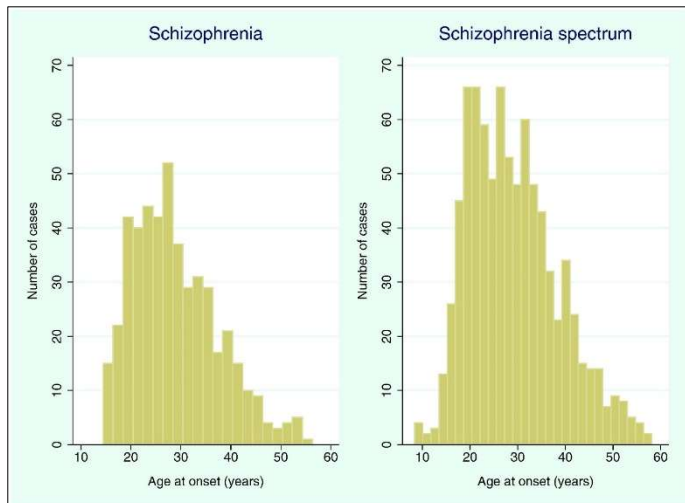
### Age at SMI onset found by other authors

The distribution of age at onset of schizophrenia found by three different studies are shown in Appendix figure XXVII.1 to Appendix figure XXVII.3. Appendix figure XXVII.4 and Appendix figure XXVII.5 show age at onset of BD in two further studies. All show peaks in early adulthood.



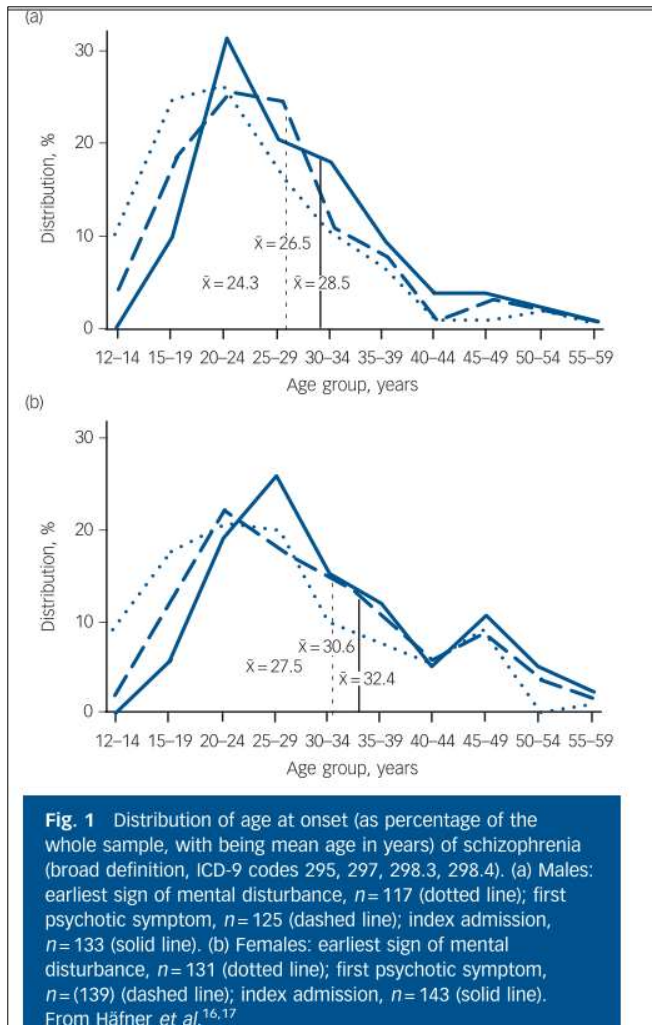
Source : Kirkbride JB, Errazuriz A, Croudace TJ, Morgan C, Jackson D, Boydell J, et al. Incidence of Schizophrenia and Other Psychoses in England, 1950–2009: A Systematic Review and Meta-Analyses. PLoS ONE. 2012;7(3):e31660, reproduced here under CC BY 4.0 licence.

