The association between the reproductive health of young women and cardiovascular disease across the lifespan

by

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Abstract

Background: In women, cardiovascular disease (CVD) is the leading cause of death, accounting for one-third of all deaths worldwide. Traditionally, CVD has been perceived as a male-dominated condition, with reproductive-age group women perceived to be protected from CVD. Recent analyses of age-and sex-specific data from high-income countries have revealed that the observed ongoing decline in CVD mortality was sustained in older adults (> 55 years) but had slowed in young adults (≤ 55 years). The rate of decline was slowest in young women. Contemporary data describing CVD trends among young adults from the United Kingdom (UK) are scarce. Several lines of evidence suggest that reproductive factors (adverse pregnancy outcomes and fertility-related endocrine factors) in young women may serve as markers of their cardiometabolic health throughout the lifespan (young adulthood, midlife, and old age). The breadth, level, and quality of evidence on the relationship between reproductive factors and CVD is unclear. Also, awareness of these reproductive factors as factors that enhance CVD is low among healthcare providers and women themselves.

Aim: The aim of this thesis was to examine the association between female reproductive factors and cardiovascular disease across the lifespan.

Methods: A series of annual cohort and cross-sectional studies (1998-2017) were constructed to estimate incidence rates and prevalence among 16-50-year-old men and women (Objective 1). An umbrella review (tertiary level review of existing systematic reviews and meta-analyses) was conducted to consolidate higher-level evidence on the association between female reproductive factors and CVD (Objective 2). Cochrane, Medline and Embase were searched for relevant systematic reviews and meta-analyses from inception until 31st August 2019. Three separate retrospective matched cohort studies were conducted using UK primary care data. Cox proportional hazard models were fitted to estimate adjusted hazard ratio's (aHR) and corresponding 95% confidence interval (95% CI) for CVD in women with (i)

endometriosis (Objective 3), (ii) pelvic inflammatory disease (Objective 4), (iii) menstrual cycle characteristics including irregular and frequent or infrequent cycles (Objective 5) versus a matched comparator group.

Results: Overall, from 1998 to 2017, the incidence and prevalence of ischaemic heart disease (IHD) and angina decreased, while coronary revascularisation, stroke/transient ischaemic attack (TIA), and heart failure (HF) increased in both sexes. (P for trend <0.05 for all except MI incidence and prevalence in men, revascularisation incidence in men, and stroke/TIA incidence in women). The umbrella review analysis included a total of 32 reviews evaluating multiple reproductive factors. The average period of follow-up was 7 to 10 years. All reviews were rated moderate in quality except three. In summary, the effect sizes for CVD ranged from 1.01 to 4-fold. The effect sizes were greatest (2-fold) for stillbirth, gestational diabetes, pre-term birth, current use of oral contraceptives (combined oral contraceptives or progesterone only pill), pre-eclampsia and recurrent pre-eclampsia. The effect size for HF was 4-fold in pre-eclampsia. The aHR for composite CVD were: 1.24 (95% CI 1.13–1.37) for endometriosis; 1.10 (95% CI 0.93-1.30) for pelvic inflammatory disease; 1.08 (95% CI 1.00-1.19) for irregular menstrual cycles; and 1.24 (1.02-1.52) for frequent or infrequent menstrual cycles.

Conclusion: Overall, among young adults in the UK, the incidence and prevalence (1998-2017) of IHD and angina exhibited a downward trend while stroke/TIA, HF, and revascularisation, exhibited an upward trend. MI incidence increased in women but remained stable in men. From menarche to menopause, female reproductive factors were associated with CVD throughout the lifespan. Physicians addressing health indicators should consider the adverse impact of female reproductive factors on CVD. Policymakers should consider including female reproductive risk factors in clinical guidelines as part of CVD risk evaluation.

Dedication

This thesis is dedicated to my parents. Thank you for everything.

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List of manuscripts arising from PhD thesis.

The following five manuscripts are associated with the five separate studies described in Chapter 3 to 7 of this thesis. The studies described in Chapter 3, Chapter 4, Chapter 5, Chapter 6, and Chapter 7 have all been published.

Okoth K, Crowe F, Marshall T, Thomas GN, Nirantharakumar K, Adderley NJ. Sex-specific temporal trends in the incidence and prevalence of cardiovascular disease in young adults: a population-based study using UK primary care data. Eur J Prev Cardiol. 2022 Feb 9; https://academic.oup.com/eurjpc/article/29/10/1387/6525229 **(Published)**

Okoth K, Chandan JS, Marshall T, Thangaratinam S, Thomas GN, Nirantharakumar K, et al. Association between the reproductive health of young women and cardiovascular disease in later life: Umbrella review. Vol. 371, The BMJ. BMJ Publishing Group; 2020. https://www.bmj.com/content/371/bmj.m3502 **(Published)**

Okoth K, Wang J, Zemedikun D, Thomas GN, Nirantharakumar K, Adderley NJ. Risk of cardiovascular outcomes among women with endometriosis in the United Kingdom: a retrospective matched cohort study. BJOG. 2021 Sep 1;128(10):1598–609. https://obgyn.onlinelibrary.wiley.com/doi/10.1111/1471-0528.16692 **(Published)**

Okoth K, Thomas GN, Nirantharakumar K, Adderley NJ. Risk of cardiometabolic outcomes among women with a history of pelvic inflammatory disease: A retrospective matched cohort study from the UK. https://bmcwomenshealth.biomedcentral.com/articles/10.1186/s12905-023-02214-5 (**Published**)

Okoth K, Parry-Smith W, Thomas GN, Nirantharakumar K, Adderley NJ. The association between menstrual cycle characteristics and cardiometabolic outcomes in later life: A retrospective matched cohort study of 704,743 women from the UK. https://doi.org/10.1186/s12916-023-02794-x (**Published)**

List of other selected manuscripts published during PhD study.

Okoth K, Subramanian A, Chandan JS, Adderley NJ, Thomas GN, Nirantharakumar K, et al. Long term miscarriage-related hypertension and diabetes mellitus. Evidence from a United Kingdom population-based cohort study. PLoS One. 2022 Jan 1;17(1):e0261769.

Subramanian A, Anand A, Adderley NJ, **Okoth K,** Toulis KA, Gokhale K, et al. Increased COVID-19 infections in women with polycystic ovary syndrome: a population-based study. Eur J Endocrinol. 2021 May 1;184(5):637–45.

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Benson RA, **Okoth K**, Keerthy D, Gokhale K, Adderley NJ, Nirantharakumar K, et al. Analysis of the relationship between sex and prescriptions for guideline-recommended therapy in peripheral arterial disease, in relation to 1-year all-cause mortality: a primary care cohort study. BMJ Open. 2022 Mar 1;12(3):e055952.

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Singh M, Crowe F, Thangaratinam S, Abel KM, Black M, **Okoth K**, et al. Association of pregnancy complications/risk factors with the development of future long-term health

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Šumilo D, Nirantharakumar K, Willis BH, Rudge GM, Martin J, Gokhale K, et al. Long term impact of prophylactic antibiotic use before incision versus after cord clamping on children born by caesarean section: longitudinal study of UK electronic health records. BMJ. 2022 May 17;377:e069704.

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List of abbreviations

Abbreviation	Description
ACS	Acute coronary syndrome
AMR	Acceptable Mortality Reporting
AMSTAR 2	A Measurement Tool to Assess Systematic Reviews
APC	Annual percentage change
APO	Adverse pregnancy outcome
BNF	British National Formulary
CCA	Corrected covered area
COC	Combined oral contraceptive
CPRD	Clinical Practice Research Datalink
CVD	Cardiovascular disease
EHR	Electronic Health Records
EMIS	Egton Medical Information Systems
EPIC	Epidemiology and Pharmacology Information Core
GDM	Gestational diabetes mellitus
GP	General practitioner
GRPD	General Practice Research Database
HDP	Hypertensive disorders of pregnancy.
HR	Hazard ratio
ICD	International Classification of Diseases
IHD	Ischaemic heart disease
IMRD	IVQIA Medical Research Data
IMS	Intercontinental Medical Statistics Health Incorporation
InPS	In Practice System
MRC	Medical Research Council
NHS	National Health Service
OPCS	Office of Population Censuses and Surveys Classification
OXMIS	Oxford Medical Information System
PCOS	Polycystic ovary syndrome
PID	Pelvic inflammatory disease
POI	Premature ovarian insufficiency
POP	Progesterone only pill
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-analysis.
QOF	Quality and Outcomes Framework
THIN	The Health Improvement Network
TPP	The Phoenix Partnership
UK	United Kingdom
VAMP	Value Added Medical Products

Chapter 1. General introduction

Introduction

The research in this thesis focuses on the association between female-sex-specific factors and cardiovascular disease across the lifespan. This section provides a general introduction to the thesis and lays the ground for justification for the research.

The rationale for examining cardiovascular disease in women: The female disadvantage

Cardiovascular disease (CVD) is a significant public health burden and the leading cause of morbidity and mortality in women. Recent global estimates indicate that CVD was responsible for 35% of the total deaths in women.[1] Patients living with CVD have diminished quality of life following functional impairments and limited mobility. Moreover, CVD leads to increased economic costs of health care and loss of productivity. Differences between men and women exist in morbidity, mortality, clinical course, and management of CVD. In medical research, the terms sex and gender are frequently used interchangeably, causing confusion. Sex refers to a person's biological characteristics as determined by sex chromosomes (XY for males and XX for females).[2] Loosely speaking, gender is not a trait we are born with or have but something we perform or do. Gender is derived from behavioural, cultural, and social factors. It is a broad concept that includes an inner sense of identity, societal expectations, and societal power distribution.[2] Despite increased awareness of sex and gender differences in CVD, CVD in women continues to be undertreated, underestimated, and underappreciated.[1,3]

Undertreated

Dr Bernadine Healy, the first female director of the US National Institutes of Health, raised the issue of sex and gender differences in CVD diagnosis in an article titled 'The Yentyl Syndrome.'[4] Healy highlighted the results of two US studies to demonstrate sex bias in managing CVD.[5,6] Yentyl was named after Isaac Bashevis Singer's story Yentyl. Yentyl was a heroine who disguised herself as a man to attend school and receive an education she would

not have otherwise received. In both studies highlighted by Healy, women were less likely to receive standard CVD care, including coronary procedures, unless they presented with male pattern CVD.[5,6]. Healy concluded that women were unlikely to receive optimal care for CVD complications unless they presented with symptoms similar to men's (Yentyl syndrome).[4] Several decades after Healy's clarion call, women continue to receive subpar CVD-related care.[7] A recent meta-analysis of 2.3 million participants showed lower women to men pooled prevalence ratios for CVD medication prescription, including statin therapy (0.90; 95% CI, 0.85 to 0.95), aspirin (0.81; 95% CI, 0.72 to 0.92) and angiotensin-converting enzyme inhibitors (0.85; 95% CI, 0.81 to 0.89).[8]

Underestimated

Historically CVD is perceived to be predominantly a man's disease. Women of reproductive age, in particular, are mistakenly believed to be protected from CVD.[9] Consequently, efforts to improve female cardiovascular health have focused on postmenopausal age-group women. Despite commendable progress in lowering the CVD burden over several decades, analyses of current age-and-sex-specific data from several high-income countries revealed that CVD mortality trends have continued to decline in older adults (> 55 years) but have plateaued in younger adults (≤55 years).[10–12] The slowing down of the decline in IHD mortality was most pronounced in young women (≤ 55 years), with some countries reporting a reversal of the declining mortality trends. Moreover, morbidity in young women is on an upward trend, with several high-income countries reporting a rise in myocardial infarction in younger women.[13,14]. Although several countries have seen a slowing of CVD mortality and morbidity in younger adults, the underlying causes remain unknown. The increased prevalence of established risk factors, including obesity and diabetes among young adults, may partly explain the slowing down of CVD in this age group. Given that up to 20% of CVD risk is unexplained by traditional risk factors, attention has shifted to novel CVD risk factors.[15]

Several emerging lines of evidence suggest that female reproductive factors, such as adverse pregnancy outcomes (APO) and reproductive endocrine factors, are linked to an increased risk of CVD throughout life. Pregnancy is physiological stress that may unmask women with underlying cardiovascular vulnerabilities.[16] Women who have had a negative pregnancy outcome are at a higher risk of developing premature CVD.[17,18] Existing CVD risk prediction models are designed for the general population and do not account for female-specific CVD risk factors.[19] Because they were developed and validated in older age groups (> 55 years), these models perform sub-optimally in women of reproductive age).[20,21]

Underappreciated

Both health care professionals and women underappreciate CVD risk in younger women. A US nationwide survey of 1011 women aged 25-60 reported that 45% of women included in the survey were unaware that CVD was the leading cause of mortality.[22] In the same survey, only 39% of primary care physicians rated CVD as a major concern for women's health. Less than half (42%) of cardiologists and only 22% of primary care physicians felt that they were very well prepared to evaluate CVD risk in women.[22]

This thesis, therefore, examines the association between reproductive factors and CVD across the lifespan.

Definition of cardiovascular disease and its subtypes

Cardiovascular disease (CVD) is a group of heart and blood vessel disorders. Subtypes of CVD include ischaemic heart disease (IHD), cerebrovascular accidents (stroke and transient ischaemic attack), peripheral arterial disease, rheumatic heart disease, congenital heart disease, deep vein thrombosis and pulmonary embolism.[23] This thesis will focus on IHD, cerebrovascular disease (stroke and transient ischaemic attack) and heart failure as these are the most significant contributors to disease morbidity and mortality. In this thesis, composite CVD will refer to the combination of IHD, stroke, transient ischaemic attack (TIA) and heart failure.

IHD is a subtype of CVD referring to a group of diseases that affect the blood supply to the heart. It is composed of several subtypes, including angina pectoris, acute myocardial infarction, and sudden cardiac death, varying in severity and chronicity.[24] Stroke and TIA refer to clinical signs of an acute focal or global brain disturbance that is exclusively vascular in origin and lasts for more than 24 hours (stroke) or less than 24 hours (TIA). Ischaemic stroke occurs if the blood vessels supplying the brain are occluded or stenosed, while haemorrhagic stroke refers to the rupture of blood vessels supplying the brain.[24] Heart failure is a syndrome with typical symptoms (fatigue, ankle swelling and breathlessness) and signs (raised jugular venous pressure, basal crepitations, peripheral oedema) as a result of structural or functional abnormality.[24]

Evidence of unfavourable CVD trends in younger women

Foremost, it is necessary to define the term "young" in connection to CVD to comprehend the burden of CVD among young individuals. Different studies use vastly different cut-offs for what constitutes “young”, with definitions ranging from < 35 years to < 55 years of age. The focus of this thesis is reproductive age group women. Therefore, the term young will refer to adults $\leq$ 50 years of age unless specified otherwise. Public health efforts and advances in

CVD care have fuelled a remarkable decline in CVD mortality over the last four decades.[25] However, analyses of contemporary data from several high-income countries have unmasked unequal decline in CVD trends between older (>55 years) and younger (≤ 55 years) age groups. When compared to similarly aged men, younger women had shown minimal improvements with stagnation or reversal of declining trends. For instance, Wilmot et al. analysed CHD mortality trends across three decades (1979-2011). They examined CHD mortality across three age groups: 55, 55 to 64, and 65 years. Over the entire period (1979-2011), the average annual percentage change (AAPC) was lower in adults 55 years of age than in older groups, and it was lower in young and middle-aged women (< 65 years) than males in the same age group; women < 55 years of age experienced the smallest fall, with an AAPC of 1.9%.[10] Izadnegahdar and colleagues examined 10-year hospitalisation rates for acute myocardial infarction in adults aged 20 years and over in British Columbia, Canada.[14] Overall, rates declined in both men and women. However, age-stratified analyses revealed increased hospitalisation in younger (20-55 years) women (1.72% per year 95% CI, 0.08 to 3.39) compared to similarly aged men (0.32% per year 95% CI, -0.73 to 1.38). Nedkoff et al. investigated 12-year trends (1996-2007) in Western Australia's acute coronary syndrome (ACS) hospitalisation rates.[26] Overall, during the study period, the rates of ACS declined in both men and women. Analysis of age-specific (35-54 years) data revealed an increase in rate among women (APC 2.0; 95% CI 1.0 to 3.8) versus the decrease noted in men (APC −1.0; 95% CI −1.7 to −0.3). Ekker et al. examined the incidence of stroke in young (18-50 years) compared to older (>50 years) Dutch adults.[27] During the study period (1998-2010), the incidence of stroke increased in young adults (23%; p for trend <0.001) compared to a decreased noted in older adults (-11%; p for trend = 0.009). Among adults aged 18-44, the incidence was higher in women than men.[27] There is limited data on sex differences in heart failure trends. A Danish study investigated age-specific trends in the incidence of heart

failure between 1995 and 2012.[28] The incidence of heart failure doubled in young (≤ 50 years) adults but decreased in older (> 50 years) adults.

The excess risk in women for shared CVD risk factors

Although men and women share traditional risk factors, their impact differs between the sexes. Hypertension, total and low-density lipoprotein cholesterol have a greater effect in men than in women.[29] Diabetes, smoking, and triglycerides impact women more than men.[29] A Danish study showed that the pooled ratio of relative risks for myocardial infarction was 50% higher among female than male smokers (RR 1.57; 95% CI, 1.25 to 1.97).[30] For type 2 diabetes, a meta-analysis of 29 studies showed that the pooled ratio of relative risks for diabetes was 46% higher among women compared to men with diabetes (RR 1.46 1.14 to 1.88).[31]

Sex-specific risk factors for CVD

Scoping search

I scoped the Medline database, Google Scholar (first 200 hits) and a database of systematic reviews (Epistemonikos.org),[32] to identify studies examining the relationship between female sex-specific (biological) factors and their association with CVD. There were no restrictions to the study design or language. The scoping search aimed to: (i) determine the breadth of sex-specific factors associated with CVD; (ii) map studies according to hierarchy or level of evidence; and (iii) identify gaps to inform potential areas for future research. Table 1.1 presents the scoping search results (list of sex-specific factors). The highest level of evidence for most of the sex-specific factors were secondary studies (systematic reviews). The majority of the studies were published after 2007. Several of the reproductive factors had more than one systematic review examining their relationship with CVD (overlapping reviews). Overlap occurs when two or more reviews address the same question and include similar primary studies.[33] Results from some of the overlapping reviews reported inconsistent

findings. For example, in the review by Chen et al.,[34] each 1-year increase in age at menarche was associated with a reduced risk of ischaemic heart disease mortality (adjusted RR 0.969; 95% CI, 0.947 to 0.993). The study by Charalampopoulos et al.[35] found no association between early age at menarche (< 12 years) compared to median menarcheal age group and ischaemic heart disease mortality (adjusted HR 1.22; 95% CI, 0.95 to 1.56). A review by Kleijin et al. examined the association between reproductive history, including age at menarche and CVD in postmenopausal women,[36] but found no association. The meta-analysis by Smith et al.[37] showed that one standard deviation increase in offspring birth weight was associated with decreased maternal mortality from CVD (adjusted HR 0.75; 95% CI, 0.67, 0.84). Grandi et al. found no association between birth weight and fatal and non-fatal CVD (adjusted OR 1.29; 95% CI, 0.91–1.83) in the analyses comparing history of low birth weight (< 2500g) compared to birthweight ≥ 2500g at delivery.[38] The highest available evidence was contained in primary studies for a few reproductive factors (endometriosis, pelvic inflammatory disease, anaemia in pregnancy, menstrual cycle characteristics). The few studies that examined the relationship between endometriosis and CVD were limited to hypertension and coronary heart disease outcomes in nurses from the US.[39,40] Two Taiwanese studies showed that women with a history of pelvic inflammatory disease (PID) were at an increased risk of myocardial infarction (aHR 1.86, 95% CI; 1.23-2.81) and stroke (aHR 1.63; 95% CI; 1.45–1.85) compared to those without PID. However, these studies did not adjust for key confounders, including smoking, BMI, and hypertension. Due to differences in exposure and outcome definition, studies investigating the relationship between menstrual cycle characteristics and future CVD risk have reported contradictory findings. There is limited UK data on the relationship between menstrual cycle characteristics and subsequent risk of CVD.

Table1.1: List of reproductive factors linked to cardiovascular outcomes as identified from a scoping search

Reproductive factor	Study design-highest level of available evidence	Year of publication (Range)	No of studies	Outcome studied
Fertility-related (reproductive endocrine)				
Menarche	Systematic review and meta-analysis	2014-2018	4	Composite CVD, Stroke, IHD
Menstrual cycle characteristics	Cohort study	2010-2017	3	Composite CVD, IHD, Stroke.
Progesterone only contraceptive pills (POP)	Systematic review and meta-analysis	2009-2018	4	Myocardial infarction, Stroke
Combined oral contraceptives. (COC)	Systematic review and meta-analysis	1990-2015	17	Myocardial infarction, Stroke
Oral contraceptive pills (COC or POP)	Systematic review and meta-analysis	2015-2018	2	Stroke
Cardiovascular risk associated with hormonal contraceptive use in women with pre-existing medical conditions	Systematic review and meta-analysis	2005-2016	8	Myocardial infarction, Stroke
Polycystic ovary syndrome	Systematic reviews and meta-analysis	2002-2018	7	Composite CVD, IHD, Stroke
Endometriosis	Cohort study	2016	1	IHD
Pelvic inflammatory disease	Cohort study	2011-2016	3	Myocardial infarction, Stroke Intracerebral haemorrhage
Premature ovarian insufficiency	Systematic review and meta-analysis	2016	2	Composite CVD, IHD, Stroke
Fertility therapy	Systematic review and meta-analysis	2017	1	Composite CVD, Stroke
Age at menopause	Systematic review and meta-analysis	2006-2016	4	Composite CVD, IHD, Stroke
Menopausal symptoms	Systematic review and meta-analysis	2016	1	Composite CVD, IHD, Stroke
Breastfeeding	Systematic review and meta-analysis	2015-2017	2	Composite CVD
Adverse pregnancy outcomes and other pregnancy related factors				
Parity & Pregnancy	Systematic review and meta-analysis	1996-2018	7	Composite CVD
Age at first birth	Systematic review and meta-analysis	2017	1	Composite CVD, IHD, Stroke
Miscarriage	Systematic review and meta-analysis	2013	1	IHD, Stroke
First trimester bleeding without miscarriage	Cohort study	2012	1	IHD
Anaemia in pregnancy	Cohort study	2015	1	Composite CVD
Hypertensive disorders of pregnancy	Systematic review and meta-analysis	2007-2018	6	Composite CVD, IHD, Stroke, HF
Gestational diabetes mellitus	Systematic review and meta-analysis	2015-2018	2	Composite CVD, IHD, Stroke
Stillbirths	Systematic reviews and meta-analysis.	2019	1	Composite CVD
Placental abruption	Systematic review	2017-2019	2	Composite CVD
Preterm birth	Systematic review and meta-analysis	2014-2018	3	Composite CVD, stroke, IHD
Low birth weight & Small for gestational age	Systematic review and meta-analysis	2007-2019	3	Composite CVD

CVD= Cardiovascular disease, IHD= Ischaemic heart disease, HF= Heart failure

Among UK women, Iliodromiti and Nelson found no association between irregular menstrual cycles compared to regular menstrual cycles and fatal and non-fatal IHD (aHR: 0.88 95% CI; 0.58 to 1.34). The UK study treated irregular menstrual cycles and cycles lasting more than 34 days as a single composite exposure. In a prospective cohort of US women, compared to regular menstrual cycles, the risk of fatal and non-fatal CHD was increased among women with very irregular cycles (aRR 1.53; 95% CI 1.24-1.90) and usually irregular menstrual cycles (aRR 1.22; 95% CI, 1.04-1.44).[41]

Definition of reproductive factors associated with CVD

Fertility-related factors

Reproductive endocrine factors can affect fertility may have an impact on long-term cardiovascular health. In women the main reproductive hormones include oestrogen and progesterone. The hypothalamus–pituitary–ovary axis (HPO) is the primary regulator of female reproductive function. Dysregulation of the HPO axis may lead reproductive endocrine disorders. The most common reproductive endocrine disorders include menstrual cycle disorders (amenorrhoea, irregular cycles) polycystic ovary syndrome (PCOS), and endometriosis.

Age at menarche

Menarche refers to a woman's first-ever menstrual period. It heralds the onset of a woman's reproductive capacity.[42] Onset of puberty starts at eight years of age and is marked by breast budding (thelarche). Next is pubic hair development (pubarche), growth spurt and finally, menarche. The average age at onset of menarche is 12.4 years and may vary due to differences in race, ethnicity, obesity, and environmental factors.[42] By the age of 15, approximately 98% of women will experience their first menstrual cycle. Generally, the onset of menarche is considered to be early if it occurs before 12 years of age and late if it occurs

after 15 years.[42] Menstrual cycles in the first few years after menarche are usually irregular due to immaturity of the hypothalamic pituitary ovarian axis.[42]

Menstrual cycle characteristics

Menstruation is the cyclic shedding of the uterine lining under the influence of hormones produced by the hypothalamus, pituitary, and ovary.[43] Menstrual cycle length is defined as the period between day 1 of the menstrual bleeding of one cycle to the onset of bleeding for the next cycle. The menstrual cycle length median duration is 28 days (range 25-30 days). Polymenorrhoea refers to a menstrual cycle length of fewer than 21 days, while oligomenorrhoea refers to menstrual cycle lengths exceeding 35 days. The volume of blood loss during a menstrual flow may range from spotting to 80mls (average 30 mls) per cycle.[43] Menstrual cycle characteristics may be affected by stress, BMI, ethnicity, and lifestyle factors.

Hormonal contraceptive use

Hormonal contraceptive methods contain either progesterone, oestrogen, or a combination of both. There are several forms of hormonal contraceptives, including the oral contraceptive pill, coil, implant, contraceptive patch, and vaginal ring. Globally, approximately 16% (151 million) of women in the reproductive age group use the pill as their preferred method of contraception.[44] Oral contraceptive pills are divided into progesterone only, combined oestrogen and progesterone (COC), and continuous or extended pills.[45] COC pill is the most commonly prescribed pill. In the COC pill the oestrogen component is combined with various generations (first, second, third) of the progestin component. Progesterone acts mainly by inhibiting ovulation, while oestrogen acts by inhibiting follicular development.[45]

Polycystic ovary syndrome

Polycystic ovary syndrome (PCOS) is a reproductive endocrine disorder characterised by irregular menstrual periods, polycystic ovaries or hyperandrogenism (excess male

hormone).[46] The global prevalence of PCOS ranges from 5-20% among women of reproductive age.[46] The cause of polycystic ovary syndrome is yet to be determined but is likely to be multi-factorial.[47] The pathophysiology of PCOS involves a complex interplay of genetic, foetal, metabolic and environmental factors. Key features among these factors are hyperandrogenism, aberrant gonadotrophin secretion, ovarian dysfunction, hyperinsulinaemia and follicular arrest.[48]

Endometriosis

Endometriosis is the presence of endometrial-like tissue in sites outside the uterus.[49] Approximately 10% of reproductive age group women suffer from endometriosis. The mechanisms leading to the presence of endometrial tissue outside the uterus are not entirely clear. The most widely recognised mechanism leading to presence of endometrial tissue in ectopic sites is retrograde menstruation.[49] Menstrual blood containing endometrial cells may flow back through the fallopian cavity into the abdominopelvic cavity, where they implant, mature and bleed with each menstrual cycle. A second proposed mechanism is metaplastic transformation.[49] Endometrial cells in the peritoneal cavity arise from metaplasia of coelomic epithelium due to trigger by unknown stimuli. A third mechanism is the spread of endometrial cells through the vascular and lymphatic systems.[49]

Pelvic inflammatory disease

Pelvic inflammatory disease is inflammation of the upper genital tract (uterus, fallopian tubes and ovaries) following an ascending infection from the lower genital tracts.[50] In most cases, infection is caused by sexually transmitted bacteria (*Neisseria gonorrhoea* and *Chlamydia trachomatis*). PID is most common among women in the 15-25 age category. Short-term complications include pelvic and tubo-ovarian abscesses, while longer-term complications include infertility, chronic pelvic pain, and ectopic pregnancy.[50]

Premature ovarian insufficiency and early menopause

Menopause is the permanent cessation of menstrual activity following the loss of ovarian function. Menopause may be natural (no known organic or physiological cause) or iatrogenic (surgical).[51] In high-income countries, the mean age at natural menopause ranges between 50-52 years.[52] For about 10% of women menopause will occur between the age of 40-45 years (early menopause). Approximately 1% of women will have menopause before the age of 40 years (premature ovarian insufficiency, POI).[52] Although POI is primarily an idiopathic condition, other associated risk factors include genetic causes, metabolic disorders, autoimmune conditions, and inflammatory disorders.

Vasomotor and menopausal symptoms

Vasomotor symptoms (hot flushes and night sweats) are the hallmark of the menopausal transition and are experienced by up to 80% of women during the menopausal period.[51,53] Hot flushes are sudden dilatation of the face and neck lasting for 1-5 minutes and accompanied by sweating and can be debilitating.[51] Hot flushes are common in late perimenopause and early postmenopausal years. However, for some women vasomotor symptoms may persist for several years. The intensity of vasomotor symptoms varies widely between women and may be influenced by genetic, racial (black ethnicity), environmental and lifestyle factors (physical activity, smoking, diet).[51] Hot flushes are common during sleep. The relationship between hot flushes, night sweats and sleep arousal are not clearly understood. Declining oestrogen levels trigger a disturbance of the thermoregulatory activity in the hypothalamus resulting in sudden vasodilation.[54]

Adverse pregnancy outcomes and other pregnancy related factors

The obstetric period is characterised by increased physiological demands on the cardiovascular system to support the growing foetus. During this period cardiac output increases by 30-50% due to an increase in heart rate and stroke volume. The majority of

women withstand the physiological demands of pregnancy without any complications. However, about 30% of pregnancies result in adverse pregnancy outcomes (APOs).[55] APOs are associated with future risk of CVD and may be used to identify young women at risk of CVD who would not have otherwise be identified by traditional risk prediction tools.

Hypertensive disorders of pregnancy

Hypertensive disorders of pregnancy (HDP) refers to a group of related disorders that include gestational hypertension, pre-eclampsia, pre-eclampsia superimposed on chronic hypertension and chronic hypertension.[56] Pre-eclampsia refers to newly diagnosed hypertension after 20 weeks gestation in a previously normotensive person and with the presence of proteinuria or, in the absence of proteinuria, features of severe pre-eclampsia (pulmonary oedema, elevated liver transaminases, renal insufficiency, visual or cerebral symptoms and thrombocytopenia).[56] Gestational hypertension is hypertension diagnosed after 20 weeks' gestation in a previously normotensive person without evidence of proteinuria and other features of severe pre-eclampsia.[56] Chronic hypertension is hypertension diagnosed before pregnancy or before 20 weeks gestation. It could also refer to hypertension first diagnosed during pregnancy that persists for more than 12 weeks beyond delivery. Chronic hypertension with superimposed pre-eclampsia refers to a sudden increase in blood pressure or new onset of proteinuria or sudden increase in proteinuria in a patient diagnosed with chronic hypertension before or in early pregnancy.[56] Globally, up to 10% of all pregnancies are affected by hypertensive disorders.[57] The pathogenesis of hypertensive disorders of pregnancy are not clearly understood. HDP are characterised by aberrant spinal artery remodelling, abnormal placentation, placental ischaemia, and oxidative stress resulting in endothelial dysfunction and end organ damage.[58]

Pregnancy loss (miscarriages and stillbirths)

Spontaneous abortion or miscarriage is defined as intra-uterine foetal loss before viability (20-28 weeks). It is the most typical pregnancy complication, with 23 million (44 per minute) miscarriages recorded annually.[59] Most miscarriages occur early in pregnancy (1st trimester). The causes of miscarriage include chromosomal abnormalities, endometrial defects, demographic factors (age, body mass index, ethnicity), lifestyle factors (smoking, high alcohol consumption), and clinical factors (antiphospholipid antibodies, subclinical hypothyroidism and thyroid autoantibodies, uterine anomalies, sexually transmitted infections).[59] Stillbirth refers to foetal demise that occurs after 28 weeks' gestation.[60] Approximately 2 million stillbirths occur annually worldwide.[60] Stillbirth is antepartum if it occurs before labour or intrapartum if it occurs after labour. The causes of stillbirth include demographic factors (advanced maternal age, black ethnicity), lifestyle factors (smoking, high alcohol consumption), and clinical factors (multiple gestation, reproductive technology).[60]

Gestational diabetes mellitus

Gestational diabetes mellitus (GDM) is a glucose intolerance of variable severity detected for the first time in the second or third trimester of pregnancy.[61] Approximately 14% of all pregnancies globally, equivalent to 18 million deliveries annually, are affected by GDM.[62] The risk factors for GDM include genetic susceptibility, family history, demographic (advanced maternal age, ethnicity, low stature), lifestyle (high pre-pregnancy BMI, sedentary, poor diet), and clinical (vitamin D deficiency, polycystic ovary syndrome, twin pregnancy).[61] GDM arises from impaired glucose tolerance following β-cell dysfunction in the setting of chronic insulin resistance.[63] Decreased insulin resistance in the second or third trimester reflects decreased insulin resistance before pregnancy.

Placental abruption

Placental abruption is the separation of the placenta from the uterus lining before the second stage of labour is completed.[64] The risk factors for placental abruption include demographic (advanced maternal age), lifestyle (smoking, cocaine use) and clinical (hypertension, prior history of placental abruption) factors.[64] The placenta is the source of oxygen and nutrients and the route for excretion of foetal waste products.[64] Placental abruption occurs when maternal blood vessels detach from the placenta resulting in bleeding between the uterine lining and maternal side of the placenta. Accumulation of blood separates the uterine wall and placenta.[64]

Preterm delivery

Preterm delivery refers to live delivery prior to the completion of 37 weeks of gestation. Preterm birth is referred to as extremely preterm, very preterm and moderate to late preterm if it occurs at less than 28 weeks, 28 to 32 weeks, and 32-37 weeks, respectively.[65] Around 15 million preterm deliveries occur every year, with the rates of preterm delivery ranging from 5% to 18% globally.[65] The risk factors associated with preterm delivery include demographic (advanced maternal age, black ethnicity), lifestyle (extreme of BMI, smoking, stress), and clinical (prior preterm delivery, uterine curettage, cervical surgery, uterine malformations, antepartum haemorrhage, uterine malformations).[65] The biological mechanisms responsible for preterm delivery are unclear. Proposed mechanisms include genetic predisposition, maternal vascular under perfusion, mid-trimester increases in cell-free foetal DNA, and inflammation and infection.[65]

Low birth weight and small for gestational age

Low birth weight and small for gestation age are distinct entities. Low birth weight refers to birth weight below 2500g irrespective of gestational age.[66] Low birth weight is further classified as very low (< 1500g) or extremely low (< 1000g). Low birth weight results from

intrauterine growth restriction or preterm birth. Globally, approximately 20 million newborns (15-20% of all live births) per year are categorised as low birth weight.[66] Small for gestational age (SGA) refers to birthweight below the 10th percentile of gestational age based on appropriate reference.[67] Small for gestational age and intra-uterine growth restriction are often used interchangeably but are different. Intra-uterine growth restriction refers to newborns with malnutrition and growth restriction in-utero regardless of their birth weight percentile.[67]

Post-partum haemorrhage

Post-partum haemorrhage refers to blood loss ≥ 500 ml from the genital tract following vaginal delivery or blood loss > 1000 ml after caesarean section.[68] Primary post-partum haemorrhage (PPH) occurs within the first 24 hours of delivery. Secondary PPH refers to PPH that occurs after 24 hours and up to 6 weeks after delivery. Approximately 5-10% of all deliveries result in PPH.[69] The major risk factors associated with increased risk of PPH include demographic (advanced maternal age, Asian ethnicity) and clinical (placenta praevia, multiple pregnancy, previous PPH, pre-eclampsia). The causes of PPH include uterine atony, lacerations of the reproductive tract, retained placenta, coagulopathy, and endometritis.[69]

Parity and gravidity

Gravidity describes the number of times a woman has been pregnant. Parity refers to the number of births or deliveries of viable gestational age (≥ 24 weeks) recorded during a woman's lifetime irrespective of the outcome.[70]

Justification for this thesis

In summary, CVD is the leading cause of death in women globally. Despite this CVD in women in underappreciated, underestimated, and untreated leading to suboptimal CVD care for women. Disparities in CVD between the sexes exist. Emerging data links reproductive factors to poor cardiometabolic health. Therefore, reproductive history is a readily available tool that may be utilised to identify women potentially at risk of cardiovascular vulnerabilities. Electronic health records from UK primary care are a rich source of sociodemographic, medical, and reproductive data that may be harnessed to improve women's cardiovascular health. In chapter 2 of this thesis, I discuss data from the IVQIA Medical Research Data (IMRD-UK) database, which contains UK electronic health records. IVQIA Medical Research Data (IMRD-UK) contains information from The Health Improvement Network (THIN), a Cegedim-owned database. IQVIA and Cegedim have entered into a licence agreement to distribute and utilise the THIN database for clinical and epidemiological research. Although CVD is associated with older age groups, evidence suggests that all age groups are affected. Recent age-and sex-specific temporal trend analyses conducted in several high-income countries have revealed that CVD mortality trends continue to decline in older age groups (>55 years) but have stagnated in younger adults (< 55 years). In addition, reports from several high-income countries, including the USA, Canada, and Australia, show that younger women have increased myocardial infarction hospitalisation rates. Compared to men, women with myocardial infarction have longer in-hospital stays, higher in-hospital mortality, and worse outcomes in the long term. It is not clear whether similar trends are observable in the UK population. In Chapter 3 of this thesis, I address this gap by examining sex-specific temporal trends in the incidence and prevalence of major CVD subtypes, including IHD, cerebrovascular events and heart failure. The rising prevalence of traditional risk factors in young adults including type 2 diabetes mellitus and

obesity may have partly contributed to the slowing down of CVD mortality and morbidity declining trends in this age-group. Also, up to 20% of CVD risk cannot be explained by traditional risk factors only. Female sex-specific factors are emerging as factors that enhance the risk of CVD throughout the life span. Several systematic reviews and meta-analyses have examined the association between female reproductive factors (pregnancy complications and gynaecologic endocrine factors) and subsequent maternal CVD years beyond the post-partum period. Despite the presence of these reviews and given that pregnancy complications resolve after the peripartum period awareness about sex-specific factors for CVD is low among reproductive age group women and medical personnel alike. Moreover, reviews examining the same topic may present conflicting results; therefore, a further appraisal of the evidence is required. Thus, the next logical step is to appraise and synthesise the evidence provided by these existing reviews into a single document to guide policy making. In Chapter 4 of this thesis, I pool into one single document (an umbrella review) all secondary-level evidence (systematic reviews and meta-analyses) that examine the relationship between reproductive factors and maternal risk of cardiovascular disease. In addition, I investigate whether these reproductive factors are acknowledged in relevant UK guidelines and suggest policy recommendations where they are not. Endometriosis, pelvic inflammatory disease, and menstrual cycle characteristics are among the reproductive factors for which systematic review level evidence is lacking, and evidence of their association with CVD is limited, uncertain or contradictory. In Chapters 5 to 7 of this thesis, I address this gap by investigating whether these reproductive factors are associated with CVD in women from the UK.

Aims and Objectives

The overall aim of the thesis was to examine the association between female reproductive factors and cardiovascular disease across the lifespan.

Specific objectives

1. To examine sex-specific temporal trends in the incidence and prevalence of cardiovascular disease in young UK adults.
2. To systematically identify, appraise and synthesise into one document (umbrella review) high-level evidence from existing systemic reviews and meta-analyses that have examined the association between reproductive factors and CVD in women.
3. To examine the association between endometriosis and future risk of CVD among UK women.
4. To examine the association between pelvic inflammatory disease and future risk of CVD among UK women.
5. To examine the relationship between menstrual cycle characteristics including the regularity and frequency of menstrual cycles and future risk of CVD among UK women.

Thesis outline

Chapter 2: Overview of the study designs and data source.

Chapter 3: Temporal trends in the incidence and prevalence of CVD in young UK adults.

Using electronic health records from the UK, this chapter examines the incidence and prevalence of cerebrovascular disease (stroke and transient ischaemic attack), heart failure and ischaemic heart disease, including subtypes of angina and myocardial infarction, in young adults for the period 1998-2017.

Chapter 4: The association between the reproductive health of young women and cardiovascular disease in later life: An Umbrella review.

This chapter identifies, appraises, and synthesises evidence from systematic reviews and meta-analyses that have examined the relationship between female reproductive factors and CVD. In addition, it examines relevant UK guidelines for recognition or mention of female reproductive factors associated with CVD.

Chapter 5: The association between endometriosis and risk of cardiovascular disease.

This chapter examines the relationship between endometriosis and the future risk of CVD in women using UK primary care data.

Chapter 6: Risk of cardiometabolic outcomes among women with a history of pelvic inflammatory disease: A retrospective matched cohort study from the UK.

This chapter explores the relationship between history of pelvic inflammatory disease and subsequent risk of CVD in women using UK primary care data.

Chapter 7:

This chapter explores the relationship between menstrual cycle characteristics, including the regularity and frequency of menstrual cycles, and the risk of CVD in women using UK primary care data.

Chapter 8: Discussion

This chapter summarises the main findings of Chapters 3 to 7, provides recommendations for public health, and proposes areas for future research.

Chapter 2. Overview of study designs, data source and methods

Introduction

This chapter provides an overview of study designs, data sources and methods employed in the analyses in this thesis. Detailed descriptions of the statistical methods used in this thesis are provided within the individual studies/chapters.

Umbrella reviews

Evidence-based medicine (EBM) recognizes that not all evidence is the same and that a hierarchy of evidence exists. Study designs at the bottom of the hierarchy include case series and reports. Case-control and cohort studies are ranked in the middle, while randomised control trials, systematic reviews, and meta-analyses are placed at the top.[71] Systematic reviews and meta-analyses play a key role in evidence-based practice as they provide high-level evidence that can aid in decision-making. Over the last thirty years, published systematic reviews have increased dramatically. A study conducted in 2010 suggested that up to 11 systematic reviews were published daily.[72] Almost certainly, this number has grown exponentially. Given the rising number of systematic reviews, the next step is to summarise reviews on a given topic and compare their findings. An umbrella review is a study synthesising evidence from multiple reviews addressing a similar topic into one document.[73] An umbrella review aims to examine what is known, provide recommendations for clinical practice, identify what is unknown, and propose areas for future research.[73] The results in an umbrella review are summarised using tabular and graphical presentations.

Unique challenges in umbrella review methodology

The primary unit of synthesis for an umbrella review is the systematic review. The format and methodology required to conduct an umbrella review is similar to the one needed for a systematic review. Therefore, umbrella reviews follow the format recommended in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). PRISMA items are discussed in detail in Chapter 4.

Synthesising data from systematic reviews is a complex process and has methodological challenges. Two challenges worth mentioning are the overlap between systematic reviews and the inclusion of outdated systematic reviews. Overlap occurs when two or more existing systematic reviews examine similar research questions (similar interventions and outcomes) and consequently include similar primary studies. The degree of overlap may vary between overlapping reviews. There are several strategies to deal with overlap. One strategy (full inclusion scenario) involves including all the overlapping reviews and synthesising that data by extracting the outcome data from the primary studies one at a time. However, this process is time-consuming and labour-intensive, especially if presented with multiple overlap scenarios. In addition, the quality and reporting of overlapping reviews may vary. Other researchers opt for a restricted approach. A restricted approach involves including only one systematic review when faced with overlapping reviews. The selection criteria may involve selecting a review that is: Cochrane type, the most recent, the one with the highest quality, or the one with the highest number of participants. A limitation of this restricted approach is that the inclusion of a review based on pre-specified criteria may lead to the loss of outcome data that may have been captured by another excluded review. A separate hybrid strategy involves combining elements of the full and restricted approach. To begin with, the hybrid approach involves including all overlapping reviews in the umbrella review. Next, the degree of overlap is then assessed using a citation matrix and quantified using the corrected covered area.[33] A citation matrix is a graphical representation of the degree of overlap that includes primary studies as row data and overlapping systematic reviews as column data. The corrected covered area (CCA) is then calculated to quantify the degree of overlap. CCA expressed as a percentage is computed as N-r/(rc-r).[33] N refers to the number of checked squares in the citation matrix, r is the number of rows (primary studies included in the overlapping reviews), and c represents the number of columns (number of overlapping

reviews). The degree of overlap may range from slight (CCA 0-5%), moderate (CCA 6-10%), high (CCA 11-15%) to very high (> 15%). Finally, overlapping umbrella reviews are selected for inclusion in the umbrella review based on pre-specified criteria and degree of overlap. For instance, if overlap involves a Cochrane versus a non-Cochrane review, the Cochrane review may be given preference due to their methodological rigour and quality. Where there is a slight to moderate (CCA < 11%) degree of overlap between non-Cochrane reviews, all overlapping may be included, and the results compared. If overlap is high (CCA ≥11%) preference may be given to: highest quality as evaluated by relevant quality assessment tool, the most recent, the one with pooled effect estimates, and the one with the highest number of participants. In this thesis I adopted the hybrid approach described here to deal with the problem of overlap.

Second, eligible systematic reviews may be out of date. Newly published primary studies may change the conclusion of existing systematic reviews and alter the evidence landscape. Consequently, policy formation will not be influenced by current evidence. Rather than repeating the entire systematic review process, updating existing reviews has benefits. This thesis dealt with the issue of out-of-date reviews by adopting the framework Garner et al. recommended.[74] A review was eligible for an update if all the following criteria were met: (i) the review was rated as at least moderate in quality; (ii) there were eligible newly published primary studies; and (iii) findings from newly published studies would alter the conclusions of an existing systematic review. To determine whether findings from a study would alter the conclusion of an existing review, quantitative tests were employed for existing systematic reviews with meta-analysis as the primary form of synthesis, while qualitative tests were employed for systematic reviews with a narrative synthesis as the primary mode of analysis.[75] Quantitative tests involve combining the pooled effect estimates of an existing review with the result of a newly published primary study to generate a new pooled effect estimate.

Qualitative tests involve consulting subject matter experts to decide whether it is worthwhile to proceed with an update. Both methods are reported to be equally effective.[75]

Data sources for epidemiological analyses

Routinely collected data may be leveraged to address evidence gaps on potential sex-specific factors for cardiovascular disease.[76] This section provides background information about universal health coverage in the UK, IQVIA Medical Research Data (incorporating and formerly known as The Health Improvement Network database), Read code clinical terminology, and selecting Read codes for medical research.

Universal health coverage in the UK

The UK has provided universal health care to all its residents since the National Health Service (NHS) formation in 1948.[77] More than 98% of UK residents are registered with a general practitioner (GP) near their residence. Patients are registered in only one general practice at a time. GPs are responsible for providing non-emergency care and referrals to secondary or tertiary health care when required.[78] Thus, GPs function as 'gatekeepers' of the NHS service. At all levels of care, medical services, including consultations, emergency care, elective surgery, cancer screening and immunisations, are free of charge.[77] Electronic transfer of patient records occurs between practices if a patient relocates. This ensures that the GP holds a lifetime of patient records.

Electronic Health Records

Electronic health records (EHR) refer to the organised capture of medical information in a digital format during a medical encounter. The use of electronic health records in the UK began around the 1990s. The software used by general practices is integrated within practice systems to ensure that patient data collection is unobtrusive. There are various commercial suppliers of information systems for EHR in the UK. The main ones include Egton Medical

Information Services (EMIS), Vision managed by In Practice System (InPS) Limited, and SystemOne developed and managed by The Phoenix Partnership (TPP).[79]

IQVIA Medical Research Data (IMRD) and The Health Improvement Network Database (THIN)

Historical overview

The development of EHR databases was driven by the need to computerise medical records and conduct medical research. In Practice Systems (InPS), which in 1987 was rebranded as Value Added Medical Products Limited (VAMP Ltd), developed one of the first UK primary care databases, the General Practice Research Database (GPRD).[80,81] In 1993, due to fiscal challenges, VAMP Ltd was purchased by Reuters Health Information, who donated GPRD to the UK Department of Health one year later.[80,81] The agreement was that the GPRD would be used for research on a non-profit basis. The Office for National Statistics managed GPRD until 1999. After that, the Medicines and Health Care Products Regulatory Agency (MHRA) took control of its management. In 2012, GRPD was rebranded as the Clinical Practice Research Datalink (CPRD).[80]

After the acquisition of VAMP Ltd in 1993, some former company employees teamed up to form Epidemiology and Pharmacology Information Core (EPIC).[81,82] Between 1995-1999 EPIC had the sole rights to supply EHR data for research conducted in GPRD in the UK.[83] Meanwhile, after donating GPRD to the UK Department of Health, Reuters Health Information continued developing software systems to manage general practices. In 1995, Reuters Health Information launched the Vision EHR software system.[80] In 1999, Cegedim, a European software company, took control of Reuters Health Information and renamed it In Practice Systems (InPS).[80] Once the exclusive rights held by EPIC expired, EPIC collaborated with Cegedim to form The Health Improvement Network database (THIN). Later, Cegedim took ownership of EPIC. A series of company mergers and business

partnerships occurred after that. In 2014, Intercontinental Medical Statistics Health Incorporation (IMS Health) acquired part of Cegedim's businesses.[84,85] Two years later, Quintiles acquired IMS Health, rebranding the group as IQVIA.[86,87] IVQIA Medical Research Data (IMRD-UK) incorporates data from The Health Improvement Network (THIN) a proprietary database of Cegedim. Through a licence agreement, IQVIA and Cegedim are working together to distribute and utilise the THIN database for clinical and epidemiological studies. The use of IMRD-UK for research purposes has received approval from the NHS Research Health Authority (NHS Research Ethics Committee ref. 18/LO/0441).[88]

Participating in THIN data collection scheme

Including a patient in the THIN data collection scheme occurs when a patient registers with a GP contributing data to the scheme or when a practice joins the scheme.[88] The data is collected retrospectively for all patients (active, inactive, or transfers-out) who have not opted out. Patients can opt-out of the data collection scheme by informing their practice.[88] From that point onwards, their data will not be collected with any historical data stored in line with guidelines provided by the Medical Research Council (MRC). Three updated datasets of IMRD-UK (incorporating THIN data) are released annually for use in research. By 2019, there were 18 million patients in THIN contributed by over 800 practices spread across the UK.[88]

Validity and data quality

THIN, and consequently IMRD-UK, is representative of the UK population in terms of sociodemographic characteristics (age, sex, socioeconomic status), death rates and Quality and Outcomes Framework (QOF) condition prevalence.[89–91] Participating practices receive feedback on the completeness and quality of their data.[88] In this thesis, practices were eligible to enter studies from the later of two dates: (i) the acceptable mortality reporting (AMR) date

and (ii) a year after the practices began to use the Vision software system. AMR refers to the date when the recording of mortality in a practice is within three standard deviations of the demographically and regionally expected values as determined by the Office for Nation Statistics (ONS).[88,92]

Data architecture in IMRD-UK database

Data in IMRD-UK are contained in a set of files, namely medical, additional health data (AHD), postcode variable indicator (PVI), patient, therapy, consultation, staff, and practice. These records are linked together using a unique patient identifier that is practice specific. **Table 2.1** provides the data architecture of the IMRD-UK database.

Table 2.1 Data architecture of IMRD-UK

File	Description	Data fields
Patient	Demographic and registration details.	Year of birth Sex Date patient registered with the practice Registration status Death date
Medical	Diagnoses, symptoms, and interventions	Medcode (Diagnostic Read code) Event date- Date of diagnosis
Therapy	Prescriptions issued in primary care	Multilex code British National Formulary (BNF) code Date of prescription Dosage
AHD	Additional health data i.e., Laboratory results (Hb A1C, Hepatitis), Immunization (Tetanus, Polio, Diptheria), Lifestyle characteristics (Smoking, Alcohol), Physiological measurements (Height, weight, BP, waist circumference), Maternity pregnancy dates.	Ahdcode
Consultation	Provides the date, duration, and time of practice consultation.	
Staff	Provides information on the sex and role of practice staff that have entered the data.	

Clinical coding in UK primary care

Historical overview

The use of EHR in UK primary care practice was pioneered in the late 1960s by Dr John Preece, a GP from Exeter.[93,94] During the same period, The Oxford Medical Linkage Project, led by Dr John Perry, was developed to investigate the feasibility of automated collection of health records from general practices for the purpose of conducting epidemiological research.[95] This project led to the formation of the Oxford Medical Information System (OXMIS) clinical coding system, an extended version of the International Classification of Disease System 8 (ICD-8).[95] GPs used OXMIS codes throughout the 1980s. However, further development of the OXMIS coding system stopped after the demise of Dr John Perry. In 1980, Dr James Read and other partners at Abvie Limited developed the Read code clinical classification system.[96] Read codes are a super-set of codes derived from existing clinical terminologies. These include the International Classification of Diseases system (ICD-9), Office of Population Censuses and Surveys classification of surgical operations, procedures and occupations (OPCS-4), British National Formulary (BNF), and the International Classification of Procedures in Medicine (ICPM).[97] In 1988, the Royal College of General Practitioners and The British Medical Association recommended the national use of the Read code system. The first version of Read codes, termed the 4-byte GP set, was adopted for use by the NHS in 1990.[96] Read code version 2, or the 5-byte system, enabled hospitals to map their data to ICD-9.

Read code hierarchy

The Read code thesaurus is organised into chapters. Chapters 0 to 9 represent occupations, procedures (laboratory, diagnostic, preventative, therapeutic, surgical) and administrative codes, while chapters A to Z excluding I, V, W and X represent the different physiological systems of the body. A Read code (version 2) is made up of 7 characters composed of

alphabetical or numeric characters (medcode) and an associated descriptive component up to 60 characters long. Read code concepts are hierarchically organised within levels. Each level (stem code) is further split from left to right until finer concepts, termed a "leaf", are reached. These finer concepts represent very specific diagnoses or other finer clinically related terms. **Table 2.2** provides an example of the hierarchy of the Read code clinical system.

Table 2.2 Hierarchical organisation of Read codes

Hierarchy level	Read code	Descriptive terms
1 "Root code."	G....00	Circulatory system diseases
2	G5...00	Other forms of heart disease
3 "Stem code."	G58..00	Heart failure
4	G581.00	Left ventricular failure
5 "Leaf code."	G581000	Acute left ventricular failure

Selection of Read codes

For all epidemiological studies conducted using IMRD-UK/THIN data as part of this thesis, I used sequential steps to select Read codes. Petersen et al. and Watson et al. previously described these steps.[98,99] The first step involved the creation of a list of relevant descriptive terms (keywords) to identify the medical term of interest. Second, a search of the descriptive term column of the Read code thesaurus was performed using the keywords identified in step 1. This step helps to identify the most relevant alphanumeric codes that identify the condition of interest. For, example heart failure is coded under G58. The third step involved searching the Read code column using the relevant codes identified in step 2. For example, the Read code column was searched for 'G58' to identify all the heart failure-related codes and their synonymous terms. These steps were repeated until all the relevant descriptive terms were exhausted. To ensure that all codes were captured, I compared my list with relevant lists

published in previous literature or with lists published in online Read code suppositories, including calibreresearch.org,[100] the University of Manchester clinical codes repository,[101] and the Cambridge university repository.[102]

Strengths and limitations of IMRD-UK/THIN

Strengths

Practices that contribute to THIN are spread throughout the UK; therefore, THIN, and consequently IMRD-UK, are generally representative of the UK population. THIN database contains continuously recorded medical data, including diagnoses, prescriptions, laboratory measurements and symptoms. This facilitates longitudinal analyses covering several years. In addition, conducting retrospective analyses using EHR from the UK is cost-effective and provides large statistical power. Moreover, given the large patient population, it is possible to study rare exposures using THIN data. Data in THIN is collected unobtrusively and therefore reflects "real-world evidence" (RWE).

Limitations

Data in the THIN database is not primarily collected for research purposes; therefore, data may be poorly recorded for some conditions. For instance, recording of ethnicity data is not well captured in the THIN database. Also, data recorded in THIN primarily capture events in primary care. Prescriptions and procedures recorded in secondary care may not be captured in the THIN database unless communicated to primary care; however, diagnoses made in secondary care are communicated to a patient's general practices and are recorded in their primary care EHR.

Chapter 3. Sex-specific temporal trends in the incidence and prevalence of cardiovascular disease in young adults: A population-based study using UK primary care data

The study presented in this chapter has been published:

Okoth K, Crowe F, Marshall T, Thomas GN, Nirantharakumar K, Adderley NJ. Sex-specific temporal trends in the incidence and prevalence of cardiovascular disease in young adults: a population-based study using UK primary care data. Eur J Prev Cardiol. 2022 Feb 9; https://doi.org/10.1093/eurjpc/zwac024

KO conceived the idea of the study guided by KN, NJA, and GNT. KO carried out the data cleaning, statistical analysis, and first draft of the manuscript. All authors: KO, CF, MT, GNT, KN and NJA, reviewed and revised the manuscript.

Abstract

Aims

There is concern that cardiovascular disease (CVD) in young adults is rising; however, current trends in the UK are unknown. We investigated sex-specific trends in the incidence and prevalence of CVD in young UK adults.

Methods

A series of annual (1998-2017) cohort and cross-sectional studies were conducted to estimate incidence rates and prevalence in men and women aged 16-50. Joinpoint regression models were fitted to evaluate changes in trends.

Results

From 1998-2017, incidence and prevalence had an overall downward trend for ischaemic heart disease (IHD) and angina, while coronary revascularisation, stroke/TIA, and heart failure (HF) had an upward trend in both sexes. Myocardial infarction (MI) trends were stable in men and increased in women. For incidence, the average annual percentage change (AAPC) for men versus women, respectively, were: IHD -2.6% versus -3.4%; angina -7.0% versus -7.3%; MI 0.01% versus 2.3%; revascularisation 1.1% versus 3.9%; stroke/TIA 1.9% versus 0.6%; HF 5.6% versus 5.0% (P for trend <0.05 for all except MI and revascularisation in men and stroke/TIA in women). For prevalence, AAPCs for men versus women, respectively, were: IHD -2.8% versus -4.9%; angina -7.2% versus -7.8%; MI -0.2% versus 2.0; revascularisation 3.2% versus 4.1%; stroke/TIA 3.1% versus 3.6%; HF 5.0% versus 3.0% (P for trend <0.05 for all except MI in men). In recent years, IHD and revascularisation trends levelled off, while stroke/TIA and HF trends increased in both sexes.

Conclusion

Overall trends in incidence and prevalence of CVD are worsening in young adults. Factors behind unfavourable trends warrant investigation and public health intervention.