**Appendix figure XXVII.1: Incidence of schizophrenia by age and sex in England, 1950-2009**



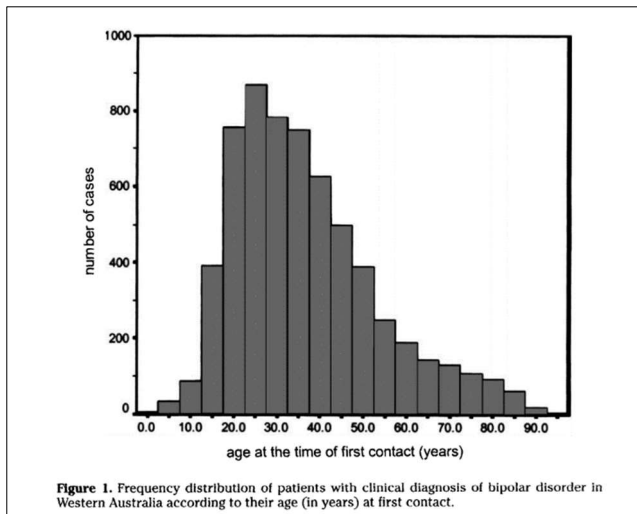
Source: Hilker R, Helenius D, Fagerlund B, Skyttke A, Christensen K, Werge TM, et al. Is an Early Age at Illness Onset in Schizophrenia Associated With Increased Genetic Susceptibility? Analysis of Data From the Nationwide Danish Twin Register. *EBioMedicine*. 2017;18:320-6, reproduced here under CC BY NC ND licence.

**Appendix figure XXVII.2: Age at onset among all twins affected with schizophrenia (N=448) and schizophrenia spectrum (N=788) in twin pairs born 1951–2000 and identified by linkage of the Danish Twin Register and the Danish Psychiatric Central Research Register.**



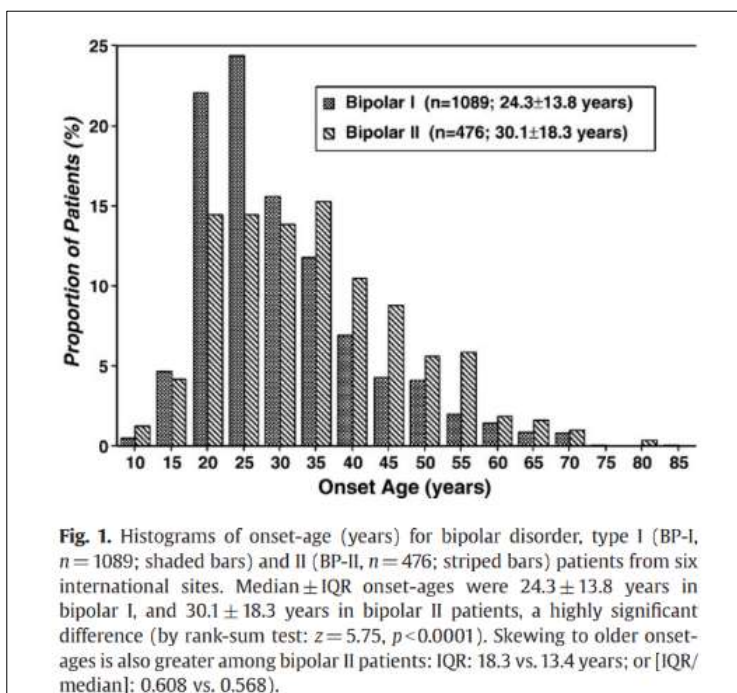
Source: Jones PB. Adult mental health disorders and their age at onset. *British Journal of Psychiatry*. 2013;202(s54):s5-s10.