Background

Cardiovascular disease (CVD) is a leading cause of mortality globally and remains a persistent public health burden. In Europe, CVD is the leading cause of premature mortality, accounting for 29% and 26% of the total deaths in men and women under 65 years.[103] Despite commendable improvements, CVD mortality rates have declined unequally in different age groups. Age and sex-disaggregated data from trend analyses conducted in countries from the western world has revealed that the rate of decline in CVD burden was sustained in older adults but had slowed down in younger adults.[10,11,104–108] Differences between the sexes were observed, with coronary heart disease (CHD) mortality trend stagnating in young women.[10] Factors contributing to the slowing down of CVD mortality trends in young adults are heterogenous. The prevalence of common traditional risk factors, including obesity and diabetes, have risen globally.[109,110] This is compounded by a lack of awareness in young adults regarding CVD and associated risk factors.[111] In addition, biological differences in CVD risk are under-appreciated in young adults. Age and sex-specific factors such as pregnancy complications which are associated with premature CVD and place women at a unique disadvantage.[112] Premature CVD translates to young adults living their productive years with ill-health, persistent disability, and increased economic burden.

Studies focussing on CVD in young UK adults are scarce and limited to ischaemic heart disease mortality statistics. To address this gap, we used UK primary care data to examine contemporary trends in the incidence and prevalence of CVD in young UK adults aged 16-50 years.

Methods

A series of cross-sectional studies were conducted on 1st January of every year from 1998 to 2017 to estimate annual prevalence of CVD. Yearly cohort studies were carried out from 1st January to 31st December over the same period to calculate annual incidence rates.

Data Source

IQVIA Medical Research Data (IMRD, incorporating The Health Improvement Network (THIN), is a database of electronic health records contributed by more than 780 general practices spread across the UK. THIN is generalisable to the UK population in terms of demographics and major condition prevalence.[90]

Practices were eligible for inclusion from the later of one year after the practice commenced using the Vision software system and one year after the practice met acceptable mortality reporting to maximise data quality.[92]

Study population

Participants aged 16-50 years were eligible for inclusion. Participants must have been registered with an eligible practice for ≥1 year before study entry to ensure documentation of all important patient data. Study period was 1st January 1998 to 31st December 2017. Study participants were eligible to enter at the latest of their 16th birthday, study start date (1st January 1998) and one year after joining an eligible practice. Participants were censored when they reached 50 years of age.

Case definition of cardiovascular diseases

Diagnoses and other health-related concepts are recorded in UK primary care using the Read code terminology.[113] The relevant cardiovascular disease Read codes were selected through a meticulous process described in **Supplemental Methods**. Cardiovascular diseases of interest included: stroke/transient ischaemic attack (TIA), heart failure (HF), revascularisation

procedures (coronary artery bypass graft (CABG) and percutaneous coronary intervention (PCI)) and ischaemic heart disease (IHD), including its subtypes angina and myocardial infarction (MI). Cardiovascular conditions are part of the Quality and Outcomes Framework and are well recorded in UK primary care.[114]

Analysis

Detailed description of the analysis is found in the **Supplemental Methods**. Briefly, annual prevalence (per 100,000 population) and incidence rate (per 100,000 person-years) were calculated for eligible males and females separately, and separately for each cardiovascular disease. The changes in incidence and prevalence trend over time were analysed using Joinpoint software (V.4.8.0.1).[115] Joinpoint software takes the trend data and fits the simplest model that the data allow.[115,116] Bayesian information criterion was used to identify the optimal model that fitted the data best. The programme calculates annual percentage change (APC) and the corresponding 95% confidence interval (95% CI) for any identified segment to estimate the change in slope between a preceding joinpoint and the next.[117] The rate of change in slope for the entire study period was summarised by the average APC (AAPC) and 95% CI.[118]

Results

Among the registered practices, there was a total of 317,344 adults aged 16-50 at the beginning of 1998. There were 160,714 (50.6%) males and 156,630 (49.4%) females with a male to female ratio of 1.03:1. The total number of eligible adults peaked at 2,248,149 in 2013, before dropping 1,475, 946 in 2017. The mean age of both men and women was 34 years and remained constant over the study period.

Incidence

IHD

The crude annual incidence rate of IHD and angina are provided in **Supplemental Table S3.1**. The annual crude incidence rate of IHD (per 100,000 person-years) decreased from 104.1 in 1998 to 64.1 in 2017 in men, compared to a decrease from 49.4 in 1998 to 24.9 in 2017 in women (**Figure 3.1**). Overall, the rate of decline of IHD incidence was steeper in women (AAPC -3.4; 95% CI -4.1 to -2.6) compared to men (AAPC -2.6; 95% CI -3.4 to -1.8) (**Figure 3.3 A**). Changes in the magnitude and direction of the trend were detected by joinpoint analysis. Between 1998 and 2008, the decline in IHD incidence was greater in women (APC -6.7; 95% CI -7.7 to -5.7) compared to men (APC -4.0%; 95% CI -5.1 to -2.9). After 2008, a slowing down of trend was observed in both sexes with the direction of trend sustained in men (APC -1.1; 95% CI -2.4 to 0.2), but a reversal of trend emerged in women (APC 0.5; 95% CI -0.8 to 1.7) **(Supplemental Table S3.2** and **Supplemental Figure S3.1)**. However, these later changes were not statistically different from a zero per cent APC.

Angina

Examination of the trend by subtypes of IHD revealed that the descending IHD incidence trend was mainly driven by falls in angina incidence. The annual incidence (per 100,000 person-years) of angina fell from 64.1 in 1998 to 15.4 in 2017 in men (AAPC -7.0%; 95% CI -9.2% to -4.8%), compared to a fall from 37.5 in 1998 to 7.7 in 2017 in women (AAPC -7.3%; 95% CI -10.5% to -4.0%) (**Figure 3.1, Figure 3.3A,** and **Supplemental Table S3.2**). From 1998-2002, a stable trend in angina incidence was exhibited in both men (APC -1.9; 95% CI -8.9 to 5.7) and women (APC -6.6; 95% C, -16.1 to 4). This was followed by a significant decline from 2002-2007 with an APC of -19.9% (95% CI, -25.6 to -13.8) per year in men compared to an APC decrease of -17.9% per year (-26.3 to -8.6) in women.

Figure 3.1: Annual incidence trend (per 100 000 person-years) of cardiovascular conditions in young men and women in the UK: 1998–2017. (A) Ischaemic heart disease. (B) Angina. (C) Myocardial infarction. (D) Revascularisation procedures (coronary bypass graft and percutaneous coronary interventions). (E) Stroke and transient ischaemic attack. (F) Heart failure.

However, after 2007, the trend slowed down in both men (APC -1.9; 95% CI -3.7 to -0.1) and women (APC -1.8 95% CI -4.3 to 0.9) **(Supplemental Table S3.2** and **Figure S3.1)**.

Myocardial infarction

Supplemental Table S3.3 provides the annual incidence of MI. The crude incidence (per 100,000 person-years) of MI decreased from 46.1 in 1998 to 44.5 in 2017 in men, compared to an increase from 9.8 in 1998 to 17.1 in 2017 in women **(Figure 3.1)**. This was reflected in a significant AAPC increase of 2.3% per year (95% CI 1.4 to 3.2) in women compared to the stable trend in men (AAPC 0.01%; 95% CI -0.5 to 0.5) **(Figure 3.3A)**. For the entire study period, no changes in the incidence trends of MI were detected in either men or women (APC=AAPC).

Coronary revascularisation

The crude annual incidence rates of revascularisation procedures are provided in **Supplemental Table S3.3** The annual incidence (per 100,000 person-years) of revascularisation procedures rose from 26.2 in 1998 to 30.0 in 2017 in men, compared to a rise from 4.6 in 1998 to 7.2 in 2017 in women **(Figure 3.1)**. This represented an AAPC of 1.1% (95% CI -0.2 to 2.5) per year in men compared to AAPC of 3.9% (95% CI 1.0 to 6.8) per year in women (**Figure 3.3A**). In men, the incidence trend of revascularisation procedures increased by an APC of 5.5% per year (95% CI 1.5 to 9.7) between 1998-2004 before flattening after 2004 (APC -0.8; 95% CI -2 to 0.4). In women, the incidence trend of revascularisation procedures increased by an APC of 8.3% per year between 1998-2007 before plateauing after 2007 (APC 0.01; 95% CI -3.9 to 4.1) **(Supplemental Table S3.2,** and **Supplemental Figure S3.1)**.

Stroke/TIA

The crude annual incidence rates of stroke/TIA are provided in **Supplemental Table S3.4**. The annual incidence (per 100,000) of stroke/TIA ranged from 32.2 in 1998 to 45.2 in 2017 (AAPC 1.9; 95% CI 1-2.9) in men, compared to 7.0 in 1998 to 35.5 in 2017 (AAPC 0.6; 95% CI -0.7 to 1.9) in women **(Figure 3.1** and **Figure 3.3A)**. The incidence trend of stroke/TIA remained stable between 1998-2006 in both males (APC 0.6; 95% CI -1.2 to 2.5) and females (APC -1.2; 95% CI -3.7 to 1.5). After 2006, the increase in stroke/TIA incidence was higher in males at an APC of 2.9% (95% CI 1.7 to 4.1) per year compared to an APC 1.9% (95% CI 0.2 to 3.6) per year in females **(Supplemental Table S3.2** and **Supplemental Figure S3.1)**.

Heart failure

The crude annual incidence rates of HF are provided in **Supplemental Table S3.4**. The annual incidence (per 100,000 person-years) of HF increased from 11.9 in 1998 to 28.3 in 2017 (AAPC 5.6%; 95% CI 2.2 to 5.8) among men, and from 6.2 in 1998 to 15.9 in 2017 (AAPC 5.0%; 95% CI 2.7 to 8.5) among women **(Figure 3.1** and **Figure 3.3A)**. In men the incidence rate of HF increased steeply by an APC of 8.3% (95% CI 3.2 to 13.6) per year from 1998 to 2004. This was followed by a flattening of the trend from 2004-2009 (APC -1.8; 95% CI -10.2 to 7.4) which was later followed by a rapid APC increase of 8.3% (95% CI 5 to 11.8) per year after 2009. In women, a stable trend in HF incidence was exhibited between 1998 and 2004 (APC 0.2; 95% CI -3 to 3.5). However, after 2009, HF incidence rapidly increased at an APC of 11.9% per year (95% CI 6.2 to 17.9) **(Supplemental Table S3.2** and **Supplemental Figure S3.1).**

Prevalence

IHD

The crude annual prevalence of IHD and angina are provided in **Supplemental Table S3.5.** The annual prevalence (per 100,000) of IHD decreased from 655.8 in 1998 to 370.6 in 2017

in men, compared to a decrease from 341.6 in 1998 to 129.8 in 2017 in women **(Figure 3.2)**. This translated to an AAPC of -2.8% (95% CI -3.3 to-2.3) per year in men, compared to an AAPC of -4.9% (95% CI -5.9 to -3.9) per year in women **(Figure 3.3B)**. There was a significant decline in the prevalence of IHD between 1998 and 2011 in both men and women. In men, the prevalence of IHD decreased from 1998 to 2001 (APC-5.9%; 95% CI -8.5 to -3.2), followed by a slowing down in trend from 2001 to 2011 (APC -2.9%; 95% CI -3.4 to -2.4). In women, the prevalence of IHD declined from 1998-2002 (APC -9.1%; 95% CI -12.5 to -5.5), followed by a slowing down in trend from 2002-2011 (APC -4.9%; 95% CI -6.2 to-3.7). However, the period from 2011 onwards was characterised by a levelling off in IHD prevalence trends in both men (APC -0.9; 95% CI -1.9 to 0) and women (APC -2%; 95% CI -4 to 0.1) **(Supplemental Table S3.6** and **Supplemental Figure S3.2)**.

Angina

The prevalence (per 100,000) of angina declined from 413.8 in 1998 to 94.6 in 2017 in men (AAPC -7.2%; 95% CI -8.1 to -6.3), compared to a decrease of 243.3 in 1998 to 51.5 in 2017 (AAPC- 7.8%; 95% CI -9.8 to -6.3) in women **(Figure 3.2, Figure 3.3B,** and **Supplemental Table S3.5)**. In men angina prevalence declined with an APC of -5.7% (95% CI -7 to -4.3) per year from 1998 to 2005, -10.4% (95% CI -12.5 to 8.3) per year from 2005 to 2011, and -5.7% (95% CI -7.4 to -4.0) per year from 2011 to 2017. In women the prevalence of angina declined with an APC of -6.6% (95% CI -16.1 to 4) from 1998 to 2006, -12.1% (95% CI -16.6 to -7.3) per year from 2006 to 2011, and -5.7% (95% CI -8.3 to -3.0) per year from 2011 to 2017 **(Supplemental Table S3.6** and **Supplemental Figure S3.2).**

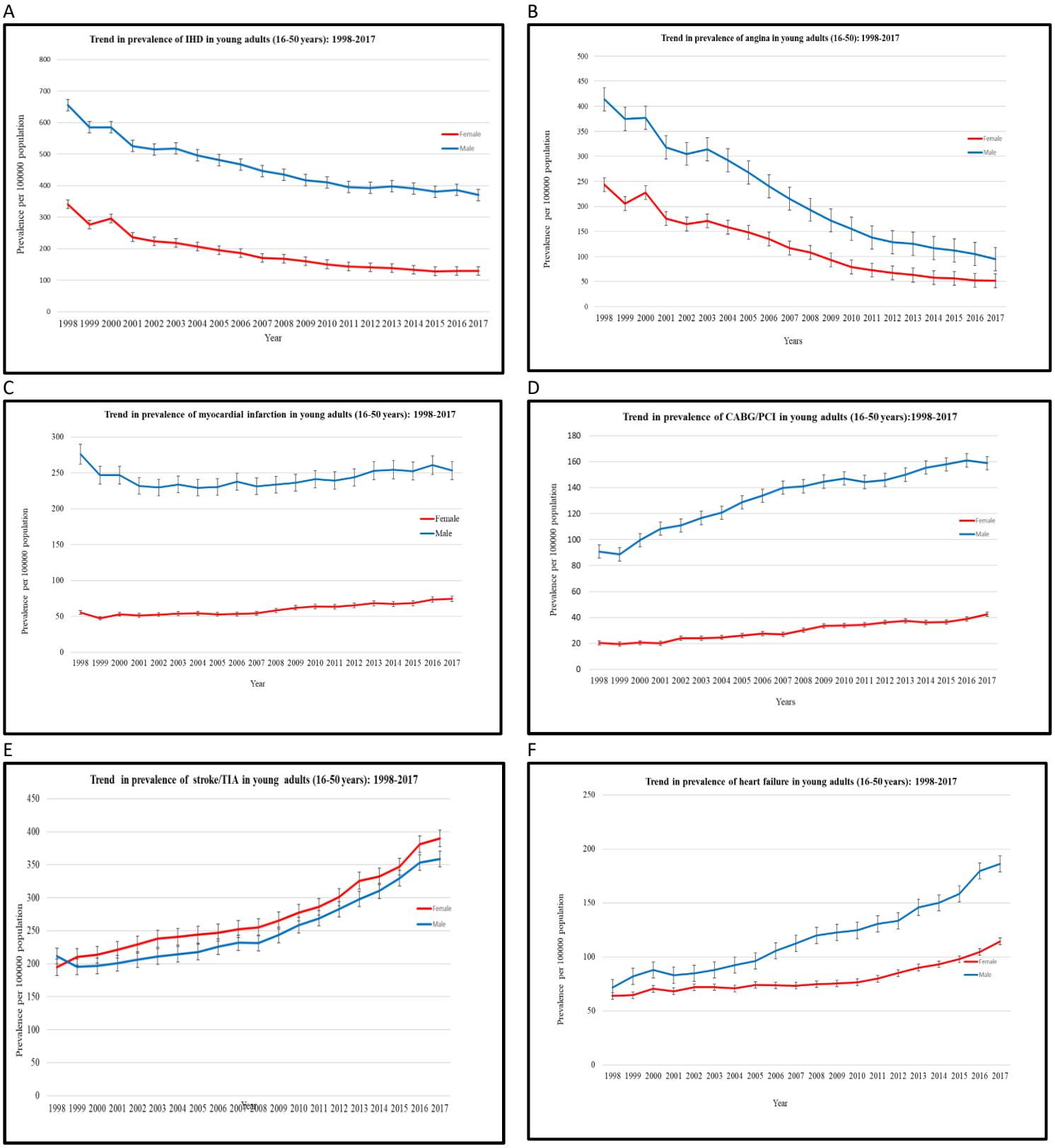
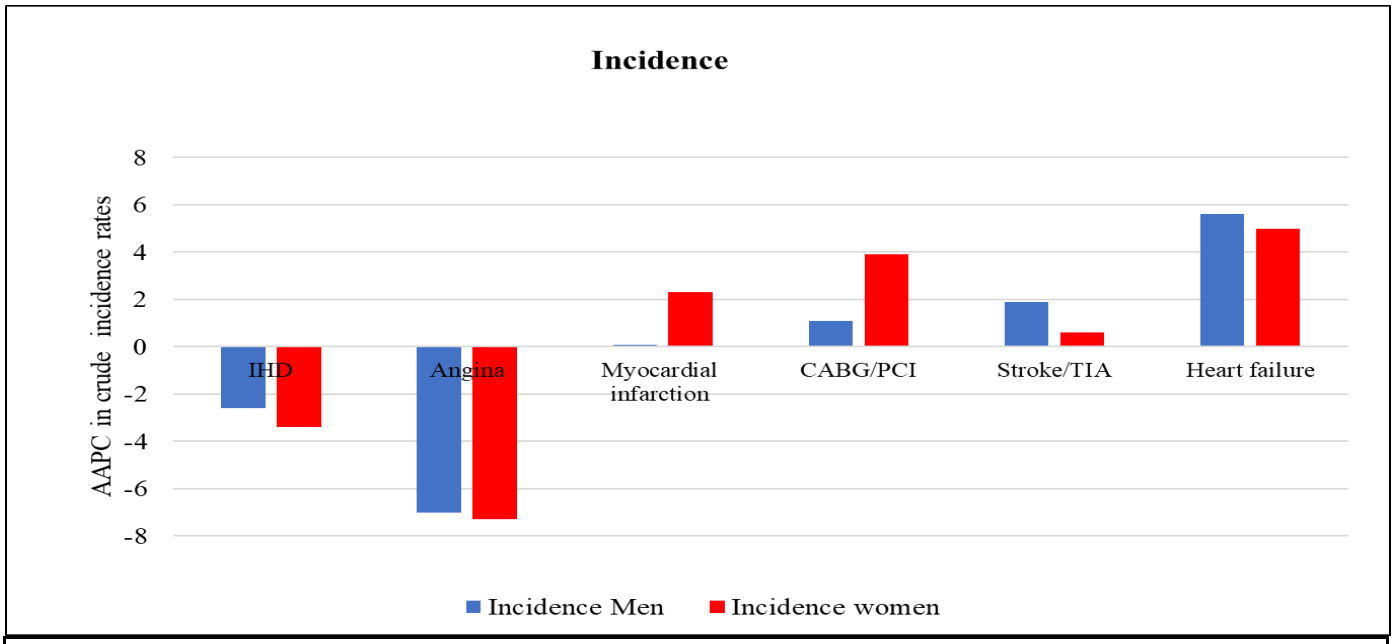


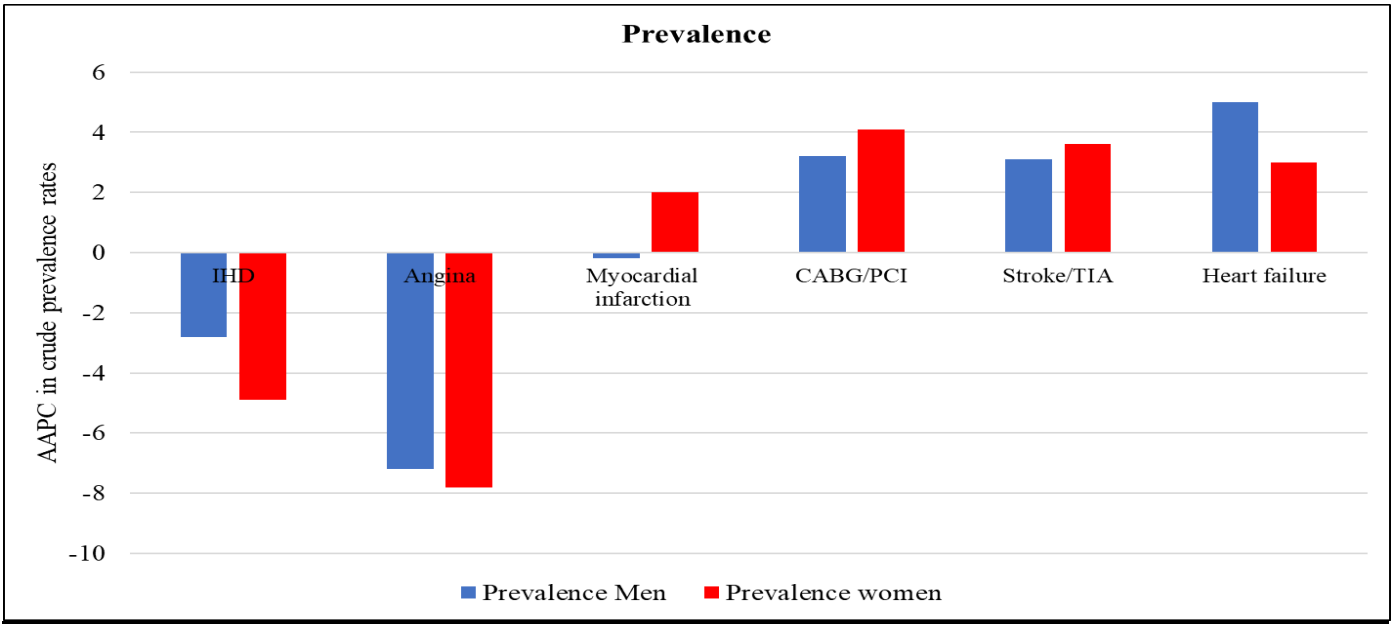
Figure 3.2: Annual prevalence trend (per 100 000 population) of cardiovascular conditions in young men and women in the UK: 1998–2017. (*A*) Ischaemic heart disease. (*B*) Angina. (*C*) Myocardial infarction. (*D*) Revascularisation procedures (coronary bypass graft and percutaneous coronary interventions). (*E*) Stroke and transient ischaemic attack. (*F*) Heart failure.

A



	IHD	Angina	MI	CABG/PCI	Stroke/TIA	Heart Failure
Men: AAPC (95%CI)	-2.6 (-3.4 to -1.8)	-7.0 (-9.2 to -4.8)	0.1 (-0.5 to 0.5)	1.1 (-0.2 to 2.5)	1.9 (1 to 2.9)	5.6 (2.7 to 8.5)
Women: AAPC (95%CI)	-3.4 (-4.1 to -2.6)	-7.3 (-10.5 to-4)	2.3 (1.4 to 3.2)	3.9 (1 to 6.8)	0.6 (0.7 to 1.9)	5 (2.2 to 7.8)

B



	IHD	Angina	MI	CABG/PCI	Stroke/TIA	Heart Failure
Men: AAPC (95%CI)	-2.8 (-3.3 to -2.3)	-7.2 (-8.1 to -6.3)	-0.2 (-0.8 to 0.4)	3.2 (2.8 to 3.6)	3.1 (2.6 to 3.5)	5.0 (4.0 to 6.1)
Women: AAPC (95%CI)	-4.9 (-5.9 to -3.9)	-7.8 (-9.3 to-6.3)	2.0 (1.3 to 2.6)	4.1(3.2 to 4.9)	3.6 (3.2 to 4.1)	3.0 (2.4 to 3.5)

Figure 3.3: Average annual percentage change in crude incidence **(A)** and prevalence **(B)** of cardiovascular disease in young UK adults (16–50 years), 1998–2017.

Myocardial infarction

The crude annual prevalence rates of MI are provided in **Supplemental Table S3.7.** Prevalence (per 100,000) of MI ranged from 276.3 in 1998 to 253.2 in 2017 in men, compared to 55.5 in 1998 to 74.6 in 2017 in women **(Figure 3.2)**. This was reflected in the stable trend (AAPC -2%; 95% CI -0.8 to 0.4) noted in men compared to a gradual increase (AAPC 2%; 95% CI 1.3 to 2.6) in women **(Figure 3.3B)**. A closer examination of MI prevalence trend in men revealed a significant decline from 1998-2001 (APC 5.2%; 95% CI -8 to -2.3), followed by a stable trend from 2001-2008 (APC 0.2 %; 95% CI -0.8 to 1.3), and an upward trend from 2008 onwards (APC 1.2%; 95% CI 0.6 to 1.7). In women, the prevalence of MI was stable from 1998-2005 (APC 0.5; 95% CI -1.1 to 2.1), followed by an upward trend from 2005 onwards (APC 2.8; 95% CI, 2.1 to 3.5) **(Supplemental Table S3.6** and **Supplemental Figure S3.2)**.

Coronary revascularisation

The crude annual prevalence of revascularisation procedures are provided in **Supplemental Table S3.7**. The prevalence (per 100,000) of revascularisation procedures increased by an AAPC of 4.1% (95% CI 3.2 to 4.9) per year in men, from 90.8 in 1998 to 150.8 in 2017, compared to an AAPC increase of 3.2% (95% CI 2.8 to 3.6) per year in women, from 20.4 in 1998 to 40.5 in 2017 **(Figure 3.2** and **Figure 3.3B)**. In men, the prevalence trend of revascularisation procedures was characterised by an APC increase of 5.5% (95% CI 4.7 to 6.3) per year between 1998 and 2006, followed by slowing down of trend to a 1.5 % (95% CI 1.1 to 2) APC increase after 2006. In women, the prevalence of revascularisation procedures increased by an APC of 4.7% (95% CI 4 to 5.5) per year from 1998 to 2011, followed by a slowing down of trend to a 2.6% (95% CI 0.3 to 5.0) APC increase after 2011 **(Supplemental Table S3.6** and **Supplemental Figure S3.2)**.

Stroke/TIA

The crude annual prevalence of stroke/TIA are provided in **Supplemental Table S3.8.** The prevalence (per 100,000) of stroke/TIA between ranged from 211.6 in 1998 to 358.7 in 2017 (AAPC 3.1%; 95% CI 2.6 to 3.5) in men, and from 194.7 in 1998 to 389.8 in 2017 (AAPC 3.6% 95% CI 3.2 to 4.1) in women **(Figure 3.2** and **Figure 3.3B)**. In men, the trend in stroke prevalence was stable until 2001 (APC -0.9%; 95% CI -2.9 to 1.3). This was followed by a 2.3% (95% CI 1.6 to 3.0) APC increase between 2001 to 2008 and a 5.0% (95% CI 4.6 to 5.4) APC increase after 2008. In women, the prevalence trend of stroke was characterised by a steep increase (APC 3.6%; 95% CI 2.6 to 4.7) between 1998 and 2003, followed by further acceleration of pace (APC 5.2% 95% CI, 4.7 to 5.7) from 2009 onwards **(Supplemental Table S3.6** and **Supplemental Figure S3.2)**.

Heart failure

The crude annual prevalence of heart failure are provided in **Supplemental Table S3.8**. The crude prevalence (per 100,000) of heart failure increased from 75.6 in 1998 to 182.3 in 2017 in men (AAPC 5%; 95% CI 4 to 6.1), compared to an increase from 63.8 in 1998 to 114.4 in 2017 in women (AAPC 3%; 95% CI 2.4 to 3.5) **(Figure 3.2** and **Figure 3.3B)**. Heart failure prevalence trend in men was characterised by a steep increase (APC 4.5%; 95% CI 4.0 to 5.0) from 1998 until 2014, which subsequently doubled in magnitude (APC 8.1%; 95% CI 1.6 to 15.0) from 2014 onwards. In women, the prevalence of heart failure exhibited a significant increase from 1998 to 2002 (APC 2.8%; 95% CI 0.8 to 4.8), followed by a stable trend from 2002 to 2010 (APC 0.8; 95% CI -0.1 to 1.6) and a steep upward trend after 2010 (APC 5.7%; 95% CI 4.8 to 6.5) **(Supplemental Table S3.6** and **Figure 3.2)**.

Discussion

We examined sex-specific temporal trends in the incidence and prevalence of CVD in young adults using UK primary care data. Generally, trends were similar between men and women, with the burden of CVD greatest in men compared to women. Overall, from 1998-2017, for both incidence and prevalence analyses, IHD exhibited descending trends while revascularisation procedures, stroke/TIA, and HF showed ascending trends. Examination of trends by subtypes of IHD revealed that the fall in angina rates was the principal driver of IHD trend. MI exhibited an upward trend in women but remained stable in men.

Joinpoint analyses captured several notable changes in the magnitude and direction of trends in recent years. In both men and women, the period after 2008 was characterised by a slowing down of angina and IHD incidence trends with a small albeit non-significant reversal of IHD trend detected in women. A flattening of incidence trends was detected for revascularisation procedures after 2004 and 2007 in men and women, respectively. For stroke/TIA, the period after 2006 was characterised by a significant rise in incidence trends in both men and women compared to the stable trends noted before this period. For HF, the period after 2009 was characterised by steep increases in incidence trends in both men and women. Overall, prevalence trends paralleled incidence trends for all cardiovascular conditions except stroke/TIA prevalence rates which were marginally higher in women compared to men.

Literature on incidence and prevalence trends in CVD in young UK adults are sparse. **Supplemental Table S3.9** highlights the comparisons of trends with findings from selected existing literature. Direct comparisons are challenging due to methodological differences in the definition of young adults, disparities in the source population (community versus hospital setting) and differences in study periods. The declining IHD observed in our study aligns with the overall findings from existing UK literature.[119,120] Between 2000 and 2010, among UK adults aged >30 years, Bhattarai et al.[119] noted similar trends in the incidence of

IHD in both sexes. Additionally, our study observed a slowing down in IHD trends in recent years. These findings complement reports from studies from the US and Western Europe which noted similar decelerations in IHD trends **(Supplemental Table S3.9)**.[10,11,106,121] Moreover, Bhattarai and colleagues reported that between 2000-2010, there was a significant decline in the incidence of angina while the incidence of MI and revascularisation procedures remained unchanged.[119] Our study provides additional evidence that the falling angina rates were the principal drivers of IHD trends. The present study identified that the incidence and prevalence of MI significantly increased in women and remained stable in men. These findings echo similar ominous trends observed among women from Australia, Canada, and the USA **(Supplemental Table S3.9**).[13,14,26,122,123]

Studies examining sex-specific trends in revascularisation procedures in young adults are limited. Recent studies conducted in the US noted that there was a downward trend in incidence of coronary revascularisation procedures.[124–126] Dani et al. reported that between 2004-2008 the volume of CABG procedures was on a downward trend among US adults aged 18-45. The greater burden of revascularisation procedures among women compared to men in the present study may be attributable to the concurrent rise in the incidence of MI **(Supplemental Table S3.9)**.

We noted that men had slightly higher incidence rates of stroke/TIA overall while women reported had higher prevalence rates of stroke/TIA. Studies examining sex-specific temporal trends in stroke report inconsistent results, with some studies reporting no difference, other studies noted differences in particular age categories, while some studies report a higher incidence in specific genders.[27] A study examining stroke incidence in young adults from fifteen European countries noted a female predominance below 34 years, while male predominance was noted in ages 40-49 years.[127] A Dutch study noted that the incidence of stroke in young adults was higher in females than in males.[27] Despite inconsistent results on

sex differences in the burden of stroke, our study concurs with the reports of increased stroke incidence in young adults noted in previous literature **(Supplemental Table S3. 9)**.[27,127–129]

The present study supports findings of rising HF incidence rates noted in cohorts from Denmark, Sweden, and the USA; however, these studies were limited by a lack of sex-specific data **(Supplemental Table S3.9)**.[28,130,131]

The factors behind unfavourable trends in CVD among young UK adults are unclear but are possibly multifactorial. The risk of CVD increases with increasing age. Throughout the study period the mean population age remained constant. Therefore, the unfavourable trends observed in our study are unlikely to be attributable to population ageing. The latest data from Health Survey England shows that the prevalence (1993-2019) of obesity and diabetes mellitus is on an upward trend while smoking and alcohol consumption are on a downward trend in men and women aged over 16 years.[132] Also, the proportion of adults with untreated hypertension has been on a downward trend since 2003. The unfavourable trends in cardiovascular conditions noted in the present study parallel the rising prevalence of obesity and diabetes mellitus. Examination of recent reports on CVD morbidity trends reveals that the incidence and prevalence trends (2005-2017) for all cardiovascular conditions are on a downward trend in in older adults (> 65 years).[133] Although strategies for the primary prevention of cardiovascular disease are the same across all age groups the disparities in CVD morbidity trends between older adults and young adults warrants investigation. The unfavourable trends reported in the present study suggests that young adults are less responsive to strategies for primary prevention of CVD. The variations in the impact of traditional risk factors may explain differences between sexes. Age, total cholesterol, low-density lipoprotein, and hypertension have a more significant effect on men. Diabetes, smoking, systolic arterial hypertension, triglycerides and high-density lipoprotein levels have a greater impact in women.[134] During the study period, we observed a stable trend in MI in

men and an upward trend in women. A study conducted using UK biobank data showed that diabetes mellitus (type 1 or type 2), current smoking, and systolic blood pressure were associated with an excess risk of MI in women.[135]. Socioeconomic deprivation could also be a key factor in young adults. A large perspective cohort study conducted in 20 low-, middle- and high-income countries found that low levels of education rather than household wealth was the marker of socioeconomic status associated with major cardiovascular events in all the countries studied.[136] O'Flaherty et al noted that the flattening of CHD mortality trends in young Scottish adults was restricted to the most deprived groups.[137] The adverse trends reported in our study may be partly influenced by young material deprived adults who not only lead unhealthy lifestyles but have a low level of awareness or education regarding primary prevention of CVD.

Sex-specific factors disadvantage women. Female reproductive complications including adverse pregnancy outcomes and reproductive endocrine factors enhance the risk of premature cardiovascular disease.[112,138] Results from an exploratory analysis of ecological data found that countries with higher rates of pre-term delivery had higher rates of stroke (correlation coefficient; r=0.65).[139] The prevalence of several of these reproductive factors are on an upward trend in high-income countries and may influence the rising trend of CVD in young women.[140,141] It is commonly accepted that endogenous oestrogen delays onset of CVD in premenopausal women; ovarian dysfunction may therefore impact CVD in women aged >45. However, evidence on the cardioprotective effects of oestrogen is debated and epidemiological evidence does not support an acceleration of CVD risk in women at menopause.[9,142] Furthermore, the average age of onset of menopause is 51, which is after the upper age cut-off for our study.

Strengths and limitations

Our study has several strengths. The long-term follow-up covering twenty years allowed detailed analysis of the changes in CVD morbidity trends. Compared to qualitative descriptions, the use of joinpoint regression is an unbiased quantitative technique used to detect changes in trend. Analysis of temporal trends was based on a primary care database that is representative of the UK population. However, some potential limitations need highlighting. First, although diagnoses for MI and other cardiovascular conditions are well-recorded in UK primary care, the sole use primary care data compared to linked primary and secondary care data, underestimates crude incidence rates.[143] Second, our analysis is descriptive in nature. The relationship between risk factors and cardiovascular disease trend was beyond the scope of the present study. Third, analysis of temporal trends in our study was limited to young adults. Comparisons with older populations was beyond the scope of the present study.

Implications for policy and future research

The adverse trends in the present study suggest an increased burden of CVD in the future as the young UK population ages. Future research should focus on identifying factors behind unfavourable trends in CVD morbidity. Public health interventions are needed to stem the ominous trends.

Conclusion

From 1998 to 2017, among young UK adults, the incidence and prevalence of IHD and angina exhibited a downward trend while revascularisation procedures, stroke/TIA, and HF exhibited an overall upward trend. MI trends remained stable in men but significantly increased in women. Several noteworthy changes in trend were detected over the period: In recent years, in both sexes, a levelling off in trends of IHD and revascularisation procedures

were detected, while stroke/TIA and HF trends exhibited significant increases. The factors behind the unfavourable trends warrant urgent investigation and intervention.

Chapter 4. Association between the reproductive health of young women and cardiovascular disease in later life: umbrella review

The study presented in this chapter has been published.

Okoth K, Chandan JS, Marshall T, Thangaratinam S, Thomas GN, Nirantharakumar K, et al. Association between the reproductive health of young women and cardiovascular disease in later life: Umbrella review. Vol. 371, The BMJ. BMJ Publishing Group; 2020. https://doi.org/10.1136/bmj.m3502

KO developed the review question guided by KN, NJA, and GNT. KO identified, searched, appraised, and extracted data as the first reviewer. JSC was the second reviewer, and NJA, KN and GNT act as the third reviewers where required. KO synthesised the data and wrote the first draft of the manuscript. All authors: KO, JSC, ST, MT, GNT, KN and NJA, reviewed and revised the manuscript.

Abstract

Objective: To consolidate evidence from systematic reviews and meta-analyses investigating the association between reproductive factors in women of reproductive age and their subsequent risk of cardiovascular disease.

Design: Umbrella review.

Data sources: Medline, Embase, and Cochrane databases for systematic reviews and meta-analyses from inception until 31 August 2019.

Review methods: Two independent reviewers undertook screening, data extraction, and quality appraisal. The population was women of reproductive age. Exposures were fertility related factors and adverse pregnancy outcomes. Outcome was cardiovascular diseases in women, including ischaemic heart disease, heart failure, peripheral arterial disease, and stroke.

Results: 32 reviews were included, evaluating multiple risk factors over an average follow-up period of 7-10 years. All except three reviews were of moderate quality. A narrative evidence synthesis with forest plots and tabular presentations was performed. Associations for composite cardiovascular disease were: twofold for pre-eclampsia, stillbirth, and preterm birth; 1.5-1.9-fold for gestational hypertension, placental abruption, gestational diabetes, and premature ovarian insufficiency; and less than 1.5-fold for early menarche, polycystic ovary syndrome, ever parity, and early menopause. A longer length of breastfeeding was associated with a reduced risk of cardiovascular disease. The associations for ischaemic heart disease were twofold or greater for pre-eclampsia, recurrent pre-eclampsia, gestational diabetes, and preterm birth; 1.5-1.9-fold for current use of combined oral contraceptives (oestrogen and progesterone), recurrent miscarriage, premature ovarian insufficiency, and early menopause; more less than 1.5-fold for miscarriage, polycystic ovary syndrome, and menopausal symptoms. For stroke outcomes, the associations were twofold or more for current use of any

oral contraceptive (combined oral contraceptives or progesterone only pill), pre-eclampsia, and recurrent pre-eclampsia; 1.5-1.9-fold for current use of combined oral contraceptives, gestational diabetes, and preterm birth; and more less than 1.5-fold for polycystic ovary syndrome. The association for heart failure was fourfold for pre-eclampsia. No association was found between cardiovascular disease outcomes and current use of progesterone only contraceptives, use of non-oral hormonal contraceptive agents, or fertility treatment.

Conclusions: From menarche to menopause, reproductive factors were associated with cardiovascular disease in women. In this review, presenting absolute numbers on the scale of the problem was not feasible; however, if these associations are causal, they could account for a large proportion of unexplained risk of cardiovascular disease in women, and the risk might be modifiable. Identifying reproductive risk factors at an early stage in the life of women might facilitate the initiation of strategies to modify potential risks. Policy makers should consider incorporating reproductive risk factors as part of the assessment of cardiovascular risk in clinical guidelines.

Systematic review registration PROSPERO CRD42019120076.

Introduction

Globally, one third, or 17.9 million, of total annual deaths are attributable to cardiovascular disease.[144] The incidence of cardiovascular disease has declined since the middle of the last century, but less so in women than in men. In developed countries,[10,26,145] the incidence of cardiovascular disease has declined in older age groups (≥55), but has stagnated or increased in adults aged less than 55.[14,26,145] For instance, in the United States, the proportion of hospital admissions for acute myocardial infarction for adults aged less than 55 rose from 27% between 1995 and 1999 to 32% between 2010 and 2014.[13] The greatest increases were recorded in women aged 35-54.[13] In Western Australia, between 1996 and 2007, in adults aged 35-54, hospital admissions for acute myocardial infarctions increased by 4% in women but decreased by 0.2% in men.[26] Other temporal trend analyses have recorded similar increases in women aged 30-54.[13,146–148]

Although many commonalities exist, several differences between men and women in terms of risk factors for cardiovascular disease are apparent. Traditional risk factors for cardiovascular disease, such as smoking and diabetes, affect women more than men.[30,31] Beyond these traditional risk factors, risk factors specific to women, such as adverse pregnancy outcomes and fertility complications, are under recognised.[149] Women experiencing adverse pregnancy outcomes and issues related to fertility have been shown to often have early manifestations of vascular changes. Endothelial dysfunction has been shown to be prevalent in women with a history of pre-eclampsia and recurrent pregnancy loss, and could remain beyond pregnancy complications, predisposing these women to further vascular complications and serving as a prognostic marker for future cardiovascular disease.[150] Biochemical risk factors for cardiovascular disease, including raised concentrations of cholesterol, glucose, and triglycerides, have been shown to persist many years after a hypertensive disorder of pregnancy.[151] A better understanding of associations with these risk factors could be explored

in future research to identify areas of modifiable risk in women to reduce their long term risk of cardiovascular disease.

In developed countries, up to a third of parous women experience one or more adverse pregnancy outcomes,[152] including hypertensive disorders of pregnancy, gestational diabetes mellitus, placental abruption, and low birth weight and preterm births.[153] Reproductive risk factors are not limited to the obstetric period. Globally, up to 10% of women are diagnosed with secondary infertility.[154] Common causes of secondary infertility, including polycystic ovary syndrome, premature ovarian insufficiency, endometriosis, and pelvic inflammatory disease, have been linked to an increased risk of cardiovascular disease.[40,155,156] Also, early age at menarche, early menopause, and use of hormonal contraceptive agents are associated with risk of cardiovascular disease.[157]

In the past three decades, the prevalence of adverse pregnancy outcomes has increased in some developed countries.[140,141,158,159] On average, young women could develop cardiovascular disease events as early as a decade after experiencing an adverse pregnancy outcome.[17,160] Young women who develop acute coronary syndromes have longer stays in hospital after admission, higher readmission rates, and higher mortality than men.[146,161] Moreover, women with pre-eclampsia have six times the risk of readmission for acute coronary syndromes at one year and tend to present with a more serious type of myocardial infarction than women without pre-eclampsia.[162] Prediction models for traditional risk factors for cardiovascular disease are less optimal in young adults.[163,164] Also, only 49% of primary care physicians in the US said they were confident in the assessment of the risk of cardiovascular disease in women.[22]

Adverse pregnancy outcomes and cardiovascular disease share common (traditional) risk factors, including hypertension, hyperglycaemia, and obesity. In a Norwegian cohort study, blood pressure and body mass index were linked to 77% of the excess risk of cardiovascular

disease in women with hypertensive disorders of pregnancy.[165] Up to 15% of the risk of coronary heart disease in young women (aged <65) could not be accounted for by traditional risk factors.[15]

Several systematic reviews have looked at risk factors specific to women and cardiovascular disease but they evaluated different risk factors and different outcomes. An umbrella review is a review of existing systematic reviews and meta-analyses.[166]

The aim of the study was to conduct an umbrella review of systematic reviews evaluating the association between risk factors specific to women (adverse pregnancy outcomes and issues related to fertility) and cardiovascular disease outcomes. This umbrella review will provide decision makers with a consolidated source of high-quality studies on this subject. This review will help in developing care pathways which consider a broader range of factors specific to women than are currently considered, in particular those risk factors that have the potential to be modified to reduce the risk of cardiovascular disease in women at high risk (such as those with pre-eclampsia, gestational diabetes, and polycystic ovary syndrome).[167–169] The results of this review are presented by the exposure of interest (over the life course of women) and by cardiovascular outcome.

Methods

An umbrella review is a narrative compilation of evidence for several related clinical questions from multiple systematic reviews and meta-analyses into one usable document with text, tables, and graphics. It aims to examine what is known and not known, and then to propose recommendations for practice and research.[73]

Objective, population, exposures, and comparator

In this review, we explored reproductive factors in women and their association with cardiovascular disease. The umbrella review followed the guidelines for Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA), and the protocol was registered

in PROSPERO (registration No CRD42019120076). The population included women of reproductive age.

Exposures were identified through a scoping search and consensus with an expert panel (clinicians and epidemiologists). The scoping search included search terms for women, cardiovascular disease, and risk factors, to identify relevant reproductive risk factors. These risk factors were related to fertility and adverse pregnancy outcomes. Factors related to fertility included: age at menarche; age at first pregnancy; age at first birth; early natural menopause; premature ovarian insufficiency; polycystic ovary syndrome; endometriosis; pelvic inflammatory disease; parity; gravidity; breastfeeding; use of hormonal contraceptive drugs; and fertility treatment. Adverse pregnancy outcomes included: pregnancy loss (miscarriage and stillbirth); hypertensive disorders of pregnancy (pre-eclampsia and gestational hypertension); low birth weight; small for gestational age; gestational diabetes; preterm birth; and placental abruption. The comparator group included women of reproductive age without the reproductive factor of interest (that is, controls or unexposed women).

Outcomes

Outcomes included: ischaemic heart disease; angina; myocardial infarction; coronary artery disease; cerebrovascular accident, including stroke and transient ischaemic attack; heart failure; peripheral arterial disease; and composite cardiovascular disease (ischaemic heart disease, cerebrovascular accident, heart failure, and peripheral arterial disease).

Study design

Systematic reviews or meta-analyses were included. A study qualified as a systematic review or meta-analysis if, at a minimum: it described the conduct of the systematic review in adequate detail; an attempt was made to identify all of the relevant primary studies in at least

one database and a search strategy was provided; and it performed a quality appraisal of the primary studies included.[170]

Excluded were guidelines, narrative reviews, literature reviews, genetic studies, reviews looking at atherosclerosis or venous thromboembolism as an outcome, and reviews assessing the association between hormonal replacement treatment and cardiovascular disease.

Search strategy

Medline, Embase, and the Cochrane Database of Systematic Reviews were searched from inception until 31 August 2019 without language restrictions. The search strategy was developed around the key terms: menarche, OR hormonal contraceptives, OR polycystic ovary syndrome, OR menopause, OR endometriosis, OR hypertensive disorders of pregnancy, OR gestational diabetes, OR miscarriage, OR stillbirth, OR placental abruption, OR low birth weight, OR preterm birth, AND cardiovascular disease. The results were limited to systematic reviews and meta-analyses with a search filter.[171] Reference lists of eligible reviews and meta-analyses were searched for additional citations. **Appendix 4.1** provides a detailed search strategy for the Medline database. This strategy was adapted for searching Embase and the Cochrane Database of Systematic Reviews.

Study selection and data extraction

Two reviewers (KO and JSC) independently carried out the study selection and data extraction from the eligible studies. Data extracted included: author, year of publication, number of participants, number and type of studies included, appraisal instrument used, method of analysis, outcomes assessed, heterogeneity, and findings. The study used the data extraction form recommended by the Joanna Briggs Institute **(Appendix 4.2)**.[172]

Quality assessment

The online AMSTAR 2 (A Measurement Tool to Assess systematic Reviews) checklist was used to assess methodological quality and assign an overall rating for the reviews included.[173]

Two reviewers (KO and JSC) rated the methodological quality of the reviews with the AMSTAR 2 quality appraisal instrument.[174] In the case of disagreements and failed consensus, a decision was reached by consulting a third reviewer (NJA).

The AMSTAR 2 quality assessment tool is a 16 item or domain checklist. Seven of these items are considered critical. Shortcomings in any of the critical domains could affect the overall validity of a review. The domains considered critical are: registration of the protocol before starting the review; conduct of an adequate search of the literature; providing justification for the exclusion of individual studies; satisfactory assessment of risk of bias in the studies included in the review; use of appropriate statistical methods in performing a meta-analysis; accounting for risk of bias when interpreting the results; and evaluation of the presence and effect of publication bias.[174]

Overlapping and outdated reviews

Associations assessed in two or more reviews overlapped if they evaluated the same exposure and outcome.[33] Incorporating results from reviews with overlapping associations could lead to the inclusion of primary studies more than once and result in biased findings and estimates.[175,176] Also, up to 50% of published systematic reviews are out of date after 5.5 years.[177] Reviews on cardiovascular disease topics have a shorter duration of currency (three years).[177] We categorised overlapping systematic reviews as outdated (reviews older than five years or published before 2013) and contemporary (reviews published after 2013). Overlapping reviews that were out of date were excluded at the full text screening stage.

For contemporary reviews found to have overlapping associations (that is, investigating the same exposure and outcome), a graphical cross tabulation (citation matrix) of the overlapping systematic reviews (in columns) and the included primary studies (in rows) was generated.[178] A citation matrix allows the degree of overlap to be quantified with a measure known as the corrected covered area (CCA).[33] CCA, expressed as a percentage, is calculated as

(N−r)/(rc−r), where N is the number of publications included in evidence synthesis (or the number of ticked boxes in the citation matrix), r is the number of rows, and c is the number of columns. Overlap is categorised as very high (CCA >15%), high (CCA 11-15%), moderate (CCA 6-10%), or slight (CCA 0-5%).[33] CCA is a validated method of quantifying the degree of overlap between two or more reviews, and helps the decision process on how to deal with overlap when it is present.

All non-overlapping systematic reviews that met the inclusion criteria (Cochrane and non-Cochrane) were included in the analysis. **Appendix 4.3** shows the citation matrices for all studies with some degree of overlap. Overlap between reviews was managed as follows:

- Where overlap involved evidence synthesis from Cochrane and non-Cochrane reviews, the Cochrane review was selected in preference.[179] A recent study examining the effect of different inclusion decisions on the comprehensiveness and complexity of overviews of reviews for healthcare interventions concluded that selecting the Cochrane review resulted in the least amount of data loss; also, Cochrane reviews were generally higher quality and tended to be more recent.[180]
- Where a high degree of overlap (CCA ≥11%) between two or more non-Cochrane reviews was found, preference was given to the review that (in hierarchical order): had the highest rating, and at a minimum was rated as moderate quality, assessed with the AMSTAR 2 quality assessment tool; was most recent; supplied pooled effect estimates or had conducted a meta-analysis; and had the highest number of studies or participants.[179]
- Where a slight or moderate degree of overlap (CCA ≤10%) was found, both reviews were retained, and the findings compared.

Data synthesis

Systematic reviews and meta-analyses that met the inclusion criteria formed the unit of analysis. Only data available from reviews were presented. Results from reviews were

synthesised with a narrative synthesis, with tabular presentation of findings and forest plots for reviews that performed a meta-analysis. Summary tables describing review characteristics and findings were also presented.

Update of eligible reviews

The framework recommended by Garner et al[74] was used to determine whether an update was necessary. An existing review qualified for an update if all of the following were met:

- The review was widely cited and achieved a minimum rating of moderate with the AMSTAR 2 quality appraisal tool.[174] Reviews with low citations or a low-quality rating were unsuitable for an update.
- With the key search terms from the search strategy of an existing review, a focused or abbreviated search of primary studies[75] identified newly published studies that met the inclusion criteria of the review.
- The findings from newly published studies would change the conclusion or credibility of the review.

Appendix 4.4 describes the search strategy used to identify newly published studies. With findings from newly published studies, we evaluated the effect of updating existing reviews which met the above eligibility criteria.[74] As proposed by Chung et al,[75] we relied on statistical methods (for reviews that conducted meta-analyses) and the informed opinion of subject experts (for reviews that did not perform meta-analyses).

In determining whether an original meta-analysis was out of date, newly published studies were sorted by sample size from the largest to the smallest. A fixed effect meta-analysis was then conducted by sequentially pooling (from the largest to the smallest) the effect estimate from newly published studies with the overall effect estimate of the original meta-analysis. The aim of this process was to identify whether a full update of the review was needed. An original meta-analysis was considered out of date if the addition of newly published studies

resulted in a change of statistical significance or a change in the relative effect size by at least 50%.

Based on the opinion of subject experts (TM and ST), the reviews that did not perform a meta-analysis were classified as definitely out of date, probably out of date, possibly out of date, and still valid. A review that was ranked definitely out of date or probably out of date was considered a high priority for update.

If an update was considered necessary, the original methods used in the conduct of the existing review were replicated. **Appendix 4.5** summarises the evaluation process for considering reviews for update.[181]

Patient and public involvement

No patients were involved in setting the umbrella review question, in conducting the study, or in interpreting and writing up the results. The umbrella review was unfunded and was used to answer a specific question, where patient and public involvement will take place later in the work. We plan to engage with local policy makers (National Institute for Health and Care Excellence, Royal College of Obstetricians and Gynaecologists, Clinical commissioning groups) and local charities (British Heart Foundation), and to disseminate the research through social media (twitter), a press release from the Institute of Applied Health Research, University of Birmingham, and sharing of the research findings at relevant conferences.

Results

Literature search

The search retrieved 11 345 articles. After removal of duplicates, and screening of titles and abstracts, 88 articles qualified for full text screening. Preliminary assessment of outdated overlapping reviews resulted in exclusion of 21 reviews. Applying the inclusion-exclusion criteria identified 39 reviews for the umbrella review. **Figure 4.1** summarises the study

selection process. **Appendix 4.6** provides the list of excluded studies, with reason for exclusion, after screening of the titles and abstracts.

Methodological quality

Thirty two reviews were rated as moderate in quality and seven reviews were rated as low in quality **(Appendix 4.7)**. All seven low quality reviews did not meet three of the seven domains considered critical: they had not stated that the review methods were established before conducting the review; they had not used a comprehensive search strategy; and they had not provided a list of excluded studies and the justification for their exclusion.[174]

Overlapping and non-overlapping associations

Twenty three reviews reported overlapping associations.[34,35,38,182–201] Overlapping associations included: current use of combined oral contraceptives and risk of myocardial infarction, n=2[195,196]; use of combined oral contraceptives and risk of ischaemic stroke, n=3[186,195,196]; use of combined oral contraceptives and risk of haemorrhagic stroke, n=2[190,196]; use of progesterone only pill and risk of stroke, n=2[191,194]; use of combined oral contraceptives in migraine and risk of stroke, n=2[193,194]; early menarche and mortality from cardiovascular disease, n=2[34,35]; early menopause and risk of fatal cardiovascular disease, n=3[197–199]; pre-eclampsia and risk of cardiovascular disease, n=2[38,200]; gestational diabetes and risk of cardiovascular disease, n=3[182,188,201]; preterm birth and risk of cardiovascular disease, n=3[38,183,184]; and polycystic ovary syndrome and risk of cardiovascular disease, n=3.[185,187,189] **Appendix 4.8** describes the general characteristics of the reviews with overlapping associations, including the decision to retain or exclude an association from the analysis.

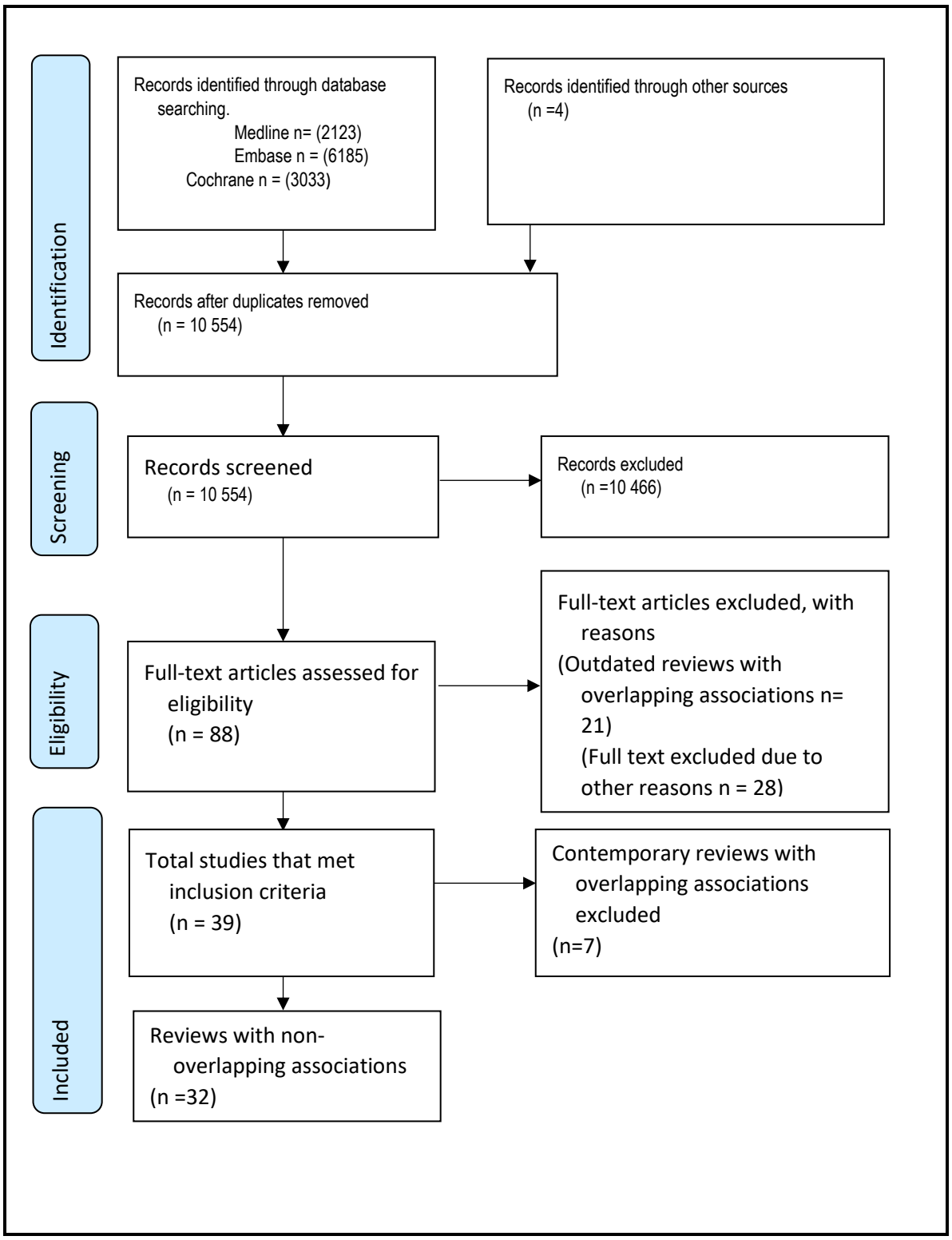


Figure 4.1: **PRISMA Flow diagram**

Appendix 4.3 provides an example of the assessment of the degree of overlap with a citation matrix. **Appendix 4.9** lists the thirty two reviews with non-overlapping associations that were included in the analysis and the seven contemporary reviews that were excluded because of overlap.

Study characteristics of reviews with non-overlapping associations

Factors related to fertility investigated in the included reviews were use of hormonal contraceptive agents (n=9), fertility treatment (n=1), early menarche (n=2), polycystic ovary syndrome (n=3), menopause (n=4), parity (n=2), and breastfeeding (n=1). Adverse pregnancy outcomes included miscarriage (n=1), pre-eclampsia (n=2), gestational diabetes (n=2), preterm births (n=3), and multiple adverse pregnancy outcomes (n=1). One study reviewed risk factors related to fertility and adverse pregnancy outcomes but was limited to heart failure as an outcome (n=1). Of the 32 reviews included in the analyses, 24 conducted meta-analyses as the main form of evidence synthesis. The median length of follow-up was about 10 years for studies on risk factors related to fertility and 7.5 years for studies on adverse pregnancy outcomes. **Supplemental Table S4.1** summarises the general characteristics of the reviews and meta-analyses included in the umbrella review.