### Appendix figure XXVII.3: Distribution of age at onset of schizophrenia for males and females



Source: Almeida OP, Fenner S. Bipolar Disorder: Similarities and Differences Between Patients With Illness Onset Before and After 65 Years of Age. *International Psychogeriatrics*. 2002;14(3):311-22.

#### Appendix figure XXVII.4: Age at onset of bipolar disorder

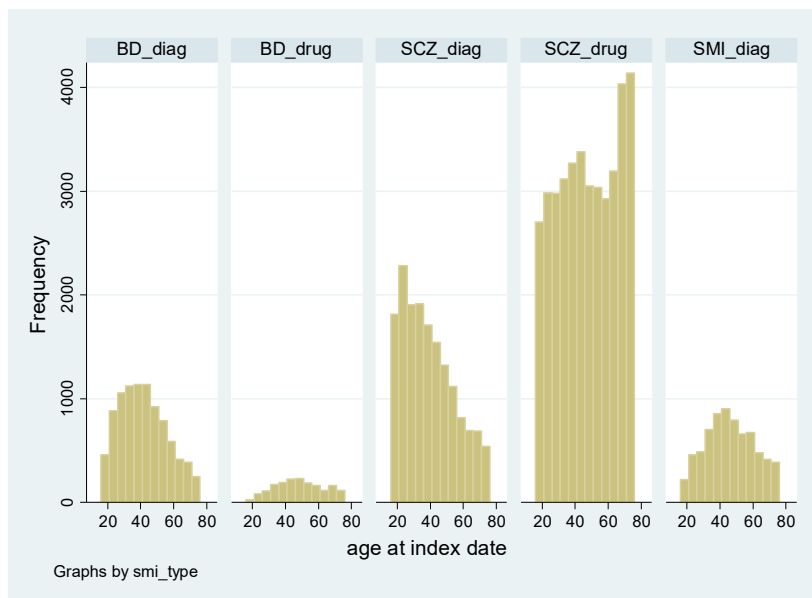


Source: Baldessarini RJ, Bolzani L, Cruz N, Jones PB, Lai M, Lepri B, et al. Onset-age of bipolar disorders at six international sites. *Journal of Affective Disorders*. 2010;121(1):143-6.

#### Appendix figure XXVII.5: Age at onset of BD I and BD II

### Age at onset for different specifications of SMI

The age distributions of SMI patients in the incident cohort defined by schizophrenia diagnosis, BD diagnosis, schizophrenia medications, BD medications and by other SMI are shown in Appendix figure XXVII.6. Cases defined by schizophrenia and BD diagnosis, *i.e.* those having a Read code indicating SMI diagnosis show peaks in early adulthood, similar in shape to those of the other authors above. However, the cases defined by drug codes for schizophrenia and BD, *i.e.* those with no Read code indicating SMI diagnosis, have peaks at later ages which do not appear to represent the typical age distribution on new diagnoses of SMI. Additionally, there are very large numbers of patients in the SCZ\_drug group compared to the other groups. The histogram of the SMI\_diag group, *i.e.* those with an SMI Read code indicating neither schizophrenia nor BD also showed a peak rather older than would be expected.



Appendix figure XXVII.6: Age at index date by SMI type, incident cohort

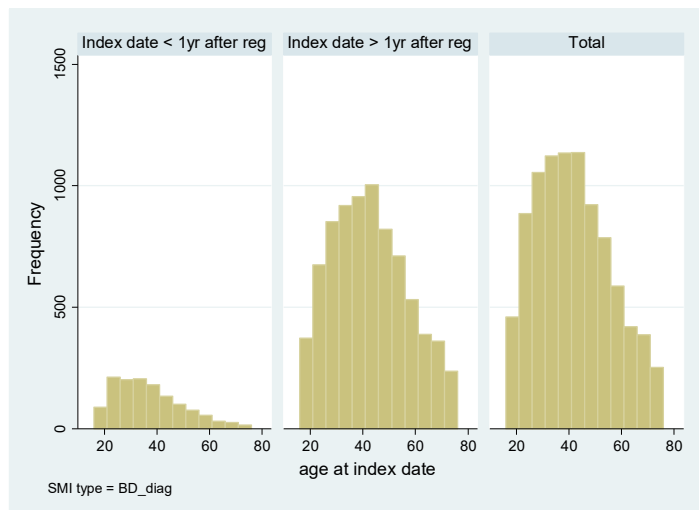
### Index date within a year of registration