Summary findings

Supplemental Table S4.2 provides a summary of the studies included in the umbrella review, with the main results, a summary of the relevant existing guidelines, and recommendations for future research and clinical practice. **Table 4.1** shows the effect sizes for each reproductive factor and the risk of cardiovascular disease.

A life course approach was adopted where exposures are presented from menarche to menopause for risk factors related to fertility, and from miscarriage to low birth weight for adverse pregnancy outcomes.

Table 4.1. Summary findings for each reproductive risk factor and their effect sizes for cardiovascular outcomes.

Reproductive factors (Fertility-related)	Fatality Type	Composite Cardiovascular Disease Effect size (95% CI)	Ischaemic Heart Disease Effect size (95% CI)	Stroke Effect size (95% CI)	Heart Failure Effect size (95% CI)
Early Menarche	Non-fatal	HR 1.15 (1.02 to 1.28)	--	-	-
	Fatal	RR 0.99 (0.98 to 1.01)	RR 0.97 (0.947 to 0.993)	RR 0.98 (0.95 to 1.01)	-
	Fatal and non-fatal	-	-		-
Oral contraceptive pill use	Non-fatal	-	-	Ischaemic subtype OR 2.47 (2.04 to 2.99)	-
	Fatal	-	-		-
	Fatal and non-fatal	-	-	Haemorrhagic subtype OR 1.39 (1.05 to 1.83)	-
Current combined oral contraceptive use	Non-fatal	-	-	-	-
	Fatal	-	-	-	-
	Fatal and non-fatal	-	Myocardial infarction RR 1.6 (1.3 to 1.9)	Ischaemic subtype RR 1.7 (1.5 to 1.9)	-
Progesterone only pill use	Non-fatal	-	Myocardial infarction RR 0.98 (0.66 to 1.47)	RR 1.02 (0.72 to 1.44)	-
	Fatal	-	-	-	-
	Fatal and non-fatal	-	-	-	-
Combined oral contraceptives in obese women	Non-fatal	-	Myocardial infarction OR 0.88 to 5.1	OR 0.59 to 4.6	-
	Fatal	-	-	-	-
	Fatal and non-fatal	-	-	-	-
Oestrogen containing contraceptives among women with migraine	Non-fatal	-	-	-	-
	Fatal	-	-	-	-
	Fatal and non-fatal	-	-	Ischaemic subtype OR 2.08 to 16.9	-
Combined oral contraceptive use among women with dyslipidaemia	Non-fatal	-	Myocardial infarction OR 25 (6 to 109)	IRR 1.76 (1.51 to 2.06)	-
	Fatal	-	-	-	-
	Fatal and non-fatal	-	-	-	-
Combined oral contraceptive use among women with hypertension	Non-fatal	-	Myocardial infarction OR 6 to 68	Ischaemic subtype OR 3.1 to 14.5	-
	Fatal	-	-	-	-
	Fatal and non-fatal	-	-	-	-
Combined non-oral hormonal contraceptives	Non-fatal	-	Myocardial infarction OR 0.2 to OR 1.6	OR 0.8 to 1.2	-
	Fatal	-	-	-	-

	Fatal and non-fatal	-	-	-	-
Polycystic ovarian syndrome	Non-fatal	OR 1.30 (1.09 to 1.56)	OR 1.44 (1.13 to 1.84)	OR 1.36 (1.09 to 1.7)	OR 3.24 (0.53 to 19.94)
	Fatal	-	-	-	-
	Fatal and non-fatal	-	-	-	-
Fertility therapy	Non-fatal	-	-	-	-
	Fatal	-	-	-	-
	Fatal and non-fatal	HR 0.91 (0.67 to 1.25)	-	HR 1.25 (0.96 to 1.63)	-
Parity	Non-fatal	RR 1.14 (1.09 to 1.18)	-	-	-
	Fatal	RR 0.79 (0.60 to 1.06)	-	-	-
	Fatal and non-fatal	-	-	-	-
Breastfeeding	Non-fatal	HR 0.77 to 0.93	-	-	-
	Fatal	-	-	-	-
	Fatal and non-fatal	-	-	-	-
Premature ovarian insufficiency	Non-fatal	-	-	-	-
	Fatal	RR 1.24 (0.98 to 1.58)	RR 1.48 (1.02 to 2.16)	RR 1.00 (0.86 to 1.16)	-
	Fatal and non-fatal	HR 1.61 (1.22 to 2.12)	HR 1.69 (1.29 to 2.21)	HR 1.03 (0.88 to 1.99)	-
Early Menopause (Natural and unnatural)	Non-fatal	-	RR 1.50 (1.28 to 1.76)	-	HR 1.36 to 1.66
	Fatal	RR 1.19 (1.08 to 1.31)	RR 1.11 (1.03 to 1.20)	RR 0.99 (0.92 to 1.07)	-
	Fatal and non-fatal		-	-	-
Early natural menopause	Non-fatal	-	-	-	-
	Fatal	RR 1.01 (0.91 to 1.13)	RR 1.09 (1.00 to 1.18)	RR 0.94 (0.86 to 1.03)	
	Fatal and non-fatal	-	-	-	-
Menopausal symptoms	Non-fatal	-	-	-	-
	Fatal	-	-	-	-
	Fatal and non-fatal	RR 1.29 (0.98 to 1.71)	RR 1.18 (1.03 to 1.35)	RR 1.08 (0.89 to 1.32)	-
Miscarriage	Non-fatal	-	-	-	-
	Fatal	-	-	-	-
	Fatal and non-fatal	OR 0.83 to 2.69	OR 1.45 (1.18 to 1.78)	OR 1.11 (0.72 to 1.69)	-
Stillbirth	Non-fatal	OR 1.49 (1.08 to 2.06)	-	-	-
	Fatal	OR 2.23 (1.90 to 2.62)	-	-	-
	Fatal and non-fatal	-	-	-	-
Pre-eclampsia	Non-fatal	OR 2.24 (1.72 to 2.93) * OR 2.74 (2.48 to 3.04) †	OR 1.73 (1.46 to 2.06)	OR 2.95 (1.10 to 7.90)	RR 4.19 (2.09 to 8.38)
	Fatal	OR 1.73 (1.46 to 2.06)	RR 2.10 (1.25 to 3.51)	RR 1.97(0.80 to 4.88)	-
	Fatal and non-fatal	-	-	-	-
Recurrent pre-eclampsia	Non-fatal	-	RR 2.40 (2.15 to 2.68)	RR 1.69 (1.21 to 2.35)	RR 2.88 (2.23 to 3.72)
	Fatal	-	-	-	-
	Fatal and non-fatal	-	-	-	-
Gestational hypertension	Non-fatal	RR 1.67 (1.28 to 2.19)	-	RR 1.83 (0.79 to 4.22)	-
	Fatal	-	-	-	-
	Fatal and non-fatal	-	-	-	-

Gestational diabetes	Non-fatal	-	RR 2.09 (1.56 to 2.80)	RR 1.25 (1.07 to 1.48)	-
	Fatal	-	-	-	-
	Fatal and non-fatal	RR 1.98 (1.57 to 2.50)	-	-	-
Placental abruption	Non-fatal	-	-	-	-
	Fatal	-	-	-	-
	Fatal and non-fatal	OR 1. 82 (1.42 to 2.33)	-	-	-
Preterm birth	Non-fatal	OR 1.63 (1.39 to 1.93)	RR 1.49 (1.38 to 1.60)	RR 1.65 (1.51 to 1.79)	-
	Fatal	OR 1.93 (1.83 to 2.03)	RR 2.11 (1.87 to 2.36)	RR 1.30 (0.94 to 1.80)	-
	Fatal and non-fatal	HR 2.01 (1.52 to 2.65)	HR 1.38 (1.22 to 1.57)	HR 1.71 (1.53 to 1.91)	-
Recurrent preterm birth	Non-fatal	-	-	-	-
	Fatal	HR 2.1 (1.2 to 3.7)	-	-	-
	Fatal and non-fatal	HR 1.4 (1.2 to 1.6)	HR 1.4 to 1.8	HR 1.8 (1.4 to 2.2)	-
Low birthweight	Non-fatal	-	-	-	-
	Fatal	-	-	-	-
	Fatal and non-fatal	OR 1.29 (0.91 to 1.83)	-	-	-
Small for gestational age	Non-fatal	-	-	-	-
	Fatal	-	-	-	-
	Fatal and non-fatal	OR 1.09 to 3.50	-	-	-

Factors related to fertility

Early age at menarche

Early age at menarche (<12), compared with menarche after the age of 12, was associated with a risk of morbidity from composite cardiovascular disease **(Table 4.1)**.[202] No association between early age at menarche and mortality from cardiovascular disease was found.[34] When examined by subtype of cardiovascular disease, an association between early age at menarche and risk of mortality from ischaemic heart disease was seen, but no association with mortality from stroke.

Use of hormonal contraceptive agents

Oral contraceptives and non-oral forms of combined hormonal contraceptives were associated with an increased risk of arteriothrombotic events **(Table 4.1)**.[186,195,203]

Use of oral contraceptives

Current users of any oral contraceptive (combined oral contraceptives containing a combination of oestrogen and progesterone, or progesterone only pill) had an increased risk of stroke compared with non-current users.[186,190] The increase in risk was greater for ischaemic stroke,[186] than haemorrhagic stroke.[190] The risk of both ischaemic and haemorrhagic stroke was greatest in women on higher doses of oestrogen, who had hypertension, were smokers, or were aged over 35 **(Supplemental Table S4.3)**.

Current users of combined oral contraceptives had a greater risk of developing myocardial infarction and stroke than non-current users of combined oral contraceptives.[195] The same review,[195] showed that the risk was increased in women on higher doses of oestrogen but was not related to the dose, generation, or type of progesterone **(Supplemental Table S4.3)**. In contrast, no association was seen between current use of the progesterone only pill and risk of myocardial infarction or stroke.[191]

Use of non-oral contraceptive agents

Comparing users of non-oral combined hormonal contraceptive agents with users of combined oral contraceptives,[203] no association with the development of myocardial infarction (the results were not meta-analysed, but odds ratios from individual primary studies ranged from 0.2 to 1.6) or stroke (odds ratio 0.8 to 1.2) was seen but the review was rated as low quality **(Table 4.1** and **Supplemental Table S4.4).**

Use of hormonal contraceptive agents in women with coexisting medical illnesses

Use of hormonal contraceptive agents was associated with an additional risk of cardiovascular disease in women who had coexisting medical conditions.[193,204,205] The risk of stroke in women diagnosed with migraine was 2-16-fold greater for those taking combined hormonal contraceptive agents than those not taking combined hormonal contraceptives **(Table 4.1)**.[193] Similarly, in women with dyslipidaemia,[204] results derived from one primary study reported in the systematic review showed that users of combined hormonal contraceptive agents were at an increased risk of myocardial infarction[206] and cerebrovascular accident compared with non-users **(Table 4.1)**.[207] Use of combined oral contraceptives in women with hypertension women was associated with a much higher risk of myocardial infarction (odds ratio 6 to 68) and ischaemic stroke (odds ratio 3.1 to 14.5) than women with normal blood pressure taking non-combined oral contraceptives.[208] But use of combined hormonal contraceptives in women with a high body mass index (>27.3 kg/m^2) was not found to be a multiplicative or additive risk factor for the development of myocardial infarction or stroke **(Table 4.1)**.[205] Reviews assessing the association between the use of combined oral contraceptives in women with a high body mass index and the risk of myocardial infarction or stroke were rated as low quality **(Appendix 4.7)**.

Polycystic ovary syndrome

Women with polycystic ovary syndrome had a 1.3-fold greater risk of developing composite cardiovascular disease than women who did not have polycystic ovary syndrome (**Table 4.1)**.[185] This increased risk was maintained when examining ischaemic heart disease[185] and stroke[209] separately **(Supplemental Table S4.3)**. Results from population-based studies suggested that, compared with healthy controls, the risk of cardiovascular events was increased in young women in the reproductive age group with polycystic ovary syndrome (hazard ratio 1.43, 95% confidence interval 1.27 to 1.61); no association was seen in postmenopausal women with polycystic ovary syndrome **(Supplemental Table S4.3)**[189] but this review was rated as low quality. Based on the results of one cross sectional study,[210] no association was found between polycystic ovary syndrome and the risk of heart failure **(Table 4.1** and **Supplemental Table S4.4)**.[211]

Fertility treatment

Women receiving fertility treatment (ovulation induction, in vitro fertilisation, and intrauterine insemination with drug treatment) had no greater risk of developing composite cardiovascular disease or stroke than infertile women not on fertility treatment.[212]

Parity and gravidity

Mortality from composite cardiovascular disease was lower in ever parous women than nulliparous women **(Table 4.1)**.[213] In a dose-response analysis, the association between ever parity and mortality from composite cardiovascular disease followed a J shaped curve with the risk lowest at a parity of four. For non-fatal events,[214] however, the risk of composite cardiovascular disease was increased in ever parous women, with the risk increasing by 4% for each live birth.[214]

Breastfeeding

Evidence synthesised from four studies suggested that breastfeeding was associated with an overall reduction in maternal cardiovascular disease.[215] Reviewers presented only a narrative review, without a meta-analysis **(Supplemental Table S4.4)**. Compared with women who did not breastfeed, two US cohort studies found that morbidity from myocardial infarction[216] and composite cardiovascular disease[217] was lower in women with a lifetime length of lactation of more than 12 months. In a cohort of Chinese women,[218] mortality from ischaemic heart disease but not stroke was lower in women who ever breastfed than in those who never breastfed. In a cohort of Norwegian women,[219] women aged 65 or younger and who never breastfed were at a higher risk of mortality from stroke than women who ever breastfed.

Menopause

Overall, women who experienced menopause earlier than age 40 (premature ovarian insufficiency) had a 1.6-fold risk of developing composite cardiovascular disease compared with women without premature ovarian insufficiency.[220] This association was related to the development of ischaemic heart disease[220]; no association was found with stroke. These findings were also reflected in the association with mortality risk from ischaemic heart disease, but not mortality from stroke or composite cardiovascular disease.[199]

Women who had experienced early (aged <45) menopause (natural and unnatural) had a 20% higher risk of mortality after cardiovascular disease than women who had experienced menopause at age 45 or older.[197] Specifically, an increased risk of developing ischaemic heart disease (fatal and non-fatal outcomes) but not stroke was seen.[197]

Early (aged <45) natural menopause was not associated with a risk of mortality from composite cardiovascular disease or stroke, but was associated with a risk of mortality as a result of ischaemic heart disease.[199] No association was seen between menopausal symptoms

and risk of composite cardiovascular disease or stroke compared with women without menopausal symptoms[221] but the risk was increased for ischaemic heart disease.

Adverse pregnancy outcomes

Pregnancy loss (miscarriage and stillbirth)

A history of miscarriage was not associated with an increased risk of composite cardiovascular disease **(Table 4.1)**.[38] In a review exploring individual cardiovascular diseases, miscarriage was linked to a higher risk of ischaemic heart disease but not of stroke.[222] Women with a history of stillbirth had a greater risk of morbidity and mortality from composite cardiovascular disease than women with no history of stillbirth.[38]

Hypertensive disorders of pregnancy (pre-eclampsia and gestational hypertension)

Overall, women with a history of pre-eclampsia (both moderate and severe pre-eclampsia) were at an increased risk of mortality and morbidity from composite cardiovascular disease compared with those without a history of pre-eclampsia **(Table 4.1)**.[38] For subtypes of cardiovascular disease, a history of pre-eclampsia was associated with a higher odds of experiencing heart failure,[200] fatal ischaemic heart disease,[200] and non-fatal stroke,[38] but not fatal stroke.[200]

A small degree (CCA 5.6%) of overlap was noted between two reviews[38,200] that investigated the association between pre-eclampsia and the risk of morbidity from ischaemic heart disease **(Appendix 4.3)**. One review[200] searched for primary studies from 2005 only. The risk of non-fatal ischaemic heart disease in women with pre-eclampsia was 1.7-2-fold in the two reviews.[38,200]

In comparison with an episode of pre-eclampsia followed by a healthy pregnancy, a history of recurrent pre-eclampsia was associated with an increased risk of composite cardiovascular disease, coronary heart disease, heart failure, and cerebrovascular accident.[223] Gestational

hypertension was linked to a greater risk of morbidity from composite cardiovascular disease but not stroke.[38]

Gestational diabetes mellitus

Women with a history of gestational diabetes had a greater risk of composite cardiovascular disease than those without gestational diabetes **(Table 4.1)**.[201] The risk was highest in the first decade after pregnancy.[201] When the analysis was limited to women who did not go on to develop diabetes mellitus after gestational diabetes, the risk was slightly less but remained statistically significant **(Supplemental Table S4.3)**.[201] The risk persisted when analysed by subtype of cardiovascular disease (coronary artery disease and stroke).[182] Evidence of an association between gestational diabetes and heart failure[211] was inconclusive however **(Supplemental Table S4.4**).[224,225]

Placental abruption

A history of placental abruption was associated with a higher odds of composite cardiovascular disease.[38]

Preterm births

Preterm delivery was associated with an increased risk of fatal and non-fatal composite cardiovascular disease.[38,226] For subtypes of cardiovascular disease, the risk was increased in non-fatal ischaemic heart disease, fatal ischaemic heart disease, and non-fatal stroke.[183] The risk of composite cardiovascular disease was greater in women with multiple preterm births than in women with one preterm birth (**Table 4.1, Supplemental Table S4.4)**.[184]

Low birth weight and small for gestational age

The risk of composite cardiovascular disease tended to be higher in women with babies of low birth weight than in women who delivered babies with an average birth weight **(Table 4.1)**.[38] Small for gestational age was linked to an increased risk of morbidity and mortality from maternal cardiovascular disease (odds ratio 1.09 to 3.50) **(Supplemental Table S4.4)**.[38]

Reviews eligible for update

We considered three reviews for update: assessing breastfeeding and the risk of cardiovascular disease,[215] assessing miscarriage and the risk of stroke,[222] and assessing gestational diabetes and the risk of stroke.[182] Breastfeeding and the risk of cardiovascular disease was considered eligible for update because of conflicting evidence in the original review; findings for breastfeeding and the risk of cardiovascular disease risk are presented as a narrative summary in line with the method used in the original review. A meta-analysis was performed for miscarriage and the risk of stroke, and for gestational diabetes and the risk of stroke, to detect a signal indicating that the review would require a full update (as outlined above; e.g., inclusion of a large new study that would result in a change to the conclusions of an existing review). After the meta-analysis, a full update was not considered necessary.

Miscarriage

A large (1 031 279 participants) Danish cohort study[227] noted that women who had a miscarriage were at a higher risk of stroke (incidence rate ratio 1.16, 95% confidence interval 1.07 to 1.25). Incorporating the results in the meta-analysis on the risk of stroke with those of the existing systematic review[222] did not alter the significance of the association between miscarriage and stroke. **Figure 4.2** shows a forest plot of the results of the individual studies and the updated meta-analysis.[227–230]

Gestational diabetes

Two recent studies[231,232] found no association between gestational diabetes and the risk of stroke (hazard ratio 1.10, 95% confidence interval 0.75 to 1.61; incidence rate ratio 0.95, 95% confidence interval 0.51 to 1.77, respectively). When the results were incorporated into the meta-analysis on gestational diabetes and risk of stroke,[182] the association between gestational diabetes and risk of stroke was maintained (risk ratio 1.21, 95% confidence

interval 1.05 to 1.40). **Figure 4.3** shows a forest plot of the results of the individual studies and the updated meta-analysis.[231–234]

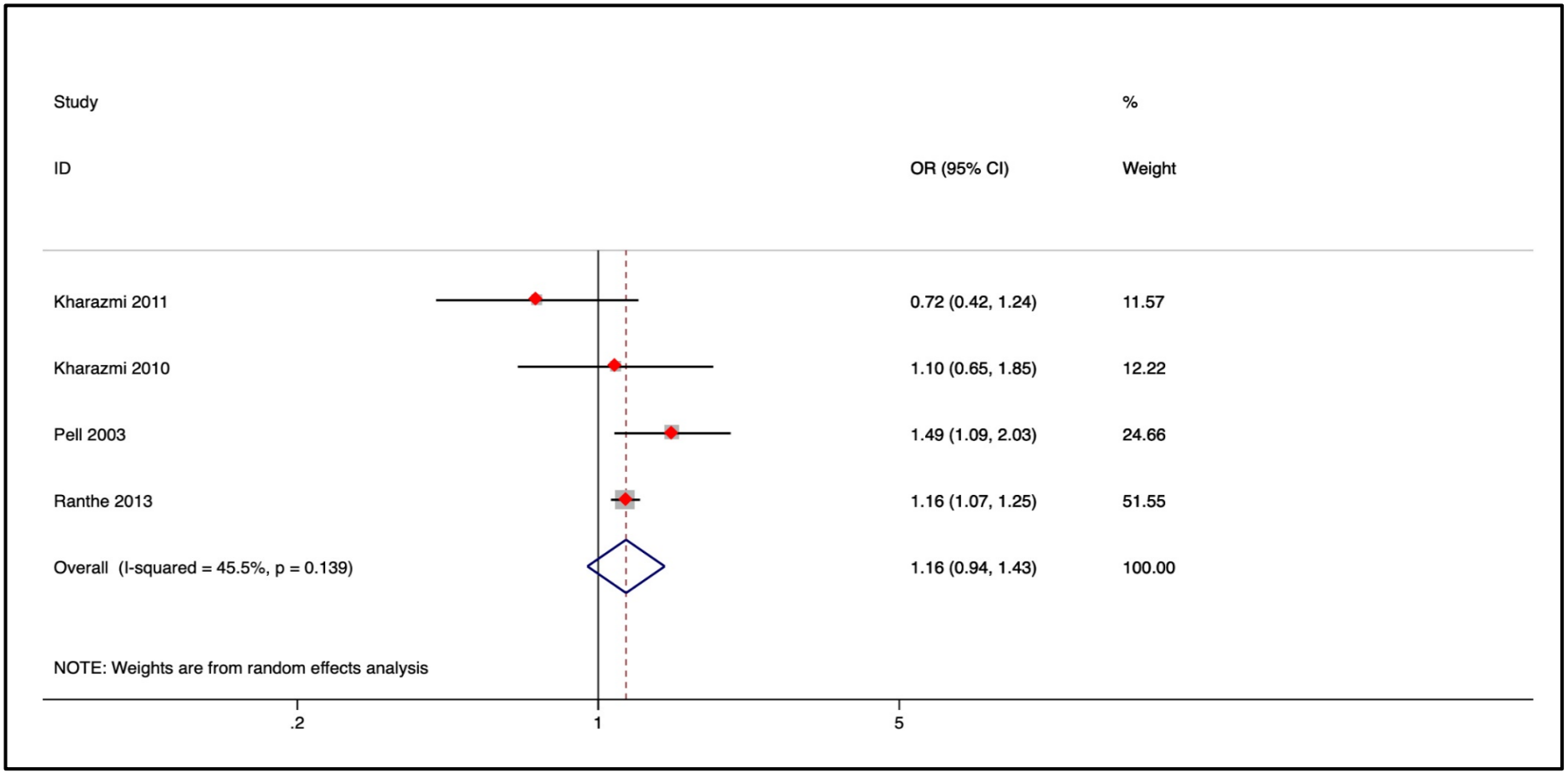


Figure 4.2: Forest plot showing studies investigating the association between miscarriage and risk of stroke. Note, weights are from random effects analysis.

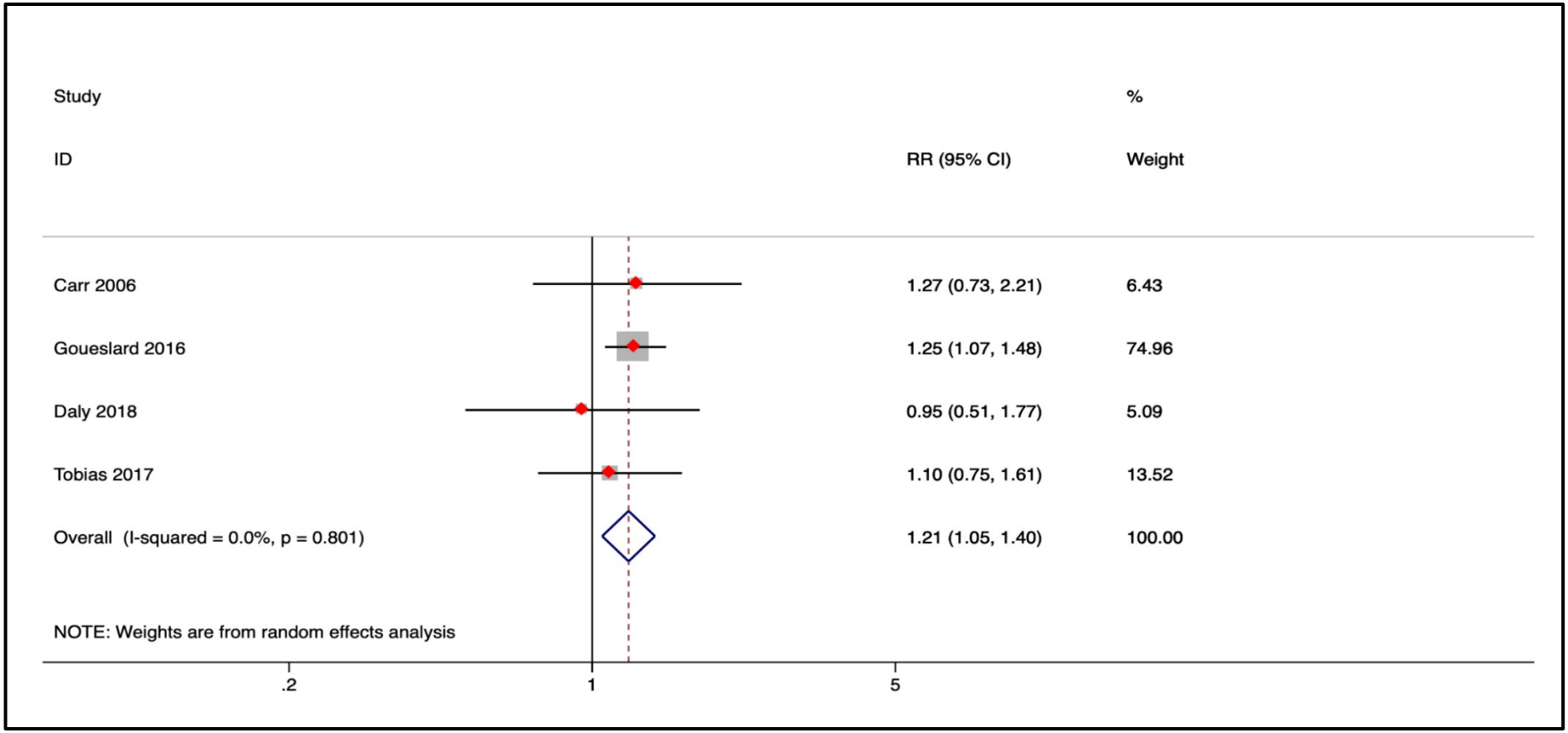


Figure 4.3: Forest plot showing studies investigating the association between gestational diabetes and risk of stroke. Note, weights are from random effects analysis.

Breastfeeding

After the original review,[215] six newly published observational studies[235–240] (five cohort and one case-control study) examined the association between length of lactation and cardiovascular disease **(Table 4.2** and **Supplemental Table S4.5** provides more results for the primary studies in the original systematic review). The quality of the studies ranged from low to high **(Appendix 4.10).** A longer length of breastfeeding was associated with a reduced risk of non-fatal composite cardiovascular disease compared with never breastfed in all three cohort studies.[235,238,240] Mortality from composite cardiovascular disease tended to be lower in women who breastfed for longer than in those who never breastfed, as assessed by two cohort studies.[235,240] Two cohort studies showed that a longer length of breastfeeding was associated with reduced morbidity from coronary heart disease compared with never breastfed.[239,240] In the case-control study, a U shaped association between length of breastfeeding and morbidity from coronary heart disease was seen, with the lowest risk in women who breastfed for 16-26 months over a total lifetime.[236] Longer length of breastfeeding versus never breastfed was associated with reduced morbidity from stroke in two cohort studies.[237,240] In summary, newly published observational studies support an inverse association between length of lactation and morbidity or mortality from cardiovascular disease.

Table 4.2: Summary of primary observational studies (Newly published) investigating association between breastfeeding and maternal cardiovascular disease risk.

Study ID/ Setting	Objective	Study design/ participants	Exposure/comparator	Outcome	Effect size (95% CI)
Nguyen 2019 New South-Wales Australia	Examine the association between breastfeeding and CVD hospitalisation and death	Cohort of 100864 middle-aged and parous women	Self-reported breastfeeding, never versus ever and average breastfeeding duration per child	CVD hospitalisation CVD mortality	*CVD hospitalisation* Never breastfed (reference) >0-6 months HR 0.86 (0.78-0.96) > 6-12 months HR 0.85(0.75-0.97) > 12 months HR 0.89 (0.71-1.12) *CVD mortality* Never breastfed (reference) >0-6 months HR 0.69 (0.51-0.94) >6-12 months HR 0.59 (0.41-0.84) > 12-month HR 0.67 (0.28-1.57)
Rajaei 2019 Stanford-USA	To evaluate the association between lactation duration and risk of developing non-fatal CAD	Hospital case-control study of 643 nulliparous and multiparous women aged 40-65 years	Exposure divided into two categories 1.Single longest duration of breastfeeding of all-live births 2. Total lifetime duration of breastfeeding	Coronary artery disease (CAD)	*1.Single highest ever duration of breastfeeding* Child and never breastfed (Ref) 1-4 months OR 1.57 (0.63-3.92) 5-9 months OR 0.53 (0.2- 1.39) 10- 18 months OR 0.71 (0.29-1.76) ≥19 months OR 0.89 (0.29-2.76) 1-4 months (Reference) 5-9 months OR 0.33 (0.14- 0.8) 10-18 months OR 0.47 (0.21-1.06) ≥19 months OR 0.57 (0.2-1.65) *2.Total lifetime duration of breastfeeding* Ref Never breastfed 0-7 months OR 1.18 (0.48 -2.86)

					8-15.5 months OR 0.88 (0.35-2.25) 16-26 months OR 0.59 (0.21-1.63) 26.5 months OR 0.71 (0.26- 1.93) Ref 0-7 months 8-15.5 months 0.78 (0.34 -1.76) 16-26 months 0.45 (0.17-1.16) ≥26.5 months 0.62 (0.26- 1.15)
Jacobson 2018 USA	To assess the association between breastfeeding and risk of stroke and whether the association differs by ethnicity and race	80191 parous women from the women's health observational study.	Never breastfeeding (< 1month) vs Ever-breastfeeding	Stroke	*Stroke risk: Ever Breastfed* No (Reference) Yes HR 0.77 (0.70-0.84) *Stroke risk: Duration of breastfeeding* Never (Reference) 1-6 months HR 0.81 (0.74- 0.90) 7-12 months HR 0.75 (0.66, 0.85) ≥ 13 months HR 0.74 (0.65, 0.83
Kirkegaard 2018 Denmark	To examine how any, partial, and full breastfeeding duration were associated with maternal risk of hypertension and CVD and how pre-pregnancy BMI and waist circumference influenced the association	Cohort study of 63 260 women with live-born singleton infants	Breastfeeding for less than 4 months vs breastfeeding for > 4months	Non-fatal CVD	*CVD risk (18 months- 15 years postpartum):* *Pre-pregnancy normal/ underweight* < 4 months (Reference) 4-10 months HR 0.68 (0.58 -0.80) >10 months HR 0.61 (0.52- 0.73) *pre-pregnancy overweight/ obese* <4 months (Reference) 4-10 months HR 0.79 (0.64-0.98) >10 months 0.88 (0.71-1.10) *CVD risk (7 years- 15 years postpartum):* *<4 months (Reference)* 4-10 months HR 0.77 (0.63- 0.94) >10 months HR 0.77 (0.62- 0.96)

Peters 2017 China	To examine the long-term CVD effects of breastfeeding among Asian (Chinese) women)	Cohort study of 289 573 Chinese women aged 30-79 years at baseline	Ever breastfeeding compared to never breastfeeding among parous women	Non-fatal CVD Non-fatal CHD Non-fatal Stroke	*<u>Lifetime lactation duration of breastfeeding among parous women</u>* *Outcome composite CVD* Never HR 1.00 (0.95-1.06) >0-12 months; HR 0.96 (0.93-0.99) 12-24 months HR 0.97 (0.95-0.99) 24-36 months HR 0.96 (0.94-0.98) 36-48 months HR 0.92 (0.89-0.94) >48 months HR 0.91 (0.88-0.93) *Outcome fatal CVD* Never 1.00 (0.77 -1.29) >0-12 months 0.88 (0.74-1.04) 12-24 months 0.98 (0.87-1.09) 24-36 months 0.93 (0.85-1.02) 36-48 months 0.81 (0.74-0.89) >48 months 0.86 (0.79-0.92) *Outcome CHD* Never HR 1.00 (0.92-1.09) >0-12 months; HR 0.93 (0.89-0.99) 12-24 months HR 0.92 (0.89-0.96) 24-36 months HR 0.86 (0.83-0.89) 36-48 months HR 0.86 (0.82-0.90) >48 months HR 0.82 (0.79-0.86) *Outcome stroke* Never HR 1.00 (0.93-1.08) >0-12 months; HR 0.93 (0.89-0.97) 12-24 months HR 0.93 (0.90-0.96) 24-36 months HR 0.91 (0.88-0.94) 36-48 months HR 0.86 (0.82-0.89) >48 months HR 0.85 (0.82-0.89)

Peters 2016 European cohort	To assess the association between breastfeeding and risk of incident coronary heart disease	Cohort 8044 parous women	Ever breastfeeding compared to never breastfeeding	CHD	*Exposure lifetime duration of breastfeeding among parous women* Never breastfed; HR 1.00 (0.75-1.34) 0-3 months; HR 0.73 (0.60-0.89) 3-6 months HR 0.68 (0.56- 0.83) 6-12 months HR 0.69 (0.55 -0.87) 12-23 months HR 0.63 (0.51-0.76) >23 months HR 0.62 (0.45 -0.86)

Summary of results by cardiovascular outcome

Composite cardiovascular disease

Preterm birth, pre-eclampsia, and stillbirth were associated with a twofold increase in the risk of composite cardiovascular disease; premature ovarian insufficiency, placental abruption, gestational hypertension, and gestational diabetes mellitus were associated with a 1.5-1.9-fold increase in the risk; and polycystic ovary syndrome, early menopause, early menarche, and ever parity were associated with a less than 1.5-fold increase in risk. Breastfeeding for longer was associated with a reduced risk of cardiovascular disease.

The forest plot (**Figure 4.4)** shows the results for reviews that conducted a meta-analysis.[34,38,185,197,199,201,202,212–214,221,226]

No association was found between cardiovascular disease outcomes and fertility treatment, current use of the progesterone only pill, or use of non-oral hormonal contraceptive agents.

Ischaemic heart disease

A history of maternal delivery of preterm infants, gestational diabetes, pre-eclampsia, and recurrent pre-eclampsia were associated with a twofold or more increase in the risk of ischaemic heart disease; current use of combined oral contraceptives (oestrogen and progesterone), premature ovarian insufficiency, early menopause, and recurrent miscarriage were associated with a 1.5-1.9-fold increased risk; and polycystic ovary syndrome, menopausal symptoms, and miscarriage were associated with a less than 1.5-fold increased risk **(Figure 4.5)**.[34,38,182,183,185,191,195,197,200,201,220–222,226]

Stroke

Current use of any oral contraceptives (combined oral contraceptives and progesterone only pill), recurrent pre-eclampsia, and pre-eclampsia were associated with a twofold or more increased risk of stroke; maternal delivery of preterm infants, gestational diabetes, and current use of combined oral contraceptives were associated with a 1.5-1.9-fold increase in

risk; and polycystic ovary syndrome was associated with a less than 1.5-fold increase in risk **(Figure 4.6**).[34,38,182,183,186,190,191,195,197,199,200,209,212,220–223,226]

Heart failure

Pre-eclampsia was associated with a fourfold increase in the risk of heart failure **(Figure 4.7)**.[200,223]

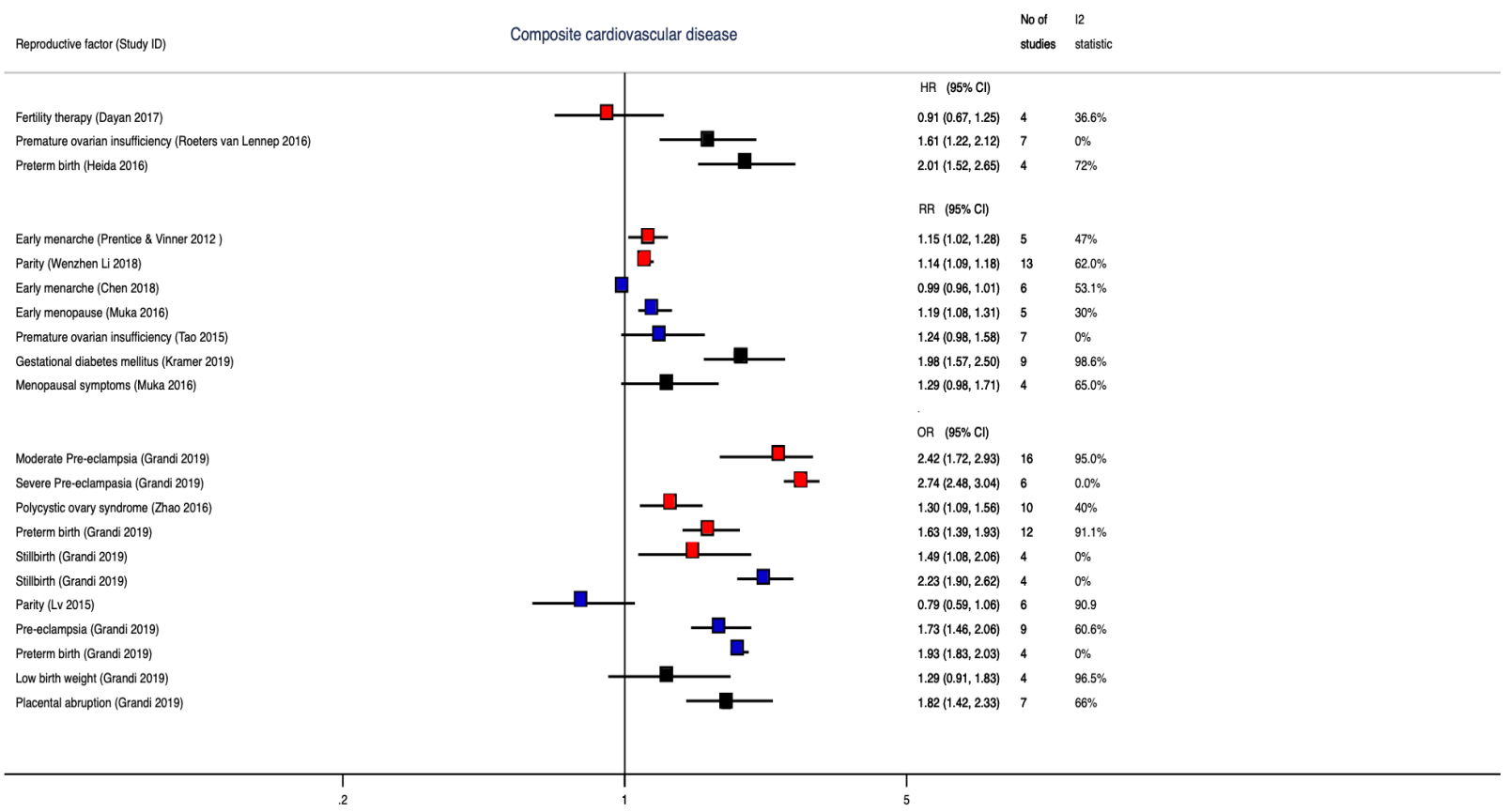


Figure 4.4: **Forest plot showing results of meta-analyses from reviews that investigated the association between various reproductive factors and risk of composite cardiovascular disease. Red indicates non-fatal outcomes, blue fatal outcomes, and black combined fatal and non-fatal outcomes**

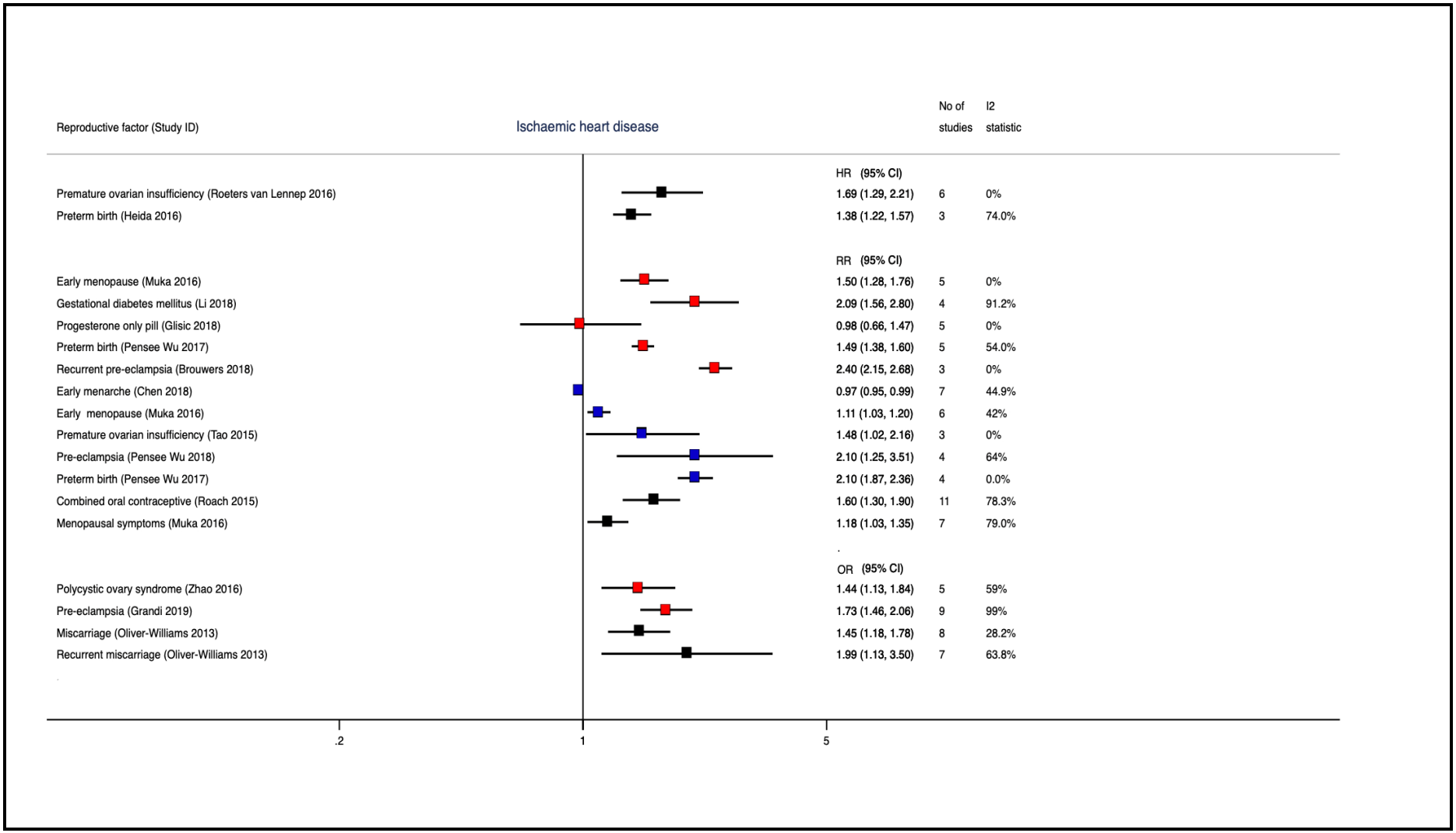


Figure 4.5: **Forest plot showing results of meta-analyses from reviews that investigated the association between various reproductive factors and risk of ischaemic heart disease. Red indicates non-fatal outcomes, blue fatal outcomes, and black combined fatal and non-fatal outcomes**

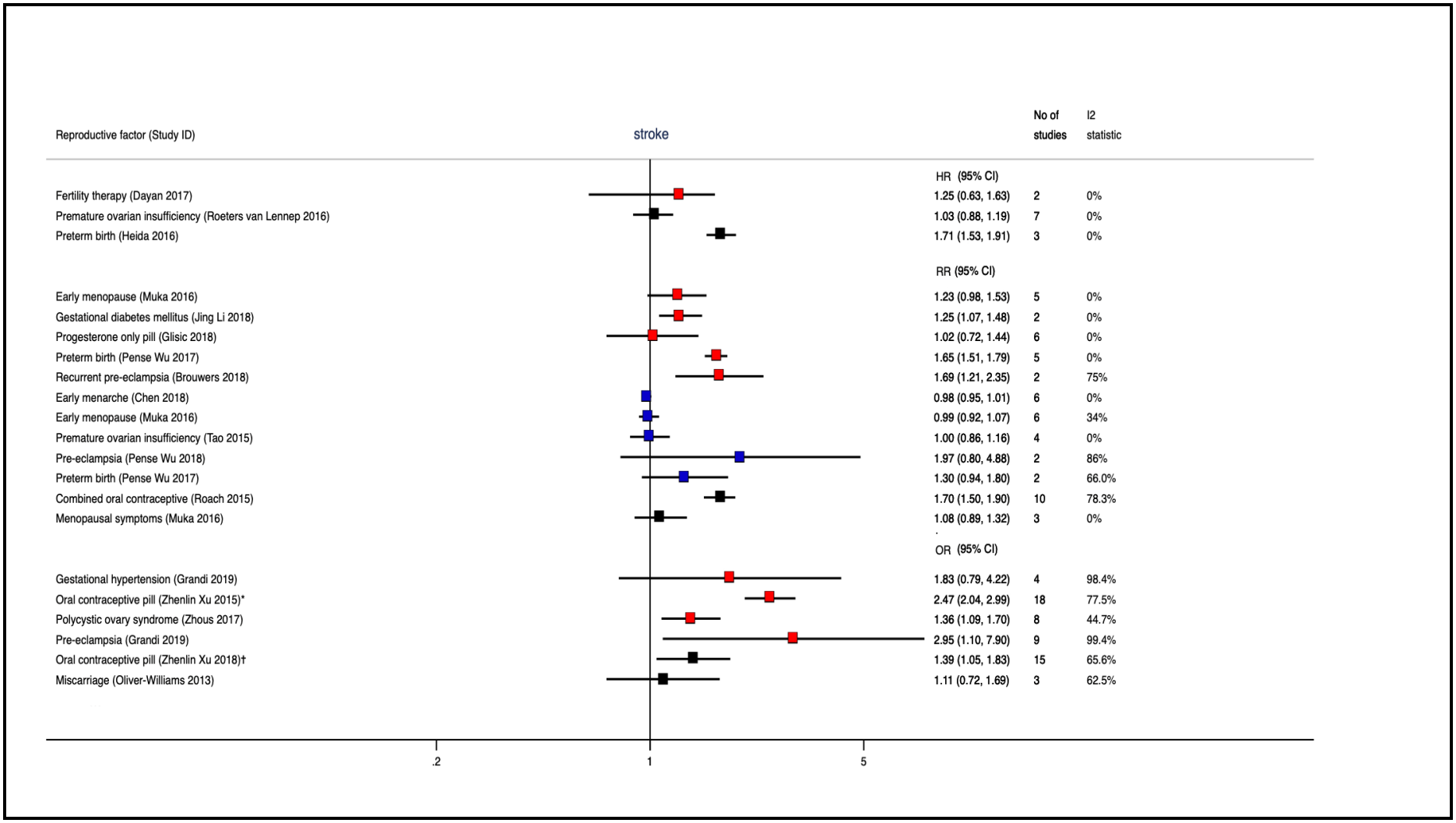


Figure 4.6: Forest plot showing results of meta-analyses from reviews that investigated the association between various reproductive factors and risk of stroke. Red indicates non-fatal outcomes, blue fatal outcomes, and black combined fatal and non-fatal outcomes. *Ischaemic stroke. †Haemorrhagic stroke

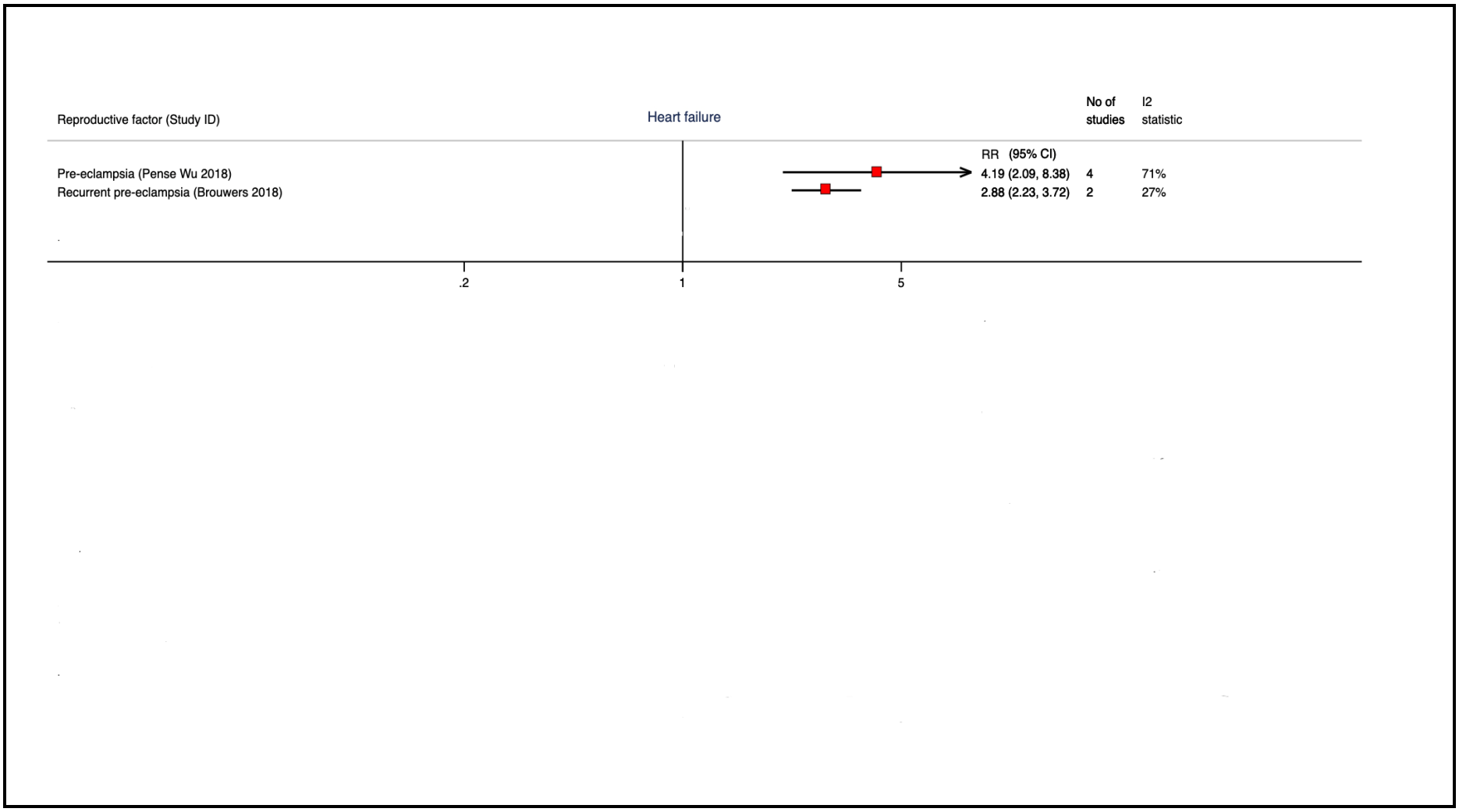


Figure 4.7: **Forest plot showing results of meta-analyses from reviews that investigated the association between various reproductive factors and risk of heart failure. Red indicates non-fatal outcomes**

Discussion

This detailed umbrella review synthesised existing systematic reviews and meta-analyses into one user friendly document. The review has updated a previous systematic review on the association between breastfeeding and maternal cardiovascular outcomes, and identified gaps and proposed recommendations for research and practice, particularly with respect to relevant UK guidelines (National Institute for Health and Care Excellence, Royal College of Obstetricians and Gynaecologists, and Faculty of Sexual and Reproductive Healthcare).

Main findings

Evidence from the umbrella review suggests that current use of combined oral contraceptives, use of combined hormonal contraceptive agents in women with dyslipidaemia, use of combined hormonal contraceptive agents in women with hypertension, use of oestrogen containing pills in women with migraine, polycystic ovary syndrome, premature ovarian insufficiency, early menarche, early menopause, menopausal symptoms, parity, pre-eclampsia, recurrent pre-eclampsia, preterm births, gestational diabetes, gestational hypertension, miscarriages, stillbirths, placental abruption, and small for gestational age are associated with an increased risk of cardiovascular disease outcomes. The review on length of lactation and the recently published studies suggests that breastfeeding for longer reduces the risk of cardiovascular disease. Length of lactation might be a proxy for general health state but never breastfed was associated with vascular characteristics (larger arterial lumen and adventitial diameters) linked to a higher risk of cardiovascular disease independent of sociodemographic characteristics, health related behaviour, family history, and body mass index.[241,242] The evidence was inconclusive on the association between use of combined hormonal contraceptive agents in women with a high body mass index (>27.3) and the risk of cardiovascular disease outcomes. No association was found between current use of progesterone only contraceptives, use of non-oral combined hormonal contraceptive agents,

fertility treatment, or gravidity and the risk of cardiovascular disease outcomes. Reviews on endometriosis, pelvic inflammatory disease, and anaemia during pregnancy were absent.

Strengths and limitations

The umbrella review has many strengths. A comprehensive search strategy was used to identify relevant reviews. The methodological quality of the studies included in the review was assessed with the AMSTAR 2 tool. Where eligible, reviews were updated to ensure the evidence was current. Evaluation of CCA and reporting of the highest quality and most current review from reviews with overlapping associations were used to eliminate double counting. Methodological rigour in the conduct of the review was achieved by following PRISMA guidelines.

Several limitations arose. Lack of data, including missing metadata (number of participants and events), hindered the reporting of some elements of the umbrella review. Certain reproductive factors, including endometriosis, pelvic inflammatory disease, first trimester bleeding without miscarriage, and anaemia in pregnancy, have been linked to an increased risk of future cardiovascular disease events.[40,156,243–245] Systematic reviews on these exposures could not be identified, however, and therefore these factors were not incorporated in our analyses. Conversely, for some reproductive factors, including age at first birth,[246] evidence from a systematic review was identified, but because of inherent methodological shortcomings,[170] the review did not meet our inclusion criteria.

With the AMSTAR 2 quality appraisal instrument, some reviews were rated as low quality, and none of the reviews was rated as high in quality. Insufficient reporting by review authors rather than shortcomings of the review methods could have inadvertently led to a downgrading of the quality of the review. Also, the reviews included were necessarily based on observational evidence; consequently, as noted by Grandi et al,[38] the possibility of confounding remains because of unknown confounders or lack of adjustment for known

confounders. The review by Grandi et al noted that a large number of studies failed to adjust for all key risk factors and therefore the results should be interpreted with caution. Misclassification of exposure or outcome status in the studies included in the review is also possible.

Methodological issues

The evidence in the umbrella review was from observational study designs which are prone to residual confounding. In some instances, evidence was derived from one study or pooled studies which recorded a small number of events, leading to imprecise results. Also, some of the evidence was derived from cross sectional studies which are poor in determining temporal associations.

Several associations between reproductive factors and cardiovascular disease had a high degree of between study heterogeneity. Several reviews could not evaluate the presence of publication bias because of the small number of studies in the meta-analyses.[247] Information from some of the primary studies was self-reported, which might lead to potential misclassification and recall bias.

Relation to evidence-based guidelines and other reviews

Factors related to fertility

Evidence presented in this review on combined hormonal contraceptive agents and combined oral contraceptives are in keeping with findings on the adverse effects of the use of hormonal contraceptive agents reported in current evidence based guidelines.[248] Also, the findings of this review agree with the consensus statement from the European Headache Federation, which reported that the risk of stroke was greater in women with migraine.[249] But caution should be exercised in the interpretation of findings on the use of combined oral contraceptives and the arteriothrombotic risk. Firstly, the between study heterogeneity was high. Secondly, publication bias was not always assessed so its presence cannot be ruled

out.[195] Finally, results on current use of combined oral contraceptives in women with dyslipidaemia and current use of combined oral contraceptives in women with obesity were imprecise because they included a small number of studies. Although the absolute risk of cardiovascular disease associated with the use of combined oral contraceptives is low (about 10 per 100 000 person years for myocardial infarction and 21 per 100 000 person years for stroke),[157] a large proportion of women (up to 18% in Europe and North America in 2019) in the reproductive age group use contraceptive pills[44]; hence clinicians should discuss this risk with patients and ensure that women are aware of the association between the use of combined oral contraceptives and the increased risk of cardiovascular disease.

The evidence reported supports the results from an overview of reviews that investigated the association between polycystic ovary syndrome and system wide complications, including cardiovascular disease.[250] The overview summarised evidence from two systematic reviews.[185,250] Our review synthesised evidence from another three reviews, including one evaluating the risk of heart failure,[189,209,211] but no evidence of an increased risk of heart failure in women with polycystic ovary syndrome was found. Results on the risk of heart failure were based on one cross sectional study that reported imprecise results. Moreover, cross sectional studies cannot be used to infer causality.

Guidelines on the prevention of cardiovascular disease recognise perimenopause and menopause as periods when women are vulnerable to cardiovascular disease.[251,252] In line with findings in the evidence-based guideline on the management of women with premature ovarian insufficiency,[253] the evidence we evaluated reported an increased risk of ischaemic heart disease and cardiovascular disease associated with premature menopause. Also, early menopause and menopausal symptoms were associated with an increased risk of ischaemic heart disease.

Adverse pregnancy outcomes

Findings from our review are consistent with European and American evidence-based guidelines on prevention of cardiovascular disease that highlighted pre-eclampsia, gestational diabetes, and preterm birth as adverse pregnancy outcomes that potentially increase the risk of cardiovascular disease.[254–257] Also, this review reports evidence of an increased risk of cardiovascular disease outcomes in women with stillbirths, small for gestational age offspring, and placental abruption. We reported that the increased risk of composite cardiovascular disease but not stroke was statistically significant (odds ratio 1.67, 95% confidence interval 1.28 to 2.19) in women with gestational hypertension. These findings are in keeping with a meta-analysis,[258] published beyond the time line of this review, which reported that women with gestational hypertension had an increased risk of composite cardiovascular disease (relative risk 1.73, 95% confidence interval 1.43 to 2.09), stroke (1.66, 0.99 to 2.79), coronary heart disease (1.56, 1.35 to 1.81), and heart failure (1.70, 1.43 to 2.02).

In an umbrella review,[259] an inverse association between birth weight and future maternal cardiovascular disease was reported (hazard ratio 0.75, 95% confidence interval 0.67 to 0.84, for every one standard deviation increase from the mean weight). An analysis reported in another review,[38] which excluded studies with self-reported low birth weight and those that reported less severe forms of cardiovascular disease, revealed a statistically significant association (odds ratio 1.46, 95% confidence interval 1.11 to 1.91) between low birth weight and cardiovascular disease,[38] in agreement with the findings of the umbrella review[259] **(Supplemental Table S4.3)**.

Biological plausibility

Multifactorial mechanisms might explain the increased risk of cardiovascular disease associated with various reproductive factors. Families of women with a history of reproductive complications were also at an increased risk of cardiovascular disease and so genetic predispositions could have a role.[260,261] Use of hormonal contraceptive agents might result in a homeostasis imbalance by favouring procoagulant factors and decreasing anticoagulant factors.[262] Metabolic derangements linked to the risk of cardiovascular disease, including weight gain, decreased insulin sensitivity, dyslipidaemia, and hypertension, are prevalent in women with risk factors for cardiovascular disease specific to women (eg, factors related to fertility and adverse pregnancy outcomes).[263–268] On the other hand, in young women aged 50 or younger, prolonged lactation was inversely linked to risk factors for cardiovascular disease, including total cholesterol, body mass index, waist circumference, and hypertension, which might be linked to the reduced risk of cardiovascular disease noted in these women.[269]

Endothelial dysfunction, which has been found in women with premature menopause and in those with adverse pregnancy outcomes, might trigger pregnancy complications and remain beyond these complications to predispose women to future cardiovascular disease.[150,270] Parity of four or more is associated with an increased risk of cardiovascular disease through an accelerated atherosclerotic process in both younger and older women.[271]

Implications for practice and public health

The implications for practice include early or routine screening and assessment for cardiovascular disease and risk factors; routine postpartum follow-up and monitoring, involving multidisciplinary healthcare professionals (eg, general practitioners, gynaecologists, cardiologists); improving education and awareness for patients and clinicians; and use of timely treatment.[272] A high proportion of women will encounter a clinician for the

first time when planning for a family and during pregnancy. Obstetricians and gynaecologists should, therefore, be involved in the referral and follow-up of patients potentially at risk. A multidisciplinary approach between general practitioners, specialist physicians, and obstetricians and gynaecologists is recommended.[273] Likewise, educating practitioners in the primary care setting on the importance of taking a thorough reproductive history and recording factors related to fertility or adverse pregnancy outcomes is essential. Information from this history could prove crucial in identifying patients at high risk for prevention of cardiovascular disease and follow-up. Our previous study found insufficient reporting of gestational diabetes and screening for cardiovascular risk factors in these women.[232] Adverse pregnancy outcomes should be communicated to primary care and reported in primary care records so these factors can be used for future risk stratification, and patients recalled for risk assessment of cardiovascular disease.

Hospital episodes related to cardiovascular disease occurred in 381 458 women in the financial year 2017-18,[274] indicating an incidence of about 113.4 cardiovascular disease episodes per 10 000 women annually. A study focusing only on coronary heart disease suggested that 15% of coronary heart disease in women younger than 65 cannot be explained by existing risk factors.[15] Therefore, we believe that if we were to look at care pathways of women with reproductive risk factors, a large proportion of cardiovascular disease would be hypothetically preventable. But quantifying how much is preventable is difficult given that many of these risk factors might cluster together; also, how many of the risk factors are modifiable, and whether, if modified, a reduction in cardiovascular events will be seen is unclear. Nevertheless, screening for risk factors in these women and management of these reproductive risk factors might not only reduce the risk of cardiovascular disease as a result of the reproductive risk factors themselves, but also reduce the risk caused by traditional risk factors for cardiovascular disease (eg, improving care pathways for women with gestational

diabetes will enable early identification of diabetes mellitus and also other risk factors, thereby reducing cardiovascular events).

Implications for future research

Several reproductive factors have been linked to an increased risk of ischaemic heart disease, stroke, and overall cardiovascular disease. These reproductive factors might be linked to the risk of peripheral arterial disease and heart failure, and therefore longitudinal studies are needed in this area.

Evidence from the review has suggested that women with adverse pregnancy outcomes are at risk of future cardiovascular disease outcomes. Current guidelines on prescription of contraceptives recommend a careful assessment of the eligibility for combined oral contraceptives in women with migraine, diabetes, and other existing conditions associated with a high risk of cardiovascular disease.[275] These guidelines do not include recommendations on the safety profile of the use of combined oral contraceptives in women with adverse pregnancy outcomes and other complications related to fertility. Also, the interaction between adverse pregnancy outcomes, factors related to fertility, and other conditions predominant in women (migraine, autoimmune diseases) that predispose to cardiovascular disease needs to be investigated.

That pregnancy complications act as a stress test that unmasks women who are at an increased risk of cardiovascular disease has been postulated.[276] Whether adverse pregnancy outcomes and reproductive factors related to fertility directly cause or act as stressors that reveal those who are already susceptible to cardiovascular disease needs to be determined. This information will help in starting preventive strategies early. Moreover, the mechanistic pathways between these reproductive factors and risk of cardiovascular disease need to be determined.[277]

Prediction models for traditional risk factors for cardiovascular disease could underestimate the true risk of cardiovascular disease in young women because they do not account for risk factors specific to women.[278] A recent systematic review on risk prediction models for cardiovascular disease in women noted that only 1.1% of the 260 articles included in the review investigated the added value of incorporating risk factors specific to women in risk prediction models.[19] Even in studies that evaluated the use of predictors specific to women, however, none included predictors such as hypertensive disorders of pregnancy, gestational diabetes, polycystic ovary syndrome, and premature ovarian insufficiency. The benefit of adding reproductive factors to risk prediction models for cardiovascular disease needs to be extensively evaluated.

Should the reproductive profile prove useful in the early prediction of cardiovascular disease, it would be equally essential to determine the effectiveness of intensive screening and monitoring.[55] Conventional risk factors for cardiovascular disease, including hypertension and body mass index, have been associated with an excess risk of cardiovascular disease in women with hypertensive disorders of pregnancy.[165] Determining whether women with reproductive profiles that place them at an increased risk of cardiovascular disease might be candidates for lifestyle changes, including statin treatment, is essential. Also, interventions to promote a healthy lifestyle, epidemiological data and trends, and randomised controlled trials that assess early intervention in women with risk factors should be evaluated.[272]

Conclusion

In summary, the evidence reported in this umbrella review suggests that, from menarche to menopause, the reproductive profile of women is associated with their future risk of cardiovascular disease. Large prospective studies are needed to confirm the association between current use of combined oral contraceptives in patients with obesity and the risk of cardiovascular disease. Similarly, prospective studies with a longer duration of follow-up are

needed to investigate the association between reproductive factors and the risk of heart failure. A large proportion of unexplained risk of cardiovascular disease in women might be attributable to reproductive risk factors but the exact magnitude of the effect is unclear. Identification of reproductive risk factors at an early stage in the life course of women might facilitate the initiation of strategies to modify potential risks. Future research on the benefit of adding risk factors specific to women to prediction models for cardiovascular disease and on the mechanistic pathways that underlie the association between reproductive factors and cardiovascular disease is required. Policy makers should consider incorporating reproductive risk factors as part of the risk assessment for cardiovascular disease in clinical guidelines.

Chapter 5. Risk of cardiovascular outcomes among women with endometriosis in the United Kingdom: A retrospective matched cohort study

The study presented in this chapter has been published.

Okoth K, Wang J, Zemedikun D, Thomas GN, Nirantharakumar K, Adderley NJ. Risk of cardiovascular outcomes among women with endometriosis in the United Kingdom: a retrospective matched cohort study. BJOG. 2021 Sep 1;128(10):1598–609. https://doi.org/10.1111/1471-0528.16692

KO conceived the idea of the study guided by KN, NJA, and GNT. KO carried out the data cleaning, statistical analysis, and first draft of the manuscript. All authors: KO, JW, DZ, GNT, KN and NJA, reviewed and revised the manuscript.

Abstract

Objective

To describe the prevalence and incidence of endometriosis and to estimate the risk of cardiovascular outcomes in women with endometriosis.

Design

Population-based cohort study using The Health Improvement Network database.

Setting

UK primary care

Population

Women aged 16-50 years were followed through from 1995 to 2018

Methods

Adjusted hazard ratios (aHR) for cardiovascular outcomes comparing women with endometriosis to those without endometriosis were estimated using multivariable Cox regression models. Prevalence and incidence of endometriosis were estimated using annual (1998-2017) sequential cross-sectional and cohort studies, respectively.

Main outcome measure

The primary outcome was composite cardiovascular disease (CVD) including, ischaemic heart disease (IHD), heart failure (HF) and cerebrovascular disease. Secondary outcomes were arrhythmia and hypertension.

Results

56090 women with endometriosis and 223669 matched controls without endometriosis were included in the analysis of cardiovascular risk. Compared to women without endometriosis,

the aHR for cardiovascular outcomes among women with endometriosis were: composite CVD, 1.24 (95% CI 1.13-1.37); IHD 1.40 (95% CI 1.22-1.61); cerebrovascular disease, 1.19 (95% CI 1.04-1.36); HF, 0.76 (95% CI 0.54-1.07); arrhythmia, 1.26 (95% CI 1.11-1.43); hypertension, 1.12 (95% CI 1.07-1.17) and all-cause mortality 0.66 (95% CI 0.59-0.74). The incidence of endometriosis was 12.3 per 10000 person-years in 1998 and 11.5 per 10000 person years in 2017. The prevalence of endometriosis increased from 119.7 per 10000 population in 1998 to 201.28 per 10000 population in 2017.

Conclusion

Endometriosis is associated with an increased risk of cardiovascular outcomes. Young women with endometriosis are a potential target for CVD risk assessment and prevention.

Background

Cardiovascular disease (CVD) is a leading cause of death and disability worldwide.[279] CVD risk in young women is under-perceived by both medical personnel and among the women themselves.[22] Age- and sex-stratified data have shown that while CVD mortality has steadily decreased in older adults (> 55 years), the decrease has slowed in younger adults (< 55 years), notably in women.[10] Attention has shifted towards investigating sex-specific risk factors for CVD to account for the differential risk between the sexes. Female sex-specific risk factors for CVD, including adverse pregnancy outcomes, polycystic ovary syndrome, and premature menopause, are well documented in the literature. However, the association between endometriosis and CVD is under-studied.

Endometriosis is the abnormal presence and growth of endometrium-like (the inner layer of the uterus) epithelium and stroma in places outside the endometrium and myometrium. It is a public health problem that affects an estimated 176 million women globally or 5-10% of women in the reproductive age group.[280] The standard for the diagnosis of endometriosis is laparoscopic visualisation ideally accompanied by histological confirmation.[281] In the UK and several other countries, the average diagnostic delay for endometriosis is 7 years.[282] The exact cause of endometriosis is unclear. Several theories, including retrograde (backflow) menstruation, transformation of peritoneal mesothelial cells into endometrial cells (coelomic metaplasia) and lymphatic and vascular spread have been postulated.[283] Ectopic endometrial tissues undergo cyclical proliferation, secretion and sloughing.[284] The result is chronic inflammation and fibrosis. Chronic inflammation triggers endothelial dysfunction and initiates premature atherosclerosis.[285] Moreover, among people with chronic inflammatory disorders, the relative risk of atherosclerotic CVD is greatest in young women.[286] Beyond

chronic inflammation, there is increased production of reactive oxygen species from oxidative stress, a known trigger of cardiac arrhythmia.[287]

Given the chronic inflammatory nature of endometriosis, coupled with diagnostic delays, young women with endometriosis may be predisposed to an increase in cardiovascular risk. Using primary care data from the UK, this study aims to investigate the association between endometriosis and cardiovascular risk, as well as to describe the incidence and prevalence of endometriosis among women of reproductive age in the UK.

Methods

Study design

To estimate yearly endometriosis prevalence, sequential cross-sectional studies were carried out on 1st January each calendar year from 1998 to 2017. Annual incidence rates were calculated by conducting a series of yearly cohort studies over the same period.

A population-based retrospective cohort study was carried out to assess the risk of long-term cardiovascular outcomes. Women with a diagnosis of endometriosis (exposed) and matched controls from the general population with no diagnosis of endometriosis (unexposed), were identified between 1st January 1995 and 31st December 2018. The rates of cardiovascular outcomes were compared in the exposed and unexposed groups.

Data source

The health improvement network (THIN) is a database that contains anonymised electronic health records contributed by 787 practices in the UK using Vision software. THIN covers approximately 6.2% of the UK population.[288] Registered practices contributing to the database are representative of the UK population.[289] Vision software is an electronic health record system which is used to collect patient data by the participating practices. THIN contains data on patient demographics, medical diagnoses, lifestyle characteristics, and prescriptions.

Practice eligibility criteria

Practices were eligible for inclusion from the later of the date on which the practice met acceptable mortality reporting (AMR) and one year after the practice began to use the Vision software system, to ensure data reporting quality and sufficient time for recording important information. AMR is a quality assurance standard that ensures practices consistently record data.[92]

Study population

For incidence and prevalence, female patients aged 16-50 years registered with an eligible practice for ≥1 year before cohort entry (to ensure documentation of all important baseline covariates) were eligible for inclusion. For the cardiovascular outcomes study, adult women aged 16-50 years at baseline were included in the study. The study period was 1st January 1995 to 31st December 2018. Participants entered the study at the latest of their 16th birthday, study start date (1st January 1995), and one year after joining the practice.

Exposure

Women with the exposure (endometriosis) were matched with up to four women without a diagnosis of endometriosis, randomly selected from a pool of eligible women. The exposed and unexposed groups were matched by age (+/- one year), local health authority, and body mass index (BMI, +/- 2kg/m^2). The exposure (endometriosis) was identified using the relevant diagnostic (Read) codes (**Supplemental Table S5.1**). Our study included both surgically confirmed and coded endometriosis cases, and physician assigned codes based on clinical suspicion. Information to distinguish surgically confirmed cases from cases diagnosed on clinical suspicion was not available. Restricting cases to surgically confirmed cases alone may lead to selection bias. Although emerging evidence suggests that the clinical diagnosis of

endometriosis is more reliable than previously thought, [290] there is potential for misclassification bias.

Follow-up period

The date of diagnosis of endometriosis served as the index date for newly diagnosed patients (incident) while for patients with pre-existing endometriosis the date the patient became eligible to take part in the study was assigned as the index date. Unexposed patients were assigned the same index date as their corresponding exposed patient to mitigate immortal time bias. Each exposed participant and matched controls were followed up from the index to the exit date. The exit date was the earliest of (i) the outcome, (ii) death, (iii) study end date, (iv) date of leaving the general practice or when the general practice stopped contributing to the database.

Outcomes

The primary outcomes were the incident diagnosis of any the following individual cardiovascular conditions: heart failure, cerebrovascular disease, and ischaemic heart disease. Secondary outcomes were the incident diagnosis of arrhythmia or hypertension, and mortality. Participants with a diagnosis of any outcome of interest at baseline were omitted from the corresponding analysis. Outcomes were defined using the relevant clinical (Read) codes.

Study covariates

The study included the following potential confounders: age, Townsend deprivation quintile, smoking status, lipid-lowering medication (current users, with a record of a prescription within 60 days prior to index date), BMI, contraceptive use (current users, i.e. those prescribed hormonal contraceptives for the last 365 days before cohort entry), alcohol use, history of pre-eclampsia, history of gestational diabetes mellitus (GDM), polycystic ovary syndrome (PCOS),

pregnancy loss (miscarriage and stillbirths), pre-term births, early menopause, premature ovarian insufficiency, pelvic inflammatory disease (PID), migraine, hysterosalpingo-oophorectomy and connective tissue disorders.

For each of the covariates, the most recently recorded variable before study entry was used. BMI in kg/m^2 was categorised as normal or underweight < $25kg/m^2$, overweight 25-30 kg/m^2, obese > $30kg/m^2$, or missing for those with missing or implausible values. The self-reported smoking status was categorised as current smoker, ex-smoker, never smoker or missing. Alcohol use was categorised as current drinkers, non-drinkers, and ex-drinkers. A record of a prescription for lipid-lowering medication was used as a proxy for elevated cholesterol levels. Current users were defined as those with lipid-lowering medication for the last sixty days before cohort entry.

Analysis

Prevalence and incidence

For annual point prevalence, the proportion of eligible females with any record ever of endometriosis was calculated on 1st January each year from 1998 to 2017. Crude incidence rates every year from 1998 to 2017 were calculated by dividing the number of newly diagnosed females (numerator) by the total number of person-years at risk (denominator) for the given year. In addition, crude incidence rates by Townsend deprivation quintiles and age categories (18-25, 26-30, 31-35, 36-40, 41-45, and 46-50 years) were estimated.

Cardiovascular outcomes

Participant characteristics at baseline were reported using the appropriate descriptive statistics: categorical variables were reported using proportions while mean (SD) or median (IQR) were used in reporting continuous variables. For each exposure group, the crude incidence rates of cardiovascular outcomes were calculated. Univariable and multivariable Cox proportional

hazards models were used to estimate the crude and adjusted hazard ratios (aHR) and 95% CI of incident cardiovascular conditions among women with endometriosis compared to those without endometriosis. In the multivariable models, adjustments were made for age, smoking status, hormonal contraceptive use, lipid-lowering medication, BMI, alcohol use, polycystic ovary syndrome, migraine, and connective tissue disorders. For each model, the proportional hazards assumption was initially checked using the Schoenfield residual test followed by a graphical confirmation using the log-log survival curves.

Sensitivity analysis

Hysterectomy, treatment with gonadotropin hormone (GnRH) agonists, PID, PCOS, and adverse pregnancy outcomes are linked to higher CVD risk.[156,291,292] Sensitivity analyses for composite CVD outcomes were therefore conducted restricting analysis to: 1) women without a record for hysterectomy or oophorectomy; 2) women without PID; 3) women without adverse pregnancy outcomes; and 4) women with incident endometriosis (exposure) and their corresponding matched controls; 5) excluding women with a current prescription for GnRH.

Statistical significance was set at $p < 0.05$. All analyses were conducted using Stata version 14.2

Missing data

Missing data and implausible patient characteristics were assigned to a separate missing category and included in the regression model.

Patient and public involvement

Patients and the public were not involved in this study.

Funding

There was no funding for this study.

Results

Incidence and prevalence

The annual incidence of endometriosis among UK women aged 16-50 years was 12.3 per 10000 person-years in 1998 and 11.5 per 10000 person-years in 2017 **(Supplemental Table S5.2**). Overall, the annual incidence of endometriosis remained relatively stable throughout the twenty years of follow-up **(Figure 5.1).** The annual prevalence of endometriosis gradually increased from 119.7 per 10000 population in 1998 to 201.3 per 10000 population in 2017 **(Figure 5.1** and **Supplemental Table S5.3)**. Women in the 26-35 years age bracket had the highest incidence of endometriosis: 16.1 per 10000 person-years for the 26-30 years age group and 15.1 per 10000 person-years for the 31-35 years age group (**Figure 5.1** and **Supplemental Table S5.4**). There was a linear decrease in the incidence of endometriosis from the least deprived to the most deprived Townsend deprivation quintile **(Figure 5.1).** Women in the least deprived Townsend quintile had the highest incidence of endometriosis (13.9 per 10000 person-years) while those in the most deprived Townsend quintile had the lowest incidence of endometriosis (10.4 per 10000 person-years) **(Supplemental Table S5.5).**

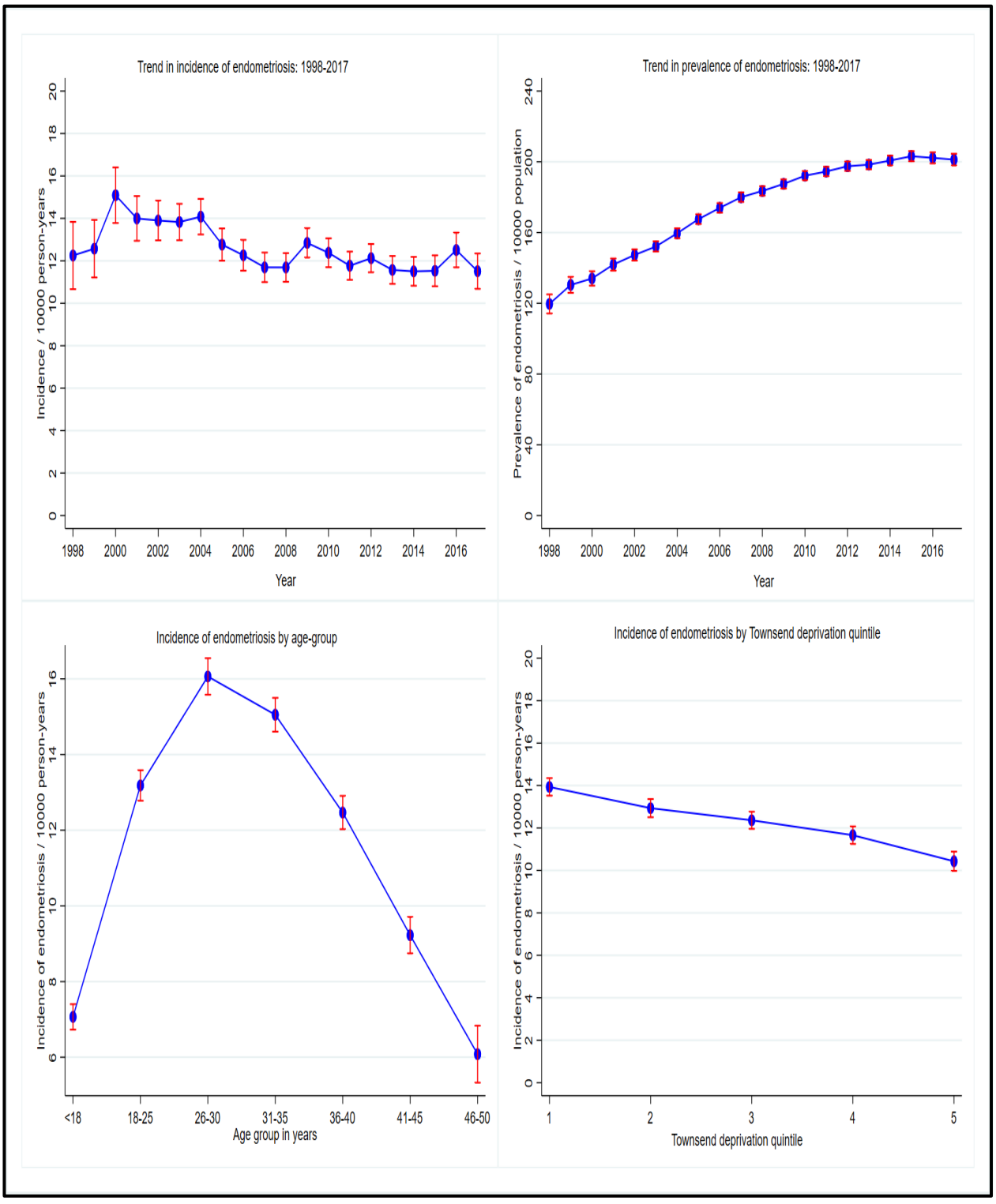


Figure 5.1: **The incidence and prevalence of endometriosis among UK women: 1998-2017**.

Cardiovascular risk

Table 1 presents the baseline characteristics of patients with diagnosis endometriosis and matched controls without a diagnosis of endometriosis. A total of 279,759 women aged 16-50 years were included in the analysis of cardiovascular risk. The exposed group was composed of 56090 (20.1%) women with a diagnosis of endometriosis while the unexposed group included 223669 (79.9%) controls matched for age, BMI, and health authority. Baseline demographic, lifestyle, medical, and reproductive characteristics were similar between the two groups. At baseline, the median age in the exposed and unexposed groups were 36.7 years (IQR; 30.9- 42.5) and 36.7 years (IQR; 30.8-42.4), respectively; while 14.2% of women in the exposed group and 14.0% of women in the unexposed group were obese. Women with endometriosis compared to those without endometriosis were more likely to have connective tissue disorders (1.1% versus 0.7%), history of miscarriage (12.2% versus 9.3%), PCOS (5.9% versus 2.3%), PID (10.1% versus 3.0%), migraine (30.2% versus 22.4%) and a current prescription for combined oral contraceptive (7.0% versus 5.6%).

Table 5.1: Baseline demographic, lifestyle, reproductive and medical characteristics among women with endometriosis and those without endometriosis

Characteristics	Endometriosis	Unexposed
	N (%)	N (%)
Median age in years (IQR)	36.7 (30.9-42.5)	36.7 (30.8-42.4)
Smoking status		
Smokers	13332 (23.8)	51458 (23)
Ex-smokers	8771 (15.6)	31100 (13.9)
Non-smokers	31 151 (55.5)	126255 (56.5)
Missing	2836 (5.1)	14856 (6.6)
BMI (kg/m ^{2})		
<18.5	1645 (2.9)	5551 (2.5)
18.5-25 kg	25557 (45.6)	103884 (46.4)
25-30 kg	12245 (21.8)	48471 (21.7)
>30 kg	7974 (14.2)	31401 (14.0)
Missing	8669 (15.5)	34402 (15.4)
Alcohol status		
Non-drinker	9549 (17.0)	37878 (16.9)
Drinker	35873 (64.0)	139609 (62.4)
Excessive drinker	1300 (2.3)	5051 (2.3)
Missing	9368 (16.7)	41131(18.4)
Townsend Deprivation Index		
1 (Least deprived)	12385 (22.1)	44710 (20.0)
2	10362 (18.5)	39580 (17.7)
3	10354 (18.5)	41 457 (18.5)
4	8567 (15.3)	37416 (16.7)
5 (Most deprived)	5480 (9.8)	26527 (11.9)
Missing	8942 (15.9)	33 979 (15.2)
Current statin prescription	481(0.9)	1889 (0.8)

Characteristics	Endometriosis	Unexposed
Connective tissue disorders	613 (1.1)	1643 (0.7)
Migraine	16,950 (30.2)	50,129 (22.4)
Outcomes at baseline		
Hypertension	1767 (3.2)	6870 (3.1)
Diabetes	573 (1.0)	2820 (1.3)
IHD	91 (0.2)	432 (0.2)
Stroke/TIA	160 (0.3)	619 (0.3)
Heart failure	16 (0.0)	93 (0.0)
Reproductive history		
Current COC prescription	3,938 (7.0)	12,584 (5.6)
Current GnRH agonists	2482 (4.4)	280 (0.1)
Nulliparity	222 (0.4)	854 (0.4)
Primiparity	392 (0.7)	1452 (0.7)
Multiparity	375 (0.7)	1398 (0.6)
Miscarriage	6836 (12.2)	20882 (9.3)
Stillbirths	181 (0.3)	726 (0.3)
Gestational diabetes mellitus	368 (0.7)	1390 (0.6)
Pre-eclampsia	294 (0.5)	1156 (0.5)
Premature delivery	231 (0.4)	994 (0.4)
Placental abruption	28 (0.1)	118 (0.1)
Polycystic ovary syndrome	3327 (5.9)	5221 (2.3)
Premature ovarian insufficiency	66 (0.1)	202 (0.1)
Pelvic inflammatory disease	5649 (10.07)	6599 (3.0)
Hysterectomy/oophorectomy	8466 (15.1)	7119 (3.2)

COC= combined oral contraceptive; GnRH= gonadotropin-releasing hormone; TIA= transient ischaemic attack

Cardiovascular diseases

Between 1995 and 2018, 574 (1.03%) and 1676 (0.75%) incidence composite CVD events were recorded among women with and without endometriosis, respectively **(Table 5.2).** The crude incidence rate of composite CVD was 1.60 per 1000 person-years among women with endometriosis and 1.36 per 1000 person-years among women without endometriosis. The crude HR of composite CVD among women with endometriosis compared to those without was 1.16 (95% CI 1.06-1.28; p = 0.002) In the adjusted model (demographic, lifestyle characteristics, hypertension, diabetes mellitus, and reproductive history) endometriosis was associated with a higher risk of composite cardiovascular disease (aHR 1.24; 95% CI 1.14-1.37; p < 0.001) **(Table 5.2** and **Figure 5.2).**

On analysis of individual CVD subtypes, comparing women with endometriosis to those without endometriosis, the unadjusted HR of IHD was 1.26 (95% CI 1.09-1.44; p = 0.001) In the adjusted model ,endometriosis was associated with a 40% higher risk of IHD (aHR 1.40; 95% CI 1.22-1.61; p < 0.001) **(Table 5.2** and **Figure 5.2).**The crude HR of cerebrovascular disease was 1.13 (95% CI 0.99-1.29; p = 0.067) in women with endometriosis compared to those without endometriosis. In the adjusted model, the association between endometriosis and cerebrovascular disease was significant (aHR 1.19; 95% CI 1.04-1.36; p = 0.010) **(Table 5.2** and **Figure 5.2)**. For heart failure, in the crude model, women with endometriosis compared to those without endometriosis had lower HF risk (HR 0.71; 95% CI 0.50-0.99; p = 0.044). In the adjusted model, there was no association between endometriosis and risk of heart failure (aHR 0.76; 95% CI 0.54-1.07; p = 0.115) **(Table 5.2** and **Figure 5.2)**.

Table 5.2: Incidence rates and hazard ratios for primary cardiovascular outcomes

	Composite CVD		**IHD**		**Cerebrovascular disease**		**Heart failure**	
	Endometriosis	Unexposed	Endometriosis	Unexposed	Endometriosis	Unexposed	Endometriosis	Unexposed
Population	55832	222556	55999	223237	55930	223050	56074	223576
Events, n (%)	574 (1.03)	1676 (0.75)	279 (0.5)	753 (0.33)	294 (0.53)	881(0.39)	41 (0.07)	195 (0.08)
Person-years	357959.8	1233555	360270.9	1241282	360076.3	1240657	362130.2	1247165
Crude incidence rate/1000 person years	1.60	1.36	0.77	0.61	0.82	0.71	0.11	0.16
Age at outcome, median (IQR)	42.6 (37.5-46.8)	43.4 (39.1-47.1)	43.2(39.4-47.1)	43.5 (40.0-46.8)	41.3 (36.3-46.6)	43.0 (38.3-47.0)	43.6 (37.0-46.7)	43.2 (39.4-47.3)
Crude HR (95% CI)	1.16 (1.06- 1.28)		1.26 (1.09-1.44)		1.13 (0.99-1.29		0.71 (0.50-0.99)	
P-value	0.002		0.001		0.067		0.044	
Adjusted HR (95% CI)	1.24 (1.14-1.37)		1.40 (1.22-1.61)		1.19 (1.04-1.36)		0.76 (0.54-1.07)	
P-value	<0.001		<0.001		0.010		0.115	

Abbreviations: CVD = composite cardiovascular disease, IHD = ischaemic heart disease, IQR = inter-quartile range, HR = hazard ratio.
Adjusted for: age, Townsend deprivation quintiles, BMI, smoking status, lipid-lowering medication, alcohol use, diabetes mellitus, hypertension, connective tissue disorders, migraine, contraceptive use, parity status, PCOS.

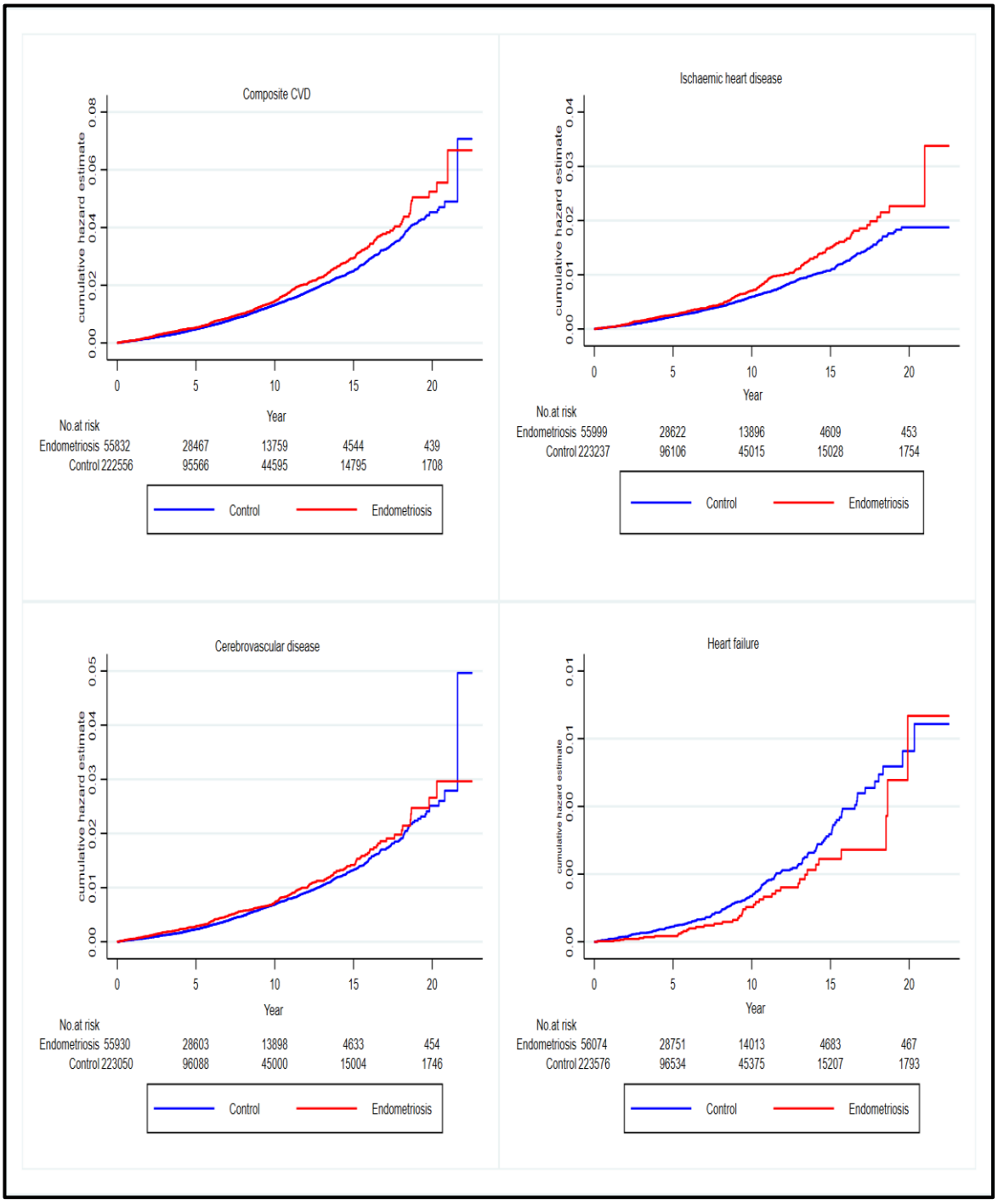


Figure 5.2: **Cumulative hazard of primary cardiovascular outcomes among women with endometriosis (exposed) and those without endometriosis (unexposed/control).**

Arrythmias

The crude incidence rate of arrhythmia was 0.92 per 1000 person-years and 0.72 per 1000 person-years among women with endometriosis and those without endometriosis, respectively. The unadjusted HR comparing women with endometriosis to those without was HR 1.26 (95% CI 1.11-1.44; p < 0.001). In the adjusted model, endometriosis was associated with a 26% higher risk of arrhythmia (aHR 1.26; 95% CI 1.11-1.43; p = 0.001) **(Supplemental Table S5.6** and **Figure S5.1).**

Hypertension

The crude incidence rate of hypertension was 6.99 per 1000 person-years and 6.52 per 1000 person-years among women with endometriosis and those without endometriosis, respectively. Comparing women with endometriosis to those without, the crude HR was 1.06 (95% CI 1.01-1.11; p = 0.016). In the adjusted model (demographic, lifestyle characteristics and diabetes mellitus, reproductive history, connective tissue disorders and migraine) endometriosis was associated with a higher risk of hypertension (HR 1.12; 95% CI 1.07-1.17; p < 0.001) **(Supplemental Table S5.6** and **Figure S5.1).**

Mortality

The crude mortality rates were 0.90 and 1.46 per 1000 person-years in women with and without endometriosis respectively. The fully adjusted HR was 0.66 (95% CI 0.59-0.74; p<0.001) in women with endometriosis compared to those without **(Supplemental Table S5.6).**

Sensitivity analysis

Supplemental Table S5.7, Supplemental Table S5.8 and **Supplemental Figure S5.2** provide the results of various restricted analyses on the association between endometriosis

and composite CVD. On exclusion of women with hysterectomy and oophorectomy, the association was attenuated (fully adjusted HR 1.17; 95 % 1.04-1.31; p=0.010). The exclusion of women with PCOS and those with a current prescription for GnRH agonist did not materially change the effect estimates for composite CVD (HR 1.25; 95% CI 1.13-1.38; p<0.001 and HR 1.25; 95% CI, 1.14-1.38; p <0.001, respectively). Exclusion of women with PID resulted in minimal change on the effect estimate (fully adjusted HR 1.22; 95% CI 1.10-1.35; = p <0.001). Restriction of the analysis to women without adverse pregnancy outcomes strengthened the effect estimate for CVD (fully adjusted HR 1.30; 95% CI 1.18-1.45; p < 0.001). On restriction to incident exposure only, the increased risk was maintained but the association was no longer statistically significant (fully adjusted HR 1.21; 95% CI 0.98-1.49; p = 0.074).

Discussion

Main findings

This population-based retrospective cohort demonstrated that cardiovascular outcomes were increased among UK women diagnosed with endometriosis compared to those without a diagnosis for endometriosis. Specifically, endometriosis was associated with a higher risk of composite CVD, IHD, cerebrovascular disease, arrhythmia, hypertension, independent of demographic, lifestyle, and reproductive confounders. No association was found between endometriosis and heart failure risk. Overall, between 1998 and 2017, the trend in the annual incidence of endometriosis was stable with only minor variations noted between the years. During the same period, there was a steady increase in the annual prevalence of endometriosis.

Interpretation of findings in the context of previous literature

Among the general female population, the prevalence of endometriosis is estimated to range from 2% to 10%.[293,294] However, prevalence estimates differ based on the study setting or diagnostic criteria.[295] The prevalence estimates in our study are similar to findings from two UK studies, a community-based study[296] and a population-based study,[297] that estimated the prevalence of endometriosis at 1.4% and 1.5%, respectively. The incidence estimates from our study align with two UK-based population studies that estimated the incidence of endometriosis at 0.97 per 1000 person-years among women aged 15-55 years,[297] and 1.46 per 1000 person-years among women aged 12-54 years. A Finnish study showed that women with endometriosis had lower all-cause mortality compared to the comparator group **(Figure S5.3)**.[298] This is consistent with the results from our study which found a significantly lower rate of mortality among women with endometriosis compared to matched controls. Longer survival among women with endometriosis compared to matched controls without

endometriosis may explain the increased annual prevalence with a stagnant annual incidence rate of endometriosis among UK women throughout the twenty years of follow-up.

Endometriosis is an oestrogen dependent condition that is common among women of reproductive age. Similar to findings in our study, a cohort study from the US, the Nurses' Health Study II (NHS II) study found that the incidence of laparoscopically confirmed endometriosis was highest among women aged 25-29 years and decreased after the age of 40 years.[299] The incidence of endometriosis decreased linearly from the least deprived quintile to the most deprived quintile. Our findings concur with reports in previous literature that noted a higher incidence of endometriosis among women of higher socioeconomic status.[300] Socioeconomic status may be a proxy marker for lifestyle risk factors associated with endometriosis in the UK. Smoking and obesity which are inversely associated with endometriosis, tend to be more prevalent among persons from more deprived socioeconomic groups; while excessive alcohol consumption, which is associated with increased risk, is more prevalent in younger high-income earners in the UK.[301] Also, the propensity to seek medical attention among women with pelvic pain and infertility is higher among women from higher compared to lower socioeconomic status groups.[302]

Findings from our study are comparable with findings from a narrative systematic review that examined the association between endometriosis and atherosclerotic cardiovascular disease. The systematic review included two population-based studies from the US Nurses' Health Study II Cohort.[39,40] The findings from these studies are summarised in **Figure S5.3**. The NHS II prospective cohort studies found that women with endometriosis compared to those without endometriosis were at a higher risk of composite IHD and hypertension **(Figure S5.3)** [39,40] We adjusted for additional confounding variables, including migraine, PCOS, and connective tissue disorders. This may partly explain the lower effect estimate of IHD risk in our study. The NHS II studies were limited to investigating the association between

endometriosis, IHD risk and hypertension risk.[39,40] On extending the research to other CVD subtypes, we found that endometriosis was associated with increased risk of cerebrovascular disease and composite CVD. Our findings are supported by a recent population based cohort study by Chiang et al which found an increased risk of composite cardiovascular disease including cerebrovascular events among Taiwanese women with endometriosis compared to controls **(Figure S5.3)**.[303] However, we did not find any association between endometriosis and heart failure risk. The attenuation of the increased risk of composite CVD after the exclusion of women with hysterectomy supports previous reports in the literature that both ovarian conservation and oophorectomy are linked to increased CVD risk.[304] A detailed pre-operative counselling on the benefits and risks of performing hysterectomies among women with endometriosis should be emphasised. Exclusion of women on current prescription of GnRH analogues was not associated with attenuation of CVD risk, consistent with the results from study by Chiang et al.[303] The exclusion of women with PID did not support findings of increased risk of CVD among women with PID reported in previous literature.[156,244] Further robust studies are needed since important confounding variables, including smoking, BMI and alcohol, were unaccounted for in these studies. A study by Brincat et al found that up to 10% of infertile women had endometriosis with PCOS. Exclusion of women with PCOS did not attenuate the risk of CVD suggesting the association between endometriosis and CVD was independent of PCOS.[305] It is not clear why, on sensitivity analyses, the exclusion of women with adverse pregnancy outcomes amplifies cardiovascular risk. Endometriosis is an enigmatic condition. It is probable that the phenotypes of endometriosis linked to increased adverse pregnancy outcomes are associated with greater localised pelvic inflammation but are less likely to be associated with systemic inflammation linked to cardiovascular complications. Restriction of the analysis to women with incident exposure and their matched

controls resulted in a non-significant increase in composite CVD with fewer outcomes reported. Prospective studies with a longer duration of follow-up are needed.

To the best of our knowledge, this is the first study to investigate an association between endometriosis and risk of arrhythmia. Findings in our study are supported by results from previous studies which have demonstrated that other chronic inflammatory conditions are linked to increased arrhythmia risk.

Biological plausibility

Several biological mechanisms may explain the observed association between endometriosis and higher cardiovascular risk. First, chronic inflammation promotes endothelial dysfunction. The systemic inflammatory nature of endometriosis has been demonstrated by several studies that found increased levels of pro-inflammatory markers in the peritoneal fluid and serum of women with endometriosis.[306] Moreover, chronic inflammation may favour the development of cardiac arrhythmia both directly via altered cardiac electrophysiology and indirectly via the accelerated development of IHD.[287]

Second, biomarkers of oxidative stress have been found to be elevated among women with endometriosis.[307] Prolonged exposure to reactive oxygen species (ROS) from oxidative stress has been associated with vascular and cardiac myocytes dysfunction which may lead to cardiac arrhythmias through cardiac fibrosis, ion channel conduction disturbances, early and late depolarisations.[308,309] Third, various studies have shown that endometriosis is associated with high levels of atherogenic low-density lipoproteins (LDL).[39] Fourth, the oxidation hypothesis may partly explain the association between reproductive risk factors, including endometriosis and increased CVD risk.[310] The hypothesis explains that LDL is not atherogenic on its own; for atherosclerosis to occur, ROS must oxidise LDL leading to form cell formation, a dysfunctional endothelium and finally atherogenesis.

Implications for public health and future research

Findings from this study suggest that young women with endometriosis are a potential target group for CVD disease prevention and, therefore, an extensive reproductive history should be taken by physicians. A multi-disciplinary approach that includes gynaecologists, cardiologists and primary care physicians is needed for effective CVD risk assessment and follow-up of women with endometriosis. Future research should focus on developing a non-invasive means of accurately diagnosing endometriosis, identifying phenotypes of endometriosis associated with enhanced cardiometabolic risk, and assessing whether the early identification and treatment of endometriosis will translate to reduced CVD burden.

Strengths and limitations

Several limitations arose. We were unable to distinguish surgically confirmed cases from cases diagnosed through other means; cases were identified through physician assigned diagnostic codes for endometriosis. We believe diagnostic Read codes for endometriosis are reliable and valid for several reasons. First, a recent UK study showed that 94% of patients with a diagnosis for endometriosis in UK primary care had at least one diagnostic procedure performed including ultrasound, magnetic resonance imaging, laparoscopy, and histology prior to diagnosis.[311] Therefore, the validity of the cases is likely to be high. Second, in a randomised controlled trial designed to evaluate the efficacy of leuprolide against placebo in the management of chronic pelvic pain among women with clinically diagnosed endometriosis, post-treatment laparoscopy confirmed 78% and 87% of clinically diagnosed cases in the leuprolide and placebo groups, respectively.[312] Third, in previous observational studies that used surgically confirmed endometriosis as the case definition, the inclusion of non-surgically confirmed endometriosis cases in sensitivity analyses,[40] or in stratified analyses,[297] did not lead to changes in the observed effect estimates. Furthermore, the exclusive use of laparoscopically confirmed cases may inadvertently introduce selection bias

since women referred for laparoscopy may systematically differ from those not referred for laparoscopy or those who are asymptomatic. [313]

In addition, our study may be limited by the inclusion of asymptomatic patients with endometriosis in the unexposed group. The impact of including asymptomatic cases in the unexposed cohort is uncertain and may not necessarily attenuate effect estimate.[314] .

In other chronic inflammatory conditions, the cardiovascular risk increases with the severity of the condition.[315] Due to unavailability of data, stratified analysis by the severity of endometriosis could not be carried out in our study. There remains a possibility of unmeasured confounding, for instance due to factors such as dietary patterns, physical activity, or breastfeeding history.

The strengths of this retrospective cohort study include large sample size, a long duration of follow-up, use of a database that is representative of the UK population, and the availability of data on important confounders.

Conclusion

In conclusion, this study found an association between endometriosis and a higher risk of cardiovascular outcomes. No association was found between endometriosis and risk of heart failure. Future research should focus on whether early treatment of endometriosis and primary CVD prevention strategies will be effective in reducing CVD risk among young women with endometriosis.

Chapter 6. Risk of cardiometabolic outcomes among women with a history of pelvic inflammatory disease: A retrospective matched cohort study from the UK

The content from this chapter has been published.

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https://doi.org/10.1186/s12905-023-02214-5

KO conceived the idea of the study guided by KN, NJA, and GNT. KO carried out the data cleaning, statistical analysis, and first draft of the manuscript. All authors: KO, GNT, KN and NJA, reviewed and revised the manuscript.

Abstract

Introduction

To describe the incidence and prevalence of pelvic inflammatory disease (PID) and to estimate the risk of cardiometabolic outcomes among women with PID compared to women without PID.

Methods

A UK retrospective matched cohort study using data from The Health Improvement Network. To assess cardiometabolic risk, women (aged ≥ 16 years) with PID were compared to matched controls without PID. Annual prevalence and incidence of PID (1998-2017) were estimated among women aged 16-50 years using annual cross-sectional and cohort analyses, respectively. Adjusted hazard ratios (aHR) and 95% CI for cardiometabolic outcomes were estimated using Cox proportional hazards models. The primary outcome was composite cardiovascular disease (CVD) and its subtypes, including ischaemic heart disease (IHD), heart failure (HF) and cerebrovascular disease. Secondary outcomes were hypertension, and type 2 diabetes mellitus (T2DM).

Results

Among the 715 recorded composite CVD events, the crude incidence rate per 1000 person-years was 1.5 among women with history of PID compared to 1.3 in matched controls. Compared to women without PID (N=73769), the aHRs for cardiometabolic outcomes among women with PID (N=19804) were: composite CVD 1.10 (95% CI 0.93-1.30); IHD 1.19 (95% CI 0.93-1.53); cerebrovascular disease 1.13 (95% CI 0.90-1.43); HF 0.92 (95% CI 0.62-1.35) hypertension 1.10 (95% CI 1.01-1.20); and T2DM 1.25 (95% CI 1.09-1.43). The prevalence (per 10,000 population) of PID was 396.5 in 1998 and 237 in 2017. The incidence (per 10,000 person-years) of PID was 32.4 in 1998 and 7.9 in 2017.

Conclusion

There was no excess risk of composite CVD or its subtypes among women with history of PID compared to matched controls. Findings from our study suggest that history of PID was associated with an increased risk of hypertension and type 2 diabetes mellitus, two major risk factors for CVD. Additional studies are required to support these findings.

Background

Cardiovascular disease (CVD) is a major public health burden with the most recent estimates from Europe revealing that it accounted for a third of all premature deaths among women.[316] Despite a notable reduction in CVD burden in recent decades, there is potential for a resurgence. Analysis of sex-aggregated data unmasks differential trends in CVD mortality, with rates in older age groups (>65 years) showing a steady decline, while rates in younger adults (< 55 years) show stagnation.[12] With up to 20% of CVD unexplained by traditional risk factors, non-traditional risk factors for CVD are gaining prominence.[15] Female reproductive complications are associated with cardiovascular outcomes in later life.[112] However, evidence on the association between infections of the female reproductive tract and CVD is limited. Findings from nascent literature suggest an increased risk of cardiovascular outcomes among women with a history of pelvic inflammatory disease.[156,244] However, these studies had several limitations, including a misleading case definition, a short duration of follow-up, and lack of adjustment for key confounders.

PID refers to infection of the female upper genital tract. The causative microorganisms are polymicrobial with *Chlamydia trachomatis* and *Neisseria gonorrhoea* accounting for 35% of the cases in the UK.[317] Infectious agents may aid in the development of cardiometabolic outcomes through the direct assault of the vasculature or indirect systemic effects of response to infection.[318] The present study estimated the burden of PID among UK women and explored the association between history of PID and risk of cardiometabolic outcomes.

Methods

Study design

Serial cross-sectional studies were carried out on 1st January each year from 1998-2017 to estimate the prevalence of PID. To estimate the annual incidence rate, a series of cohort studies were conducted over the same period. A population-based retrospective cohort study (1995-2018) was conducted to assess risk of long-term cardiometabolic outcomes.

Data source

This work used de-identified data provided by patients as a part of their routine primary care. Study data was extracted from IQVIA Medical Research Data (IMRD-UK), which incorporates data from The Health Improvement Network (THIN). The Health Improvement Network is one of the largest UK primary care databases containing electronic health records from England, Wales, Scotland, and Northern Ireland. By 2019, more than 800 practices spread throughout the UK had contributed data to THIN.[88] Validation studies have demonstrated that THIN is representative of the UK with regard to demographics, mortality (adjusted for demographics and deprivation) and prevalence of major conditions.[89–91] Participating practices record patient data using Vision software, an electronic health records system. Practices were eligible for inclusion from the later of one year after the date on which the practice met acceptable mortality reporting (a quality assurance standard and one year after the practice began to use the Vision system, to maximise data quality and recording).

Study population

For incidence and prevalence, female patients aged 16-50 years and registered with an eligible practice for ≥1 year before study entry (to ensure documentation of all-important baseline covariates) were eligible for inclusion.[319] For the cardiometabolic outcomes study, women aged ≥ 16 years at baseline were included in the study. The study period was 1st

January 1995 to 31st December 2018. Participants were eligible to enter the study at the latest of their 16th birthday, study start date and one year after joining the practice.[319]

Exposure

Women with PID (exposed group) were matched with up to four randomly selected women without PID (unexposed group). The exposed and unexposed groups were matched by age (± one year), general practice, and body mass index, BMI (± 2 kg/m^2). Diagnoses of PID were identified using UK primary care diagnostic codes (Read codes). The present study adopted the version of the PID Read code list developed by French and colleagues who grouped diagnostic codes for PID in UK primary care into three separate categories, defined as "definite", "probable" and "possible".[320] The present study combined "definite" and "probable" into a single category; only participants who fulfilled this definition of PID were included in the study. A search of the Read code dictionary did not reveal any additional codes beyond the list developed by French and colleagues. Patients with a record of "possible" PID were excluded from the study.

Follow-up period

The date of diagnosis of PID served as the index date for exposed patients. Unexposed patients were assigned the same index date as their corresponding exposed patient in order to mitigate immortal time bias.[321] Each exposed participant and matched controls were followed up from the index to the exit date. The exit date was the earliest of (i) the outcome, (ii) death, (iii) study end date, (iv) date of leaving the general practice or when the general practice stopped contributing to the database.[319]

Outcomes

The primary outcomes were an incident diagnosis of composite CVD and the following individual cardiovascular outcomes: heart failure, cerebrovascular accident (stroke and

transient ischaemic attack (TIA)), and IHD. Secondary outcomes were an incident diagnosis of type 2 diabetes mellitus and hypertension. Patients with a record of any CVD at baseline were excluded from the analysis for primary outcomes; patients with a record of type 2 diabetes or hypertension at baseline were excluded from the respective analyses. For example, patients with a record for type 2 diabetes mellitus at baselines were excluded from the analyses examining the association between PID and risk of type 2 diabetes mellitus. The Read codes used in the presented study were selected through a meticulous process similar to the methodology proposed by Davé and Peterson and Watson et al.[98,99] First, a list of relevant medical terms relating to the outcomes were developed. Second, the description and alpha-numeric fields (columns) of the Read code dictionary were searched for relevant codes using the medical terms identified in the first step. Third we compared the codes identified in the previous step to codes published in online Read code repositories (caliberresearch.org, clinicalcodes.org, Cambridge code lists index),[100–102] and codes published in supplemental material of existing literature.[322,323] Finally, we consulted UK clinicians to develop the final set of codes to be used in the study. All the outcomes in the present study are part of the UK quality and outcomes framework (QOF), a pay for performance scheme. The QOF was created to improve chronic disease management by financially rewarding primary care practices for providing interventions linked to improved health outcomes.[324] Chronic conditions that fall under the QOF domains are well-recorded in UK general practices. Validation studies have demonstrated that the prevalence of chronic conditions in THIN database is comparable to national estimates.[89–91]

Potential confounders

The study included the following potential confounders: age, Townsend deprivation quintile, BMI (categorised as <18.5 kg/m^2 (underweight, 18.5-25 kg/m^2 (normal weight), 25-30 kg/m^2 (overweight), >30 kg/m^2 (obese) and missing), smoking status (categorised as non-smokers,

smokers, ex-smokers and missing), lipid medication (current users, with a record of a prescription within 60 days prior to index date), diabetes mellitus, hypertension, contraceptive use (current users, defined as those prescribed combined oral contraceptive pills within the last 365 days prior to cohort entry), and reproductive conditions (gestational diabetes mellitus, pre-term delivery, miscarriage, pre-eclampsia, stillbirths, polycystic ovary syndrome, endometriosis). For each of the covariates, the most recently recorded measurement before study entry was used.[319,325]

Analysis

Prevalence and incidence

For annual point prevalence, the proportion of eligible females with any record ever of PID was calculated on 1st January each year from 1998-2017. Crude incidence rates every year from 1998-2017 were calculated by dividing the number of newly diagnosed females (numerator) by the total number of person-years at risk (denominator) for the given year. Incidence rates by Townsend quintiles of deprivation and age-specific categories were also calculated using data for the whole period (1998-2017).[319,325]

Cardiometabolic outcomes

Participant characteristics at baseline were reported using mean (SD) or median (IQR) for continuous variables and numbers (%) for categorical data. Both unadjusted and adjusted Cox proportional hazards models were used to estimate the hazard ratios (HR) and 95% CI of incident cardiometabolic conditions among women exposed to PID compared to those unexposed to PID. In the multivariable models, adjustments were made for age, smoking status, hormonal contraceptive use, lipid profile, BMI, pre-eclampsia, gestational diabetes, pregnancy loss, and endometriosis.[319,325] For each model, the proportional hazards assumption was checked using the Schoenfeld residuals test followed by a graphical

confirmation using the log-log survival curves. Statistical significance was set at 0.05. All analyses were conducted in Stata SE version 17.0.

Sensitivity analysis

We hypothesised that women diagnosed with PID may have frequent primary care contacts after the index date therefore, some degree of surveillance bias cannot be ruled out. Surveillance bias is a type of bias in which the exposure group has a higher or lower chance of being screened for the outcome than the comparator group or the general population.[326] In a sensitivity analysis, a two-year lag period was introduced after the index date to investigate the possibility of surveillance bias.

Results

Prevalence and incidence

Overall, both the annual prevalence and incidence of PID among women in the UK decreased throughout the twenty-year period of study **(Figure 6.1, Supplemental Table S6.1,** and **Supplemental Table S6.2)**. The prevalence (per 10,000 population) of PID decreased from 396.5 in 1998 to 237.0 in 2017. The incidence (per 10,000 person-years) of PID decreased from 32.4 per in 1998 to 7.9 in 2017.