Appendix table XXVII.1 shows the percentage of SMI patients and matched non-SMI comparators who had index date within a year of practice registration. Patients with SMI defined by BD and schizophrenia Read codes were twice as likely as those without SMI to have their index date within one year of registration. 14.5% of people with BD Read codes and 14.4% with schizophrenia Read codes were diagnosed between 60 days and one year of registration, compared with 7.4% of the matched comparison group.

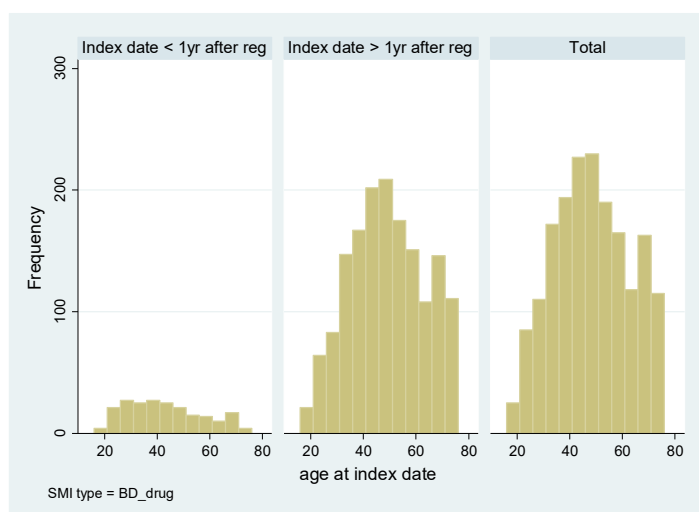
**Appendix table XXVII.1: Index date between 60 days and one year of registration by SMI definition and age, percentages**

| Age group       | Cases by definition of SMI |                    |                      |                      |                     | Non-SMI comparators<br>n=219,092 |
|-----------------|----------------------------|--------------------|----------------------|----------------------|---------------------|----------------------------------|
|                 | BD_diag<br>n=9,153         | BD_drug<br>n=1,794 | SCZ_diag<br>n=16,361 | SCZ_drug<br>n=38,811 | SMI_diag<br>n=7,052 |                                  |
| 16-24           | 21.8                       | 27.9               | 15.4                 | 18.1                 | 18.1                | 11.4                             |
| 25-34           | 19.7                       | 17.6               | 19.1                 | 19.9                 | 16.8                | 13.2                             |
| 35-44           | 14.3                       | 13.0               | 15.2                 | 14.0                 | 11.8                | 7.6                              |
| 45-54           | 10.2                       | 9.0                | 12.3                 | 10.1                 | 7.2                 | 5.0                              |
| 55-64           | 9.3                        | 8.3                | 8.8                  | 8.2                  | 6.1                 | 3.7                              |
| 65-74           | 6.2                        | 7.5                | 7.4                  | 8.1                  | 6.8                 | 3.0                              |
| <b>All ages</b> | <b>14.5</b>                | <b>11.7</b>        | <b>14.4</b>          | <b>12.6</b>          | <b>10.6</b>         | <b>7.4</b>                       |

Appendix figure XXVII.7 to Appendix figure XXVII.11 show the age distribution of patients for different SMI definitions, for a) people diagnosed between 60 days and a year of registration only, b) excluding those diagnosed within 60 days and a year and c) including all those diagnosed after 60 days of registration. Excluding people diagnosed within a year of registration did not appear to greatly affect the age distribution.