The incidence of PID decreased with increasing age. The incidence of PID was highest among women aged 20-24 years (19.1 per 10,000 person-years at risk) and lowest among women aged 45-50 years (5.0 per 10,000 person-years at risk) **(Figure 6.1** and **Supplemental Table S6.3)**. The incidence of PID was highest among women from the most deprived population (18.5 per 10,000) and lowest among the least deprived population (11.2 per 10,000 person-years at risk) **(Figure 6.1** and **Supplemental Table S6.4).**

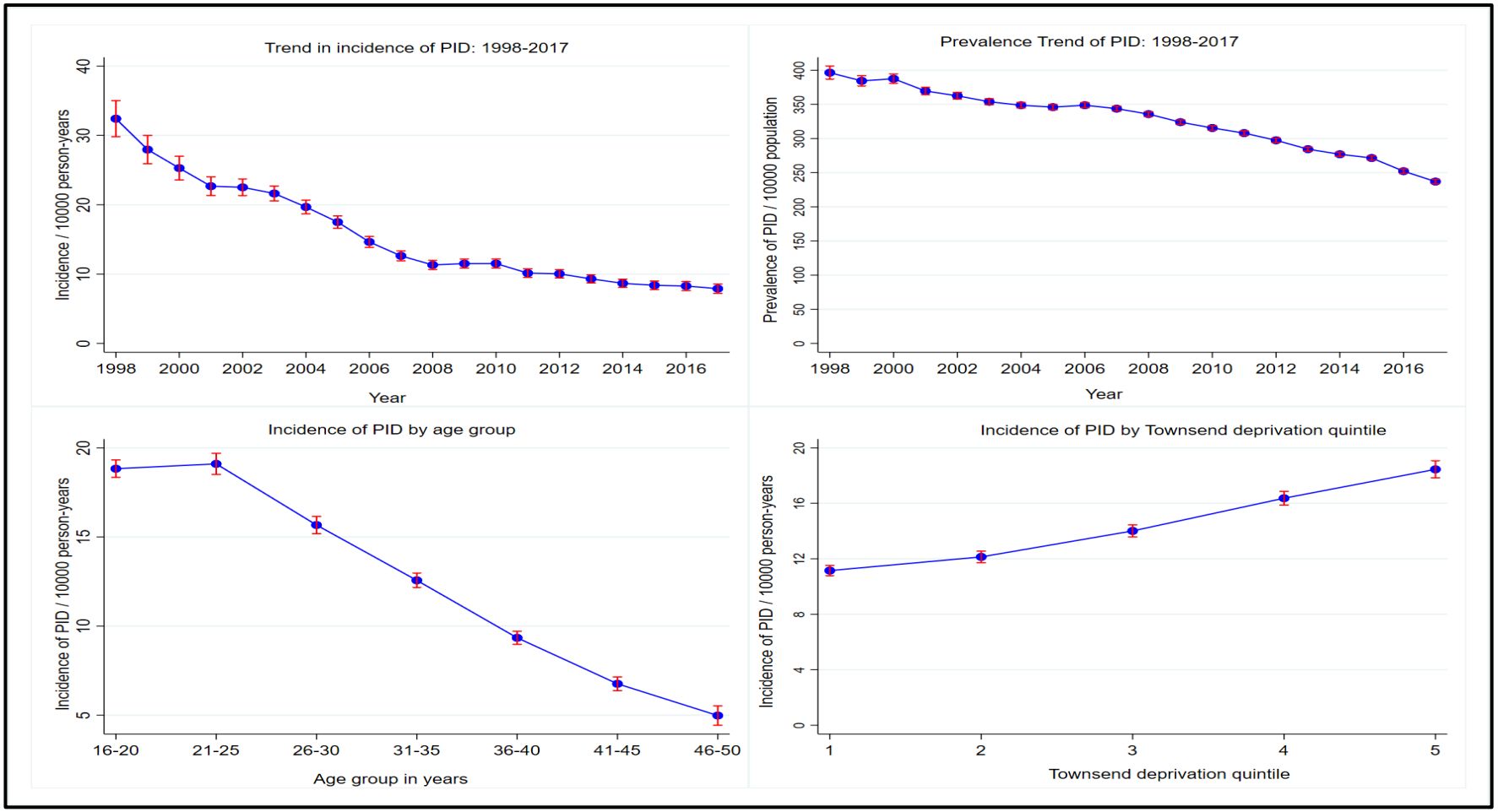

Figure 6.1: **The incidence and prevalence of pelvic inflammatory disease among UK women: 1998-2017. Townsend quintiles: 1 – least deprived, 5 – most deprived.**

Cardiometabolic outcomes

Supplemental Figure S6.1 presents the study participants flow chart. After application of inclusion and exclusion criteria, 19,804 (21%) and 73,769 (79%) women were included in the exposed and comparator groups, respectively. The baseline characteristics of the study participants are summarised in **Table 6.1.** Women with a history of PID compared to those without a history of PID were more likely to: be from the most deprived quintile (16.1% versus 13.3 %), be smokers (33.3% versus 22.3%), have a history of miscarriage (12.5% versus 6.4%), have a diagnosis of polycystic ovary syndrome (3.3% versus 1.9 %), be diagnosed with endometriosis (3.2% versus 0.9%), and have a current prescription for combined oral contraceptive pills (10.3% versus 7.9%).

The incidence rates (per 1000 person-years) of composite CVD among women with a history of PID compared to those without a history of PID were 1.5 and 1.3, respectively **(Table 6.2)**. The median (inter-quartile range) follow-up time was 4.5 (1.7-9.0) years. In the unadjusted model, the aHR for composite CVD was 1.11 (95% CI, 0.94-1.31). The multivariable model included demographic, lifestyle, medical (hypertension, diabetes mellitus) and reproductive characteristics. Adjustment did not impact the hazard ratio of composite CVD (aHR 1.10; 95% CI 0.93-1.30) **(Table 6.2** and **Figure 6.2).**

Table 6.1: **Baseline demographic, lifestyle, reproductive and medical characteristics among women with pelvic inflammatory disease (PID) and those without PID**

Characteristic	Pelvic inflammatory disease (n = 19,804)	Without pelvic inflammatory disease (n = 73,769)
	n (%)	n (%)
Age (years)		
<20	3,319 (16.8)	14,315 (19.4)
21-30	6,865(34.7)	24,942 (33.8)
31-40	5,786 (29.2)	21,027 (28.5)
41-50	2,368 (12.0)	8,325 (11.3)
>50	1466 (7.4)	5160 (7.0)
BMI categories (kg/m^2)		
<18.5	779 (3.9)	2,569 (3.5)
18.5-25	8,374 (42.3)	29,109 (39.5)
25-30	3,880 (19.6)	12,808 (17.4)
>30	2,858 (14.4)	9,771 (13.3)
Missing or implausible	3,913 (19.8)	19,512 (26.5)
Townsend deprivation quintile		
1 (least deprived)	3,361 (17.0)	14,744 (20.0)
2	3,179 (16.1)	12,815 (17.4)
3	3,765 (19.0)	13,807 (18.7)
4	3,862 (19.5)	13,380 (18.1)
5 (most deprived)	3,178 (16.1)	9,843 (13.3)
Missing	2,459 (12.4)	9,180 (12.4)
Smoking status		
Non-smokers	9,212 (46.5)	39,957 (54.2)
Ex-smokers	2,826 (14.3)	8,368 (11.3)
Smokers	6,599 (33.3)	16,462 (22.3)
Missing	1,167 (5.9)	8,982 (12.2)
Current Lipid	318 (1.6)	1,021 (1.4)
Hypertension	803 (4.1)	2,522 (3.4)
Diabetes	290 (1.5)	861 (1.2)
Reproductive history		
Gestational diabetes	126 (0.6)	273 (0.4)
Pre-term delivery	163 (0.8)	458 (0.6)
Miscarriage	2,471 (12.5)	4,738 (6.4)
Stillbirth	80 (0.4)	195 (0.3)
Pre-eclampsia	92 (0.5)	281 (0.4)
Polycystic ovary syndrome	643 (3.3)	1,405 (1.9)
Endometriosis	638 (3.2)	672 (0.9)
Current combined oral contraceptive pills	2,043 (10.3)	5,848 (7.9)

BMI = Body mass index, kg = kilograms, m = metre

The incidence rates (per 1000 person-years) of composite CVD among women with a history of PID compared to those without a history of PID were 1.5 and 1.3, respectively **(Table 6.2)**. The median (inter-quartile range) follow-up time was 4.5 (1.7-9.0) years. In the unadjusted model, the aHR for composite CVD was 1.11 (95% CI, 0.94-1.31). The multivariable model included demographic, lifestyle, medical (hypertension, diabetes mellitus) and reproductive characteristics. Adjustment did not impact the hazard ratio of composite CVD (aHR 1.10; 95% CI 0.93-1.30) **(Table 6.2** and **Figure 6.2)**.

Table 6.2: Incidence rates and hazard ratios for composite cardiovascular disease (CVD) and CVD subtypes for women with a history of PID compared to those without a history of PID

	Composite CVD		Ischaemic Heart Disease		Cerebrovascular disease		Heart failure	
	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed
Population	19,559	72,994	19,659	73,305	19,687	73,400	19,747	73,605
Events, n (%)	184	531	86	228	100	283	33	120
Person-years	126220.7	413438.4	127279.9	416644.2	127453.4	417432.6	128107.8	419306.3
Crude incidence rate/1000 person years	1.5	1.3	0.7	0.5	0.8	0.7	0.3	0.3
Crude HR (95% CI)	1.11 (0.94-1.31)		1.20 (0.93-1.54)		1.13 (0.90-1.42)		0.87 (0.59- 1.28)	
P-value	0.238		0.154		0.289		0.486	
Adjusted HR (95% CI)	1.10 (0.93-1.30)		1.19 (0.93-1.53)		1.13 (0.90-1.43)		0.92 (0.62-1.35)	
P-value	0.275		0.176		0.284		0.671	

CVD = composite CVD, HR= Hazard ratio,.

Model adjusted for age, Townsend deprivation quintile, BMI, smoking status, lipid-lowering medication (current users, with a record of a prescription within 60 days prior to index date), diabetes mellitus hypertension contraceptive use (current users, defined as those prescribed combined oral contraceptive pills within the last 365 days prior to cohort entry) and reproductive conditions (premature delivery, miscarriage, stillbirths, gestational diabetes mellitus, polycystic ovary syndrome, pre-eclampsia, endometriosis.

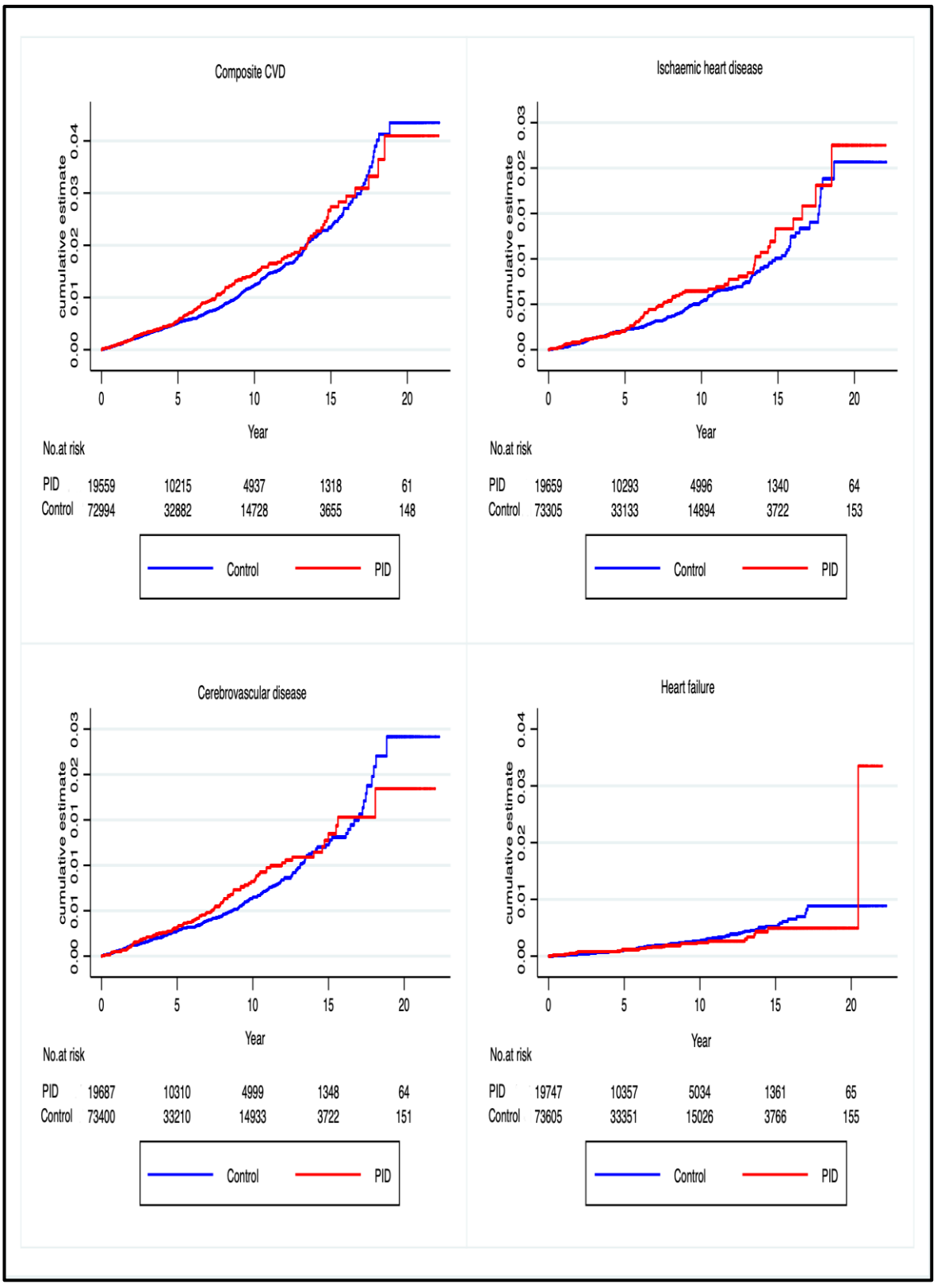

Figure 6.2: Cumulative hazard of primary cardiometabolic outcomes among women with a history of PID (exposed) and those without a history of PID (unexposed).

On examination of CVD subtypes, compared to women without history of PID, the aHR for CVD subtypes in women with history of PID were: 1.19 (95% CI 0.93-1.53) for IHD; 1.13 (95% CI 0.90-1.43) for cerebrovascular disease; 0.92 (95% CI 0.62-1.35) for heart failure **(Table 6.2** and **Figure 6.2).**

In the crude model, the HR for hypertension was marginally increased (HR 1.09; 95% CI 1.00-1.19) among women with history of PID compared to controls without history of PID. In the adjusted model, the aHR for hypertension was 1.11 (95% CI, 1.01-1.21; p = 0.023) among women with history of PID compared to those without history of PID **(Table 6.3** and **Figure 6.3)**. The crude HR for type 2 diabetes among women with history of PID compared controls without history of PID was 1.31 (95% CI, 1.14-1.50). In the adjusted model the HR was slightly attenuated but remained significant (aHR 1.25; 95% CI 1.09-1.43) **(Table 6.3** and **Figure 6.3)**.

In a sensitivity analysis, the introduction of a two-year lag period to investigate the possibility of surveillance bias had minimal impact on the results. The adjusted HRs for cardiometabolic outcomes in women with history of PID compared to matched controls were: 1.13 (95% CI 0.93-1.36) for composite CVD; 1.20 (95% CI 0.91-1.58) for IHD; 1.18 (95% CI 0.91-1.53) for cerebrovascular disease; 0.64 (95% CI 0.40-1.04) for heart failure 1.11 (95% CI 1.00-1.23) for hypertension; and 1.26 (95% CI 1.08-1.47) for type 2 diabetes mellitus **(Supplemental Table S6.5 and Supplemental Table S6.6)**

Table 6.3: **Incidence rates and hazard ratios for hypertension and type 2 diabetes mellitus for women with a history of pelvic inflammatory disease (PID) compared to those without a history of PID**

	Hypertension		Type 2 Diabetes mellitus	
	Exposed	Unexposed	Exposed	Unexposed
Population	18,984	71,188	19,496	72,849
Events, n (%)	658	1942	294	720
Person-years	119,971.3	394,438.7	125,431.3	411,909.9
Crude incidence rate/1000 person years	5.5	4.9	2.3	1.7
Crude HR (95% CI)	1.09 (1.00-1.19)		1.31 (1.14-1.50)	
P-value	0.051		<0.001	
Adjusted HR (95% CI)	1.10 (1.01-1.20) *		1.25 (1.09-1.43)#	
P-value	0.038		<0.002	

CVD = composite CVD, HR= hazard ratio.
Model adjusted for age, Townsend deprivation quintiles, BMI, smoking status, lipid-lowering medication (current users, with a record of a prescription within 60 days prior to index date) contraceptive use (current users, defined as those prescribed combined oral contraceptive pills within the last 365 days prior to cohort entry) and reproductive conditions (premature delivery, miscarriage, stillbirths, gestational diabetes mellitus, polycystic ovary syndrome, pre-eclampsia, endometriosis).
* = Model adjusted for diabetes mellitus, # = Model adjusted for hypertension.

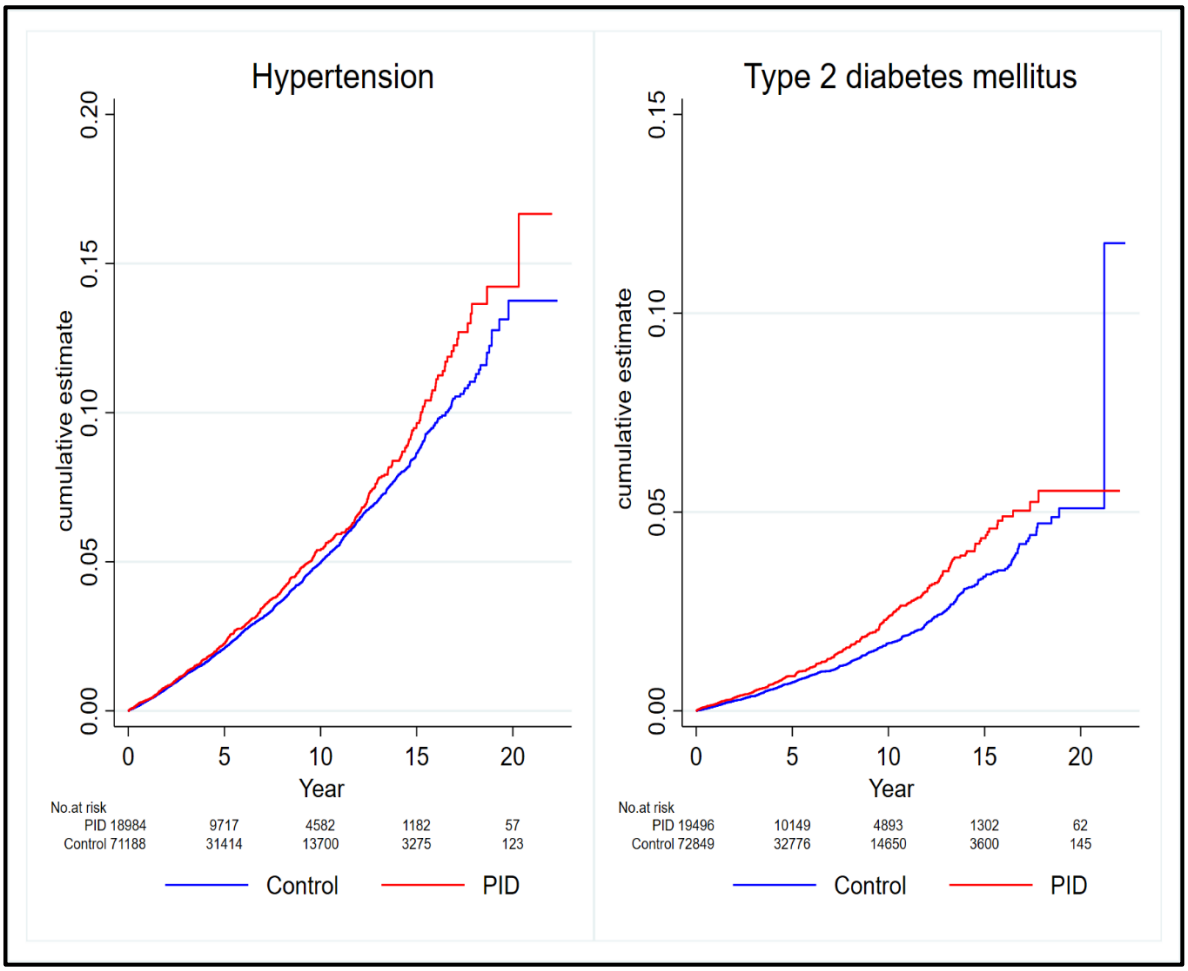

Figure 6.3: **Cumulative hazard of secondary cardiometabolic outcomes among women with a history of PID (exposed) and those without a history of PID (unexposed).**

Discussion

This study explored risk of cardiometabolic outcomes among women with a history of PID compared to a matched comparator group of women without a history of PID. We found no evidence of association between a history of PID and risk of composite CVD or subtypes of CVD. The evidence from our study suggests that women with a history of PID were at a significantly higher risk of hypertension and T2DM.

The main strengths of our study include a large sample size from a population representative of the general UK population, a long duration of follow-up and the availability of information on known and potential confounders.

Our study has several limitations. We lacked information on the mode of diagnosis; therefore, we could not distinguish cases diagnosed through laparoscopy or endometrial biopsy from those diagnosed by other means. Diagnoses based on clinical findings are practicable, cost-effective and capture a vast majority of PID cases as demonstrated by several studies.[327–329] Although diagnoses based on clinical findings captures the vast majority of cases, there are no studies that have examined the validity of PID diagnoses in UK primary care databases. Since CVD is part of the Quality and Outcomes Framework, this is well recorded in UK primary care. Second, the case definition used in our cohort study relied on physician assigned codes for PID. We used a restricted definition for PID in our analyses to minimise the use of non-specific symptom codes to diagnose PID. Consequently, the true incidence and prevalence estimates of PID may be underestimated. Third, the exposed cohort was composed of only clinically diagnosed PID cases; there is therefore a likelihood for the inclusion of subclinical PID cases in the unexposed group. However, any observed associations are likely to be biased towards the null. Fourth, ethnicity data is not well-recorded in the THIN database, therefore, it was not included in the adjusted analyses. Fifth, because we made no adjustments for multiple comparisons, it is possible that the significant

results observed in the study may be affected by type 1 error. Sixth, eligible patients (exposed and corresponding matched controls) were identified using the Data Extraction for Epidemiological Research (DExtER) tool.[330] Controls were defined as patients who did not have a record of PID at the index date or at any time-point afterward until the end of study. The use of future exposure information to define cohort membership at baseline may lead to bias.[331] However, since the incidence of PID is low, the effect estimates are unlikely to be affected.

Three studies examined the incidence rate and demographic characteristics of PID in the UK primary care setting.[320,332,333] French and colleagues reported a decline in the incidence rate of PID between 2000 to 2008 among women aged 15-44 years.[320] Likewise, reports from Public Health England reported a decline in rates between 2000 to 2011.[333] The drivers behind the decline in rates of PID in the UK are not entirely clear. Improved testing technology and increased screening rates (national chlamydia screening programme in 2002) for chlamydia infection may have contributed to early treatment before the onset of PID.[334] In addition, a negative test on chlamydia screening may have contributed to a reduction in the coding for PID cases.[334] Our findings are consistent with previous UK studies which reported higher rates of PID among young persons aged 16-24 and those from lower socioeconomic groups. A major risk factor for PID infection is sexual behaviour. National UK surveys on sexual attitudes and lifestyles have consistently shown that younger individuals are more likely to have multiple partners and engage in risky sexual behaviour.[335] A lower index of deprivation may be a surrogate marker for sexual behaviour.[336]

A search of the literature suggests that all the previously published studies evaluating the risk of cardiovascular outcomes among women with a history of PID were from Taiwan.[156,244,337] The Taiwanese studies noted that compared to women without history of PID, women with history of PID were at a significantly higher risk of myocardial infarction and ischaemic

stroke but at a significantly lower risk of intracerebral haemorrhage. Methodological differences may explain the discordant findings between the present study and the Taiwanese studies. Foremost, the Taiwanese studies relied on data from administrative health databases which are typically designed for financial reimbursements and lacked additional health data on potential confounders. The present study adjusted for these missing variables. Also, in the Taiwanese studies, the lax case definition for PID that included ICD-9 codes for infections of the lower genital tract may have been misleading.[338] In addition, the because the study population is young a lower number of CVD events were recorded.

To the best of our knowledge, this is the first study to show a temporal association between an increased risk of hypertension and diabetes mellitus among women with a history of PID compared to women without PID. The exact mechanisms explaining the association between infections and elevated cardiometabolic risk are uncertain. One potential mechanism includes direct invasion of arterial vasculature.[318] Several studies have identified Chlamydia trachomatis in cardiovascular tissue suggesting that it may have a role cardiovascular disease development through local effects.[339–341] A second potential mechanism involves systemic responses to infection (indirect) effects. The molecular components of pathogens may be structurally similar (molecular mimicry) to host proteins resulting in a cross-reaction as the immune system recognises host proteins as foreign.[342] Systemic response to infections involves the release of cytokines and other acute phase reactant proteins (CRP). An increase in pro-inflammatory cytokines and acute phase proteins promotes cardiovascular disease via increased oxidative stress, impairment of endothelial nitric oxidase synthase, insulin resistance induction of endothelial cell apoptosis, increased uptake of low-density lipoproteins by macrophages, and adherence of monocytes into the arterial wall.[343–345]

History of PID may serve as a marker for the future development of hypertension and diabetes mellitus (type 2), two prominent risk factors for CVD. The integration of the female

reproductive history into routine primary care consultations may impact CVD risk factor screening.[346] Areas that warrant further research include: the variability in cardiometabolic risk based on the type of microbe causing PID or severity of PID.

Conclusion

This study found no evidence of excess risk of composite CVD or its subtypes among women with history of PID compared to matched controls. Findings from our study suggests that history of PID was associated with an increased risk of hypertension and type 2 diabetes mellitus, two major risk factors for CVD. Additional studies are required to support these findings.

Chapter 7. The association between menstrual cycle characteristics and cardiometabolic outcomes in later life: A retrospective matched cohort study of 704,743 women from the UK

The content of this chapter has been published.

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https://doi.org/10.1186/s12916-023-02794-x

KO conceived the idea of the study guided by KN, NJA, and GNT. KO carried out the data cleaning, statistical analysis, and first draft of the manuscript. All authors: KO, WPS, GNT, KN and NJA, reviewed and revised the manuscript.

Abstract

Background

Female reproductive factors are gaining prominence as factors that enhance cardiovascular disease (CVD) risk; nonetheless, menstrual cycle characteristics are under-recognised as a factor associated with CVD. Additionally, there is limited data from the UK pertaining to menstrual cycle characteristics and CVD risk.

Methods

A UK retrospective cohort study (1995-2021) using data from a nationwide database (The Health Improvement Network). Women aged 18-40 years at index date were included. 252,325 women with history of abnormal menstruation were matched with up to two controls. Two exposures were examined: regularity and frequency of menstrual cycles; participants were assigned accordingly to one of two separate cohorts. The primary outcome was composite cardiovascular disease (CVD). Secondary outcomes were ischaemic heart disease (IHD), cerebrovascular disease, heart failure (HF), hypertension, and type 2 diabetes mellitus (T2DM). Cox proportional hazards regression models were used to derive adjusted hazard ratios (aHR) of cardiometabolic outcomes in women in the exposed groups compared matched controls.

Results

During 26 years of follow-up, 20,605 cardiometabolic events occurred in 704,743 patients. Compared to women with regular menstrual cycles, the aHRs (95% CI) for cardiometabolic outcomes in women with irregular menstrual cycles were: composite CVD 1.08 (95% CI 1.00-1.19); IHD 1.18 (1.01-1.37); cerebrovascular disease 1.04 (0.92-1.17); HF 1.30 (1.02-1.65); hypertension 1.07 (1.03-1.11); T2DM 1.37 (1.29-1.45). The aHR comparing frequent or infrequent menstrual cycles to menstrual cycles of normal frequency were: composite

CVD 1.24 (1.02-1.52); IHD 1.13 (0.81-1.57); cerebrovascular disease 1.43 (1.10-1.87); HF 0.99 (0.57-1.75); hypertension 1.31 (1.21-1.43); T2DM 1.74 (1.52-1.98).

Conclusion

History of either menstrual cycle irregularity or frequent or infrequent cycles were associated with an increased risk of cardiometabolic outcomes in later life. Menstrual history may be a useful tool in identifying women eligible for periodic assessment of their cardiometabolic health.

Background

Cardiovascular disease (CVD) is a major public health burden and remains the leading cause of mortality in women accounting for 35% of the total deaths worldwide based on estimates from the global burden of disease study.[1,347] Recent literature reviews and consensus statements from professional societies in the US and Europe have highlighted the association between female reproductive factors and risk of CVD in later life.[112,348–350] However, menstrual cycle history and its relation to CVD was not included despite evidence of its association with CVD risk.[351–353]

The menstrual life course begins at menarche and ends at menopause. The regulation of menstrual cycles involves an intricate balance between hypothalamic, pituitary, and gonadal axis hormones. A disruption of this balance may result in changes in menstrual characteristics that may affect one or more of four menstrual cycle domains: frequency, regularity, duration, or volume of flow.[354] The years immediately after menarche and the menopausal transition period are characterised by irregular and unstable menstrual cycles.[355] When menstrual cycles are stable, a typical menstrual period will last for 3 to 5 days while the average menstrual cycle will last for 28 days (range 21-35 days).[355] Long or irregular menstrual cycles are associated with cardiovascular risk factors including hyperinsulinemia and dyslipidaemia, hypertension and diabetes mellitus.[356,357] The American College of Obstetricians and Gynaecologists recommends the inclusion of menstrual cycle history as a vital sign to improve the timely identification of potential adverse health outcomes in later life.[358] However, the management of abnormal menstruation focuses primarily on addressing associated infertility challenges with other potential longer-term risks underappreciated.

The UK provides universal health care to all its residents. The first point of call for UK women with clinically significant changes in the menstrual cycle patterns will be the primary care practice. The present study will harness electronic health data from UK primary care to

shed more light on the association between menstrual cycle characteristics and risk of cardiometabolic outcomes in the future.

Methods

Study design

A population-based retrospective cohort study was conducted to evaluate the association between menstrual cycle characteristics and long-term risk of cardiometabolic outcomes. Only domains relating to the regularity and frequency of menstrual cycle were used in the present study **(Supplemental Table S7.1**).[354] Therefore, two study cohorts were created. The first cohort was composed of women with irregular or no menstrual cycle (exposed group) and matched controls from the general population without a history of irregular menstrual cycles. The second cohort was composed of women with infrequent or frequent menstrual cycles (exposed group) and matched controls from the general population without a history of infrequent or frequent menstrual cycles. The study period was 1st January 1995 to 31st December 2021. The rates of cardiometabolic outcomes were compared in the exposed and control groups.

Data source

IQVIA Medical Research Data (IMRD) incorporates data from The Health Improvement Network (THIN), a Cegedim database. Reference made to THIN is intended to be descriptive of the data asset licensed by IQVIA. The proposed study used de-identified data provided by patients as a part of their routine primary care. IMRD-UK (formerly THIN) is a nationwide UK-based database containing anonymised electronic health records contributed by 787 general practices. Registered practices contributing to the database are representative of the UK population.[90,289] Participating practices collect patient data using an electronic health records software system known as Vision software.

Practice eligibility criteria

Practices were eligible for inclusion from the later of the date on which the practice met acceptable mortality reporting (a quality assurance standard) or one year after the practice began to use the Vision software system.[92]

Study population

The study population was composed of women aged 18-40 years at baseline. Participants entered the study at the latest of their 18th birthday, study start date (1st January 1995), or one year after joining the practice (to ensure sufficient time for recording of baseline information).

Exposure

The coding of diagnoses and other health-related care processes in UK primary care is based on the Read code clinical terminology (computable phenotype).[113] The exposures of interest were identified by the presence of a diagnostic Read code describing menstrual cycle irregularity or frequent or infrequent cycles as reported in primary care. Menstrual cycle characteristic self-report has been validated in other studies and is regarded as reliable.[359,360] Where a patient had a diagnostic record for both irregularity and frequent or infrequent menstrual cycles, exposure status was assigned to the first ever recorded domain. Characteristics relating to the regularity of the menstrual cycle defined a composite exposure that included irregular cycles, amenorrhoea, menometrorrhagia, and Metropathia haemorrhagica. Attributes relating to menstrual cycle frequency defined a composite exposure that included too frequent (polymenorrhoea, epimenorrhoea) or infrequent (oligomenorrhoea) cycles. Details are provided in **Supplemental Table S7.2**. Women with the exposure of interest were matched with up to two women without a record of the exposure (controls), randomly selected from a pool of eligible women. The exposed and unexposed groups were matched by age (+/- one year) and general practice. Women with a

record of other menstrual related conditions including intermenstrual bleeding, menstrual disorders, and complications of duration or volume of flow were excluded from the study.

Follow up period

For newly (incident) diagnosed exposures (irregular cycles and frequent or infrequent cycles) the date of diagnosis served as the index date. For patients with a pre-existing record relating to complications in the regularity or frequency of menstrual cycles, the date the patient became eligible to participate in the study served as the index date. To mitigate immortal time bias, exposed patients were assigned the same index date as their corresponding controls and matched on this date.[321] Each exposed and matched control participant contributed follow-up time from the index to the exit date. The exit date was the earliest of (i) the outcome, (ii) death, (iii) study end date, (iv) date of leaving the general practice or when the general practice stopped contributing to the database.

Outcomes

The primary outcome was the incident diagnosis of cardiovascular disease, a composite of ischaemic heart disease, heart failure or cerebrovascular disease (stroke or transient ischaemic attack). Secondary outcomes were the cardiovascular conditions separately, hypertension and type 2 diabetes mellitus. Participants with a diagnosis of the outcome of interest at baseline were excluded from the corresponding crude and adjusted regression analysis. Outcomes were identified using the relevant Read codes. The Read codes used in the present study were selected using a method comparable to that proposed by Davé and Peterson and Watson et al.[98,99] First, a list of pertinent medical terms associated with the outcomes was compiled. Using the medical terms identified in the first step, the description, and numeric fields (columns) of the Read code dictionary were searched for relevant diagnostic codes related to the outcomes of interest. Third, we compared the codes identified in the previous step with codes published in online Read code repositories (caliberresearch.org, clinicalcodes.org,

Cambridge code lists index),[100–102] as well as codes published in supplementary material of existing literature.[361] Finally, we consulted with UK clinicians to determine the final set of codes to be used in the study. All the outcomes in this study are included in the United Kingdom's Quality and Outcomes Framework (QOF), a pay-for-performance system. The QOF was established to improve chronic disease management by financially rewarding primary care practises for providing interventions associated with better health outcomes. Chronic conditions falling under the QOF domains are well documented in UK general practises. Validation studies demonstrate that the prevalence of chronic diseases in THIN databases is comparable to national estimates.[89–91]

Study covariates

The following potential confounders were included in the study: sociodemographic characteristics (age and Townsend index of deprivation), lifestyle characteristics (body mass index [BMI], smoking status, alcohol use,), medical characteristics (current lipid medication, connective tissue disorders, migraine), and reproductive factors (current oral contraceptive [COC] pill use, preeclampsia, gestation diabetes mellitus, pregnancy loss, pre-term delivery, polycystic ovary syndrome [PCOS], endometriosis, pelvic inflammatory disease and uterine fibroids). Age was calculated at index date. The Townsend deprivation index is a measure of material deprivation derived from census data and linked to residential area.[362] The Townsend deprivation index is computed using the following domains: unemployment as a percentage of economically active individuals aged 16 and older, car ownership as a percentage of all households, home ownership as a percentage of all households, and overcrowding. BMI was calculated as weight divided by height in metres squared and categorised using WHO criteria (< 18.5, 18.5-24.9. 24-29.9 and > 30 kg/m^2).[363] Smoking (non-smokers, current smokers, ex-smokers) and alcohol use (non-drinkers, drinkers with excess, drinker without excess, ex-drinker) were self-reported. Self-reported smoking status

and self-reported alcohol use are reliably recorded in THIN database.[364,365] Current lipid medication was defined as the prescription of lipid medication within 60 days of cohort entry. Connective tissue disorders included rheumatological diseases (systemic lupus erythematosus, polymyositis, mixed connective tissue disease, polymyalgia rheumatica, moderate to severe rheumatoid arthritis). Current combined oral contraceptive (COC) pills use was defined as contraceptive use within 1 year of cohort entry. For each of the covariates, the latest record of the variable prior to study entry was used.

Analysis

Participant characteristics at baseline were reported using median (IQR) for continuous variables and counts (%) for categorical variables. The crude incidence rates of cardiometabolic outcomes were estimated for each exposure group. Unadjusted and adjusted Cox proportional hazard models were used to derive hazard ratios (HR) and 95% confidence intervals (95% CI) for the associations between menstrual cycle characteristics (regularity or frequency) and incident cardiometabolic outcomes. In the multivariable models, adjustments were made for age, BMI, Townsend deprivation quintiles, smoking status, COC pills use, lipid-lowering drug use, alcohol use, connective tissue disorders, reproductive complications, and migraine. A separate category called missing was created for categorical data with missing data and incorporated in the regression analysis. For each model, the proportional hazards assumption was evaluated using the Schoenfeld residual test and graphical confirmation using the log-log survival curves.

Sensitivity analysis

We performed several sensitivity analyses on the primary outcome to evaluate the robustness of our findings. Women with several reproductive characteristics, including polycystic ovary syndrome (PCOS), amenorrhoea, endometriosis, fibroids, and current contraceptive use were excluded to evaluate whether these conditions drove any observed associations. We also

examined, separately, the association between frequent or infrequent menstrual cycles and their relationship to cardiometabolic outcomes.

A two-tailed p-value of 0.05 was considered statistically significant. All analyses were conducted using Stata SE version 17.0.

Results

Supplemental Figure S7.1 presents the study participants flow chart. There were 704,743 patients in the present study including 215,378 with a history of irregular menstrual cycles and 36,947 with a history of frequent or infrequent menstrual cycles **(Table 7.1)**. By design, the median age of women in the exposed and unexposed groups was similar (approximately 27 years). Compared to women who had regular cycles, women with irregular menstrual cycles were more likely to be obese (15.4% versus 10.9%), be current smokers (24.9% versus 21.1%), be in the most deprived Townsend quintile (14.8% versus 13.1%), have migraine (27.8% versus 21.3%), have a current prescription for COC pills before cohort entry (30.6% versus 27.0.%), have a history of miscarriage (9.2% versus 6.2%), and have a diagnosis of polycystic ovary syndrome (5.6% versus 1.7%). A similar pattern in baseline differences was present in the group examining women with frequent or infrequent menstrual cycles compared to women with menstrual cycles of normal frequency.

Table 7.1: Baseline characteristics by menstrual characteristics status

Characteristics	Irregular cycles (N= 215 378)	Regular cycles (N=386 825)	Frequent / infrequent cycles (N= 36 947)	Normal cycle frequency (N=65 593)
	n (%)	n (%)	n (%)	n (%)
***Age**; Median (IQR)*	27.5 (22.1-33.2)	27.2 (22.0-32.7)	27.5 (21.8-33.8)	27.4 (21.9-33.4)
Townsend deprivation quintile				
1 (Least deprived)	36877 (17.1)	71109 (18.4)	6913 (18.7)	12912 (19.7)
2	33111 (15.4)	61786 (16.0)	5916 (16.0)	10949 (16.7)
3	38970 (18.1)	70821 (18.3)	6765 (18.3)	12014 (18.3)
4	39909 (18.5)	68329 (17.7)	6630 (17.9)	11310 (17.2)
5 (Most deprived)	31911 (14.8)	50707 (13.1)	5054 (13.7)	8171 (12.5)
Missing	34600 (16.1)	64073 (16.6)	5669 (15.3)	10237 (15.6)
BMI categories in kg/m^2				
18.5-25	87884 (40.8)	157658 (40.8)	14245 (38.6)	26492 (40.4)
<18.5	10107 (4.7)	15996 (4.1)	1561 (4.2)	2589 (4.0)
25-30	37110 (17.2)	61591 (15.9)	6233 (16.9)	10537 (16.1)
>30	33194 (15.4)	41996 (10.9)	6234 (16.9)	6925 (10.6)
Missing	47083 (21.9)	109584 (28.3)	8674 (23.5)	19050 (29.0)
Smoking status				
Non-smokers	121477 (56.4)	220926 (57.1)	20922 (56.6)	37065 (56.5)
Current smokers	53576 (24.9)	81706 (21.1)	8629 (23.4)	13766 (21.0)
Ex-smokers	23951 (11.1)	38887 (10.1)	4012 (10.9)	6434 (9.8)
Missing	16374 (7.6)	45306 (11.7)	3384 (9.2)	8328 (12.7)
Alcohol status				
Non-drinker	40821 (19.0)	65386 (16.9)	6469 (17.5)	10345 (15.8)
Drinker with excess	4720 (2.2)	5887 (1.5)	737 (2.0)	932 (1.4)
Drinker no excess	111018 (51.6)	192483 (49.8)	18887 (51.1)	32934 (50.2)
Ex-drinker	2329 (1.1)	3397 (0.9)	348 (0.9)	580 (0.9)
Missing	56490 (26.2)	119672 (30.9)	10506 (28.4)	20802 (31.7)
Current lipid medication	456 (0.2)	527 (0.1)	87 (0.2)	79 (0.1)
Connective tissue disorders	999 (0.5)	1498 (0.4)	168 (0.5)	289 (0.4)
Migraine	59873 (27.8)	82328 (21.3)	10550 (28.6)	13877 (21.2)
Reproductive factors				
Current combined oral contraceptive pills	65820 (30.6)	104274 (27)	10266 (27.8)	17339 (26.4)
Polycystic ovary syndrome	11970 (5.6)	6448 (1.7)	3755 (10.2)	1017 (1.6)
Pelvic inflammatory disease	6283 (2.9)	6941 (1.8)	1100 (3.0)	1193 (1.8)
Endometriosis	2353 (1.1)	3730 (1.0)	417 (1.1)	639 (1.0)
Fibroids	698 (0.3)	1268 (0.3)	144 (0.4)	210 (0.3)
Miscarriage	19745 (9.2)	23954 (6.2)	3083 (8)	4225 (6)

Characteristics	Irregular cycles (N= 215 378)	Regular cycles (N=386 825)	Frequent / infrequent cycles (N= 36 947)	Normal cycle frequency (N=65 593)
Gestational diabetes	1280 (0.6)	1603 (0.4)	232 (0.6)	253 (0.4)
Pre-eclampsia	812 (0.4)	1081 (0.3)	134 (0.4)	203 (0.3)
Pre-term births	1452 (0.7)	2403 (0.6)	228 (0.6)	378 (0.6)
Baseline cardiovascular diseases				
Hypertension	2631 (1.2)	3181 (0.8)	471 (1.3)	562 (0.9)
Diabetes	1898 (0.9)	2359 (0.6)	334 (0.9)	392 (0.6)
Ischaemic heart disease	119 (0.1)	123 (0.0)	14 (0.0)	22 (0.0)
Stroke/TIA	307 (0.1)	379 (0.1)	50 (0.1)	73 (0.1)
Heart failure	46 (0.0)	76 (0.0)	12 (0.0)	14 (0.0)

Footnotes: BMI, Body mass index; IQR = Inter quartile range; Kg/m^2 = Kilogrammes per metre square. There were no missing data for age. The total number (%) of missing data for Townsend deprivation quintile, BMI and alcohol status were 114 579 (16.3%), 184391 (26.2%) and 73392 (10.4%), respectively. For current lipid medication, connective tissue disorders, migraine, reproductive factors, and baseline cardiovascular diseases absence of a diagnostic code for these conditions was assumed to indicate absence of disease.

Composite CVD

Menstrual cycle regularity

Between 1995 and 2021, 896 and 1056 composite CVD events were recorded among women with irregular versus regular menstrual cycles, respectively. Median (IQR) follow-up was 4.5 (1.7-9.6) years in the exposed and 3.8 (1.4-8.3) years in the unexposed group. The crude incidence rate (per 1000 years) of composite CVD was 0.67 in women with irregular menstrual cycles versus 0.50 in women with regular menstrual cycles. The HR for composite CVD comparing irregular with regular menstrual cycles were 1.26 (95% CI 1.15-1.38; p<0.001) in the crude model and 1.08 (95% CI 1.00-1.19; p=0.062) in the model adjusting for sociodemographic, lifestyle, medical and reproductive characteristics (**Figure 7.1, Figure 7.2,** and **Supplemental Table S7.3)**.

Menstrual cycle frequency

During the study period, 205 versus 202 composite CVD events were recorded in women with frequent or infrequent menstrual cycles compared to controls with menstrual cycles of normal frequency, respectively. Median (IQR) follow-up was 5.1 (2.0-10.5) years in the exposed and 4.0 (1.5-8.8) years in the unexposed group. The crude incidence rate (per 1000 person years) of composite CVD was 0.83 in women with frequent or infrequent cycles compared to 0.53 in women with menstrual cycles of normal frequency with a crude HR of 1.46 (95% CI 1.20-1.78; p<0.001) **(Supplemental Table S7.3)**. In the adjusted model, the association between frequent or infrequent cycles and composite CVD was maintained. (aHR 1.24, 95% CI 1.02-1.52; p=0.031) **(Figure 7.1, Figure 7.3)**.

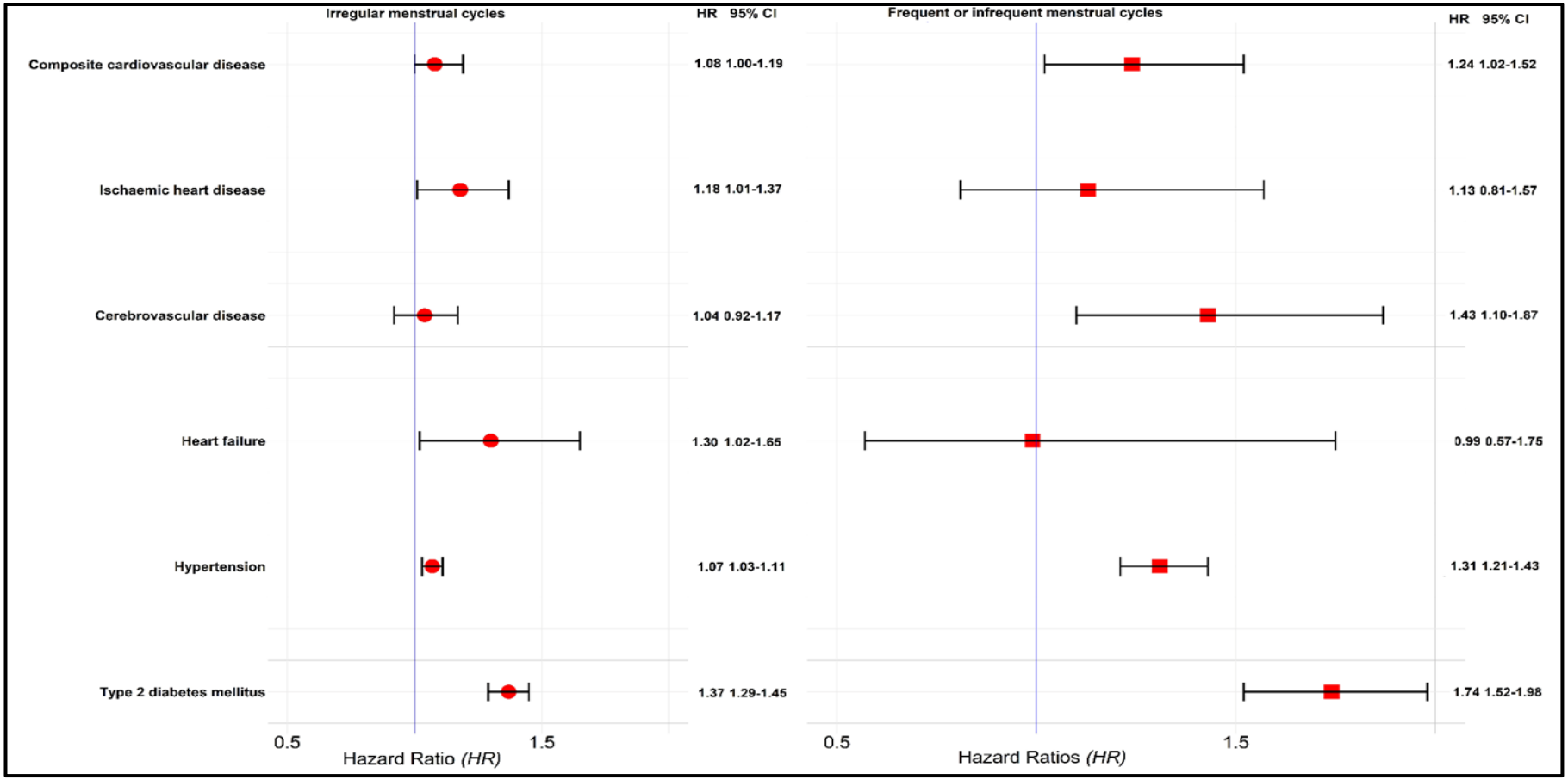

Figure 7.1: **Forest plot showing the fully adjusted effect estimates and 95% CI for cardiometabolic outcomes in women with history of irregular menstrual cycles or frequent or infrequent menstrual cycles.**

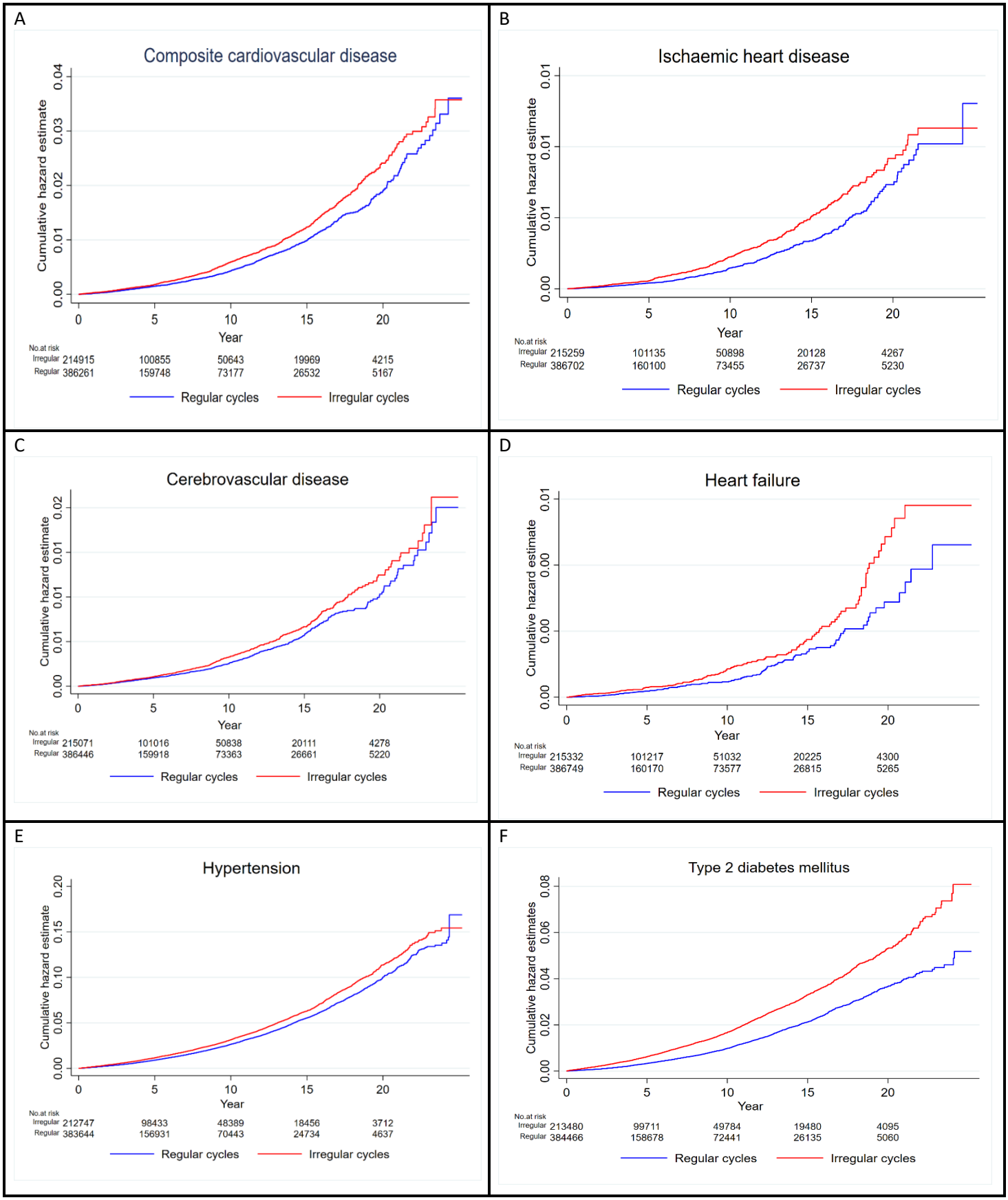

Figure 7.2: Cumulative hazard estimates of cardiometabolic outcomes in women with irregular cycles compared to those with regular cycles.

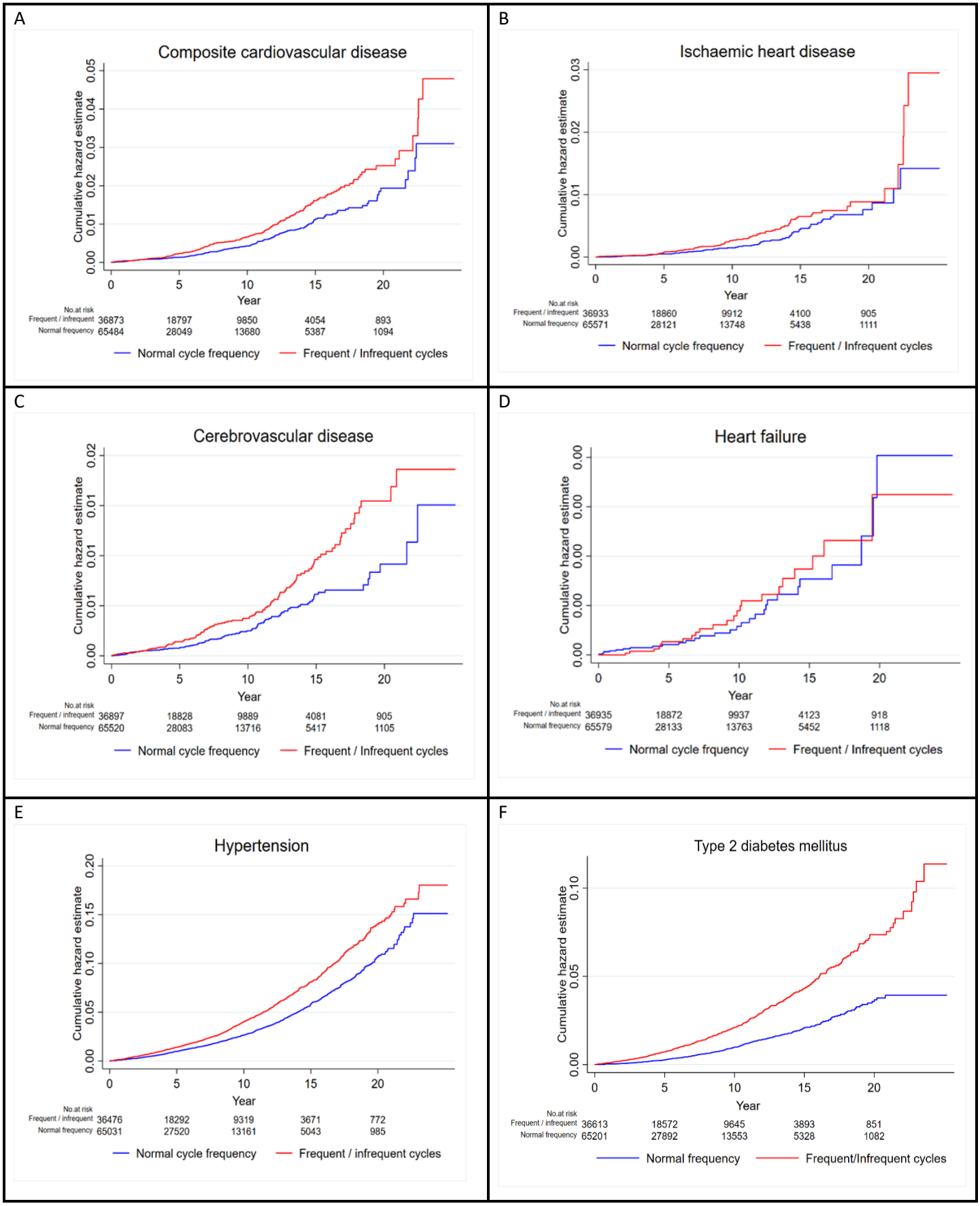

Figure 7.3: **Cumulative hazard estimates showing cardiometabolic outcomes in women with frequent or infrequent cycles compared to those with normal cycle frequency.**

CVD subtypes

Menstrual cycle regularity

In the model comparing irregular to regular menstrual cycles, the adjusted HR for CVD subtypes were; 1.18 (95% CI 1.01-1.37; p=0.033) for ischaemic heart disease; 1.04 (95% CI 0.92-1.17; p= 0.508) for cerebrovascular disease; and 1.30 (95% CI 1.02-1.65; p=0.033) for heart failure **(Figure 7.1, Figure 7.2** and **Supplemental Table S7.3).**

Menstrual cycle frequency

In the model comparing frequent or infrequent menstrual cycles to menstrual cycles of normal frequency, the adjusted HR for CVD subtypes were 1.13 (95 % CI 0.81-1.57; p=0.464) for ischaemic heart disease; 1.43 (95% CI 1.10-1.87; p=0.007) for cerebrovascular disease; and 0.99 (95% CI 0.57-1.75; p=0.985) for heart failure **(Figure 7.1, Figure 7.2,** and **Supplemental Table S7.3)**.

Hypertension

Menstrual cycle regularity

During follow-up, the crude incidence rate (per 1000 person-years) of hypertension was 3.48 in women with irregular menstrual cycles versus 2.79 in controls with regular menstrual cycles. Compared to those with regular menstrual cycles, women with irregular menstrual cycles had a HR of subsequent hypertension of 1.19 (95% CI 1.14-1.24; p<0.001) and 1.07 (95% CI 1.03-1.11; p=0.001) in the unadjusted and adjusted models, respectively **(Figure 7.1, Figure 7.2,** and **Supplemental Table S7.3)**.

Menstrual cycle frequency

The crude incidence rate (per 1000 person-years) of hypertension was 4.42 in women with frequent or infrequent menstrual cycles compared to 3.0 in women with menstrual cycles of normal frequency, with a crude HR of 1.41 (95% CI 1.30-1.54; p<0.001). In the adjusted

model women with frequent or infrequent cycles were 32% more likely to develop hypertension (HR 1.31; 95% CI 1.21-1.43; p<0.001) **(Figure 7.1, Figure 7.3,** and **Supplemental Table S7.3).**

Type 2 diabetes mellitus

Menstrual cycle regularity

The crude incidence rate (per 1000 person-years) of type 2 diabetes mellitus was 1.82 in women with irregular menstrual cycles and 1.05 in those with regular menstrual cycles. Compared to women with regular menstrual cycles, women with irregular menstrual cycles were more likely to develop type 2 diabetes mellitus in both the crude (HR 1.66; 95% CI 1.34-1.49; p<0.001) and adjusted (1.37; 95% CI 1.29-1.45; p<0.001) models **(Figure 7.1, Figure 7.2,** and **Supplemental Table S7.3).**

Menstrual cycle frequency

The crude incidence rate (per 1000 years) of type 2 diabetes mellitus was 2.38 in women with frequent or infrequent menstrual cycles versus 1.02 in women with menstrual cycles of normal frequency. Women with frequent or infrequent cycles were twice as likely to develop type 2 diabetes mellitus compared to women with menstrual cycles of normal frequency (crude HR 2.25; 95% CI 1.96-2.53; p <0.001). The association was maintained in the adjusted model (HR 1.74; 95% CI 1.52-1.98; p <0.001) **(Figure 7.1, Figure 7.3,** and **Supplemental Table S7.3)**.

Sensitivity analyses

Menstrual cycle regularity

The effect estimate for the association between menstrual cycle irregularity and composite CVD showed only minimal changes on exclusion of women with amenorrhea (aHR 1.09; 95% CI 0.96-1.24; p=0.173), polycystic ovary syndrome (aHR 1.09; 95% CI 0.99-1.19;

p=0.080), endometriosis (aHR 1.09; 95% CI 0.99-1.20; p=0.068), fibroids (aHR 1.09; 95% CI, 0.99-1.19; p=0.067), or current oral contraceptive use (aHR 1.03; 95% CI 0.94-1.15; p=0.445) **(Supplemental Table S7.4)**. Also, the effect estimate for the association between menstrual cycle irregularity and composite CVD showed only minimal changes (aHR 1.09 (95% CI, 1.00-1.20; p=0.052) on excluding polycystic ovary syndrome, endometriosis, and fibroids as covariates included in the multivariable Cox proportional hazard model **(Supplemental Table S7.5)**.

Menstrual cycle frequency

The association between frequent or infrequent cycles and composite CVD was no longer maintained on exclusion of women with amenorrhea (aHR 1.18; 95% CI 0.95-1.47; p=0.130) and on current oral contraceptive use (aHR 1.14; 95% CI 0.91-1.42; p=0.259). The association between frequent or infrequent cycles and risk of composite CVD was sustained on exclusion of women with history of polycystic ovary syndrome (aHR 1.23; 95% CI 1.01-1.51; p=0.043), endometriosis (aHR 1.24; 95% CI 1.02-1.52; p=0.035) or uterine fibroids (aHR 1.26; 95% CI 1.03-1.54; p=0.025) **(Supplemental Table S7.6)**. The effect estimate for composite CVD for the association between frequent or infrequent cycles and composite CVD was not materially affected (aHR 1.28 95% CI, 1.05-1.55 p=0.016)) on exclusion of polycystic ovary syndrome, endometriosis, and fibroids as covariates included in adjusted Cox proportional hazard model **(Supplemental Table S7.5)**. In the analysis comparing frequent menstrual cycles to menstrual cycles of normal frequency, the adjusted HRs for cardiometabolic outcomes were: 1.42 (95% CI 1.09-1.85; p=0.009) for composite CVD; 1.13 (95% CI 0.74-1.72; p=0.570) for IHD; 1.88 (95% CI 1.33-2.67; p<0.001) for cerebrovascular disease; 0.93 (95% CI, 0.42-2.06; p=0.858) for heart failure; 1.37 (95% CI 1.22-1.54; p <0.001) for hypertension; and 1.37 (95% CI 1.13-1.65; p<0.001) for type 2 diabetes mellitus (**Supplemental Table S7.7**). For the analysis examining infrequent menstrual cycles versus

menstrual cycles of normal frequency, the adjusted HRs for cardiometabolic outcomes were 1.06 (95% CI 0.78-1.45; p=0.704) for composite CVD; 1.16 (95% CI 0.68-1.97; p=0.582) for IHD; 1.01 (95% CI 0.66-1.53; p=0.980) for cerebrovascular disease; 1.13 (95% CI 0.50-2.54; p=0.770) for heart failure; 1.24 (95% CI 1.85-2.72; p<0.001) for type 2 diabetes mellitus **(Supplemental Table S7.7)**.

There was no evidence of interaction between cycle dysfunction (irregular and frequent or frequent) and lifestyle characteristics including BMI, smoking, and alcohol consumption **(Supplemental Figure S7.2)**.

Discussion

Main findings

In this nationwide cohort study of more than 700 thousand women from the UK, history of both irregular menstrual cycles and frequent or infrequent menstrual cycles were associated with an increased risk of several cardiometabolic outcomes. The associations were strongest for women with abnormal patterns in the frequency of their menstrual cycles with frequent or infrequent cycles being associated with a significant increase in hazard of composite CVD. History of menstrual cycle irregularity was associated with a borderline increase in the hazard of composite CVD. On examination by subtypes of CVD, menstrual cycle irregularity was associated with an increased risk of ischaemic heart disease and heart failure but not stroke. Frequent or infrequent cycles were associated with an increased risk of cerebrovascular disease but not ischaemic heart disease or heart failure. On examination by subtype of menstrual cycle frequency, frequent menstrual cycles were associated with an elevated risk of composite CVD and cerebrovascular disease but not ischaemic heart disease or heart failure. No association was observed between infrequent menstrual cycles and composite CVD or any of the CVD subtypes. Both irregular menstrual cycles and frequent or infrequent cycles were linked with an increased risk of hypertension and type 2 diabetes mellitus.

Comparison with previous literature

A summary of the study characteristics of selected existing literature are provided in **Supplemental Table S7.8**. Overall, results from our study support and expand existing literature that have examined the association between menstrual characteristics and cardiometabolic outcomes. A UK prospective cohort study of 40896 premenopausal women aged 50 years and below at baseline examined the association between irregular menstrual cycles and risk of fatal and non-fatal cardiovascular disease.[366] During a median duration of follow-up of 6.9 years (IQR: 6.2 to 7.6), no relationship was found between irregular

menstrual cycles compared to regular menstrual cycles and risk of fatal and non-fatal CVD outcomes **(Supplemental Table S7.8)**. Three United States (US) prospective cohort studies that were all conducted by Wang et al. examined the relationship between menstrual cycle characteristics and cardiometabolic outcomes (CVD and diabetes mellitus) in a cohort of female nurses.[352,353,367] The studies by Wang et al. typically defined menstrual cycle regularity as very regular, regular, usually irregular, and always irregular or no period while cycle length was defined as ≤ 25 days, 26-31 days, 32-39 days, ≥ 40 days. The most recent study by Wang et al.[353] followed up 80630 women for a period of 24 years to examine relationship between menstrual cycle regularity and risk of CVD (fatal and non-fatal). Compared to women who had very regular cycles at ages 14 to 17 years, 18 to 22 years and 29 to 46 years, women with always irregular cycles or no periods at ages 18 to 22 and 29-46 age-groups were at an elevated risk of CVD in later life. **(Supplemental Table S7.8)** In the second prospective cohort study,[352] Wang and colleagues followed up 79505 premenopausal women for a period of 24 years to evaluate the association between menstrual cycle characteristics and risk of premature mortality. Always irregular cycle or no period at ages 18-46 was associated with mortality from CVD **(Supplemental Table S7.8)**.[367] Wang et al. followed 75456 participants followed for a period of 24 years to investigate the association between menstrual cycle characteristics and type 2 diabetes mellitus. Both irregular menstrual cycles and menstrual cycle length of ≥ 40 days were associated with an elevated risk of type 2 diabetes mellitus **(Supplemental Table S7.8)**. A recent Australian study of 13714 participants investigated the relationship between irregular menstrual cycles compared to regular menstrual cycles (never, sometimes, or rarely) and risk of non-fatal heart disease (myocardial infarction, angina).[368] During the 20-year period of follow-up irregular menstrual cycles compared to regular menstrual cycles was linked to higher risk of heart disease and diabetes mellitus **(Supplemental Table S7.8)**. We observed a relationship between frequent

(short) but not infrequent (long) menstrual cycles and CVD. This contrasted with a US cohort study which found an association between long menstrual cycles but not short menstrual cycles and CVD.[353] In the US study, compared to women with a menstrual cycle length of 26-31 days, the adjusted HRs for cardiovascular disease were: 1.00 (95% CI 0.83-1.20) for cycle lengths of $\leq$ 25 days, 1.05 (95% CI 0.89-1.24) for cycle lengths of 32-39 days and 1.30 (95% CI 1.09-1.57) for cycle lengths of $\geq$ 40 days or too irregular to estimate (Additional file: Table S8).[353] In our study menstrual cycle frequency was classified as either frequent or infrequent. Our study could not differentiate menstrual cycle frequency by cycle length in days. Therefore, our results should be interpreted with caution given that the relationship between infrequent (long) menstrual cycles and CVD appears to be greatest with increasing length ($\geq$ 40 days) in menstrual cycles, as suggested by the findings from the US study.[353] The association between frequent (short) menstrual cycles and elevated CVD risk is biologically plausible. Frequent menstrual cycles are a marker of diminished ovarian reserve.[369] Previous studies have reported a relationship between diminished ovarian reserve and elevated CVD risk.[370,371]

An Iranian study followed up 2128 women aged 18-49 years at baseline to investigate the association between irregular menstrual cycles compared regular menstrual cycles and risk of cardiometabolic outcomes.[372] During the 15-year period of follow-up irregular menstrual cycles compared to regular menstrual cycles were associated with higher risk of type 2 diabetes mellitus but not hypertension. The present study found that irregular menstrual cycles were associated with an increased risk of heart failure. However, due to the low number of events we did not find any association between changes in menstrual cycle frequency and heart failure risk. Direct comparisons between the existing literature and the present study are challenging due to several differences which may partly explain some of the contrasting findings. The main methodological differences relate to the stratification of

irregular menstrual cycles by severity into four categories (US studies);[352,353,367] case definition of the exposure to include both regularity and frequency of menses as a single exposure (Iranian study);[372] case definition of the unexposed group (regular menstrual cycles) as never, rarely, or sometimes (Australian study);[368] restriction of the study participants exclusively to nurses (US studies);[352,353,367] and inclusion of fatal CVD events in the outcomes (US and UK studies).[353,366]

Biological plausibility

Several mechanisms yet to be fully elucidated are suspected to play a role in the association between menstrual cycle characteristics and elevated risk of cardiometabolic outcomes. First, PCOS which a common cause of amenorrhoea, irregular menstrual cycles and oligomenorrhoea, is characterised by cardiovascular risk factors including metabolic syndrome, obesity, insulin resistance, dyslipidaemia, and hypertension.[373] The present study found that the association between menstrual complications and cardiometabolic outcomes was independent of PCOS. That PCOS is associated with an increased risk of CVD is debatable. Some studies report an increased risk of CVD among women with PCOS while other studies argue that any observed association is minimal or restricted to severe phenotypes of PCOS.[374] Second, other reproductive factors (endometriosis, fibroids) associated with changes in menstrual characteristics and linked to adverse cardiometabolic health may partly account for the observed association.[325,375] However, exclusion of women with a record for endometriosis or fibroids in sensitivity analyses did not alter the observed effect estimates. Attenuation of the effect size on exclusion of women on current prescription for combined oral contraceptive (COC) suggests that increased CVD risk may be partly mediated by COC use.[376] Third, changes in menstrual cycle characteristics is strongly linked to hyperinsulinemia. Hyperinsulinemia suppresses the production of sex hormone binding globulin resulting in elevated level of free testosterone. This hormonal environment is

associated with higher risk of cardiometabolic outcomes.[377–380] Fourth, oestrogen modulates vascular inflammation.[381,382] Abnormal menstrual patterns may favour pro-inflammatory process which may result in atherosclerotic CVD. Fifth, differences in mechanistic pathways between menstrual cycle characteristics may partly account for the differences in findings. A longer cycle length may be indicative of fewer ovulations and, consequently, lower mean oestrogen levels.[383] Higher levels of endogenous estradiol before menopause have been associated with a decreased risk of subclinical atherosclerosis after menopause.[384] Short menstrual cycle length may be an indicator of ovarian ageing.[369,385] Markers of diminished ovarian reserve including anti-müllerian hormone (AMH) and elevated follicle stimulating hormone (FSH) have been associated with CVD risk factors.[386,387] In addition, low AMH levels may act independently to promote atherogenesis.[370,388]

Strengths and limitations

The main strength of the present study is the use of a large sample size that is representative of the UK population and a long duration of follow-up that allows sufficient time for the development of cardiometabolic outcomes. Unlike previous studies that relied on self-reports of the exposure several years after their occurrence, the present study relied on electronic health data documented at point of clinical consultation which helped to minimise recall bias. In addition, we adjusted for several key sociodemographic, lifestyle, medical and reproductive characteristics. Several limitations should be acknowledged. Foremost, we could not characterize menstrual cycle characteristics by grades of severity or duration as this information was not coded in UK electronic health records. Second, the exposure of interest relies on self-report and is therefore susceptible to misclassification. Third, although we adjusted for several known and potential confounders, the possibility of unmeasured confounding remains; for instance, we were not able to adjust for dietary habits, physical activity, or family history of CVD as this information is not well recorded in UK primary

care data. Fourth, where a patient had a diagnostic code for both irregularity and frequent or infrequent cycles, exposure status was assigned as the first ever recorded menstrual cycle characteristic domain. This makes the implicit assumption that the order in which these conditions are recorded is random; however, this may not be the case. Nevertheless, given that participants impacted by any potential classification bias will have had both menstrual cycle characteristics (and could therefore contribute to either exposure definition), and the direction of effect for most outcomes was similar for the two exposures, we expect this to have a limited impact on the findings. Fifth, there is potential for exposure misclassification among women who were included in the unexposed cohort but had abnormal menstrual cycle characteristics not recorded in primary care or who were on hormonal contraceptives. Also, we did not exclude women with abnormal cycle characteristic shortly after pregnancy or during lactation. Although history of breastfeeding compared to no breastfeeding is associated with reduced maternal risk CVD, hypertension and diabetes mellitus,[389,390] we were not able to adjust for history of breastfeeding in the analysis. Sixth, a further drawback is the possibility for selection bias due to differential loss to follow-up between exposure groups: 40.7% of women in the exposed groups and 46.0% in the unexposed groups were lost to follow-up due to leaving the general practice.

Implications for public health and research

Findings from the present study support calls for the inclusion of menstrual cycle history as an additional vital sign in the assessment of the overall health status of young women. Specifically, abnormal menstruation may act as a window into the future cardiometabolic health of women. Therefore, women with history of irregular menstrual cycles or frequent or infrequent menstrual cycles may benefit from periodic evaluation of their cardiometabolic health. Current UK guidelines should consider incorporating reproductive factors including menstrual cycle characteristics as risk enhancing factors for cardiometabolic disease given

the low awareness about these factors among UK physicians.[391] Future research should determine the pathophysiological mechanisms linking menstrual cycle complications and adverse cardiometabolic health and the factors behind the differential impact of different menstrual cycle characteristics and poor cardiometabolic outcomes.

Conclusion

History of irregular menstrual cycles or frequent or infrequent menstrual cycles is associated with increased risk of cardiometabolic outcomes in later-life. Research is needed to unravel the pathophysiological links behind changes in menstrual cycle and adverse cardiometabolic health. Incorporating reproductive history including menstrual cycle characteristics as part of routine medical evaluation may help identify potential candidates for periodic assessment of cardiometabolic health.

Chapter 8. General discussion

Chapter overview

This thesis examined the association between female reproductive factors in young women and risk of cardiovascular disease across the lifespan. There were three major aims: (i) to describe the burden (incidence and prevalence) of cardiovascular disease in young UK adults, including contemporary (1998-2017) sex-specific temporal trends (chapter 3); (ii) to identify, appraise and synthesise high level evidence, namely systematic reviews and meta-analyses, examining the association between female reproductive factors and risk of cardiovascular disease in the long term (chapter 4); (iii) Using data from UK primary care, address gaps identified in the review of literature (chapter 4) on the relationship between female reproductive factors namely endometriosis (chapter 5), pelvic inflammatory disease (chapter 6) and menstrual cycle characteristics (chapter 7) and the risk of cardiovascular disease (CVD). This chapter will begin by summarising the main findings from the individual studies in this thesis. It will summarise what was already known and highlight the contributions of this thesis to the existing body of literature. Next, this chapter will address the implications for women, public health policy and clinical practice and suggest potential areas for future research. Finally, the chapter will close with an overall conclusion for the thesis.

Sex-specific temporal trends in incidence and prevalence of cardiovascular disease in young UK adults

Summary of main findings

Adverse pregnancy outcomes and other reproductive endocrine complications are associated with higher CVD risk in the short-term (1-10 years) and long-term (> 10 years).[17,392] The prevalence of several of these reproductive factors have been on an upward trend in several countries.[140,393,394] These sex-specific factors uniquely expose reproductive age group women to a higher risk of CVD. To set the tone for the thesis, I conducted a series of yearly (1998-2017) cross-sectional and cohort studies to estimate the burden of cardiovascular disease in

young (16-50 years) men versus women and characterise the sex-specific temporal (1998-2017) trends in this age group. Results showed that for all CVD subtypes, the burden was greatest in men compared to women (Table 8.1). Overall, during the study period, in both sexes, the incidence and prevalence trends of IHD and angina decreased, while revascularisation procedures, stroke/TIA and heart failure exhibited an upward trend. Myocardial infarction trends were stable in men but significantly increased in women. (Table 8.1)

Table 8.1 Summary of the main findings on the sex-specific temporal (1998-2017) trends in incidence and prevalence of CVD in young (16-50 years) UK adults.

Condition	Sex	Incidence / 100000 person-years		AAPC	Prevalence per 10000 population		AAPC
		1998	2017		1998	2017	
IHD	Men	104.1	64.1	-2.6	655.8	370.5	-2.8
	Women	49.4	24.9	-3.4	341.6	129.8	-4.9
Angina	Men	64.1	15.4	-7.0	413.8	94.6	-7.2
	Women	37.5	7.7	-7.3	243.3	51.5	-7.8
MI	Men	46.1	44.5	+ 0.01*	276.3	253.2	-0.2
	Women	9.8	17.1	+ 2.3	55.5	74.6	+ 2.0
CABG/PCI	Men	26.2	30.0	+ 1.1	90.8	158.8	+ 3.2
	Women	4.6	7.2	+ 3.9	20.4	42.5	+ 4.1
Stroke/TIA	Men	33.2	45.2	+ 1.9	211.6	358.7	+ 3.1
	Women	37.0	35.5	+ 0.6*	194.7	389.8	+ 3.6
HF	Men	11.9	28.3	+ 5.6	71.6	186.2	+ 5.0
	Women	6.2	15.9	+ 5.0	63.8	114.4	+ 3.0

AAPC = Average annual percentage change, CABG = Coronary artery Bypass graft, HF = Heart failure, MI = Myocardial infarction, PCI = Percutaneous coronary intervention, TIA = Transient ischaemic attack. P for trend = <0.05 except *(stable trend).

What was already known?

Although the overall burden of cardiovascular disease mortality has been on a downward trend for several decades, analysis of age and sex-specific data revealed a worrisome picture. For instance, data from high-income countries showed that CVD mortality declines were sustained in older adults (> 55 years) but had slowed down in younger (< 55 years) adults, with the rate of decline slowest in younger women.[10,12]. Habits that increase the risk of CVD, including cigarette smoking, unhealthy eating, and illicit drug use, are established and accumulate in young adulthood. Also, for women, biological risk factors associated with CVD, including pregnancy complications and reproductive endocrine conditions, are prominent in this age group. Despite this, few studies had focussed on cardiovascular disease incidence and prevalence trends in young adults. Epidemiological data from North America had shown that myocardial infarction trends were on a rising trend in young adults, with the

greatest rise recorded among young women.[13,14] Data from Scandinavian countries (Denmark and Sweden) had revealed that heart failure incidence had increased among young adults (< 50 years) but had declined in older individuals (>50 years).[28,131] However, these studies had not reported sex differences in heart failure trends. For stroke, studies from France and the Netherlands had shown that the incidence of stroke had increased in young adults (<55 years), with the incidence higher in women than men.[129,395] Contemporary data on cardiovascular disease burden and temporal trends in young UK adults were scarce.

What this study adds

The study in chapter 3, conducted using UK primary care data, provides a fresh perspective into the burden and temporal trends of major cardiovascular diseases in young adults and should concern UK public health practitioners involved in CVD prevention. The fall in IHD incidence and prevalence trends were driven by falls in angina rates. Although there was an upward trend in several CVD conditions, the rate of change was disproportionate between men and women, suggesting that there are sex differences. The rate of increase in the incidence and prevalence trends for myocardial infarction and coronary artery bypass graft/ percutaneous coronary intervention (CABG/PCI) were higher in women than men. The rate of increase in heart failure incidence and prevalence trends was higher in men compared to women. The rate of increase in stroke/TIA incidence was higher in men compared to women.

The association between the reproductive health of young women and CVD in later-life: Umbrella review

Summary of main findings

To achieve the second aim, in chapter 4 I conducted an umbrella review examining the association between female reproductive factors in young women and the risk of cardiovascular disease across the lifespan. A total of 32 systematic reviews and meta-analyses met the inclusion criteria and were included in the analysis. All reviews included in

the analysis were rated moderate in quality except 4. The reviews rated low in quality related to: the use of non-oral combined hormonal contraceptives[203]; combined hormonal contraceptive use in obese women[205]; combined oral contraceptive use in hypertensive women[208]; CVD events among reproductive and menopausal age group women with polycystic ovary syndrome.[189] Table 8.2 provides a summary of the main results from the umbrella review. Given the large number of reproductive factors and outcomes under review, and for ease of reporting, the magnitude of the reported effect estimates were summarised within the categories presented in Table 8.2. The effect sizes for composite CVD were greatest (2-fold) for stillbirth, pre-eclampsia, preterm birth, and recurrent preterm birth. The effect sizes for IHD were 2-fold for pre-eclampsia, recurrent pre-eclampsia, and preterm birth. For stroke, the magnitude of the effect sizes was greatest (2-fold) for combined oral contraceptive use and pre-eclampsia. The association for heart failure was four-fold for women history of pre-eclampsia. Apart from guidelines relating to pre-eclampsia and use of hormonal contraceptives, existing UK guidelines on other reproductive factors are silent on the relationship between female reproductive factors and CVD risk.

Table 8.2 Umbrella review summary of main findings on the association between reproductive factors and cardiovascular disease

Reproductive factor	Composite CVD	IHD	Stroke/TIA	Heart failure	Recognition in UK guidelines (RCOG, NICE, FSRH)
	Magnitude of effect estimates				
Early menarche	>1 to 1.5	>1 to 1.5	>1 to 1.5	-	No mention
Any oral contraceptive pill use	-	-	2.0- 2.5	-	FSRH cautions on potential CVD risk associated with combined oral contraceptive use
Progesterone only pill use	-	-	Null	-	
COC pill use	-	1.5 to 2.0	1.5 to 2.0	-	
COC use in obese women	-	Null	Null	-	
COC use in women with migraine	-	-	2.08 to 16.9*	-	
COC use in women with dyslipidaemia	-	OR 25 (6-109) *	1.5 to 2.0	-	
COC use in women with hypertension	--	-	>5.0	-	
Combined non-oral hormonal contraceptives	-	Null	Null	-	
PCOS	>1 to 1.5	>1 to 1.5	>1 to 1.5	Null	
Fertility treatment	Null	-	Null	-	No mention
Parity	>1 to 1.5	-	-	-	No mention
Breastfeeding	>0.5 to < 1.0	-	-	-	No mention
Premature ovarian insufficiency	>1 to 1.5	>1 to 1.5	Null	-	
Early menopause (natural and unnatural	>1 to 1.5	>1 to 1.5	Null	>1 to 1.5	
Menopausal symptoms	Null	>1 to 1.5	Null	Null	
Miscarriage	Null	>1 to 1.5	Null	-	No mention
Stillbirths	2.0 to 2.5	-	-	-	No mention
Pre-eclampsia	2.5 to 3.0	2.0 to 2.5	2.5 to 3.0	4.0 to 4.5	NICE guidelines recognise increased risk associated with HDP
Recurrent pre-eclampsia	-	2.0 to 2.5	1.5 to 2.0	-	
Gestational hypertension	1.5 to 2.0	-	1.5 to 2.0	-	
Gestational diabetes	1.5 to 2.0	-	-	-	No mention
Placental abruption	1.5 to 2.0	-	-	-	No mention
Pre-term birth	2.0 to 2.5	2.0 to 2.5	1.5 to 2.0	-	No mention
Recurrent pre-term birth	2.0 to 2.5	1.5 to 2.0	1.5 to 2.0		No mention
Low birth weight	>1 to 1.5	-	-	-	No mention
Small for gestational age	>1 to 1.5	-	-	-	No mention

COC= combined oral contraceptive use, PCOS= Polycystic ovary syndrome, *=narrative synthesis involving few studies with wide confidence intervals.

What was already known?

I conducted a scoping review of published literature to identify what was already known about the relationship between female sex-specific factors and CVD. The scoping search revealed several lines of evidence that suggested that reproductive factors (adverse pregnancy outcomes and fertility-related factors) were associated with maternal CVD risk. A sizeable proportion of the literature was documented in systematic reviews and meta-analyses. Several systematic reviews addressed the same topic, with some of the reviews providing conflicting evidence. Also, the quality of these reviews was uncertain. To the best of my knowledge, there were no tertiary-level studies (umbrella reviews) on this topic. Clinicians and policymakers may be overwhelmed by an abundance of systematic reviews on a given topic. Therefore, the next logical step was to identify, appraise and summarise available secondary evidence (systematic reviews and meta-analyses) on the relationship between reproductive factors and CVD in a single document.

What this study adds

The umbrella review in this thesis provides clinicians and policymakers with a central source of high-level evidence examining the relationship between female reproductive factors and CVD risk in later life by providing a comprehensive and accessible summary of this topic. A wide range of outcomes, including composite CVD, IHD, stroke/TIA and heart failure were included. In addition, the umbrella review updated evidence relating to breastfeeding and maternal risk of CVD. Furthermore, a review of relevant UK guidelines was carried out, and recommendations for clinical practice were provided where a gap in clinical guidelines was identified.

Risk of cardiovascular outcomes among women with endometriosis in the United Kingdom: a retrospective matched cohort study

Summary of main findings

In chapter 5, I leveraged data from UK primary care to compare the risk of cardiovascular outcomes in women with a record of endometriosis (N=56090) compared to matched controls without a record for endometriosis (N=223669). The adjusted hazard ratios for cardiovascular outcomes were composite CVD 1.24 (95% CI 1.13-1.37); IHD 1.40 (95% CI 1.22-1.61); heart failure 0.76 (95% CI 0.54-1.07); cerebrovascular disease 1.19 (95% CI 1.04-1.36); hypertension 1.12 (95% CI 1.07-1.17) and arrhythmia 1.26 (95% CI 1.11-1.43).

What was already known?

Endometriosis is a common gynaecological condition marked by systemic inflammation.[396] The study in chapter 5 was motivated by a paucity of studies examining the association between endometriosis and CVD. In addition, there were no studies from the UK on this topic. At the time of conducting the study in chapter 5, a search of literature identified two US cohort studies that examined the association between laparoscopically confirmed endometriosis and risk of IHD in one study,[40] and hypertension risk in another study.[39]. The populations included in the two US cohort studies were composed exclusively of nurses from the US and therefore the results may not have been representative of the wider US population.[39,40] IHD was defined as a composite outcome that included myocardial infarction, coronary artery procedures (graft, angioplasty, stents), and angiographically confirmed angina. In the US studies, the adjusted hazard ratios for IHD and hypertension in women with endometriosis compared to those without were 1.62 (95% CI, 1.39-1.89) and 1.14 (95% CI, 1.39-1.89).[39,40]

What this study adds

This study adds to the limited body of literature on the link between endometriosis and cardiovascular disease. The study supported and expanded findings from previous studies with additional outcomes examined including composite CVD, cerebrovascular disease, heart failure and arrhythmia. Unlike previous studies, additional potential confounders, including adverse pregnancy outcomes and gonadotropin-releasing hormone (GnRH) analogues, were accounted for in our analysis. In addition, I harnessed the power of UK primary care data to provide contemporary data on the incidence and prevalence of endometriosis among UK women including examining the incidence by age-group and socioeconomic status (Townsend deprivation quintile).

Risk of cardiometabolic outcomes among women with a history of pelvic inflammatory disease: A retrospective matched cohort study

Summary of main findings.

In chapter 5, using data from UK primary care, I evaluated the risk of cardiovascular outcomes among women with a diagnosis of pelvic inflammatory disease (PID) (N=19804) compared matched controls without a record for of PID (N=73,769). The adjusted hazard ratios for cardiometabolic outcomes were: composite CVD 1.10 (95% CI 0.93-1.31); IHD 1.19 (95% CI 0.93-1.53); cerebrovascular disease 1.13 (95% CI 0.90-1.43); HF 0.92 (95% CI 0.64-1.36); hypertension 1.10 (95% CI 1.01-1.21); and T2DM 1.26 (95% CI 1.09-1.44).

What was already known?

The study was motivated by the results of a scoping search which identified three cohort studies from Taiwan that had investigated the relationship between pelvic inflammatory disease and risk of cardiovascular disease.[156,244,337] It is plausible for infections to cause vascular inflammation including infections by Chlamydia species, a common causative agent for PID.[339–341] In the Taiwanese studies, compared to controls without a history of PID, a

history of PID was associated with an elevated risk of myocardial infarction (aHR1.86; 95% CI 1.23-2.81) and stroke (aHR1.63; 95% CI 1.45-1.85), and reduced risk of intracerebral hemorrhage (aHR 0.67; 95% CI 0.50-0.90). However, these studies had several methodological shortcomings including a misleading definition for PID,[338] a short duration of follow-up and lack of adjustments for known confounders including BMI and smoking. I therefore conducted a retrospective cohort study to provide further clarity on the association between PID and long-term risk of CVD.

What this study adds

Findings from the study in chapter 5 did not support an association between history of PID and risk of cardiovascular outcomes including composite CVD, IHD, cerebrovascular disease or heart failure. Instead, PID was associated with a modest increase in the risk of hypertension and type 2 diabetes mellitus, two major risk factors for cardiovascular disease. To the best of my knowledge, this is the first study to show a potential association between PID and type 2 diabetes mellitus.

The association between menstrual cycle characteristics and cardiometabolic outcomes in later life: A retrospective matched cohort study of 704743 women from the UK

Summary of main findings

In chapter 6, I examined the relationship between menstrual cycle characteristics and future risk of cardiometabolic outcomes. The menstrual characteristics under examination were the regularity and frequency of menstrual cycle; therefore, two cohorts were created. In the first cohort, women with irregular menstrual cycles (N= 215378) were compared to matched controls without a record of irregular menstrual cycle (N=386825). In the second cohort, women with a history of frequent or infrequent menstrual cycles (N=36947) were compared to matched controls without a record of frequent or infrequent menstrual cycles (N=65593).

The adjusted hazard ratios for cardiometabolic outcomes for women with a history of irregular menstrual cycles compared to those without irregular menstrual cycles were: composite CVD 1.08 (95% CI 1.00-1.19); IHD 1.18 (1.01-1.37); cerebrovascular disease 1.04 (0.92-1.17); heart failure 1.30 (1.20-1.65); hypertension 1.07 (1.03-1.11); type 2 diabetes mellitus 1.37 (1.29-1.45). The adjusted hazard ratios for cardiometabolic outcomes comparing women with frequent or infrequent menstrual cycles to women with menstrual cycles of normal frequency were: composite CVD 1.24 (1.02-1.52); IHD 1.13 (0.81-1.57); cerebrovascular disease 1.43 (1.10-1.87); heart failure 0.99 (0.57-1.75); hypertension 1.31 (1.21-1.43); type 2 diabetes mellitus 1.74 (1.52-1.98).

What was already known?

Clinically significant changes in menstrual cycle characteristics are associated with poor health profiles including osteoporosis, reproductive cancers, and cardiometabolic health.[397] The American college of obstetricians and gynecologists recommends the inclusion of menstrual cycle history as part of routine medical history taking, given its potential as a marker of adverse health outcomes.[358,397] Despite this, few studies had investigated the relationship between menstrual cycle characteristics and long-term cardiovascular outcomes. Also, data from the UK on this topic is scarce. In a US prospective cohort study,[41] very irregular menstrual cycles compared to regular menstrual cycles were associated with an increased risk of fatal and nonfatal CHD (aRR 1.53; 95% CI 1.24-1.90) but not fatal and nonfatal stroke (1.30; 95% CI 0.97-1.74). In a Dutch study,[398] irregular menstrual cycles compared to regular cycles was associated with an elevated risk of CHD (aHR 1.28; 95% CI 1.05-1.56). However, whether this association was independent of polycystic ovary syndrome was unclear.

What this study adds

The results from the study in chapter 6 support and expand findings in previous literature that examined the link between menstrual cycle characteristics and cardiovascular outcomes. In a cohort of UK women, menstrual cycle characteristics (irregular or abnormal cycle frequency) was associated with an elevated risk of composite CVD, ischemic heart disease, cerebrovascular disease, and heart failure. Also, to the best of my knowledge, this is the first study to show an association between menstrual cycle irregularity and heart failure risk.

Implications for women

The relative risk of developing GDM was shown to be 15–38% lower in people who followed diets like the Mediterranean Diet (MedDiet), the Dietary Approaches to Stop Hypertension (DASH), or the Alternate Healthy Eating Index (AHEI). Pre-pregnancy and early-pregnancy physical activity were each associated with a 30% (OR 0.70; 95% CI, 0.57–0.85) and 21% (OR 0.79; 95% CI, 0.64–0.97) lower risk of GDM, respectively, compared to no physical activitty.[399] Adopting a heart-healthy diet and increasing physical activity are key lifestyle interventions to reduce CVD risk in women with APOs. Women who are breastfeeding have healthier cardiometabolic profiles than nonlactating women due to reduced fasting blood glucose, triglyceride, insulin resistance,[400] and blood pressure,[401] and greater high-density lipoprotein cholesterol.[215,402]

Implications for policy and clinical practice

The study in chapter 3 of this thesis showed that, overall, the incidence and prevalence of cardiovascular diseases in young adults are rising. Notable sex differences include steeper increases in the incidence of myocardial infarction and CABG/PCI in women and stroke/TIA in men. In young women, myocardial infarction is associated with longer hospital stays and a greater risk of 30-day mortality than in men.[14,146] Irrespective of age, mortality is higher in women compared to men within one (26% versus 19%) and five (47% versus 36%) years

following a diagnosis of myocardial infarction.[403] The growing burden of CVD in young adults warns of a potential rise in CVD burden in the future as the young population ages. The incidence of CVD in young adults has risen in tandem with a rise in the prevalence of obesity and diabetes mellitus in this age group. It is often stated that an ounce of prevention is worth a pound of cure. To stem the rising trend in CVD burden, proactive steps in the primary prevention of CVD in this young age group are needed. Measures may include sin tax, controlled marketing and messaging on harmful products including alcohol, tobacco and shisha use, and promotion of healthy foods. The findings in the umbrella review (chapter 4) and cohort studies (chapter 5-7) have several implications for clinicians and policymakers involved in reducing the burden of CVD. First, analyses in the umbrella review (Chapter 4) revealed that on the relationship between reproductive factors and CVD risk was limited in relevant UK guidelines, with only pre-eclampsia and hormonal contraceptive use recognised as factors that enhance CVD risk. This finding is in line with the results of a UK study which found that awareness of link between reproductive complications and CVD risk was low among UK healthcare professionals.[391] Guidelines from the European Society for Cardiologists (ESC) and the American Heart Association (AHA) recommend that women with a history of reproductive complications should be monitored periodically for cardiovascular complications.[348] Recognition of female sex-specific factors in UK clinical guidelines will help increase awareness among clinicians and facilitate the timely follow-up of the affected women. Second, a multi-disciplinary collaboration between various clinical professionals, including primary care doctors, cardiologists, obstetricians, and gynaecologists, will be needed for effective follow-up of patients with adverse pregnancy outcomes or reproductive endocrine complications. Third, improved medical records linkage between specialist units (obstetrics and gynaecology) and primary care will be required to facilitate periodic follow-up of these women in primary care.

Implications for future research

Epidemiological research

Several findings from this thesis may be used as a basis for future research. The risk factor profiles of younger patients may differ from those of older patients. Furthermore, the magnitude of the changes in CVD risk factors has varied between younger and older adults.[404,405] Future studies are needed to link the trends in common (traditional) and sex-specific factors to the rising trend in the incidence and prevalence of CVD in young adults. In the reviews relating to hormonal contraceptives use among women with dyslipidaemia, combined oral contraceptive use among women with hypertension, and non-oral use of combined hormonal contraceptives and risk of thromboembolism, the evidence was based on a single study or a few studies with a low total number of documented events, resulting in imprecise results. Larger well-conducted studies are needed to support the findings of these reviews. Observational studies suggest that first trimester bleeding without miscarriage, and anaemia in pregnancy have both been associated to an elevated risk of future cardiovascular disease events.[243,245] However, data on these reproductive factors and their association with CVD is limited. Additional research is needed to support the findings. Endometriosis is an enigmatic disease with no identified biomarkers or established clinical stages. Future research should identify phenotypes of endometriosis associated with cardiometabolic risk. This would enable targeted treatment and as well as generate hypotheses regarding potential causes. For PID, potential areas for epidemiological research include variability in risk of cardiometabolic outcomes (hypertension and type 2 diabetes mellitus) based on severity or type microorganism causing PID. Future studies should explore the relationship between female reproductive factors and other cardiovascular outcomes including peripheral vascular diseases and arrythmia.

Mechanistic research.

Although these reproductive factors are linked to elevated CVD risk, research is required to establish whether they directly cause CVD or whether they act as physiological tests that reveal women already predisposed to higher CVD risk. Also, it is important to determine whether targeting the mechanistic pathways behind reproductive factors and CVD risk can yield new treatment strategies. Likewise, the cardioprotective mechanisms associated with breastfeeding need to be clearly elucidated to determine whether these can be targeted for therapeutic benefits.

Translational research

Existing cardiovascular disease risk prediction models may underestimate young women's risk since they don't account for sex-specific factors.[278] The next logical step is to exhaustively investigate the utility of including reproductive risk factors in existing risk prediction models for CVD. Future clinical trials should examine the efficacy of dietary adjustments to avoid CVD risk factors in women with prior history of an APO. Pharmacotherapy including low-dose aspirin, metformin calcium supplementation, and antioxidants for APO prevention have been the subject of numerous research efforts.[167,406,407] It is not known pharmacological agents have a role in the prevention of cardiovascular disease after APOs.

Conclusion

This thesis examined the association between female reproductive factors and cardiovascular disease across the lifespan. The thesis began by examining contemporary (1998-2017) trends in the incidence and prevalence of cardiovascular disease in young UK adults. Overall, among young adults in the UK, the incidence and prevalence of IHD and angina exhibited a downward trend while stroke/TIA, HF, and revascularisation, exhibited an upward trend. MI incidence increased in women but remained stable in men. The factors that are behind

unfavourable trends need to be investigated and addressed. The results from this thesis suggest that reproductive factors from early age at menarche through to menopausal symptoms are linked to an increased risk of cardiovascular diseases. Endometriosis and abnormal menstrual cycle characteristics (irregular and frequent or infrequent cycles) were associated with an elevated risk of CVD among UK women. No association was found between PID and CVD among women from the UK. Physicians addressing health indicators should consider the adverse impact of female reproductive factors on CVD. Future studies are needed to investigate the mechanistic links that underlie these associations and whether these can be targeted for therapeutic benefits. Policymakers in the UK should consider updating relevant UK guidelines to highlight the relationship between reproductive factors and CVD to raise awareness among health care professionals and by extension, among the affected women.

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Chapter 3 Supplemental methods, tables, and figures.

Methods

1. Cardiovascular disease Read code selection process
2. Calculation of annual incidence rates for ischaemic heart disease and angina
3. Joinpoint analyses for incidence trends of cardiovascular disease

Tables

Supplemental Table S3.1: Crude annual incidence rates for ischaemic heart disease and angina
Supplemental Table S3.2: Annual percentage change (APC) in the incidence of CVD
Supplemental Table S3.3: Crude annual incidence rates for myocardial infarction and revascularisation procedures
Supplemental Table S3.4: Crude annual incidence rates for stroke/TIA and heart failure

Supplemental Table S3.5: Crude annual prevalence of ischemic heart disease and angina
Supplemental Table S3.6: Annual percentage change (APC) in the prevalence of CVD
Supplemental Table S3.7: Crude annual prevalence of myocardial infarction and revascularisation procedures
Supplemental Table S3.8: Crude annual prevalence of stroke/TIA and heart failure

Supplemental Table S3.9: Comparisons of trends with findings from existing literature

Figures

Supplemental Figure S3.1: Joinpoint analyses for incidence trends of cardiovascular disease
Supplemental Figure S3.2: Joinpoint analyses for prevalence trends of cardiovascular disease

Chapter 3 Supplemental Methods

1. Read code selection process

All UK residents are entitled to universal health care through the National Health Service with more than 98% of the population registered with a primary care physician (General practitioner). General practitioners (GPs) handle all non-emergency cases and refer to secondary care as needed. Secondary care physicians feedback to general practices including information on hospital events, diagnoses and procedures. UK primary care electronic health records are a rich source of data for medical research

Electronic health records in UK primary care use The Read Code Clinical Classification system to store information on a health-related concept. The Read code clinical coding terminology is a hierarchically organised system of that uses alpha-numeric codes to describe patient related diagnoses, symptoms, investigations, and other process of care.[408] Higher level codes describe broad concepts while lower level codes describe health related concepts in greater detail. Chapter 0-9 of the Read codes system describes occupations, symptoms, investigations, procedures, and other administrative information.[408] Chapters A-Z describes diagnoses. Diagnoses related to the cardiovascular system are classified under chapter G "Circulatory system diseases". An example of the Read code hierarchy is provided below.[408]

Level	Read code	Descriptive term
1	G....00	Circulatory system diseases
2	G3...00	Ischaemic heart disease
3	G30..00	Acute myocardial infarction
4	G30y.00	Other acute myocardial infarction
5	G30y100	Acute papillary muscle infarction

The process of developing code lists (electronic health records phenotyping) used to identify and select patients coded with cardiovascular conditions of interest is summarised in the table below. The selection process was similar to the methods described by Watson et al. and Dave and Petersen.[98,99]

Steps	Description	Examples of heart failure
1	Creation of a set of key words, phrases, synonyms, and related terms used to define the condition of interest.	heart failure, cardiac failure, ventricular dysfunction, ventricular failure, New York Heart Association (NYHA),
2	A search of the description term column of the Read codes dictionary using the using the set of key words developed in step 1 above	The term "heart failure" was searched for in the description term column of the Read code dictionary.
3	A search of the alpha-numeric column of the Read code dictionary for any additional codes or synonymous terms	The alpha-numeric codes "G58" was searched for to identify all heart failure codes and synonymous terms coded under G58 at hierarchy level 3 and lower.
4	Differentiate between codes that identify new diagnoses, (incident cases) from those that identify patient with pre-existing condition (Prevalent cases)	Examples of prevalent heart failure cases are "14A6.00 H/O: heart failure", "662W.00 Heart failure annual review"
5	A comparison of the selected codes with relevant codes published in Read code repositories or supplemental data of previous literature.	Read code repositories included caliberresearch.org,[100] clinicalcodes.org,[101] and Cambridge primary care code lists.[102]

		Additional sources of published codes lists from comparison included: Heart failure codes,[322] ischaemic heart disease,[119] angina,[119] myocardial infarction,[119] coronary bypass graft and percutaneous coronary intervention,[119] and stroke.[409–411]
6	Assign of codes a rating of "Definite" "probable" and "unlikely" based on the level of sensitivity of the description of the code.	
7	Consult general practitioners and other clinical specialist to agree on the final set of codes.	

The Read codes used for the study in Chapter 3, Chapter 5, Chapter 6, and Chapter 7 are provided in the Table below.

Ischaemic Heart Disease	
Read code	**Description**
322..00	ECG: myocardial ischaemia
3222	ECG: shows myocardial ischaemia
322Z.00	ECG: myocardial ischaemia NOS
323..00	ECG: myocardial infarction
3232	ECG: old myocardial infarction
3233	ECG: antero-septal infarct.
3234	ECG: posterior/inferior infarct
3235	ECG: subendocardial infarct
3236	ECG: lateral infarction
323Z.00	ECG: myocardial infarct NOS
662K.00	Angina control
889A.00	Diab mellit insulin-glucose infus acute myocardial infarct
8H2V.00	Admit ischaemic heart disease emergency
G3...00	Ischaemic heart disease
G3...11	Arteriosclerotic heart disease
G3...12	Atherosclerotic heart disease
G3...13	IHD - Ischaemic heart disease
G30..00	Acute myocardial infarction
G30..11	Attack - heart
G30..12	Coronary thrombosis
G30..13	Cardiac rupture following myocardial infarction (MI)
G30..14	Heart attack
G30..15	MI - acute myocardial infarction
G30..16	Thrombosis - coronary
G30..17	Silent myocardial infarction
G300.00	Acute anterolateral infarction
G301.00	Other specified anterior myocardial infarction

G301000	Acute anteroapical infarction
G301100	Acute anteroseptal infarction
G301z00	Anterior myocardial infarction NOS
G302.00	Acute inferolateral infarction
G303.00	Acute inferoposterior infarction
G304.00	Posterior myocardial infarction NOS
G305.00	Lateral myocardial infarction NOS
G306.00	True posterior myocardial infarction
G307.00	Acute subendocardial infarction
G307000	Acute non-Q wave infarction
G307100	Acute non-ST segment elevation myocardial infarction
G308.00	Inferior myocardial infarction NOS
G309.00	Acute Q-wave infarct
G30A.00	Mural thrombosis
G30B.00	Acute posterolateral myocardial infarction
G30X.00	Acute transmural myocardial infarction of unspecif site
G30X000	Acute ST segment elevation myocardial infarction
G30y.00	Other acute myocardial infarction
G30y000	Acute atrial infarction
G30y100	Acute papillary muscle infarction
G30y200	Acute septal infarction
G30yz00	Other acute myocardial infarction NOS
G30z.00	Acute myocardial infarction NOS
G31..00	Other acute and subacute ischaemic heart disease
G310.00	Postmyocardial infarction syndrome
G310.11	Dressler's syndrome
G311.00	Preinfarction syndrome
G311.11	Crescendo angina
G311.12	Impending infarction
G311.13	Unstable angina
G311.14	Angina at rest
G311000	Myocardial infarction aborted
G311011	MI - myocardial infarction aborted
G311100	Unstable angina
G311200	Angina at rest
G311300	Refractory angina
G311400	Worsening angina
G311500	Acute coronary syndrome
G311z00	Preinfarction syndrome NOS
G312.00	Coronary thrombosis not resulting in myocardial infarction
G31y.00	Other acute and subacute ischaemic heart disease
G31y000	Acute coronary insufficiency

G31y100	Microinfarction of heart
G31y200	Subendocardial ischaemia
G31y300	Transient myocardial ischaemia
G31yz00	Other acute and subacute ischaemic heart disease NOS
G32..00	Old myocardial infarction
G32..11	Healed myocardial infarction
G33..00	Angina pectoris
G330.00	Angina decubitus
G330000	Nocturnal angina
G330z00	Angina decubitus NOS
G331.00	Prinzmetal's angina
G331.11	Variant angina pectoris
G332.00	Coronary artery spasm
G33z.00	Angina pectoris NOS
G33z000	Status anginosus
G33z100	Stenocardia
G33z200	Syncope anginosa
G33z300	Angina on effort
G33z400	Ischaemic chest pain
G33z500	Post infarct angina
G33z600	New onset angina
G33z700	Stable angina
G33zz00	Angina pectoris NOS
G34..00	Other chronic ischaemic heart disease
G340.00	Coronary atherosclerosis
G340.11	Triple vessel disease of the heart
G340.12	Coronary artery disease
G340000	Single coronary vessel disease
G340100	Double coronary vessel disease
G341.00	Aneurysm of heart
G341.11	Cardiac aneurysm
G341000	Ventricular cardiac aneurysm
G341100	Other cardiac wall aneurysm
G341111	Mural cardiac aneurysm
G341200	Aneurysm of coronary vessels
G341300	Acquired atrioventricular fistula of heart
G341z00	Aneurysm of heart NOS
G342.00	Atherosclerotic cardiovascular disease
G343.00	Ischaemic cardiomyopathy
G344.00	Silent myocardial ischaemia
G34y.00	Other specified chronic ischaemic heart disease
G34y000	Chronic coronary insufficiency

G34y100	Chronic myocardial ischaemia
G34yz00	Other specified chronic ischaemic heart disease NOS
G34z.00	Other chronic ischaemic heart disease NOS
G34z000	Asymptomatic coronary heart disease
G35..00	Subsequent myocardial infarction
G350.00	Subsequent myocardial infarction of anterior wall
G351.00	Subsequent myocardial infarction of inferior wall
G353.00	Subsequent myocardial infarction of other sites
G35X.00	Subsequent myocardial infarction of unspecified site
G36..00	Certain current complication follow acute myocardial infarct
G360.00	Haemopericardium/current comp folow acut myocard infarct
G361.00	Atrial septal defect/curr comp folow acut myocardal infarct
G362.00	Ventric septal defect/curr comp fol acut myocardal infarctn
G363.00	Ruptur cardiac wall w'out haemopericard/cur comp fol ac MI
G364.00	Ruptur chordae tendinae/curr comp fol acute myocard infarct
G365.00	Rupture papillary muscle/curr comp fol acute myocard infarct
G366.00	Thrombosis atrium,auric append&vent/curr comp foll acute MI
G37..00	Cardiac syndrome X
G38..00	Postoperative myocardial infarction
G380.00	Postoperative transmural myocardial infarction anterior wall
G381.00	Postoperative transmural myocardial infarction inferior wall
G382.00	Postoperative transmural myocardial infarction other sites
G383.00	Postoperative transmural myocardial infarction unspec site
G384.00	Postoperative subendocardial myocardial infarction
G38z.00	Postoperative myocardial infarction, unspecified
G39..00	Coronary microvascular disease
G3y..00	Other specified ischaemic heart disease
G3z..00	Ischaemic heart disease NOS
G501.00	Post infarction pericarditis
Gyu3.00	[X]Ischaemic heart diseases
Gyu3000	[X]Other forms of angina pectoris
Gyu3100	[X]Other current complicatns following acute myocard infarct
Gyu3200	[X]Other forms of acute ischaemic heart disease
Gyu3300	[X]Other forms of chronic ischaemic heart disease
Gyu3400	[X]Acute transmural myocardial infarction of unspecif site
Gyu3500	[X]Subsequent myocardial infarction of other sites
Gyu3600	[X]Subsequent myocardial infarction of unspecified site
Angina	
Read code	**Description**
14A5.00	H/O: angina pectoris
14AJ.00	H/O: Angina in last year
187..00	Frequency of angina

661M000	Angina self-management plan agreed
661N000	Angina self-management plan review
662K.00	Angina control
662K000	Angina control - good
662K100	Angina control - poor
662K200	Angina control - improving
662K300	Angina control - worsening
662K400	Angina self management plan commenced
662K500	Angina self management plan completed
662Kz00	Angina control NOS
8B27.00	Antianginal therapy
8IEY.00	Referral to Angina Plan self-management programme declined
8T04.00	Referral to Angina Plan self-management programme
G311.00	Preinfarction syndrome
G311.11	Crescendo angina
G311.12	Impending infarction
G311.13	Unstable angina
G311.14	Angina at rest
G311100	Unstable angina
G311200	Angina at rest
G311300	Refractory angina
G311400	Worsening angina
G33..00	Angina pectoris
G330.00	Angina decubitus
G330000	Nocturnal angina
G330z00	Angina decubitus NOS
G331.00	Prinzmetal's angina
G331.11	Variant angina pectoris
G332.00	Coronary artery spasm
G33z.00	Angina pectoris NOS
G33z000	Status anginosus
G33z100	Stenocardia
G33z200	Syncope anginosa
G33z300	Angina on effort
G33z400	Ischaemic chest pain
G33z600	New onset angina
G33z700	Stable angina
G33zz00	Angina pectoris NOS
Gyu3000	[X]Other forms of angina pectoris
Myocardial infarction	
Read code	**Description**
14A3.00	H/O: myocardial infarct <60

14A4.00	H/O: myocardial infarct >60
14AH.00	H/O: Myocardial infarction in last year
14AT.00	History of myocardial infarction
14AW.00	H/O acute coronary syndrome
323..00	ECG: myocardial infarction
3232	ECG: old myocardial infarction
3233	ECG: antero-septal infarct.
3234	ECG:posterior/inferior infarct
3235	ECG: subendocardial infarct
3236	ECG: lateral infarction
323Z.00	ECG: myocardial infarct NOS
889A.00	Diab mellit insulin-glucose infus acute myocardial infarct
G30..00	Acute myocardial infarction
G30..11	Attack - heart
G30..12	Coronary thrombosis
G30..13	Cardiac rupture following myocardial infarction (MI)
G30..14	Heart attack
G30..15	MI - acute myocardial infarction
G30..16	Thrombosis - coronary
G30..17	Silent myocardial infarction
G300.00	Acute anterolateral infarction
G301.00	Other specified anterior myocardial infarction
G301000	Acute anteroapical infarction
G301100	Acute anteroseptal infarction
G301z00	Anterior myocardial infarction NOS
G302.00	Acute inferolateral infarction
G303.00	Acute inferoposterior infarction
G304.00	Posterior myocardial infarction NOS
G305.00	Lateral myocardial infarction NOS
G306.00	True posterior myocardial infarction
G307.00	Acute subendocardial infarction
G307000	Acute non-Q wave infarction
G307100	Acute non-ST segment elevation myocardial infarction
G308.00	Inferior myocardial infarction NOS
G309.00	Acute Q-wave infarct
G30B.00	Acute posterolateral myocardial infarction
G30X.00	Acute transmural myocardial infarction of unspecif site
G30X000	Acute ST segment elevation myocardial infarction
G30y.00	Other acute myocardial infarction
G30y000	Acute atrial infarction
G30y100	Acute papillary muscle infarction
G30y200	Acute septal infarction

G30yz00	Other acute myocardial infarction NOS
G30z.00	Acute myocardial infarction NOS
G31..00	Other acute and subacute ischaemic heart disease
G310.00	Postmyocardial infarction syndrome
G310.11	Dressler's syndrome
G311500	Acute coronary syndrome
G31y100	Microinfarction of heart
G31y200	Subendocardial ischaemia
G32..00	Old myocardial infarction
G32..11	Healed myocardial infarction
G32..12	Personal history of myocardial infarction
G33z500	Post infarct angina
G35..00	Subsequent myocardial infarction
G350.00	Subsequent myocardial infarction of anterior wall
G351.00	Subsequent myocardial infarction of inferior wall
G353.00	Subsequent myocardial infarction of other sites
G35X.00	Subsequent myocardial infarction of unspecified site
G36..00	Certain current complication follow acute myocardial infarct
G360.00	Haemopericardium/current comp folow acut myocard infarct
G361.00	Atrial septal defect/curr comp folow acut myocardal infarct
G362.00	Ventric septal defect/curr comp fol acut myocardal infarctn
G363.00	Ruptur cardiac wall w'out haemopericard/cur comp fol ac MI
G364.00	Ruptur chordae tendinae/curr comp fol acute myocard infarct
G365.00	Rupture papillary muscle/curr comp fol acute myocard infarct
G366.00	Thrombosis atrium,auric append&vent/curr comp foll acute MI
G38..00	Postoperative myocardial infarction
G380.00	Postoperative transmural myocardial infarction anterior wall
G381.00	Postoperative transmural myocardial infarction inferior wall
G382.00	Postoperative transmural myocardial infarction other sites
G383.00	Postoperative transmural myocardial infarction unspec site
G384.00	Postoperative subendocardial myocardial infarction
G38z.00	Postoperative myocardial infarction, unspecified
G501.00	Post infarction pericarditis
Gyu3100	[X]Other current complicatns following acute myocard infarct
Gyu3400	[X]Acute transmural myocardial infarction of unspecif site
Gyu3500	[X]Subsequent myocardial infarction of other sites
Gyu3600	[X]Subsequent myocardial infarction of unspecified site
Heart failure	
Read code	**Description**
14A6.00	H/O: heart failure
14AM.00	H/O: Heart failure in last year
14S3.00	H/O: heart recipient

14T7.00	H/O: artificial heart
1O1..00	Heart failure confirmed
23E1.00	O/E - pulmonary oedema
2JZ..00	On optimal heart failure therapy
33BA.00	Impaired left ventricular function
388D.00	New York Heart Assoc classification heart failure symptoms
585f.00	Echocardiogram shows left ventricular systolic dysfunction
585g.00	Echocardiogram shows left ventricular diastolic dysfunction
661M500	Heart failure self-management plan agreed
661N500	Heart failure self-management plan review
662f.00	New York Heart Association classification - class I
662g.00	New York Heart Association classification - class II
662h.00	New York Heart Association classification - class III
662i.00	New York Heart Association classification - class IV
662p.00	Heart failure 6 month review
662T.00	Congestive heart failure monitoring
662W.00	Heart failure annual review
679W100	Education about deteriorating heart failure
7900	Transplantation of heart and lung
7900000	Allotransplantation of heart and lung
7900100	Revision of transplantation of heart and lung
7900y00	Other specified transplantation of heart and lung
7900z00	Transplantation of heart and lung NOS
7901	Other transplantation of heart
7901000	Allotransplantation of heart NEC
7901100	Xenotransplantation of heart
7901300	Piggy back transplantation of heart
7901500	Revision of transplantation of heart NEC
7901y00	Other specified other transplantation of heart
7901z00	Other transplantation of heart NOS
7933	Transluminal heart assist operations
7933000	Transluminal insertion of pulsation balloon into aorta
7933100	Transluminal insertion of heart assist system NEC
7933200	Transluminal maintenance of heart assist system
7933400	Implantation of ventricular assist device
7933500	Implantation of right ventricular assist device
7933600	Implantation of left ventricular assist device
7933700	Implantation of biventricular assist device
7933y00	Other specified transluminal heart assist operation
7933z00	Transluminal heart assist operation NOS
7936000	Implantation of intravenous cardiac pacemaker system
7936J00	Implantat intravenous biventricular cardiac pacemaker system

7937900	Implantation of biventricular cardiac pacemaker system
793L.00	Open heart assist operations
793L000	Open implantation of ventricular assist device
793Ly00	Other specified open heart assist operations
793Lz00	Open heart assist operations NOS
8B29.00	Cardiac failure therapy
8CeC.00	Preferred place of care for next exacerbation heart failure
8CL3.00	Heart failure care plan discussed with patient
8CMK.00	Has heart failure management plan
8CMW800	Heart failure clinical pathway
8H2S.00	Admit heart failure emergency
8HBE.00	Heart failure follow-up
8Hg8.00	Discharge from practice nurse heart failure clinic
8HgD.00	Discharge from heart failure nurse service
8HHb.00	Referral to heart failure nurse
8HHz.00	Referral to heart failure exercise programme
8Hk0.00	Referred to heart failure education group
8HTL.00	Referral to heart failure clinic
8HTL000	Referral to rapid access heart failure clinic
8IE1.00	Referral to heart failure exercise programme declined
9N0k.00	Seen in heart failure clinic
9N2p.00	Seen by community heart failure nurse
9Or0.00	Heart failure review completed
G1yz100	Rheumatic left ventricular failure
G210.00	Malignant hypertensive heart disease
G210000	Malignant hypertensive heart disease without CCF
G210100	Malignant hypertensive heart disease with CCF
G211100	Benign hypertensive heart disease with CCF
G21z100	Hypertensive heart disease NOS with CCF
G230.00	Malignant hypertensive heart and renal disease
G232.00	Hypertensive heart&renal dis wth (congestive) heart failure
G234.00	Hyperten heart&renal dis+both(congestv)heart and renal fail
G400.00	Acute cor pulmonale
G41z.11	Chronic cor pulmonale
G554000	Congestive cardiomyopathy
G554011	Congestive obstructive cardiomyopathy
G58..00	Heart failure
G58..11	Cardiac failure
G580.00	Congestive heart failure
G580.11	Congestive cardiac failure
G580.12	Right heart failure
G580.13	Right ventricular failure