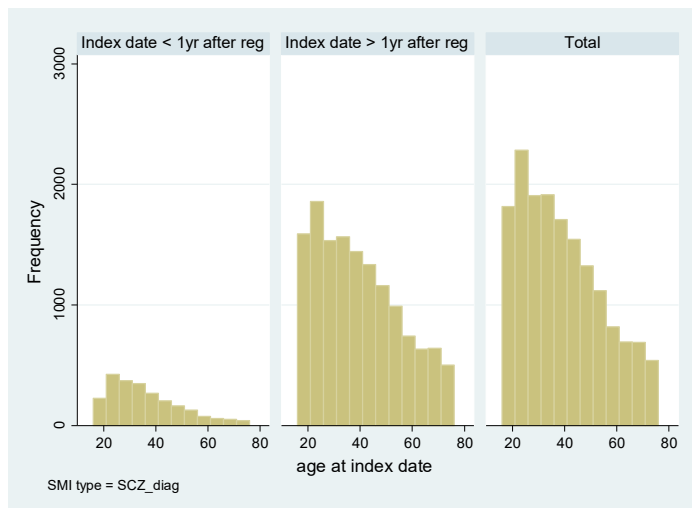


**Appendix figure XXVII.7: Age distribution of SMI: defined by BD Read code, including and excluding people diagnosed within 1 yr of registration**



**Appendix figure XXVII.8: Age distribution of SMI: defined by BD drug prescription, including and excluding people diagnosed within 1 yr of registration**

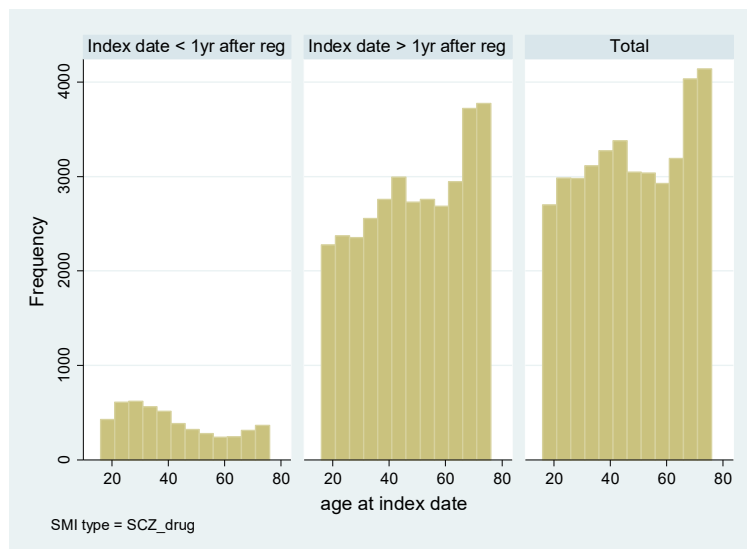




**Appendix figure XXVII.9: Age distribution of SMI: defined by schizophrenia Read code, including and excluding people diagnosed within 1 yr of registration**



**Appendix figure XXVII.10: Age distribution of SMI: defined by other SMI Read code, including and excluding people diagnosed within 1 yr of registration**



**Appendix figure XXVII.11: Age distribution of SMI: defined by schizophrenia drug prescription, including and excluding people diagnosed within 1 yr of registration**