G580.14	Biventricular failure
G580000	Acute congestive heart failure
G580100	Chronic congestive heart failure
G580200	Decompensated cardiac failure
G580300	Compensated cardiac failure
G580400	Congestive heart failure due to valvular disease
G581.00	Left ventricular failure
G581.11	Asthma - cardiac
G581.12	Pulmonary oedema - acute
G581.13	Impaired left ventricular function
G581000	Acute left ventricular failure
G582.00	Acute heart failure
G583.00	Heart failure with normal ejection fraction
G583.11	HFNEF - heart failure with normal ejection fraction
G583.12	Heart failure with preserved ejection fraction
G584.00	Right ventricular failure
G58z.00	Heart failure NOS
G58z.11	Weak heart
G58z.12	Cardiac failure NOS
G5y4z00	Post cardiac operation heart failure NOS
G5yy900	Left ventricular systolic dysfunction
G5yyA00	Left ventricular diastolic dysfunction
G5yyD00	Left ventricular cardiac dysfunction
H54..00	Pulmonary congestion and hypostasis
H541.00	Pulmonary congestion
H541000	Chronic pulmonary oedema
H541z00	Pulmonary oedema NOS
H54z.00	Pulmonary congestion and hypostasis NOS
H584.00	Acute pulmonary oedema unspecified
H584z00	Acute pulmonary oedema NOS
R2y1000	[D]Cardiorespiratory failure
SP08400	Heart transplant failure and rejection
SP08500	Heart-lung transplant failure and rejection
SP11111	Heart failure as a complication of care
SP11200	Cardiorespiratory failure as a complication of care
TB00000	Heart transplant with complication, without blame
ZRad.00	New York Heart Assoc classification heart failure symptoms
ZV42100	[V]Heart transplanted
ZV45M00	[V]Biventricular pacemaker in situ
Stroke/TIA	
Read code	**Description**
14A7.00	H/O: CVA/stroke

14A7.11	H/O: CVA
14A7.12	H/O: stroke
14AB.00	H/O: TIA
14AB000	H/O amaurosis fugax
14AK.00	H/O: Stroke in last year
661M700	Stroke self-management plan agreed
661N700	Stroke self-management plan review
662e.00	Stroke/CVA annual review
662e.11	Stroke annual review
662M.00	Stroke monitoring
662M100	Stroke 6 month review
662M200	Stroke initial post discharge review
7P24200	Delivery of rehabilitation for stroke
8HBJ.00	Stroke / transient ischaemic attack referral
8Hd6.00	Admission to stroke unit
8HHM.00	Ref to multidisciplinary stroke function improvement service
8HTQ.00	Referral to stroke clinic
9N0p.00	Seen in stroke clinic
F423600	Amaurosis fugax
Fyu5500	[X]Other transnt cerebral ischaemic attacks+related syndroms
Fyu5600	[X]Other lacunar syndromes
G60..00	Subarachnoid haemorrhage
G600.00	Ruptured berry aneurysm
G601.00	Subarachnoid haemorrhage from carotid siphon and bifurcation
G602.00	Subarachnoid haemorrhage from middle cerebral artery
G603.00	Subarachnoid haemorrhage from anterior communicating artery
G604.00	Subarachnoid haemorrhage from posterior communicating artery
G605.00	Subarachnoid haemorrhage from basilar artery
G606.00	Subarachnoid haemorrhage from vertebral artery
G60X.00	Subarachnoid haemorrh from intracranial artery, unspecif
G60z.00	Subarachnoid haemorrhage NOS
G61..00	Intracerebral haemorrhage
G61..11	CVA - cerebrovascular accid due to intracerebral haemorrhage
G61..12	Stroke due to intracerebral haemorrhage
G610.00	Cortical haemorrhage
G611.00	Internal capsule haemorrhage
G612.00	Basal nucleus haemorrhage
G613.00	Cerebellar haemorrhage
G614.00	Pontine haemorrhage
G615.00	Bulbar haemorrhage
G616.00	External capsule haemorrhage
G617.00	Intracerebral haemorrhage, intraventricular

G618.00	Intracerebral haemorrhage, multiple localized
G619.00	Lobar cerebral haemorrhage
G61X.00	Intracerebral haemorrhage in hemisphere, unspecified
G61X000	Left sided intracerebral haemorrhage, unspecified
G61X100	Right sided intracerebral haemorrhage, unspecified
G61z.00	Intracerebral haemorrhage NOS
G63y000	Cerebral infarct due to thrombosis of precerebral arteries
G63y100	Cerebral infarction due to embolism of precerebral arteries
G64..00	Cerebral arterial occlusion
G64..11	CVA - cerebral artery occlusion
G64..12	Infarction - cerebral
G64..13	Stroke due to cerebral arterial occlusion
G640.00	Cerebral thrombosis
G640000	Cerebral infarction due to thrombosis of cerebral arteries
G641.00	Cerebral embolism
G641.11	Cerebral embolus
G641000	Cerebral infarction due to embolism of cerebral arteries
G64z.00	Cerebral infarction NOS
G64z.11	Brainstem infarction NOS
G64z.12	Cerebellar infarction
G64z000	Brainstem infarction
G64z100	Wallenberg syndrome
G64z111	Lateral medullary syndrome
G64z200	Left sided cerebral infarction
G64z300	Right sided cerebral infarction
G64z400	Infarction of basal ganglia
G65..00	Transient cerebral ischaemia
G65..11	Drop attack
G65..12	Transient ischaemic attack
G65..13	Vertebro-basilar insufficiency
G650.00	Basilar artery syndrome
G650.11	Insufficiency - basilar artery
G651.00	Vertebral artery syndrome
G651000	Vertebro-basilar artery syndrome
G652.00	Subclavian steal syndrome
G653.00	Carotid artery syndrome hemispheric
G654.00	Multiple and bilateral precerebral artery syndromes
G655.00	Transient global amnesia
G656.00	Vertebrobasilar insufficiency
G657.00	Carotid territory transient ischaemic attack
G65y.00	Other transient cerebral ischaemia
G65z.00	Transient cerebral ischaemia NOS

G65z000	Impending cerebral ischaemia
G65z100	Intermittent cerebral ischaemia
G65zz00	Transient cerebral ischaemia NOS
G66..00	Stroke and cerebrovascular accident unspecified
G66..11	CVA unspecified
G66..12	Stroke unspecified
G66..13	CVA - Cerebrovascular accident unspecified
G660.00	Middle cerebral artery syndrome
G661.00	Anterior cerebral artery syndrome
G662.00	Posterior cerebral artery syndrome
G663.00	Brain stem stroke syndrome
G664.00	Cerebellar stroke syndrome
G665.00	Pure motor lacunar syndrome
G666.00	Pure sensory lacunar syndrome
G667.00	Left sided CVA
G668.00	Right sided CVA
G676000	Cereb infarct due cerebral venous thrombosis, nonpyogenic
G6W..00	Cereb infarct due unsp occlus/stenos precerebr arteries
G6X..00	Cerebrl infarctn due/unspcf occlusn or sten/cerebrl artrs
Gyu6000	[X]Subarachnoid haemorrhage from other intracranial arteries
Gyu6100	[X]Other subarachnoid haemorrhage
Gyu6200	[X]Other intracerebral haemorrhage
Gyu6300	[X]Cerebrl infarctn due/unspcf occlusn or sten/cerebrl artrs
Gyu6400	[X]Other cerebral infarction
Gyu6500	[X]Occlusion and stenosis of other precerebral arteries
Gyu6600	[X]Occlusion and stenosis of other cerebral arteries
Gyu6E00	[X]Subarachnoid haemorrh from intracranial artery, unspecif
Gyu6F00	[X]Intracerebral haemorrhage in hemisphere, unspecified
Gyu6G00	[X]Cereb infarct due unsp occlus/stenos precerebr arteries
ZLEP.00	Discharge from stroke serv
ZV12511	[V]Personal history of stroke
ZV12512	[V]Personal history of cerebrovascular accident (CVA)
ZV12D00	[V]Personal history of transient ischaemic attack
Hypertension	
Read code	**Description**
14A2.00	H/O: hypertension
661M600	Hypertension self-management plan agreed
661N600	Hypertension self-management plan review
6627	Good hypertension control
6628	Poor hypertension control
6629	Hypertension:follow-up default
662b.00	Moderate hypertension control

662c.00	Hypertension six month review
662d.00	Hypertension annual review
662F.00	Hypertension treatm. started
662G.00	Hypertensive treatm.changed
662H.00	Hypertension treatm.stopped
662O.00	On treatment for hypertension
662P.00	Hypertension monitoring
662P000	Hypertension 9 month review
662P100	Telehealth hypertension monitoring
662q.00	Trial reduction of antihypertensive therapy
662r.00	Trial withdrawal of antihypertensive therapy
66b2.00	Hypertension monitoring not required
8B26.00	Antihypertensive therapy
8BL0.00	Patient on maximal tolerated antihypertensive therapy
8CR4.00	Hypertension clinical management plan
8I3N.00	Hypertension treatment refused
8IA5.00	Trial withdrawal of antihypertensive therapy declined
8IA6.00	Trial reduction of antihypertensive therapy declined
G2...00	Hypertensive disease
G2...11	BP - hypertensive disease
G20..00	Essential hypertension
G20..11	High blood pressure
G20..12	Primary hypertension
G200.00	Malignant essential hypertension
G201.00	Benign essential hypertension
G202.00	Systolic hypertension
G203.00	Diastolic hypertension
G20z.00	Essential hypertension NOS
G20z.11	Hypertension NOS
G21..00	Hypertensive heart disease
G210.00	Malignant hypertensive heart disease
G210000	Malignant hypertensive heart disease without CCF
G210100	Malignant hypertensive heart disease with CCF
G210z00	Malignant hypertensive heart disease NOS
G211.00	Benign hypertensive heart disease
G211000	Benign hypertensive heart disease without CCF
G211100	Benign hypertensive heart disease with CCF
G211z00	Benign hypertensive heart disease NOS
G21z.00	Hypertensive heart disease NOS
G21z000	Hypertensive heart disease NOS without CCF
G21z011	Cardiomegaly - hypertensive
G21z100	Hypertensive heart disease NOS with CCF

G21zz00	Hypertensive heart disease NOS
G22..00	Hypertensive renal disease
G22..11	Nephrosclerosis
G220.00	Malignant hypertensive renal disease
G221.00	Benign hypertensive renal disease
G222.00	Hypertensive renal disease with renal failure
G22z.00	Hypertensive renal disease NOS
G22z.11	Renal hypertension
G23..00	Hypertensive heart and renal disease
G230.00	Malignant hypertensive heart and renal disease
G231.00	Benign hypertensive heart and renal disease
G232.00	Hypertensive heart&renal dis wth (congestive) heart failure
G233.00	Hypertensive heart and renal disease with renal failure
G234.00	Hyperten heart&renal dis+both(congestv)heart and renal fail
G23z.00	Hypertensive heart and renal disease NOS
G24..00	Secondary hypertension
G240.00	Secondary malignant hypertension
G240000	Secondary malignant renovascular hypertension
G240z00	Secondary malignant hypertension NOS
G241.00	Secondary benign hypertension
G241000	Secondary benign renovascular hypertension
G241z00	Secondary benign hypertension NOS
G244.00	Hypertension secondary to endocrine disorders
G24z.00	Secondary hypertension NOS
G24z000	Secondary renovascular hypertension NOS
G24z100	Hypertension secondary to drug
G24zz00	Secondary hypertension NOS
G25..00	Stage 1 hypertension (NICE - Nat Ins for Hth Clin Excl 2011)
G25..11	Stage 1 hypertension
G250.00	Stage 1 hyperten (NICE 2011) without evidnce end organ damge
G251.00	Stage 1 hyperten (NICE 2011) with evidnce end organ damge
G26..00	Severe hypertension (Nat Inst for Health Clinical Ex 2011)
G26..11	Severe hypertension
G27..00	Hypertension resistant to drug therapy
G28..00	Stage 2 hypertension (NICE - Nat Ins for Hth Clin Excl 2011)
G2y..00	Other specified hypertensive disease
G2z..00	Hypertensive disease NOS
Gyu2.00	[X]Hypertensive diseases
Gyu2000	[X]Other secondary hypertension
Gyu2100	[X]Hypertension secondary to other renal disorders
Type 2 diabetes	
Read codes	Description

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	Diabetic diet - poor compliance
66AA.11	Injection sites - diabetic
66Ab.00	Diabetic foot examination
66AB.00	Urine sugar charts
66Ac.00	Diabetic peripheral neuropathy screening
66AC.00	Blood sugar charts
66aD.00	X-ray evidence of poor mineralisation
66Ad.00	Hypoglycaemic attack requiring 3rd party assistance
66AD.00	Fundoscopy - diabetic check
66Ad000	Hypo atck - atndn ambulan crew
66Ae.00	HBA1c target
66Ae000	HbA1c target level - IFCC standardised
66Af.00	Patient diabetes education review
66Ag.00	Insulin needles changed daily
66AG.00	Diabetic drug side effects
66Ah.00	Insulin needles changed for each injection
66AH.00	Diabetic treatment changed
66AH000	Conversion to insulin
66AH100	Conversion to insulin in secondary care
66AH200	Conversion to insulin by diabetes specialist nurse
66AH300	Conversion to non-insulin injectable medication
66Ai.00	Diabetic 6 month review
66AI.00	Diabetic - good control
66Aj.00	Insulin needles changed less than once a day
66AJ.00	Diabetic - poor control
66AJ.11	Unstable diabetes
66AJ000	Chronic hyperglycaemia
66AJ100	Brittle diabetes
66AJ200	Loss of hypoglycaemic warning
66AJ300	Recurrent severe hypos

66AJ400	Hypoglycaemic warning absent
66AJz00	Diabetic - poor control NOS
66Ak.00	Diabetic monitoring - lower risk albumin excretion
66AK.00	Diabetic - cooperative patient
66Al.00	Diabetic monitoring - higher risk albumin excretion
66AL.00	Diabetic-uncooperative patient
66Am.00	Insulin dose changed
66AM.00	Diabetic - follow-up default
66AN.00	Date diabetic treatment start
66Ao.00	Diabetes type 2 review
66AO.00	Date diabetic treatment stopp.
66Ap.00	Insulin treatment initiated
66AP.00	Diabetes: practice programme
66Aq.00	Diabetic foot screen
66AQ.00	Diabetes: shared care programme
66AQ000	Unsuitable for diabetes year of care programme
66AQ100	Declined consent for diabetes year of care programme
66Ar.00	Insulin treatment stopped
66AR.00	Diabetes management plan given
66As.00	Diabetic on subcutaneous treatment
66AS.00	Diabetic annual review
66AS000	Diabetes Year of Care annual review
66At.00	Diabetic dietary review
66AT.00	Annual diabetic blood test
66At000	Type I diabetic dietary review
66At100	Type II diabetic dietary review
66At111	Type 2 diabetic dietary review
66Au.00	Diabetic erectile dysfunction review
66AU.00	Diabetes care by hospital only
66Av.00	Diabetic assessment of erectile dysfunction
66AV.00	Diabetic on insulin and oral treatment
66Aw.00	Insulin dose
66AW.00	Diabetic foot risk assessment
66Ax.00	Checking accuracy of blood glucose meter
66AX.00	Diabetes: shared care in pregnancy - diabetol and obstet
66AY.00	Diabetic diet - good compliance
66Az.00	High risk of diabetes mellitus annual review
66AZ.00	Diabetic monitoring NOS
66o2.00	Diabetic on non-insulin injectable medication
66o5.00	Diabetic on oral treatment and glucagon-like peptide 1
C100112	Non-insulin dependent diabetes mellitus
C107400	NIDDM with peripheral circulatory disorder

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 comps
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 complications
C109112	Type 2 diabetes mellitus with ophthalmic complications
C109200	Non-insulin-dependent diabetes mellitus with neuro comps
C109211	Type II diabetes mellitus with neurological complications
C109212	Type 2 diabetes mellitus with neurological complications
C109300	Non-insulin-dependent diabetes mellitus with multiple comps
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 retinopathy
C109611	Type II diabetes mellitus with retinopathy
C109612	Type 2 diabetes mellitus with retinopathy
C109700	Non-insulin dependent 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 complication
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 nephropathy
C109C11	Type II diabetes mellitus with nephropathy
C109C12	Type 2 diabetes mellitus with nephropathy
C109D00	Non-insulin dependent diabetes mellitus with hypoglyca coma
C109D11	Type II diabetes mellitus with hypoglycaemic coma

C109D12	Type 2 diabetes mellitus with hypoglycaemic coma
C109E00	Non-insulin depend diabetes mellitus with diabetic cataract
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 angiopathy
C109F12	Type 2 diabetes mellitus with peripheral angiopathy
C109G00	Non-insulin dependent diabetes mellitus with arthropathy
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
C10F.00	Type 2 diabetes mellitus
C10F.11	Type II diabetes mellitus
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
C10FS00	Maternally inherited diabetes mellitus
C10P100	Type II diabetes mellitus in remission
C10P111	Type 2 diabetes mellitus in remission
L180600	Pre-existing diabetes mellitus, non-insulin-dependent
ZC2CA00	Dietary advice for type II diabetes
ZC2CA11	Dietary advice non-insulin-dependent diabetes

2. Annual incidence of ischaemic heart disease and angina in males and females (16-50 years): 1998-2017

Annual prevalence and incidence rate were calculated for eligible males and females separately, and separately for each cardiovascular disease. Annual point prevalence (1998 - 2017) was estimated as the number of eligible adults with any record ever of the cardiovascular condition of interest on 1st January each year divided by the total number of eligible adults at the same time point each year. Prevalence was expressed per 100,000 population. For each cardiovascular condition of interest, the annual crude incidence rate (per 100,000 person-years) was calculated as the number of newly diagnosed cases (numerator), divided by the total number of person-years at risk for each calendar year (denominator). Person-years follow up was defined as the exit date minus the entry date. The entry date was defined as latest of: 16th birthday, one year after the patient joined an eligible practice, or study start date. The exit date was defined as the earliest of: outcome date (date of diagnosis of CVD), age 50 years (patients were censored once they reached 50 years of age), death date, transfer date (when the patient was transferred out of practice), collection date (the last date the practice contributed to THIN data), or 31st December each year.

The computation of incidence and prevalence was performed using Stata SE version 16.1.

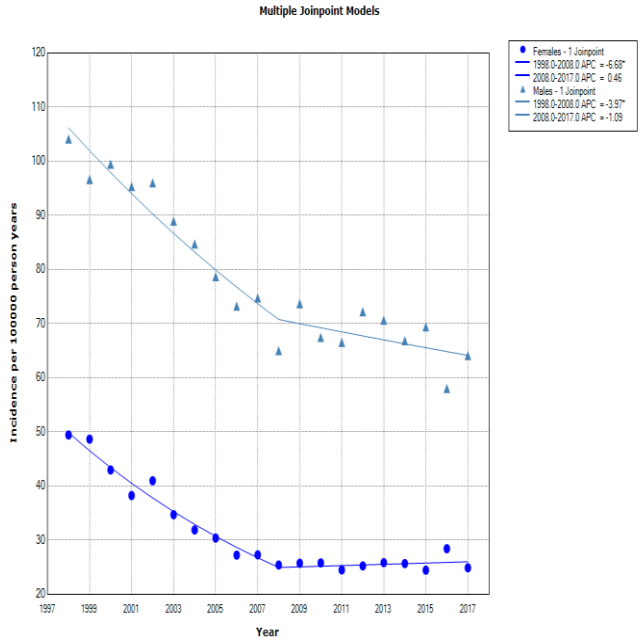
3. Joinpoint analyses for incidence trends of cardiovascular disease

The changes in incidence and prevalence trend over time were analysed using the Joinpoint regression software programme (V.4.8.0.1, April 2020, Statistical Research and Application Branch, National Cancer Institute).[115] Joinpoint software takes the trend data and fits the simplest model that the data allow.[115] Given the study period (20 data points), we restricted the model to a maximum of three joinpoints (four segments) as recommended in the software's manual.[116] The minimum number of observations from a joinpoint to either end of the data was set at three, while the minimum number of observations between joinpoints was set at four. The programme begins with a minimum of zero joinpoints (a single straight line on the log scale) representing no change in trend and tests whether additional joinpoints are statistically significant and should be added to the model. The joinpoints represent years (independent variable) where a statistically significant change in magnitude or direction in linear trends occurs. Additional joinpoints connect a series of straight lines (segments) on the log scale. Bayesian information criterion was used to identify the optimal model that fitted the data best. The programme calculates annual percentage change (APC) and the corresponding 95% confidence interval (95% CI) for any identified segment to estimate the change in slope between a preceding joinpoint and the next.[117] The rate of change in slope for the entire study period (1997-2018) was summarised by the average APC (AAPC) and 95% CI to facilitate the comparison of trends between men and women.[118] For each trend analysis, AAPC was calculated as the geometrically weighted average of each segment's APCs.[118] The weights are proportional to the length of each linear segment. Trends were interpreted to be stable if the 95% confidence interval crossed zero; otherwise, the term statistically significant was used.

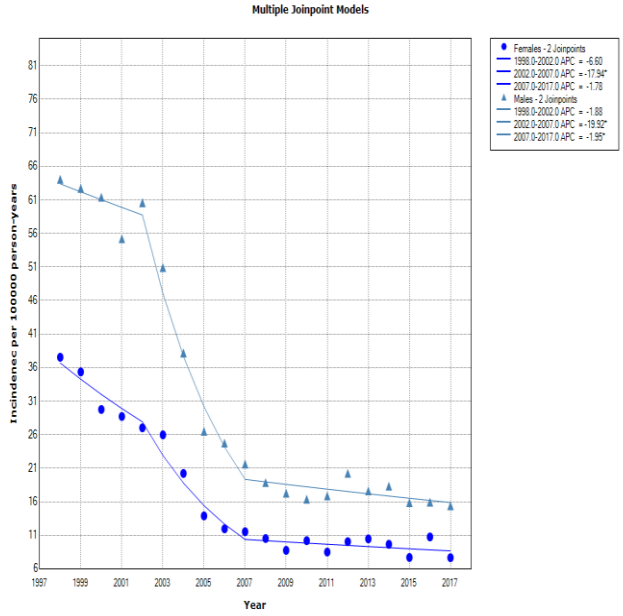
Supplemental Table S3.1: Annual incidence of ischaemic heart disease and angina in males and females (16-50 years): 1998-2017

	Male Cohort	Female cohort	Male IHD			Females IHD			Male Angina			Female Angina		
Year	Mean age in years	Mean age in years	Incident cases	Person-years	Incidence per 100000 person-years	Incident cases	Person-years	Incidence per 100000 person-years	Incident cases	Person-years	Incidence per 100000 person-years	Incident cases	Person-years	Incidence per 100000 person-years
1998	33.7	33.8	209	200814.5	104.1	96	194268.2	49.4	129	201318.3	64.1	73	194445.7	37.5
1999	33.6	33.7	272	281510.3	96.6	132	271346.5	48.6	177	282163.2	62.7	96	271561.3	35.4
2000	33.6	33.8	362	364035.3	99.4	150	349231.9	43.0	224	364869.2	61.4	104	349487.2	29.8
2001	33.6	33.8	503	527690.9	95.3	193	504659.7	38.2	292	528915.3	55.2	145	505001.2	28.7
2002	33.6	33.8	637	663667.4	96.0	259	632264.6	41.0	403	665213.3	60.6	171	632691.1	27.0
2003	33.6	33.8	709	797381.6	88.9	263	758022.1	34.7	407	799247	50.9	197	758531.4	26.0
2004	33.6	33.8	728	859433.1	84.7	260	815290.6	31.9	329	861480.9	38.2	165	815819	20.2
2005	33.6	33.8	740	940550.8	78.7	271	891762.1	30.4	250	942886.8	26.5	124	892361.1	13.9
2006	33.6	33.8	729	995539.1	73.2	257	943372.3	27.2	247	998165.1	24.7	113	944032.8	12.0
2007	33.6	33.8	772	1032738	74.8	267	978356	27.3	224	1035517	21.6	113	979069.3	11.5
2008	33.6	33.8	708	1089252	65.0	263	1035107	25.4	206	1092268	18.9	109	1035913	10.5
2009	33.6	33.8	837	1135986	73.7	279	1083759	25.7	197	1139225	17.3	95	1084656	8.8
2010	33.6	33.8	759	1125650	67.4	278	1077282	25.8	185	1128932	16.4	110	1078198	10.2
2011	33.5	33.8	747	1122454	66.6	265	1081041	24.5	190	1125793	16.9	92	1081959	8.5
2012	33.5	33.7	832	1152457	72.2	281	1113390	25.2	234	1155969	20.2	112	1114367	10.1
2013	33.5	33.6	791	1119973	70.6	281	1087366	25.8	198	1123464	17.6	114	1088323	10.5
2014	33.5	33.6	698	1044478	66.8	260	1012812	25.7	192	1047723	18.3	98	1013724	9.7
2015	33.4	33.5	640	922425.1	69.4	219	895464.4	24.5	147	925298.8	15.9	69	896271	7.7
2016	33.3	33.5	460	792950.7	58.0	219	770430.9	28.4	127	795443.7	16.0	83	771147.3	10.8
2017	33.3	33.4	456	711298.2	64.1	172	690627.9	24.9	110	713497.4	15.4	53	691275.2	7.7

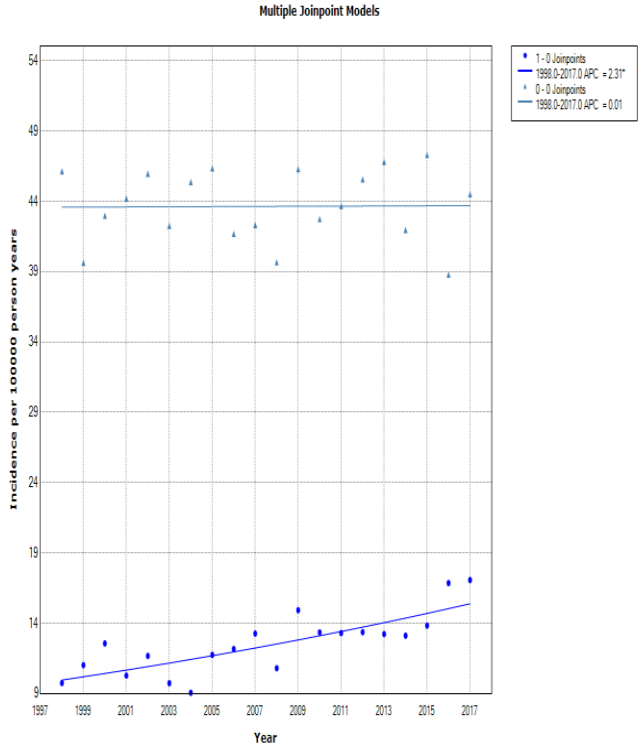
A


Multiple Joinpoint Models
Females - 1 Joinpoint
1998.0-2008.0 APC = -6.68*
2008.0-2017.0 APC = 0.46
Males - 1 Joinpoint
1998.0-2008.0 APC = -3.97*
2008.0-2017.0 APC = -1.09
Incidence per 100000 person years
Year

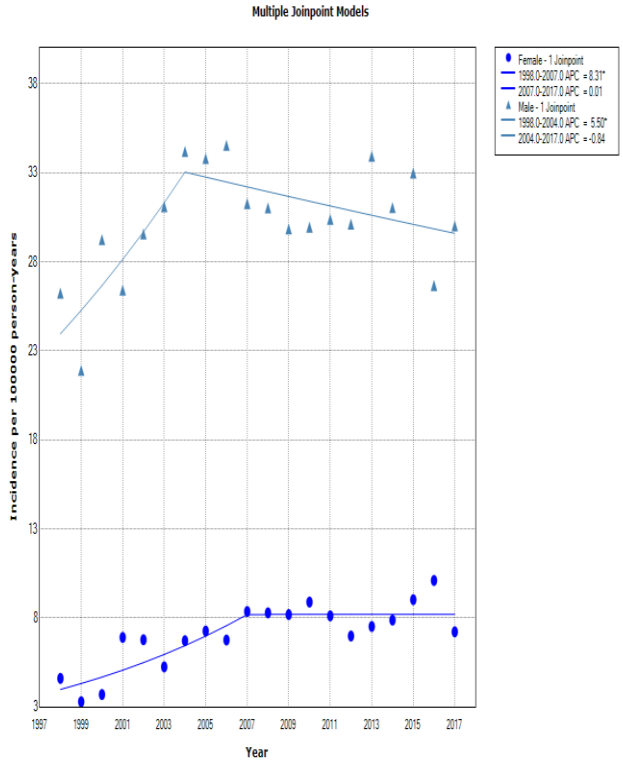
B

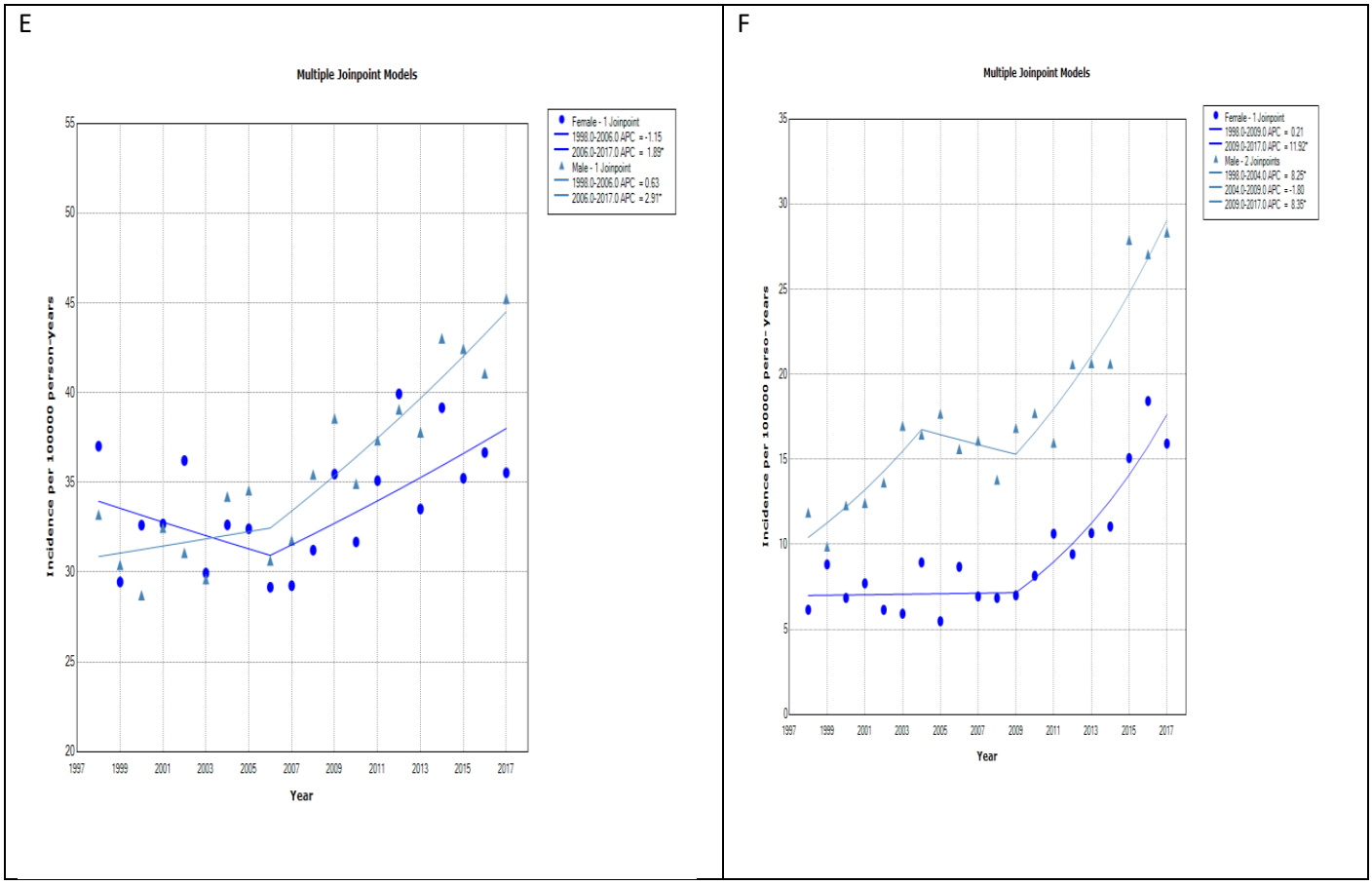

Multiple Joinpoints Models
Females - 2 Joinpoints
1998.0-2002.0 APC = -6.60
2002.0-2007.0 APC = -17.94*
2007.0-2017.0 APC = -1.78
Males - 2 Joinpoints
1998.0-2002.0 APC = -1.88
2002.0-2007.0 APC = -19.92*
2007.0-2017.0 APC = -1.95*
Incindenec per 100000 person-years
Year

C


Multiple Joinpoint Models
1 - 0 Joinpoints
1998.0-2017.0 APC = 2.31*
0 - 0 Joinpoints
1998.0-2017.0 APC = 0.01
Incidence per 100000 person years
Year

D


Multiple Joinpoint Models
Female - 1 Joinpoint
1998.0-2007.0 APC = 8.31*
2007.0-2017.0 APC = 0.01
Male - 1 Joinpoint
1998.0-2004.0 APC = 5.50*
2004.0-2017.0 APC = -0.84
Incidence per 100000 person-years
Year



Supplemental Figure S3.1: **Joinpoint regression analysis of trends in incidence of cardiovascular disease in young adults. A = ischaemic heart disease, B = Angina, C = Myocardial infarction, D = Coronary artery bypass graft (CABG)/percutaneous coronary intervention (PCI) procedures, E = Stroke/transient ischemic attack, F = Heart failure**.

Supplemental Table S3.2: Annual percentage change (APC) in the incidence of cardiovascular disease in UK adults (16-50 years), 1998-2017

Incidence trends		Period 1			Period 2			Period 3		
		Year	APC	95% CI	Year	APC	95% CI	Year	APC	95% CI
IHD	Male	1998-2008	-4*	-5.1 to -2.9	2008-2017	-1.1	-2.4 to 0.2			
	Female	1998-2008	-6.7*	-7.7 to -5.7	2008-2017	0.5	-0.8 to 1.7			
Angina	Male	1998-2002	-1.9	-8.9 to 5.7	2002-2007	-19.9*	-25.6 to -13.8	2007-2017	-1.9*	-3.7 to -0.1
	Female	1998-2002	-6.6	-16.1 to 4	2002-2007	-17.9*	-26.3 to -8.6	2007-2017	-1.8	-4.3 to 0.9
Myocardial infarction	Male	1998-2017	-0.01	-0.5 to -0.5						
	Female	1998-2017	2.3*	1.4 to 3.2						
Revascularisation procedures	Male	1998-2004	5.5*	1.5 to 9.7	2004-2017	-0.8	-2 to 0.4			
	Female	1998-2007	8.3*	3.4 to 13.5	2007-2017	0.01	-3.9 to 4.1			
Stroke/TIA	Male	1998-2006	0.6	-1.2 to 2.5	2006-2017	2.9*	1.7 to 4.1			
	Female	1998-2006	-1.2	-3.7 to 1.5	2006-2017	1.9*	0.2 to 3.6			
Heart failure	Male	1998-2004	8.3*	3.2 to 13.6	2004-2009	-1.8	-10.2 to 7.4	2009-2017	8.3*	5 to 11.8
	Female	1998-2009	0.2	-3 to 3.5	2009-2017	11.9*	6.2 to 17.9			

IHD = Ischaemic heart disease, TIA = Transient Ischaemic attack, * = $p < 0.05$

Supplemental Table S3.3: Annual incidence of myocardial infarction (MI) and revascularisation procedures (CABG/PCI) in males and females (16-50 years): 1998-2017

	Male Cohort	Female cohort	Male MI			Female MI			Male CABG/PCI			Females CABG/PCI		
Year	Mean age in years	Mean age in years	Incident cases	Person-years	Incidence per 100000 person-years	Incident cases	Person-years	Incidence per 100000 person-years	Incident cases	Person-years	Incidence per 100000 person-years	Incident cases	Person-years	Incidence per 100000 person-years
1998	33.7	33.8	93	201583.4	46.1	19	194809.9	9.8	53	201964.8	26.2	9	194874.4	4.6
1999	33.6	33.7	112	282551.2	39.6	30	272030.7	11.0	62	283006.5	21.9	9	272116.6	3.3
2000	33.6	33.8	157	365293.2	43.0	44	350055.2	12.6	107	365826.7	29.2	13	350171.4	3.7
2001	33.6	33.8	234	529348.2	44.2	52	505635.8	10.3	140	530023.9	26.4	35	505790.5	6.9
2002	33.6	33.8	306	665706.3	46.0	74	633420.2	11.7	197	666526.3	29.6	43	633605.3	6.9
2003	33.6	33.8	338	799746.7	42.3	74	759308.4	9.7	249	800703.5	31.1	40	759545.3	5.3
2004	33.6	33.8	391	861830.4	45.4	74	816590.9	9.1	295	862819.6	34.2	55	816827.6	6.7
2005	33.6	33.8	437	942966.9	46.3	105	893068.6	11.8	319	943962.8	33.8	65	893326.4	7.3
2006	33.6	33.8	416	997945.8	41.7	115	944653.7	12.1	345	998983.6	34.5	64	944919.2	6.8
2007	33.6	33.8	438	1035085	42.3	130	979539	13.3	324	1036083	31.3	82	979828.2	8.4
2008	33.6	33.8	433	1091545	40.0	112	1036294	10.8	339	1092620	31.0	86	1036590	8.3
2009	33.6	33.8	527	1138166	46.3	162	1084859	14.9	340	1139275	29.8	89	1085176	8.2
2010	33.6	33.8	482	1127674	42.7	144	1078280	13.4	338	1128769	29.9	96	1078607	8.9
2011	33.5	33.8	491	1124347	43.7	144	1081963	13.3	342	1125468	30.4	88	1082286	8.1
2012	33.5	33.7	526	1154331	45.6	149	1114305	13.4	348	1155539	30.1	78	1114641	7.0
2013	33.5	33.6	525	1121720	46.8	144	1088196	13.2	381	1122936	34.0	82	1088545	7.5
2014	33.5	33.6	439	1046016	42.0	133	1013543	13.1	325	1047077	31.0	80	1013874	7.9
2015	33.4	33.5	437	923708.7	47.3	124	896063.3	13.8	305	924634.7	33.0	81	896361.5	9.0
2016	33.3	33.5	308	794030.3	38.8	130	770913.8	16.9	212	794835.2	26.7	78	771189.3	10.1
2017	33.3	33.4	317	712196.9	44.5	118	691026.2	17.1	214	712888.9	30.0	50	691269.7	7.2

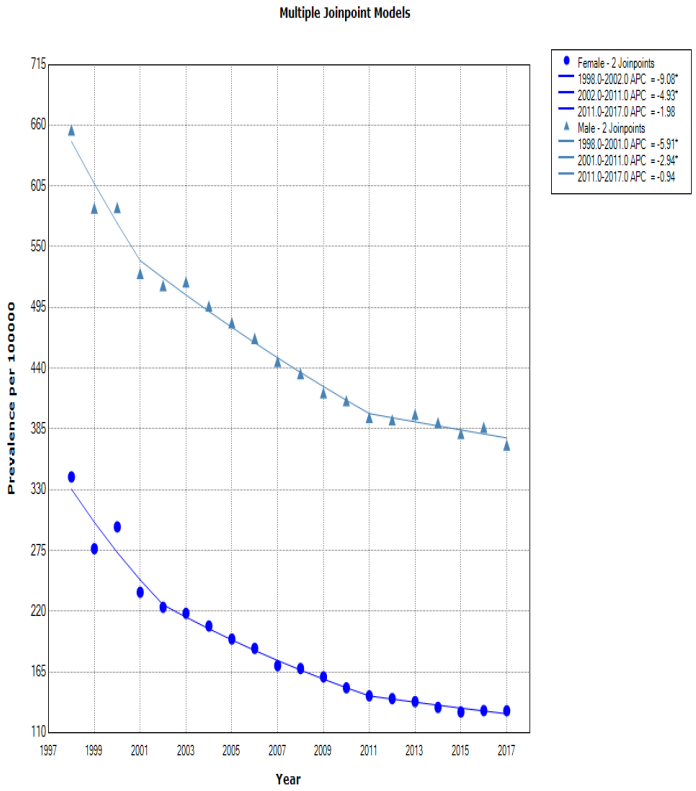
Supplemental Table S3.4: Annual incidence of stroke/transient ischaemic attack (TIA) and heart failure (HF) in males and females (16-50 years): 1998-2017

	Male Cohort	**Female cohort**	Male Stroke/TIA			Female Stroke/TIA			Male HF			Females HF		
Year	**Mean age in years**	**Mean age in years**	Incident cases	Person-years	Incidence per 100000 person-years	Incident cases	Person-years	Incidence per 100000 person-years	Incident cases	Person-years	Incidence per 100000 person-years	Incident cases	Person-years	Incidence per 100000 person-years
1998	33.7	33.8	67	201733.8	33.2	72	194519.7	37.0	24	202036	11.9	12	194802.8	6.2
1999	33.6	33.7	86	282715.9	30.4	80	271590.2	29.5	28	283097.9	9.9	24	272021.7	8.8
2000	33.6	33.8	105	365493.7	28.7	114	349477.6	32.6	45	365973.9	12.3	24	350053.4	6.9
2001	33.6	33.8	172	529545.4	32.5	165	504770.1	32.7	66	530270.3	12.4	39	505612.1	7.7
2002	33.6	33.8	207	665947.5	31.1	229	632291.8	36.2	91	666859.7	13.6	39	633378.2	6.2
2003	33.6	33.8	237	800013.1	29.6	227	757916.3	29.6	136	801092.3	17.0	45	759284.6	5.9
2004	33.6	33.8	295	862088.3	34.2	266	815069.6	32.6	142	863218.9	16.4	73	816531.9	8.9
2005	33.6	33.8	326	943190.1	34.6	289	891408.3	32.4	167	944444.3	17.6	49	893019.8	5.5
2006	33.6	33.8	306	998174.5	30.7	275	942886.3	29.2	156	999473.6	15.6	82	944580	8.9
2007	33.6	33.8	329	1035264	31.8	286	977704.9	29.3	167	1036573	16.1	68	979495.2	6.9
2008	33.6	33.8	387	1091724	35.4	323	1034369	31.2	151	1093103	13.8	71	1036266	6.8
2009	33.6	33.8	439	1138301	38.7	384	1082788	35.5	192	1139813	16.8	76	1084866	7.0
2010	33.6	33.8	394	1127754	34.9	341	1076225	31.7	200	1129285	17.7	88	1078287	8.2
2011	33.5	33.8	420	1124343	37.4	379	1079845	35.1	180	1125919	16.0	115	1081941	10.6
2012	33.5	33.7	451	1154300	39.1	444	1112021	39.9	238	1155925	20.6	105	1114265	9.4
2013	33.5	33.6	424	1121692	37.8	364	1085886	33.5	232	1123278	20.7	116	1088136	10.6
2014	33.5	33.6	450	1045869	43.0	396	1011373	39.2	216	1047380	20.6	112	1013435	11.1
2015	33.4	33.5	392	923439.2	42.4	315	894099.2	35.2	258	924784.4	27.9	135	895918.6	15.1
2016	33.3	33.5	326	793745.6	41.1	282	769177.9	36.7	215	794842.1	27.0	142	770768.9	18.4
2017	33.3	33.4	322	711840.4	45.2	245	689467.6	35.5	202	712835.2	28.3	110	690891.7	15.9

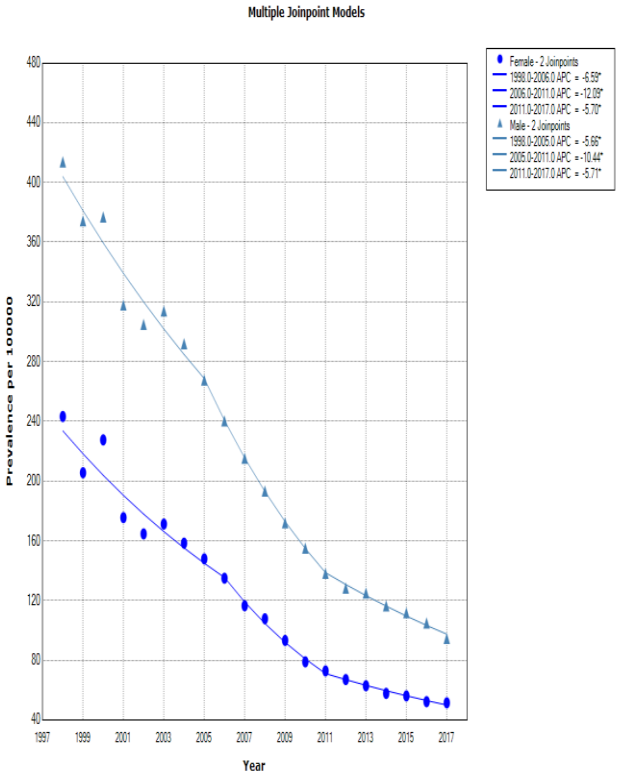
Supplemental Table S3.5: Annual prevalence of ischaemic heart disease and angina in males and females (16-50 years): 1998-2017

	Male Cohort	Female cohort	Male IHD			Female IHD			Male Angina			Female Angina		
Year	Mean age in years	Mean age in years	Prevalent cases	Total population	Prevalence per 100000 population	Prevalent cases	Total population	Prevalence per 100000 population	Prevalent cases	Total population	Prevalence per 10000 population	Prevalent cases	Total population	Prevalence per 10,000 population
1998	34.4	34.6	1054	160714	655.8	535	156630	341.6	665	160714	413.8	381	156630	243.3
1999	34.3	34.5	1499	256219	585.0	682	246598	276.6	959	256219	374.3	507	246598	205.6
2000	34.3	34.5	1870	319394	585.5	909	306733	296.3	1204	319394	377.0	698	306733	227.6
2001	34.2	34.5	2577	490051	525.9	1109	467696	237.1	1558	490051	317.9	821	467696	175.5
2002	34.3	34.6	3060	594243	514.9	1260	563755	223.5	1812	594243	304.9	928	563755	164.6
2003	34.3	34.6	3847	742387	518.2	1536	704436	218.0	2331	742387	314.0	1206	704436	171.2
2004	34.3	34.6	4117	829457	496.3	1622	785251	206.6	2422	829457	292.0	1244	785251	158.4
2005	34.3	34.6	4280	889274	481.3	1637	840414	194.8	2381	889274	267.7	1243	840414	147.9
2006	34.3	34.6	4560	976248	467.1	1719	922729	186.2	2346	976248	240.3	1245	922729	134.9
2007	34.3	34.6	4530	1015096	446.3	1637	958980	170.7	2186	1015096	215.3	1117	958980	116.5
2008	34.3	34.6	4586	1053888	435.1	1672	994539	168.1	2037	1053888	193.3	1072	994539	107.8
2009	34.3	34.6	4675	1119061	417.8	1707	1063695	160.5	1925	1119061	172.0	992	1063695	93.3
2010	34.3	34.6	4639	1129760	410.6	1622	1076777	150.6	1752	1129760	155.1	850	1076777	78.9
2011	34.2	34.6	4410	1114980	395.5	1529	1066644	143.3	1541	1114980	138.2	777	1066644	72.9
2012	34.2	34.5	4419	1123567	393.3	1524	1082059	140.8	1442	1123567	128.3	726	1082059	67.1
2013	34.1	34.4	4556	1143787	398.3	1526	1104362	138.1	1431	1143787	125.1	695	1104362	62.9
2014	34.1	34.4	4165	1065853	390.8	1371	1031610	132.9	1242	1065853	116.5	596	1031610	57.8
2015	34.0	34.3	3765	988331	380.9	1232	956722	128.8	1105	988331	111.8	537	956722	56.1
2016	33.9	34.2	3200	827733	386.6	1042	801646	130.0	869	827733	105.0	419	801646	52.3
2017	33.9	34.1	2777	749361	370.5	943	726315	129.8	709	749361	94.6	374	726315	51.5

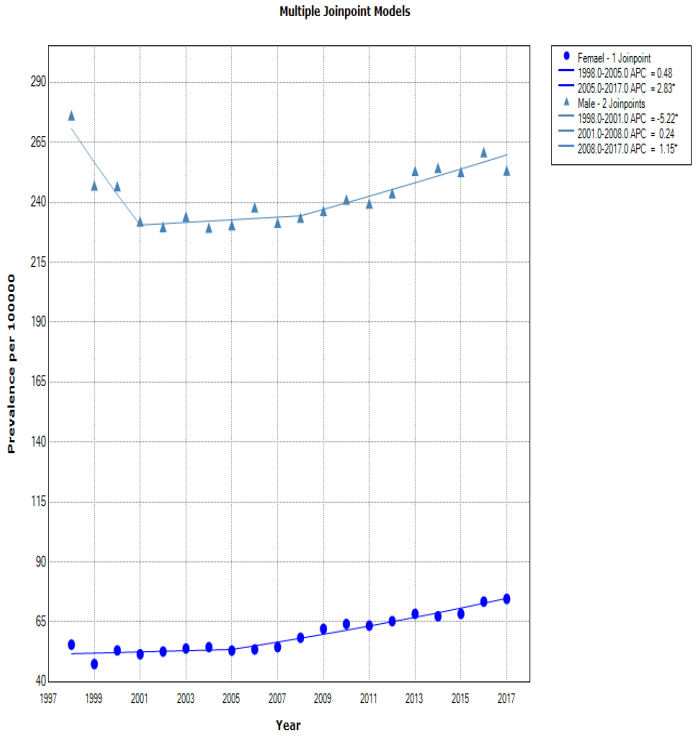
A


Multiple Joinpoint Models
Female - 2 Joinpoints
1998.0-2002.0 APC = -9.08*
2002.0-2011.0 APC = -4.93*
2011.0-2017.0 APC = -1.98
Male - 2 Joinpoints
1998.0-2001.0 APC = -5.91*
2001.0-2011.0 APC = -2.94*
2011.0-2017.0 APC = -0.94
Prevalence per 100000
Year

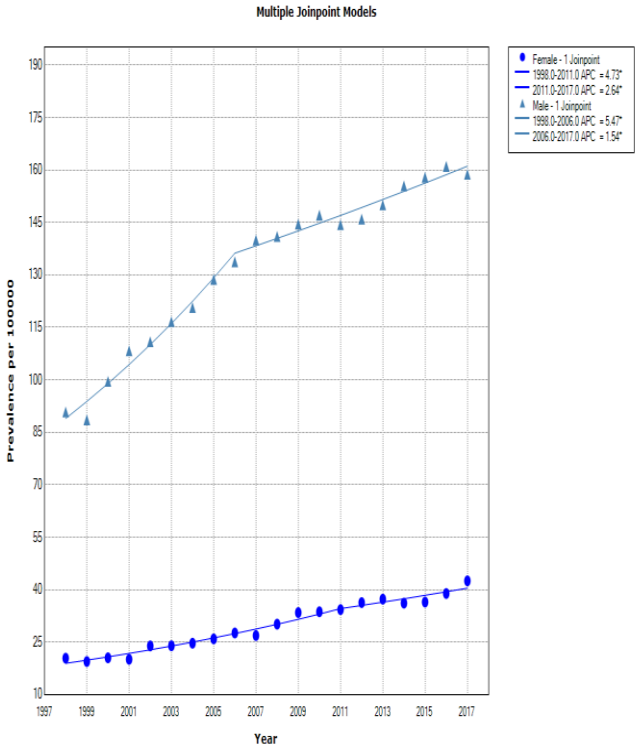
B


Multiple Joinpoint Models
Female - 2 Joinpoints
1998.0-2006.0 APC = -6.59*
2006.0-2011.0 APC = -12.09*
2011.0-2017.0 APC = -5.70*
Male - 2 Joinpoints
1998.0-2006.0 APC = -5.66*
2006.0-2011.0 APC = -10.44*
2011.0-2017.0 APC = -5.71*
Prevalence per 100000
Year

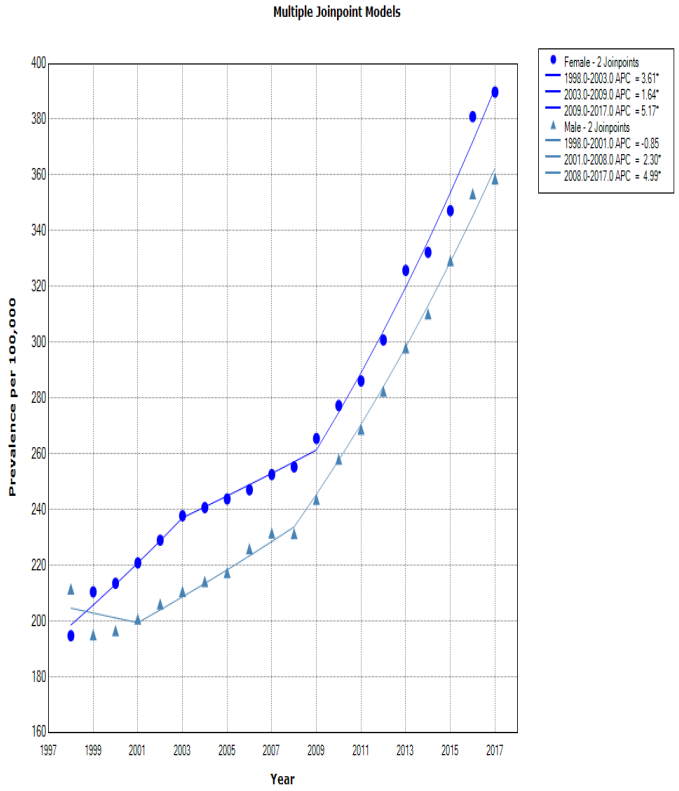
C


Multiple Joinpoint Models
Female - 1 Joinpoint
1998.0-2005.0 APC = 0.48
2005.0-2017.0 APC = 2.83*
Male - 2 Joinpoints
1998.0-2001.0 APC = -5.22*
2001.0-2008.0 APC = 0.24
2008.0-2017.0 APC = 1.15*
Prevalence per 100000
Year

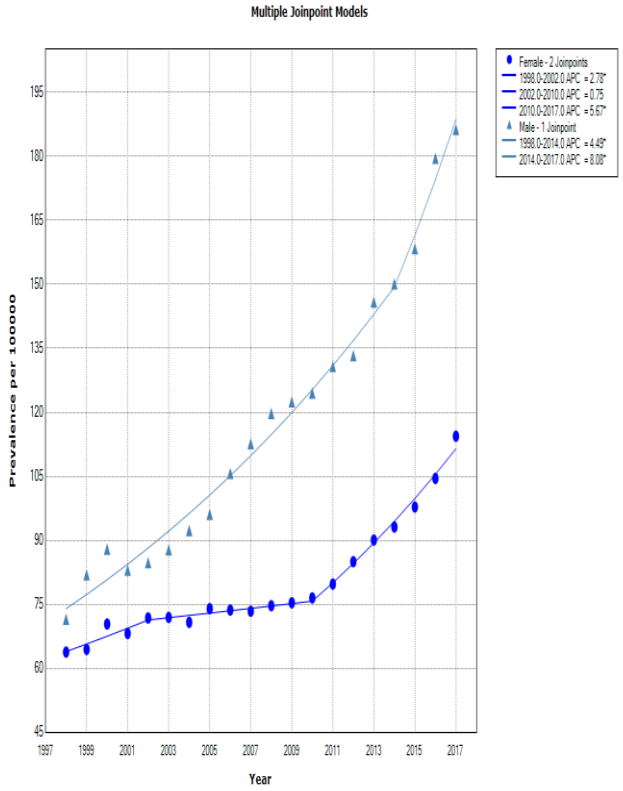
D


Multiple Joinpoint Models
Female - 1 Joinpoint
1998.0-2011.0 APC = 4.73*
2011.0-2017.0 APC = 2.64*
Male - 1 Joinpoint
1998.0-2006.0 APC = 5.47*
2006.0-2017.0 APC = 1.54*
Prevalence per 100000
Year

E



F



Supplemental Figure S3.2: Joinpoint regression analysis of trends in prevalence of cardiovascular disease in young adults. A = ischaemic heart disease, B = Angina, C = Myocardial infarction, D = Coronary artery bypass graft (CABG)/percutaneous coronary intervention (PCI) procedures, E = Stroke/transient ischemic attack, F = Heart failure

Supplemental Table S3.6: Annual percentage change (APC) in the prevalence of cardiovascular diseases in UK adults (16-50 years), 1998-2017

Prevalence trends		Period 1			Period 2			Period 3		
	Period	Year	APC	95% CI	Year	APC	95% CI	Year	APC	95% CI
IHD	Male	1998-2001	-5.9*	-8.5 to -3.2	2001-2011	-2.9*	-3.4 to -2.4	2011-2017	-0.9	-1.9 to 0
	Female	1998-2002	-9.1*	-12.5 to -5.5	2002-2011	-4.9*	-6.2 to -3.7	2011-2017	-2	-4 to 0.1
Angina	Male	1998-2005	-5.7*	-7 to -4.3	2005-2011	-10.4*	-12.5 to -8.3	2011-2017	-5.7*	-7.4 to -4
	Female	1998-2006	-6.6*	-8.3 to -4.9	2006-2011	-12.1*	-16.6 to -7.3	2011-2017	-5.7*	-8.3 to -3
Myocardial infarction	Male	1998-2001	-5.2*	-8 to -2.3	2001-2008	0.2	-0.8 to 1.3	2008-2017	1.2*	0.6 to 1.7
	Female	1998-2005	0.5	-1.1 to 2.1	2005-2017	2.8*	2.1 to 3.5			
Revasularization procedures	Male	1998-2006	5.5*	4.7 to 6.3	2006-2017	1.5*	1.1 to 2			
	Female	1998-2011	4.7*	4 to 5.5	2011-2017	2.6*	0.3 to 5			
Stroke/TIA	Male	1998-2001	-0.9	-2.9 to 1.3	2001-2008	2.3*	1.6 to 3	2008-2017	5*	4.6 to 5.4
	Female	1998-2003	3.6*	2.6 to 4.7	2003-2009	1.6*	0.6 to 2.7	2009-2017	5.2*	4.7 to 5.7
Heart failure	Male	1998-2014	4.5*	4 to 5.5	2014-2017	8.1*	1.6 to 15			
	Female	1998-2002	2.8*	0.8 to 4.8	2002-2010	0.8	-0.1 to 1.6	2010-2017	5.7*	4.8 to 6.5