## Dementia

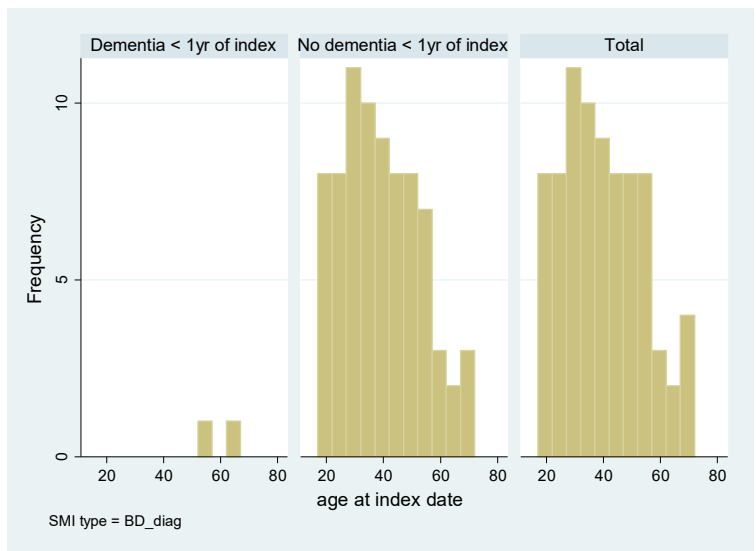
Appendix table XXVII.2: Numbers of SMI patients and non-SMI comparators with dementia diagnosis, 1% THIN sample shows the number of SMI patients and non-SMI comparators diagnosed with dementia. 6.2% of those with SMI had ever received a dementia diagnosis and 5.1% received a dementia diagnosis prior to or within a year of SMI diagnosis.

**Appendix table XXVII.2: Numbers of SMI patients and non-SMI comparators with dementia diagnosis, 1% THIN sample**

| 1% sample                              | SMI patients (n = 729) | Non-SMI comparators (n=1703) |
|----------------------------------------|------------------------|------------------------------|
| Ever had dementia Read code:           | 45 (6.2%)              | 8 (0.5%)                     |
| Dementia prior to index date           | 35 (4.8%)              | 0 (0%)                       |
| Dementia after index but within 1 year | 2 (0.3%)               | 0 (0%)                       |
| Dementia after 1 year of index         | 8 (1.1%)               | 8 (0.5%)                     |

Appendix figure XXVII.12: Age distribution of SMI: defined by BD Read code, including and excluding people diagnosed with dementia prior to or within 1 yr of SMI diagnosis to

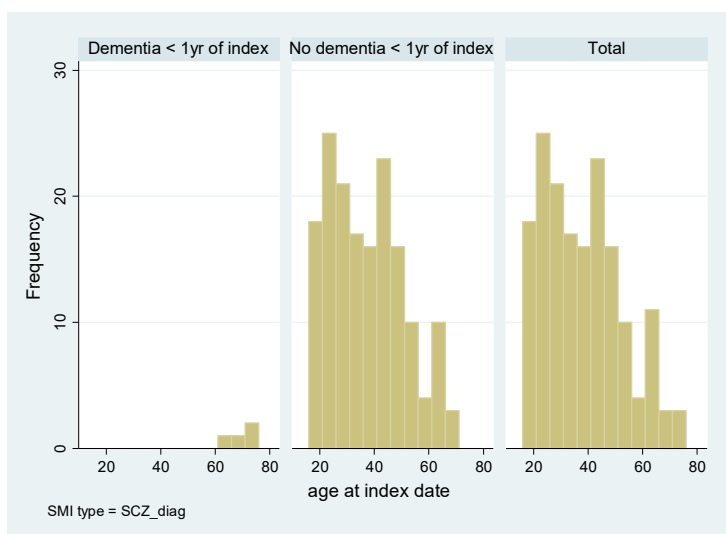
Appendix figure XXVII.16: Age distribution of SMI: defined by schizophrenia drug code, including and excluding people diagnosed with dementia prior to or within 1 year of SMI diagnosis show the age distribution of SMI patients for different SMI definitions, for a) people diagnosed with dementia prior to, or within a year of SMI diagnosis, b) excluding those diagnosed with dementia prior to, or within a year of SMI diagnosis, and c) including all those diagnosed with dementia before or after SMI diagnosis. Numbers of patients with dementia were relatively small and did not appear to account for the unexpected peaks in the age distributions of SMI onset.



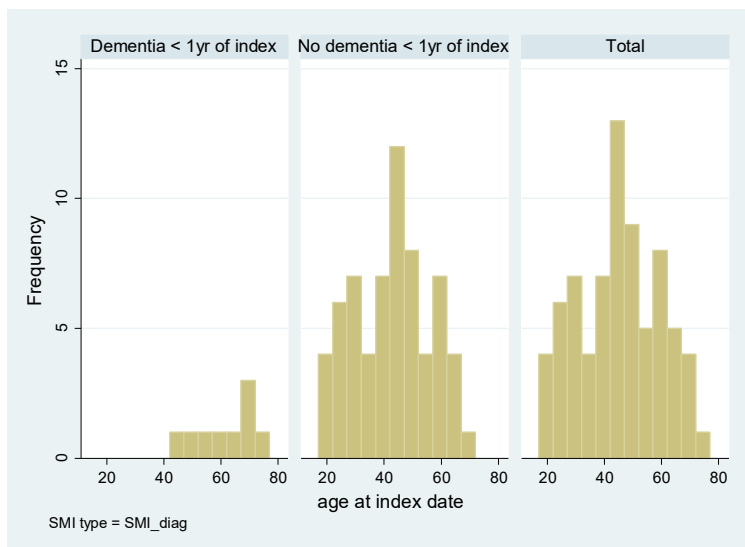
**Appendix figure XXVII.12: Age distribution of SMI: defined by BD Read code, including and excluding people diagnosed with dementia prior to or within 1 yr of SMI diagnosis**



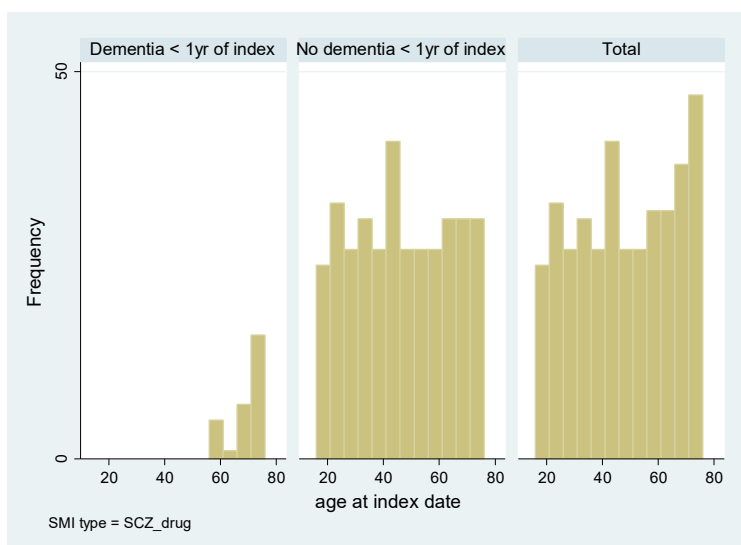
**Appendix figure XXVII.13: Age distribution of SMI: defined by BD drug prescription, including and excluding people diagnosed with dementia prior to or within 1 yr of SMI diagnosis**



**Appendix figure XXVII.14: Age distribution of SMI: defined by schizophrenia Read code, including and excluding people diagnosed with dementia prior to or within 1 yr of SMI**



**Appendix figure XXVII.15: Age distribution of SMI: defined by other SMI Read code, including and excluding people diagnosed with dementia prior to or within 1 yr of SMI diagnosis**



**Appendix figure XXVII.16: Age distribution of SMI: defined by schizophrenia drug code, including and excluding people diagnosed with dementia prior to or within 1 year of SMI diagnosis**

## Discussion

Three possible explanations for the older than expected age distribution of SMI patients were explored. Two of these: the inclusion of patients between 60 days and one year of

registration, and the inclusion of patients with a recent dementia diagnosis appeared to make little difference to the age distribution of SMI cases. The final cohorts selected excluded SMI patients with a diagnosis of dementia within a year of SMI diagnosis but included patients within a year of registration. By including this latter group, some prevalent SMI patients may have been added to the incident cases in the cohort. For these patients it would mean that the start of their SMI diagnosis was earlier than the reported date. They would thus have a shorter follow-up time until any outcome, which would apply to both SMI patients and the matched comparison group. Numbers affected are likely to have been small (<15% of SMI patients had first diagnosis within a year of registration and most of these will not be prevalent cases). Additionally, steps were taken to only include Read codes for SMI that were indicative of a new diagnosis.

The main reason for the older than expected age distribution appears to be the large numbers with a prescription for schizophrenia-specific antipsychotic medication, who did not have a Read code for schizophrenia. This is concerning and warrants further investigation but is outside the scope of this PhD. The age distributions for patients with Read codes for schizophrenia and BD appeared broadly in line with other studies, so it was decided to focus on these two groups only. The peaks may be slightly older than expected, which could be due to the inclusion of some prevalent patients as discussed above.

## References

- Almeida OP, Fenner S. Bipolar Disorder: Similarities and Differences Between Patients With Illness Onset Before and After 65 Years of Age. *International Psychogeriatrics*. 2002;14(3):311-22.
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- Kirkbride JB, Errazuriz A, Croudace TJ, Morgan C, Jackson D, Boydell J, et al. Incidence of Schizophrenia and Other Psychoses in England, 1950–2009: A Systematic Review and Meta-Analyses. *PLoS ONE*. 2012;7(3):e31660.

## APPENDIX XXVIII CALCULATIONS SHOWING HOW THE PERCENTAGE MEDIATED BY DIABETES IS HIGHER FOR THOSE AT HIGHER CVD RISK THAN LOWER CVD RISK

The percentage mediated by diabetes was higher for individuals at higher risk (males, older, smokers) than those at lower risk (females, younger, non-smokers); BD: 36% vs 4%, schizophrenia: 55% vs 14%. Some further calculations illustrate how this apparently counter intuitive finding comes about.

### 1. Odds of DM for SZ is stronger for low risk than high risk patients

High risk (male, age 65-74, current smoker at baseline):

|        | No DM at baseline | DM at baseline (%) |
|--------|-------------------|--------------------|
| No SMI | 38,516            | 4,346 (10.14)      |
| SZ     | 553               | 84 (13.19)         |

$$OR = ad/bc = 1.35$$

Low risk (female, age 45-54, not current smoker):

|        | No DM at baseline | DM at baseline (%) |
|--------|-------------------|--------------------|
| No SMI | 434,908           | 14,257 (3.17)      |
| SZ     | 2,915             | 257 (8.10)         |

$$OR = ad/bc = 2.69$$

Interpretation: high risk (older, male, smoker) more likely to have diabetes at start of follow-up than low risk (younger, female, non-smoker), so effect of SZ on odds of diabetes is stronger in low risk



2. Also, HR for association between DM and CVD is much higher in low risk than high risk

High risk:

|                   | No CVD at endpoint | CVD at endpoint (%) |
|-------------------|--------------------|---------------------|
| No DM at baseline | 34,294             | 4,775 (12.22)       |
| DM at baseline    | 3,822              | 608 (13.72)         |

RR =  $13.72/12.22 = 1.12$

Low risk:

|                   | No CVD at endpoint | CVD at endpoint (%) |
|-------------------|--------------------|---------------------|
| No DM at baseline | 426,796            | 11,027 (2.52)       |
| DM at baseline    | 13,493             | 1,021 (7.03)        |

RR =  $7.03/2.52 = 2.79$

Interpretation: high risk patients (older, male, smoker) more likely to have CVD by end of follow-up, compared with low risk (younger, female, non-smoker), so the effect of DM on CVD is stronger in low risk compared with high risk patients

So, DM is more strongly associated with SZ in low risk than high risk patients because high risk have other causes of DM than SZ. Also, DM is more likely to lead to CVD in low risk than high risk patients because high risk have other causes of CVD than DM.