IHD = Ischaemic heart disease, TIA = Transient Ischaemic attack, * = $p < 0.05$

Supplemental Table S3.7: Annual prevalence of myocardial infarction (MI) and revascularisation procedures (CABG/PCI) in males and females (16-50 years): 1998-2017

	Male Cohort	Female cohort	Male MI			Female MI			Male CABG/PCI			Female CABG/PCI		
Year	Mean age in years	Mean age in years	Prevalent cases	Total population	Prevalence per 100000 population	Prevalent cases	Total population	Prevalence per 100000 population	Prevalent cases	Total population	Prevalence per 10000 population	Prevalent cases	Total population	Prevalence per 10,000 population
1998	34.4	34.6	444	160714	276.3	87	156630	55.5	146	160714	90.8	32	156630	20.4
1999	34.3	34.5	633	256219	247.0	117	246598	47.4	227	256219	88.6	48	246598	19.5
2000	34.3	34.5	788	319394	246.7	163	306733	53.1	318	319394	99.6	63	306733	20.5
2001	34.2	34.5	1137	490051	232.0	241	467696	51.5	531	490051	108.4	94	467696	20.1
2002	34.3	34.6	1365	594243	229.7	297	563755	52.7	659	594243	110.9	135	563755	23.9
2003	34.3	34.6	1738	742387	234.1	380	704436	54.0	866	742387	116.7	169	704436	24.0
2004	34.3	34.6	1903	829457	229.4	428	785251	54.50	1001	829457	120.7	194	785251	24.7
2005	34.3	34.6	2050	889274	230.5	446	840414	53.1	1145	889274	128.8	218	840414	26.0
2006	34.3	34.6	2323	976248	237.6	494	922729	53.5	1306	976248	133.8	255	922729	27.6
2007	34.3	34.6	2350	1015096	231.5	523	958980	54.5	1421	1015096	140.0	258	958980	26.9
2008	34.3	34.6	2462	1053888	233.6	581	994539	58.4	1486	1053888	141.0	300	994539	30.2
2009	34.3	34.6	2646	1119061	236.4	661	1063695	62.1	1618	1119061	144.6	356	1063695	33.5
2010	34.3	34.6	2725	1129760	241.2	691	1076777	64.2	1662	1129760	147.1	363	1076777	33.7
2011	34.2	34.6	2671	1114980	239.6	677	1066644	63.5	1610	1114980	144.4	366	1066644	34.3
2012	34.2	34.5	2739	1123567	243.8	707	1082059	65.3	1640	1123567	146.0	393	1082059	36.3
2013	34.1	34.4	2895	1143787	253.1	755	1104362	68.4	1716	1143787	150.0	412	1104362	37.3
2014	34.1	34.4	2712	1065853	254.4	695	1031610	67.3	1657	1065853	155.5	373	1031610	36.2
2015	34.0	34.3	2497	988331	252.6	654	956722	68.4	1561	988331	157.9	349	956722	36.5
2016	33.9	34.2	2160	827733	261.0	589	801646	73.5	1333	827733	161.0	312	801646	38.9
2017	33.9	34.1	1898	749361	253.2	542	726315	74.6	1190	749361	158.8	309	726315	42.5

Supplemental Table S3.8: Annual prevalence of stroke/transient ischaemic attack (TIA) and heart failure (HF) in males and females (16-50 years): 1998-2017

	Male Cohort	Female cohort	Male stroke/TIA			Female Stroke/TIA			Male	Male H.F			Female HF		
Year	Mean age in years	Mean age in years	Prevalent cases	Total population	Prevalence per 100000 population	Prevalent cases	Total population	Prevalence per 100000 population	Year	Prevalent cases	Total population	Prevalence per 10000 population	Prevalent cases	Total population	Prevalence per 10,000 population
1998	34.4	34.6	340	160714	211.6	305	156630	194.7	1998	115	160714	71.6	100	156630	63.8
1999	34.3	34.5	500	256219	195.1	519	246598	210.4	1999	210	256219	82.0	159	246598	64.5
2000	34.3	34.5	628	319394	196.6	655	306733	213.5	2000	281	319394	88.0	216	306733	70.4
2001	34.2	34.5	984	490051	200.8	1033	467696	220.9	2001	407	490051	83.1	319	467696	68.2
2002	34.3	34.6	1225	594243	206.1	1291	563755	229.0	2002	504	594243	84.8	405	563755	71.8
2003	34.3	34.6	1564	742387	210.7	1675	704436	237.8	2003	652	742387	87.8	507	704436	72.0
2004	34.3	34.6	1777	829457	214.2	1890	785251	240.7	2004	766	829457	92.3	556	785251	70.8
2005	34.3	34.6	1934	889274	217.5	2049	840414	243.8	2005	855	889274	96.1	622	840414	74.0
2006	34.3	34.6	2206	976248	226.0	2280	922729	247.1	2006	1032	976248	105.7	680	922729	74,0
2007	34.3	34.6	2351	1015096	231.6	2422	958980	252.6	2007	1144	1015096	112.7	704	958980	73.4
2008	34.3	34.6	2439	1053888	231.4	2539	994539	255.3	2008	1262	1053888	119.7	743	994539	74.7
2009	34.3	34.6	2727	1119061	243.7	2824	1063695	265.5	2009	1371	1119061	122.5	802	1063695	75.4
2010	34.3	34.6	2916	1129760	258.1	2986	1076777	277.3	2010	1407	1129760	124.5	824	1076777	76.5
2011	34.2	34.6	2998	1114980	268.9	3052	1066644	286.1	2011	1458	1114980	130.8	851	1066644	79.8
2012	34.2	34.5	3174	1123567	282.5	3255	1082059	300.8	2012	1498	1123567	133.3	920	1082059	85.0
2013	34.1	34.4	3409	1143787	298.0	3598	1104362	325.8	2013	1668	1143787	145.8	995	1104362	90.1
2014	34.1	34.4	3307	1065853	310.2	3428	1031610	332.3	2014	1600	1065853	150.1	961	1031610	93.2
2015	34.0	34.3	3255	988331	329.3	3322	956722	347.2	2015	1565	988331	158.3	936	956722	97.8
2016	33.9	34.2	2925	827733	353.3	3054	801646	381.0	2016	1486	827733	179.5	838	801646	104.5
2017	33.9	34.1	2688	749361	358.7	2831	726315	389.8	2017	1396	749361	186.2	831	726315	114.4

Supplemental Table S3.9: Comparisons of trends with findings from existing literature

Condition	Study ID/ (Setting)	Study Objective	Source population	"Young adult" age group	Study period	Temporal trend summary	Comments
CHD Angina MI Revascularisation (CABG/PCI)	Bhattarai 2012 UK[119]	To evaluate the coding, recording and incidence of coronary heart disease In UK electronic health records.	General practise research database UK primary care data	>30 years	2000-2010	Incidence (per 100,000) CHD: -28*% in men versus -38*% in women relative rates in year 2000 Angina: -65*% in men versus women -66*% relative to rates in the year 2000 MI: +8% Men versus +15% women relative to rates in the year 2000 CABG/PCI: +2% Men versus +200% women relative to rates in the year 2000.	Overall incidence of CHD and angina declined, MI and CABG/PCI remained unchanged.
IHD incidence	Vancheri 2021[121] 20 countries Western Europe	To investigate changes in ischaemic heart disease	2020 Global burden of disease database	Not defined	1990-2019	Ischaemic heart disease incidence declined by 36% between 1990-2019. Decline was largest between 1990-2009 (32%) compared to 2010-2019 (5.9%)	Slowing down of IHD incidence and mortality with some countries a flattening of trend observed.
CHD Incidence	Meirhaeghe 2020 [106] France	To investigate whether acute coronary events had decreased between 2006 and 2014 in French adults and whether there are age and sex differences	French Monica registry	35-54 years and 45-54 years	2006-2014	Age-standardised incidence rates decreased in both men (-0.9*%) and in women (-1.8*%) due to declines in the 65-74 year age group.	Decreasing trend in CHD incidence was observed between 2006 and 2014. No substantial declines were observed in younger age groups. (35-54 years, 45-54 years, and 55-64 years)
CHD Prevalence CHD incidence	Davies 2007[120] UK	To evaluate how trends in incidence of CHD and mortality among people with CHD influence the prevalence of CHD in the UK	The Health Improvement Network UK Primary care data	>35 years	1996-2005	Prevalence Age standardised: 1.3*% in men versus 1.7*% in women. 35-44 years: AAPC -0.08 in men versus 1.14 in women 45-54 years: AAPC -0.44* in men versus 0.96* in women Incidence Age standardised: -2.2*% versus -2.3*% 35-44 years: AAPC -0.07 in men versus 5.04* in women 45-54 years: AAPC- 0.46 in men versus 0.61 in women	In UK adults aged 35 year and over, between 1996 and 2005 the age-standardised incidence in CHD significantly decreased in men and women while age standardised prevalence increased in men and women. Increasing prevalence was largely due to decrease in mortality. In the 35–44-year age group, between 1996-2005, CHD prevalence trends remained stable both sexes, while incidence remained stable in men and significantly increased in women. In the 45–54-year age group, between 1996 and 2005, CHD prevalence decreased in men and increased in women, while CHD incidence remained stable in both sexes
CHD mortality	O'Flaherty, 2008[11] (UK)	To examine trends in age specific CHD mortality rates	Office of National statistics data	>35 years	1984-2004	Age 35-44 years Men EAPC; -3.7* for periods 1984 to 1991 versus -2.4 for the period 2000 to 2004. Women EAPC; -3.2* for the period 1984 to 2004 Age 45-54 years	Coronary heart disease mortality trends are slowing down in young adults.

						Men EAPC; -3.4* for the period 1984 to 1987 versus -1.8* for the period 1999 to 2004. Women EAPC -6.6* 1984 to 1990 versus -3.5* for per period 1995 to 2004	
CHD mortality	Wilmot 2015[10] (USA)	Examine CHD mortality trends by age and sex	US vital national statistics data	< 55 years	1979-1989 1989-1999 2000-2011	EAPC: −5.5%* in men versus −4.6%* in women EAPC: −1.2%* in men versus 0.1% in women EAPC - −1.8%* in men versus −1.0 in women	CHD mortality trends are slowing down in young adults.
MI Prevalence	Towfighi 2009 [122] (USA)	Determine sex specific trends in prevalence of MI among midlife adults	National survey	35-54 years	1988-1994 1999-2004	- 2.5% in men versus + 0.7% in women - 2.2% in men versus +1.0% women	MI increased in women and decreased among men. However, results were not statistically significant
MI Incidence	Yang 2020[108] (USA)	To compare risk factors profiles and outcomes of patients who experienced MI at a very young age (<40 years) and young age (41-50 years)	Young MI Registry Brigham & Women and Massachusetts General Hospital	<40 years (very young) 41-50 years (young)	2000-2016	MI increased in over the study period among very young (≤40) The increase was significant between 2006-2016 (1.7% per year p=0.0002)	Very young adults had similar one year and long-term outcomes when compared to those age 41-50 years.
MI Incidence	Guo 2018[123] (USA)	To investigate trends in acute myocardial infarction in very young adults	Nationwide Inpatient Sample Database	≤30 years	2005-2012	During 2005-2012, Annual AMI hospitalisations for women increased from 363-470 cases During 2005-2012, Annual hospitalisation for Men reduced from 1242 to 1130 cases An increasing trend for PCI utilization was observed for both sexes (p= < 0.0001 for trend for men and women.)	AMI frequency has increased in very young adults (≤30 years)
MI Incidence	Arora 2019[13] (USA)	To examine incidence and risk factors for AMI in young patients	Hospital surveillance data from 4 US communities	35-54 years	1995-2014	Proportion of AMI increased from 21% to 31% in women versus increased from 30% to 33% in men	There was annual increase in the incidence of AMI hospitalisations in females and a decrease in males.
MI incidence Unstable angina (UA) incidence ACS incidence	Nedkoff 2011[26] (Australia)	To examine incidence of hospitalised ACS	Linked administrative health data Western Australia	35-54 years	1996-2007	MI: - 0.2 in men versus +4.0* increase in women UA: -2.5* in men versus +0.9 in women ACS: -1.0* in men versus +2.3* in women	Notable increase in ACS noted in women.
MI Incidence	Izadnegahdar 2014[14] (Canada)	Investigate trends in AMI hospitalisation in young adults	Hospital discharge abstract database British Columbia	20-55 years	2000-2009	EAPC: 0.32% in men versus 1.72%* in women	Hospitalisation rates for young women (<55years) with MI increased
Revascularisation	Gerber 2020[124] (USA)	To examine the evolution of coronary disease by examining	Linked medical records Olmstead	>25 years	2000-2018	Any revascularisation (CABG/PCI) age and sex adjusted.	Trends in revascularisation procedures decreased and then levelled-off

		trends in angiography and revascularisation	County, Minnesota, USA			2005 versus 2000 RR 0.88; 95% CI 0.80 to 0.97 2009 versus 2005 RR 0.76; 0.71 to 0.80 2018 versus 2010 RR 1.10; 95% CI 1.00 to 1.22	
Revascularisation	Alkhaouli [125]2020 (USA)	To evaluate contemporary trends in characteristics and outcomes of patients undergoing PCI/CABG	National inpatient Sample (NIS) claims database	>18 years	2003-2016	PCI -51% decrease relative to rates in 2003.; p for trend <0.001. CAGB – 48% decrease relative to rates in 2003; p for trend <0.001.	A decrease in the annual volume of CABG & PCI procedure was detected between 2003 and 2016
Heart failure incidence	Christiansen 2017[28] (Denmark)	To examine age-specific trends in incidence and 1 year mortality following index heart failure diagnosis	Hospital records-Danish nationwide registries	< 50 years	1995-2012	+ 50% in incidence of HF (men and women) under 50 years	Incidence of heart failure has increased among young individuals but decreased among older individuals.
Heart failure incidence	Barasa 2013 (Sweden)[131]	To evaluate trends in incidence and mortality among young adults diagnosed with HF	Swedish National Hospital discharge registry	< 45 years	1987–2006	1987-2006; 18-34 years, APC, +2.5%* 1987-1990; 35-44 years APC, -1.7 (Reference) 1987-1990; 35-44 years APC, +2.4* 1987-1990: 55-84 years APC, -3.8%* (Reference) 1998-2006: 55-84 years APC, -2.3*	Heart failure increased in young adults as opposed to decrease noted in older patients.
Heart failure	Vasan 2019[130] (USA)	Investigate age, sex, race, and region, specific temporal trends in morbidity and mortality due to heart failure	National Centre for Health Statistics	30-49 years	1993-2014	Age 30-39: APC, +2.91* Age 40-49 APC, +1.10* Age 50-59 APC, −1.15* Age 60-69 APC, −2.38* Age 70-79 APC, −2.17* Age >80 APC, −1.50*	Increase in HF hospitalisations noted among younger age groups compared to older age groups.
Stroke	Ekker 2019[395] (Netherlands)	To investigate the incidence of stroke and its subtypes in young adults	Dutch Hospital Discharge Register	18–50 years	1998-2010	1998 incidence per 100,000 12.1 in Men versus 15.9 in Women 2010 incidence per 100,000 15.6 in Men versus 18.9 in women +29% % in men versus +19% in women Adults > 50 year -11%	Incidence of stroke increased in young adults compared to older adults. Incidence of stroke higher in women than in men.
Stroke	Putaala 2012[127] (Europe)	To compare the distribution of risk factors among young patients with ischaemic stroke	Stroke registries from 15 cities in Europe	15-49 years	1998-2001	Age < 34 years: Male to female ratio 0.7 45-49 years: Male to female ratio 1,7	Female predominance of stroke incidence at a young age (<34 years) with male predominance at ages 40-49
Stroke	Béjot 2021 (France)[129]	To assess changes in the incidence of ischaemic stroke	Dijon Stroke registry France	18-55 years	1985-2017	(Age 18-45 years) incidence rates (per 100,000 per year Before 2003 Men: 4.1 (2.7–6.0) Before 2003 Women 6.7 (4.9–9.0)	Incidence rate of ischaemic stroke increased in the early 2000's and remained stable afterwards, Excess risk not in women disappeared over time.

						After 2003 Men: 12.0 (9.2–15.4) After 2003 Women 13.6 (10.6–17.0) Male to Female IRR 0.78 (95% CI: 0.62–1.26) (Age 45-45 years) incidence rates per 100,000 per year Before 2003 Men: 47 (37–61) Before 2003 Women: 25 (17–35) After 2003 Men 82 (67–100) After 2003 Women 46 (35–59) IRR 1.79 (95% CI: 1.29–2.49	
Stroke	Béjot 2013[128] (France)	Evaluate changes in stroke in young adults (< 55 years) over the previous 3 decades	Dijon stroke registry France	< 55 years	1985-2011	Age specific incidence males and females (< 55 years): Period 1985-1993: 11.6 per 100,000 per year Period 2003-2011 20.2 per 100,000 per year IRR 2003-2011 versus 1994-2002 Men IRR 1.67; 95% CI, 1.23 to 2.26 Women IRR 1.51; 95% CI, 1.102 to 2.08	Stroke incidence increased in young adults

- = decreasing trend; + = increasing trend; * = statistically significant results

Chapter 4 Appendices

Appendix 1: Search Strategy for systematic review

Appendix 2: Data extraction form

Appendix 3: Citation matrices for reviews with overlapping associations

Appendix 4: Search strategy for newly published studies

Appendix 5: Evaluation process for considering reviews for update

Appendix 6: List of excluded studies

Appendix 7: AMSTAR 2 quality appraisal scores

Appendix 8: General characteristics of reviews with overlapping associations

Appendix 9: A: List of studies with non-overlapping associations included in umbrella review
Analysis
B: List of contemporary overlapping studies excluded from review

Appendix 10: Newcastle Ottawa scale appraisal scores for newly published studies

Appendix 1: Medline Search Strategy.

	Concept	Search Strategy	Results
1		exp reproductive history/ or exp pregnancy/ or exp contraception behavior/ or exp Parity/	851996
2		exp Breast Feeding/	34875
3		exp hypertension, pregnancy-induced/ or exp eclampsia/ or exp hellp syndrome/ or exp pre-eclampsia/	33911
4		(pre-eclamp* or eclamp* or gestosis or tox?mia or (hypertens* and pregnan*) or (hypertens* disorder* adj2 prenancy) or gestation* hypertens* or transient hypertens* or maternal hypertens*).ti,ab.	36317
5		3 or 4	52448
6		(maternal placental syndrom?e* or placent* abrupti*).ti,ab.	1952
7		exp abortion, spontaneous/ or exp abortion, threatened/	35185
8		(pregnancy loss or miscarriage* or recurrent miscarriage* or foetal death or fetal death). ti,ab.	21811
9		7 or 8	49261
10		gestational diabetes.mp. or exp Diabetes, Gestational/	15248
11		(gdm or gestatio* diabet* or (diabet* adj2 pregn*) or ((impair* glucose tolerance or insulin resistan* or pre-diabet*) and pregn*)).ti,ab.	18562
12		10 or 11	21200
13		(pre-matur* or prematur* or preterm or pre-term or LBW or low birth weight). ti,ab.	193847
14		exp Birth Weight/ or Birth weight.mp. or exp Infant, Small for Gestational Age/ or small for gestational age.mp. or exp Fetal Growth Retardation/	100480
15		13 or 14	249950
16		1 or 2 or 5 or 6 or 9 or 12 or 15	1048419
17		exp Polycystic Ovary Syndrome/ or Polycystic Ovary Syndrome*.mp.	15491
18		(((sclerocystic or polycystic or micropolycystic) and ovar*) or (polycystic ovar* disease or polycystic ovar* syndro?me or PCO or PCOS or stein leventhal)).ti,ab.	19306
19		17 or 18	20881
20		endometri*.mp. or exp Endometriosis/ or exp HYSTERECTOMY, VAGINAL/ or exp HYSTERECTOMY/ or hysterectomy.mp. or oophorectomy.mp. or exp Ovariectomy/	153466
21		exp Contraceptives, Oral/ or exp Contraception/ or contracept*.mp.	103604
22		(birth control or family planning or hormon* method* or progest* or ethinyl estradiol).ti,ab.	118126
23		21 or 22	194628

24	exp menopause, premature/ or exp primary ovarian insufficiency/ or menarche.mp. or exp MENARCHE/	12196
25	19 or 20 or 23 or 24	353844
26	exp Cardiovascular Diseases/ or cardiovascular disease*.mp. or heart disease*.mp. or exp Heart Diseases/	2321196
27	(isch?mic heart or IHD or CHD or coronary artery or coronary heart or atheroscleros* or CVA or cerebrovascular event* or cerebrovascular accident or stroke or TIA or CV or CVD or heart failure).ti,ab.	696132
28	26 or 27	2505448
29	16 or 25	1320410
30	28 and 29	109156
31	MEDLINE.tw.	95359
32	systematic review.tw.	112686
33	meta-analysis.pt.	94442
34	intervention$.ti.	123799
35	31 or 32 or 33 or 34	332105
36	30 and 35	2123

Appendix 2: The Joanna Briggs Institute data extraction form for review for systematic reviews and research syntheses.

Study details	
Author year	
Participants (characteristics/total number)	
Setting/context	
Description of interventions/ phenomena of interest.	
Search details	
Sources searched	
Range years of included studies	
Number of studies included	
Type of studies included	
Country of origin of included studies	
Appraisal	
Appraisal instruments used	
Appraisal rating	
Analysis	
Method of analysis	
Outcomes assessed	
Result /findings	
Significance/direction	
Heterogeneity	
Comments.	

Source: Aromataris E, Fernandez R, Godfrey C, Holly C, Khalil H, Tungpunkom P. Methodology for JBI Umbrella Reviews.
Joanna Briggs Inst Rev Man. 2014;1–34.

Appendix 3. Citation matrices for reviews with overlapping associations.

A. Gestational diabetes

Systematic reviews: gestational diabetes mellitus (exposure)	Kramer 2019	Grandi 2019	Jing Li 2018	Hopman 2015
Overlapping association	Fatal and non-fatal cardiovascular disease	Fatal and non-fatal cardiovascular disease	Fatal and non-fatal cardiovascular disease	Fatal and non-fatal cardiovascular disease
Primary Study				
Carr 2206			X	X
Daly 2018	X			
Dawson 2009		X		
Freibert 2011				X
Fadl 2014	X			
Goueslard 2016	X	X	X	
Heida 2015		X		
Kaul 2015	X	X	X	
Kessous 2013	X	X	X	X
Mackenzie-Sampson 2018	X			
Pintaudi 2015		X		
Retnakaran and Shah 2017	X		X	
Savitz 2014	X	X		
Shah 2008		X	X	
Shostrom 2017			X	X
Tobias 2017	X			
Total (No of publications per review)	9	8	7	4
Grand Total (N)	**28**			
Rows (r)	**16**			
Columns (c)	**4**			
Corrected covered area (CCA)	**25%**			

Formula for calculating the corrected covered area, **CCA (%) = N-r / rc-r**

Where N = number of included publications (sum of checked boxes), r = number of rows (primary publications), c = number of columns (number of reviews).

B. Preterm birth

Systematic review ID	Grandi 2019	Pensee Wu 2018	Robbins 2014	Grandi 2019	Pensee wu 2018	Heida 2016	Robbins 2014	Heida 2016	Robbins 2014	Pense Wu 2018	Robbins 2014
Overlapping associations	Non-Fatal CVD	Non-Fatal CVD	Non-Fatal CVD	Fatal CVD	Fatal CVD	Fatal & non-fatal stroke	Fatal & non-fatal stroke	Fatal and non-fatal coronary heart disease	Fatal and non-fatal coronary heart disease	Fatal coronary heart disease	Fatal coronary heart disease
Primary Study											
Bonammy 2011	X	X					X				
Catov 2007		X	X								
Catov 2010	X	X			X	X					X
Cirillo 2015				X						X	
Davey Smith 2001					X						
Davey Smith 2005					X					X	
Freibert 2011		X									
Hastie 2011	X							X	X	X	X
Hovi 2014		X									
Irgens 2001						X					
Kessous 2013	X	X									
Lykke 2010	X			X	X			X			X
Nardi 2006	X		X						X	X	
Ngo 2015	X	X									
Ngo 2017	X										
Pell 2004						X	X				
Rich Edwards 2015				X						X	
Smith 2000											X
Smith 2001				X	X				X		X
Soh 2016	X										
Tanz 2017	X	X									
Wang 2011	X										
Wilkstrom 2005	X							X			
Total (No of publications per review)	12	8	2	4	5	3	2	3	3	5	5
Grand Total (N)	22			9		5		6		10	
Rows (r)	15			7		4		5		9	
Columns (c)	3			2		2		2		**2**	
CCA	**23.3%**			**28.6%**		**25%**		**20%**		**11.1%**	

CVD = cardiovascular disease, CCA = Corrected covered area. Calculation = **CCA (%) = N-r/ rc-r**:

Where N = number of included publications (sum of checked boxes), r = number of rows (primary studies), c = number of columns (number of systematic reviews).

C. Pre-eclampsia

Systematic review ID	Grandi 2019	Pense Wu 2017	Grandi 2019	Pense Wu 2017	Grandi 2019	Pense Wu 2017	Grandi 2019	Pense Wu 2017
Overlapping associations	Fatal CVD	Fatal CVD	Non-Fatal coronary heart disease	Non-Fatal coronary heart disease	Non-fatal stroke	Non-fatal stroke	Fatal stroke	Fatal stroke
Primary Study								
Auger 2017					X			
Bhattacharya 2012				X	X	X		X
Funai 2005	X	X	X					
Gordin 2017				X				
Hannaford 1998					X			
Haukamaa 2009				X				
Hovsepian 2014						X		
Ingress 2001							X	
Iversen 2010	X		X					
Kaaja 2005				X				
Kestenbaum 2003								
Lin 2016					X			
Lin 2011 and Tang 2009		X		X	X	X		
Luoto 2008	X		X					
Lykke 2009 and Lykke 2010	X	X	X	X	X	X		
Mannisto 2013				X		X		
Mongraw Chaffin 2010	X		X					
Ray 2005								
Riise 2017	X		X					
Savitz 2014				X	X	X		
Sjaekerven 2012	X	X	X				X	X
Smith 2001	X		X					
Stuart 2013				X		X		
Tang 2009					X			
Wilkstrom 2005				X				
Wilson 2003	X		X		X		X	
Total (No of publications per review)	9	4	9	10	9	7	3	2
Grand Total (N)	13		19		16		5	
Rows (r)	10		18		12		4	
Columns (c)	2		2		2		2	
CCA	**30%**		**5.6%**		**33%**		**25%**	

CVD = cardiovascular disease, CCA = Corrected covered area. Calculation = **CCA (%) = N-r/ rc-r**:
Where N = number of included publications (sum of checked boxes), r = number of rows (primary studies), c = number of columns (number of systematic reviews).

D. Use of oestrogen containing pills in migraine

Systematic review	Sheikh 2017	Tepper 2016
Overlapping associations	Fatal CVD	Fatal CVD
Primary Study		
Collaborative group	X	X
Champaloux 2017	X	X
Chang 1999	X	X
Lidegaard 1995	X	X
MacClellan 2007		X
Nightinghale 2004		X
Schwartz 1998	X	X
Tzurio 1995	X	X
Total (No of publications per review)	6	8
Grand Total (N)	14	
Rows (r)	8	
Columns (c)	2	
CCA	**75%**	

CVD = cardiovascular disease, CCA = Corrected covered area. Calculation = **CCA (%) = N-r/ rc-r**:
Where N = number of included publications (sum of checked boxes), r = number of rows (primary studies), c = number of columns (number of systematic reviews).

E. Early natural menopause

Systematic review	Muka 2016	Tao 2015	Gong 2015	Muka 2016	Tao 2015	Gong 2015	Muka 2016	Tao 2015	Gong 2015
Overlapping associations	Fatal CVD	Fatal CVD	Fatal CVD	Fatal coronary heart disease	Fatal coronary heart disease	Fatal coronary heart disease	Fatal stroke	Fatal stroke	Fatal stroke
Primary Study									
Cooper 1998		X		X	X	X	X	X	X
Cui 2006	X			X			X		
Gallagher 2011		X			X			X	
Hong 2007	X		X	X			X		X
Jacobsen 1999				X	X	X	X	X	X
Jacobsen 2004									
Li 2003			X						
Li S 2013	X	X	X						
Mondul 2005		X		X	X	X	X	X	X
Osserwarde 2005	X			X			X		
Snowdon 1989		X						X	
Tom 2012	X		X						
Wu 2014						X			X
Total (No of publications per review)	5	5	4	6	4	4	6	5	5
Grand Total (N)	14			14			16		
Rows (r)	10			8			9		
Columns (c)	3			3					
CCA	**20%**			**37.5%**			**38.9%**		

CVD = cardiovascular disease, CCA = Corrected covered area. Calculation = **CCA (%) = N-r/ rc-r**:
Where N = Number of included publications (sum of checked boxes), r = number of rows (primary studies), c = number of columns (number of systematic reviews).

F. Progesterone only Contraceptives

Systematic review	Glisic 2018	Tepper 2016	Glisic 2018	Tepper 2016
Overlapping associations	Myocardial infarction	Myocardial infarction	Stroke	Stroke
Primary Study				
Dunn 1999	X	X		X
Heinemann 1999	X	X	X	X
Lidegaard 1993			X	X
Lidegaard 2002				X
Lidegaard 2012	X	X	X	X
Petitti 1998	X	X	X	X
Poulter 1999		X		X
Thorogood 1991	X	X		
Tzourio 1995			X	X
WHO 1998		X	X	X
WHO 1999	X			
Total (No of publications per review)	6	6	6	9
Grand Total (N)	12		15	
Rows (r)	8		9	
Columns (c)	2		2	
CCA	**50%**		**66%**	

CCA = Corrected covered area. Calculation = **CCA (%) = N-r/ rc-r**:
Where N = Number of included publications (sum of checked boxes), r = number of rows (primary studies), c = number of columns (number of systematic reviews).

G. Oral contraceptive use

Systematic review	Zhenlin Xu 2015	Peragallo 2013	Zhenlin Xu 2018	Peragallo 2013
Overlapping associations	Non-fatal ischaemic stroke	Non-fatal ischaemic stroke	Fatal & non-fatal haemorrhagic stroke	Non-fatal haemorrhagic stroke
Primary Study				
Carolei 1996	X			
CGSS 1973	X		X	
Chang 1999		X		X
Gallagher 2011			X	
Hannaford 1994	X			
Heinemann 1998	X			
Hirvonen 1990			X	
Inman 1979			X	
Kemmeren 2002	X			
Lewis 199		X		
Li 2006			X	
Lidegaard 1993	X			
Lidegaard 2002	X			
Lindegaard 2012	X			
Longstreth 1994			X	
Mant 1998	X	X		
Martinelli 2006	X			
Nightingale 2004	X			
Petitti 1978			X	
Petitti 1996	X	X	X	X
Pezzini 2007	X			
Schwartz 1997	X	X	X	X
RCGP 1983			X	
Siritho 2003		X		
Thorogood 1981			X	
Thorogood 1992			X	
Tzourio 1995	X			
WHO-1 1996	X		X	
WHO-2 1996	X		X	
Yang 2009	X	X	X	X
Total	18	7	15	4
Grand Total (N)	25		19	
Rows (r)	21		16	
Columns (c)	2		2	
CCA	**19%**		**18.75%**	

CCA = Corrected covered area. Calculation = **CCA (%) = N-r/ rc-r**:
Where N = Number of included publications (sum of checked boxes), r = number of rows (primary studies), c = number of columns (number of systematic reviews).

H. Polycystic ovary syndrome

Systematic review ID	Tehrani 2019	Zhao 2016	Gilbert 2018
Overlapping associations	CVD	CVD	CVD
Primary Study			
Birdsall 1997		X	X
Cibula 2000		X	X
Ding 2018	X		
Glintborg 2015	X		
Hart 2014	X		
Ifitkhar 2012	X	X	X
Krentz 2007		X	X
Lo 2006	X		
Lunde 2007	X	X	X
Mani 2013	X	X	X
Merz 2016	X		
Meun 2018	X		
Okoroh 2015	X		
Pierpoint 1998	X		
Schmidt 2011	X	X	X
Shaw 2008			X
Sirmans 2014	X		
Solomon 2002		X	X
Wang 2011		X	X
Wild 2000	X	X	X
Total	14	10	11
Grand Total (N)	35		
Rows (r)	20		
Columns (c)	3		
CCA	**37.5%**		

CVD = cardiovascular disease, CCA = Corrected covered area. Calculation = **CCA (%) = N-r/ rc-r**:
Where N = Number of included publications (sum of checked boxes), r = number of rows (primary studies), c = number of columns (number of systematic reviews).

I. Oral contraceptive pills and risk of myocardial infarction

Systematic review	Roach 2015	Peragallo 2013
Overlapping associations	Fatal and non-fatal myocardial infarction	Non-fatal myocardial infarction
Primary Study		
Adam 1981	X	
Dunn 1999	X	X
Heinemann 1998/ Lewis 1997	X	X
Jick 1978	X	
Kemmeren 2002/Tanis 2001	X	X
Krueger 1980	X	
La Vecchia 1987	X	
Mann 1975a/Mann1975b	X	
Mann 1975b	X	
Mannt 1998		X
Margoslis 2007		X
Rosenberg 2001	X	X
Rossenberg 1976a	X	
Schwartz 1997	X	
Shapiro 1979/ Slone 1981	X	
Sidney 1998	X	X
Tzourio 1995	X	
WHO collaboration 1997		X
Total	15	8
Grand Total (N)	23	
Rows (r)	18	
Columns (c)	2	
CCA	**27.8 %**	

CCA = Corrected covered area. Calculation = **CCA (%) = N-r/ rc-r**:
Where N = Number of included publications (sum of checked boxes), r = number of rows (primary studies), c = number of columns (number of systematic reviews).

J. Age at menarche

Systematic review	Xu Chen 2018	Charalampopoulos 2014	Xu Chen 2018	Charalampopoulos 2014	Xu Chen 2018	Charalampopoulos 2014
Overlapping associations	Fatal CVD	Fatal CVD	Fatal coronary heart disease	Fatal coronary heart disease	Fatal stroke	Fatal stroke
Primary Study						
Canoy 2014			X			
Chang 2011	X	X	X	X	X	X
Cui 2006	X	X	X	X	X	X
Gallagher 2011			X	X	X	X
Jacobsen 2009			X	X	X	X
Lakshman 2009	X	X				
Mueller 2012	X	X	X	X	X	X
Yang 2016	X					
Wu 2014	X		X		X	
Total (No of publications per review)	6	4	7	5	6	5
Grand Total (N)	10		12		11	
Rows (r)	6		7		6	
Columns (c)	2		2		2	
CCA	**66.7 %**		**71.4 %**		**83.3 %**	

CVD = cardiovascular disease, CCA = Corrected covered area. Calculation = **CCA (%) = N-r/ rc-r**:
Where N = number of included publications (sum of checked boxes), r = number of rows (primary studies), c = number of columns (number of systematic reviews).

Appendix 4: Search strategy for newly published studies.

A. Medline search strategy for breastfeeding and maternal risk of cardiovascular disease

Concept	Search terms	Results
1	exp Breast Feeding/	36904
2	exp LACTATION/	41793
3	exp Milk, Human/	18912
4	Breast fed.mp.	5692
5	Breastfe*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	26249
6	Lactat*.mp.	208342
7	Breast milk.mp.	12848
8	1 or 2 or 3 or 4 or 5 or 6 or 7	261289
9	exp Cardiovascular Diseases/	2343673
10	exp Coronary Artery Disease/	60319
11	Ischemic heart disease.mp.	25220
12	Ischaemic heart disease.mp.	8743
13	exp Myocardial Ischemia/	423937
14	exp Heart Failure/	118451
15	exp Stroke/	130429
16	9 or 10 or 11 or 12 or 13 or 14 or 15	2349619
17	8 and 16	18330
18	limit 17 to (female and humans and yr="2015 -Current")	999

B. Medline search strategy for miscarriage and maternal risk of stroke

Concept	Search term	Results
1	exp Abortion, Spontaneous/	34727
2	exp Abortion, Habitual/	8097
3	Recurrent Abortion.mp.	614
4	Habitual Miscarriage.mp.	26
5	Miscarriage.mp.	10437
6	Foetal Death.mp.	442
7	exp Fetal Death/	29071

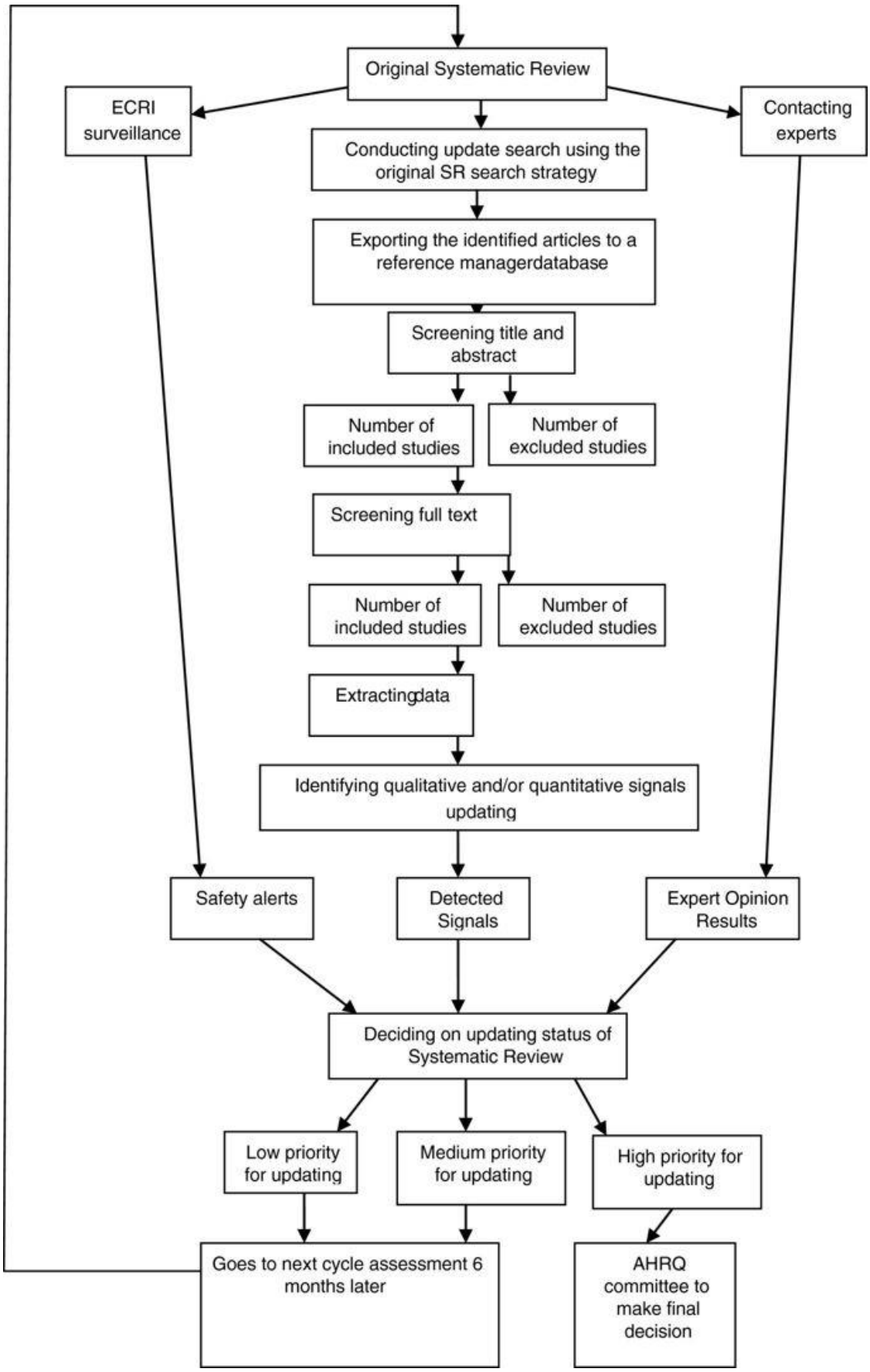
8	Pregnancy Loss.mp.	5979
9	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8	68502
10	exp Cardiovascular Diseases/	2343673
11	exp Coronary Artery Disease/	60319
12	exp Myocardial Infarction/	172659
13	Heart Attack.mp.	4229
14	Coronary Heart Disease.mp.	48640
15	Ischemic Heart Disease.mp.	25220
16	Ischaemic Heart Disease.mp.	8743
17	exp Stroke/	130429
18	exp Ischemic Attack, Transient/	20112
19	Transient Ischaemic Attack.mp.	1829
20	Vascular Accident.mp.	902
21	Apoplexy.mp. or Stroke/	100350
22	10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21	2361615
23	9 and 22	4747
24	limit 23 to (humans and yr="2011 -Current")	977

C: Medline search strategy for gestational diabetes and maternal risk of stroke

Concept	Search terms	Results
1	exp Diabetes, Gestational/	12074
2	gestational diabetes.mp.	13910
3	gestational diabetes mellitus.mp.	7903
4	GDM.mp.	6883
5	1 or 2 or 3 or 4	17764
6	exp Cardiovascular Diseases/	2343673
7	exp Coronary Disease/	214889
8	exp Coronary Artery Disease/	60319
9	exp Myocardial Infarction/	172659
10	exp Coronary Artery Bypass/	52213
11	exp Endarterectomy, Carotid/	8644
12	exp Angina Pectoris/	43142
13	exp Stroke/	130429
14	exp Peripheral Vascular Diseases/	52535

15	PVD.mp.	2441
16	exp Peripheral Arterial Disease/	7203
17	PAD.mp.	23306
18	6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17	2380697
19	5 and 18	1480
20	limit 19 to yr="2016 -Current"	409

Appendix 5: Evaluation process for considering reviews for update



Ottawa's label	Ottawa method
	Qualitative criteria for potentially invalidating signals
A1	Opposing findings: a pivotal* trial or systematic review (or guidelines) including at least one new trial that characterised the treatment in terms opposite to those used earlier
A2	Substantial harm: a pivotal trial or systematic review (or guidelines) whose results called into question the use of the treatment based on evidence of harm or that did not proscribe use entirely but did potentially affect clinical decision-making
A3	A superior new treatment: a pivotal trial or systematic review (or guidelines) whose results identified another treatment as significantly superior to the one evaluated in the original review, based on efficacy or harm
	Qualitative criteria for signals of major changes
A4	Important changes in effectiveness short of 'opposing findings'
A5	Clinically important expansion of treatment
A6	Clinically important caveat
A7	Opposing findings from discordant meta-analysis or non-pivotal trial
	Quantitative criteria signals of changes in evidence
B1	A change in statistical significance (from nonsignificant to significant)
B2	A change in relative effect size of at least 50 percent

RAND's label	RAND method indications for the need for an update
1	Original conclusion is still valid and this portion of the original report does not need updating. This conclusion was reached if we found no new evidence or only confirmatory evidence and all responding experts assessed the CER conclusion as still valid, we classified the CER conclusion as still valid
2	Original conclusion is possibly out-of-date and this portion of the original report may need updating. This conclusion was reached if we found some new evidence that might change the CER conclusion, and/or a minority of responding experts assessed the CER conclusion as having new evidence that might change the conclusion, then we classified the CER conclusion as possibly out-of-date
3	Original conclusion is probably out-of-date and this portion of the original report may need updating. This conclusion was reached if we found substantial new evidence that might change the CER conclusion, and/or a majority of responding experts assessed the CER conclusion as having new evidence that might change the conclusion, then we classified the CER conclusion as probably out-of-date
4	Original conclusion is out-of-date. This conclusion was reached if we found new evidence that rendered the CER conclusion out-of-date or no longer applicable; we classified the CER conclusion as out-of-date. Recognising that our literature searches were limited, we reserved this category only for situations where a limited search would produce *prima facie* evidence that a conclusion was out-of-date, such as the withdrawal of a drug or surgical device from the market, a black box warning from FDA, and so on

Source (flow diagram and tables): Ahmadzai N, Newberry SJ, Maglione MA, Tsertsvadze A, Ansari MT, Hempel S, et al. A surveillance system to assess the need for updating systematic reviews. Syst Rev. 2013;2:104.

Appendix 6: List of excluded studies and reasons for their exclusion

	1st Author	Year	Title	Reason for Exclusion.
1.	Chakhtoura Z [412]	2011	Progesterone only contraceptive and risk of myocardial infarction: A meta-analysis.	Overlapping review outdated
2	Chakhtoura Z [413]	2009	Progestogen-only contraceptives and the risk of stroke: a meta-analysis.	Overlapping review outdated
3	Plu-Bureau [414]	2013	Hormonal contraceptives and arterial disease: an epidemiological update.	No Quality appraisal of primary studies Overlapping review outdated
4	Khader YS [415]	2003	Oral contraceptives use and the risk of myocardial Infarction: a meta-analysis.	Overlapping review outdated
5	Septer ARW	2001	Meta-analysis shows an increased incidence of stroke in persons using oral contraceptives.	Overlapping review outdated
6.	Gillum LA [416]	2000	Ischemic stroke risk with oral contraceptives: A meta-analysis	No quality appraisal of primary studies Overlapping outdated
7	Johnston SC [417]	1998	Oral contraceptives and the risk of subarachnoid haemorrhage: a meta-analysis	No quality appraisal of primary studies Overlapping review outdated
8	Xu B, Xu Z [418]	1996	Oral contraceptive and risk of disease.	Overlapping review outdated
9	Katerndahl [419]	1992	Oral contraceptive use and cardiovascular disease risk: Is the relationship real or due to study bias?	Overlapping review outdated
10	Novotna [420]	2002	M Arterial diseases in women using combined hormonal contraceptives. [in Czech language]	Overlapping review outdated
11	Wu CQ [421]	2013	Drospirenone-containing oral contraceptive pills and the risk of venous and arterial thrombosis: a systematic review	No quality appraisal of primary studies
12	Baillargeon JP [422]	2005	Association between the current use of low-dose oral contraceptives and cardiovascular arterial disease: a meta-analysis	No quality appraisal of primary studies Overlapping review outdated
13	Chans WS [423]	2004	Risk of stroke in women exposed to low dose oral contraceptives	No quality appraisal of primary studies
14	Spitzer WO [424]	2002	Myocardial infarction and third generation oral contraceptives: aggregation of recent studies	No quality appraisal of primary studies

15	Leblanc ES [425]	1999	Benefits and risks of third-generation oral contraceptives	Overlapping review outdated Literature review No quality appraisal of primary studies
16	Luijken J [426]	2017	Association between age at menarche and cardiovascular disease: A systematic review on risk and potential mechanisms	No quality appraisal of primary studies
17	Anderson SA [155]	2014	Risk of coronary heart disease and risk of stroke in women with polycystic ovary syndrome: a systematic review and meta-analysis	Abstract; Inadequate information provided
18	Tomilson [427]	2010	Type 2 diabetes and cardiovascular disease in polycystic ovary syndrome: what are the risks, and can they be reduced?	Literature review
19	Wild RA [428]	2002	Polycystic ovary syndrome: a risk for coronary artery disease	Literature review of risk factors
20	Appiah D [429]	2016	Association of age at menopause with incident heart failure: A prospective cohort study and meta-analysis.	No quality appraisal of primary studies
21	Schwartz RH [430]	2017	the incidence of pregnancy-related stroke: A systematic review and meta-analysis	No comparator
22	Gibson [431]	2017	Incidence of myocardial infarction in pregnancy: A systematic review and meta-analysis of observational studies	No comparator
23.	Roth A [432]	1996	Acute myocardial infarction associated with pregnancy	Literature review Literature review
24.	Rosendaal NTA [246]	2017	Age at first birth and risk of later-life cardiovascular disease: a systematic review of the literature, its limitation, and recommendations for future research	No quality appraisal of primary studies. Literature review
25.	Bellamy L [160]	2007	Pre-eclampsia and risk of cardiovascular disease and cancer in later life: systematic review and meta-analysis	Overlapping review outdated No quality appraisal of primary studies
26	McDonald [433]	2008	Cardiovascular sequelae of preeclampsia/eclampsia: a systematic review and meta-analyses	Overlapping review Outdated
27	Brown MC [434]	2013	Cardiovascular disease risk in women with pre-eclampsia: systematic review and meta-analysis.	No quality appraisal

28	Li JW [435]	2014	Association of gestational diabetes mellitus (GDM) with subclinical atherosclerosis: a systemic review and meta-analysis	No hard-cardiovascular endpoints reported.
29	Huxley R [436]	2007	Is birth weight a risk factor for Ischaemic heart disease later in life?	Reports on future ischaemic heart disease as outcome among adults born with low birth weight
30	Poorthuis [437]	2017	MH Female- and Male-Specific Risk Factors for Stroke: A Systematic Review and Meta-analysis	No quality appraisal of primary studies
31	Feigin., VL [438]	2005	Risk factors for subarachnoid haemorrhage: an updated systematic review of epidemiological studies	Overlapping review outdated
32	Teunissen [439]	1996	Risk factors for subarachnoid haemorrhage: a systematic review	Overlapping review outdated
33	Aguilar Cordero [440]	2015	Breastfeeding as a method to prevent cardiovascular diseases in the mother and the child]. [in Spanish	No quality appraisal of primary studies
34	Davey Smith [37]	2007	Offspring birth weight and parental mortality: prospective observational study and meta-analysis	No quality appraisal of primary studies
35.	Sacco S [441]	2017	Contribution of hormonal contraceptive to the risk of ischaemic stroke in women with migraine: A meta-ananlysis of current data	Guideline/consensus statement
36	Wabnitz A [442]	2015	Bushnell C. Migraine, cardiovascular disease, and stroke during pregnancy: systematic review of the literature	Literature review No quality appraisal
37	Lameijer H [443]	2015	Ischaemic heart disease during pregnancy or post-partum: systematic review and case series.	No comparator
38.	Downes [444]	2017	Maternal, Labor, Delivery, and Perinatal Outcomes Associated with Placental Abruption: A Systematic Review.	No quality appraisal
39	Belbasis [259]	2016	Birth weight in relation to health and disease in later life: an umbrella review of systematic reviews and meta-analyses	No quality appraisal
40	Curtis [445]	2005	Use of combined oral contraceptives among women with migraine and nonmigraine headaches: a systematic review	Overlapping review outdated
41	Algra [446]	2012	Female risk factors for subarachnoid hemorrhage: a systematic review with emphasis on hormonal menstrual and reproductive factors	Overlapping review outdated

42	De Groot [250]	2011	PCOS coronary heart disease stroke and the influence of obesity: A systematic review and meta-analysis	Overlapping review outdated
43	M de Kleijin [36]	1999	Reproductive history and cardiovascular disease risk in postmenopausal women A review of the literature	Literature review
44	Ganesh [447]	2015	Hypertensive disorders in pregnancy and future risk of stroke: A systematic review.	Abstract: inadequate information provided
45	Culwell [448]	2009	Safety of hormonal contraceptive use among women with systemic lupus erythematosus: A systematic review	No hard cardiovascular disease end points mentioned.
46	Riley [449]	2016	Hormonal contraceptive among electronic cigarette users and cardiovascular risk: a systematic review	No cardiovascular disease outcomes reported
47	Oliver-Williams [258]	2019	Future cardiovascular disease risk for women with a history of gestational hypertension: a systematic review and meta-analysis	Abstract; inadequate information
48	Stampfer [450]	1990	Past use of oral contraceptives and cardiovascular disease: a meta-analysis in the context of the Nurses' Health Study.	Overlapping review outdated
49	Atsma [451]	2006	Postmenopausal status and early menopause as independent risk factors for cardiovascular disease: a meta-analysis	Overlapping and outdated

Appendix 7: AMSTAR 2 quality appraisal scores

Item No	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	Overall Rating
Charalampopoulos 2014	Yes	No	Yes	Partial Yes	Yes	No	No	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Moderate
Prentice and Vinner 2013	Yes	Partial Yes	No	Partial Yes	No	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	No	Yes	Moderate
Xu Chen 2018	Yes	No	No	Partial Yes	No	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Moderate
Glisic 2018	Yes	No	No	Partial Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Moderate
Tepper 2018	Yes	No	No	No	No	No	No	Yes	Yes	Yes	No MA	No MA	Yes	No	No MA	No	Low
Zhenlin Xu 2015	Yes	No	No	Partial Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Moderate
Zhenlin Xu 2018	Yes	No	No	Partial Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Moderate
Peragallo 2013	Yes	No	Yes	Partial Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Moderate
Roach 2015	Yes	No	Yes	Partial Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Moderate
Horton 2014	Yes	No	No	No	No	No	No	Yes	Yes	Yes	No MA	No MA	Yes	Yes	No MA	No	Low
Sheikh Hu 2016	Yes	No	No	Partial Yes	Yes	Yes	No	Yes	Yes	No	No MA	No MA	Yes	Yes	No MA	Yes	Moderate
Tepper 2016[a]	Yes	No	No	No	No	No	No	Yes	Yes	Yes	No MA	No MA	Yes	Yes	No MA	No	Low
Tepper 2016[b]	Yes	No	No	No	No	Yes	No	Yes	Yes	Yes	No MA	No MA	Yes	Yes	No MA	Yes	Low
Dragomann 2015	Yes	No	No	Partial Yes	Yes	No	No	Yes	Yes	Yes	No MA	No MA	Yes	Yes	No MA	Yes	Moderate
Curtis 2005	Yes	No	No	No	No	No	No	Yes	Yes	No	No	No	Yes	Yes	No	Yes	Low
Gilbert 2018	Yes	Yes	No	Partial Yes	Yes	Yes	Yes	Yes	Yes	No	No MA	No MA	Yes	Yes	No MA	Yes	Moderate
Zhous 2017	Yes	No	No	Partial	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Moderate

				Yes													
Zhao 2016	Yes	No	No	Partial Yes	Yes	Yes	No	Partial Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Moderate
Roeters van Lennep, 2014	Yes	No	No	Partial Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Moderate
Tao 2015	Yes	No	No	Partial Yes	No	No	No	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Moderate
Muka 2016a	Yes	No	No	Partial Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Moderate
Muka 2016b	Yes	No	No	Partial Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Moderate
Gong 2016	Yes	No	No	No	No	No	No	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Low
Oliver-Williams 2015	Yes	No	Yes	Partial Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Moderate
Brouwers 2018	Yes	No	No	Partial Yes	Yes	Yes	Yes	No	Yes	No	Yes	Yes	Yes	Yes	No	Yes	Moderate
Pensee Wu 2018	Yes	Yes	No	Partial Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Yes	Yes	No	No	Moderate
Jing Li 2018	Yes	No	No	Partial Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Moderate
Kramer 2019	Yes	Yes	No	Partial Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Moderate
Hopmans 2015	Yes	No	No	Partial Yes	No	No	No	Yes	Yes	No	Yes	Yes	Yes	Yes	No	Yes	Moderate
Pensee Wu 2017(HDP)	Yes	No	No	Partial Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Yes	Yes	No	Yes	Moderate
Heidi 2014	Yes	No	No	Partial Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Moderate
Robbins 2014	Yes	No	Yes	Partial Yes	Yes	No	No	Yes	Yes	No	No MA	No MA	Yes	No	No MA	Yes	Moderate
Haichen Lv 2015	Yes	No	No	Partial Yes	No	Yes	No	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Moderate
Li W 2018	Yes	No	No	Partial Yes	No	Yes	No	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Moderate
Nguyen 2017	Yes	Yes	No	Partial Yes	Yes	No	No	Yes	Yes	No	No MA	No MA	Yes	Yes	No MA	Yes	Moderate
Bojilin 2016	Yes	No	No	Partial	Yes	Yes	No	Yes	Yes	No	No	No	Yes	Yes	No	Yes	Moderate

				Yes							MA	MA			MA		
Grandi 2019	Yes	Yes	No	Partial Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Yes	Yes	No	Yes	Moderate
Dayan 2017	Yes	Yes	No	Partial Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Yes	Yes	No	Yes	Moderate
Tehrani 2019	Yes	No	No	No	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Low

No MA= No meta-analysis.

Item 1: inclusion of PICO elements? Item 2: review methods established before conduct of review? Item 3: explanation for selection of study designs to be included in review? Item 4: use of a comprehensive search strategy? Item 5: selection of studies in duplicate? Item 6: data extraction in duplicate? Item 7: provision of list of excluded studies with justification for exclusion? Item 8: description of included studies in adequate detail? Item 9: satisfactory technique for risk of bias? Item 10: sources of funding for included studies reported? Item 11: proper methods for meta-analysis? Item 12: potential risk of bias in included studies discussed? Item 13: risk of bias accounted for in interpreting results? Item 14: heterogeneity discussed? Item 15: if meta-analysis conducted was publication bias discussed? Item 16: disclosure of funding or conflict of interest?

Appendix 8: General characteristics of reviews with overlapping associations.

Index of overlapping association	Study ID	AMSTAR 2 rating	Reproductive factor	Outcome	Synthesis type (number)	Corrected covered area (CCA)	Decision to retain ✓= Yes
1	Peragallo 2013	Moderate	Current oral contraceptive pill use	Non-fatal ischaemic stroke	MA (8)	19% very high	×
	Zhenlin Xu 2015	Moderate	Oral contraceptive use	Non-fatal ischaemic stroke	MA (18)		✓
2	Roach 2015	Moderate	Current combined oral contraceptive use	Fatal and non-fatal myocardial infarction	MA (11)	27.8% very high	✓(Cochrane review)
	Peragallo 2013	Moderate	Current combined oral contraceptive use	Non-fatal myocardial infarction	MA (8)		×
3	Zhenlin Xu	Moderate	Oral contraceptive use	Fatal and non-fatal haemorrhagic stroke	MA (15)	18.7% very high	✓
	Peragallo 2013	Moderate	Current combined oral contraceptive use	Non-fatal haemorrhagic stroke	MA (4)		×
4	Glisic 2018	Moderate	Progesterone only pill use	Myocardial infarction	MA (8)	very high 50%	✓
	Tepper 2018	Low	Progesterone only pill use	Myocardial infarction	Narrative (7)		×
5	Glisic 2018	Moderate	Progesterone only pill use	Stroke	MA (8)	very high 66%	✓
	Tepper 2016	Low	Progesterone only pill use	Stroke	Narrative (8)		
6	Sheikh 2017	Moderate	Oestrogen-containing contraceptives in migraine	Stroke	Narrative (6)	75% very high	✓
	Tepper 2016	Low	Hormonal contraceptive use in migraine	Stroke	Narrative (8)		×
7	Muka 2016	Moderate	Age at menopause	Fatal CVD	MA (5)	very high 20%	✓
	Gong 2015	Low	Early natural menopause	Fatal CVD	MA (4)		×
	Tao 2015	Moderate	Early Natural menopause	Fatal CVD	MA (5)		×
8	Muka 2016	Moderate	Age at menopause	Fatal ischaemic heart disease	MA (6)	37.5% very high	✓
	Gong 2015	Low	Early natural menopause	Fatal ischaemic heart disease	MA (4)		×
	Tao 2015	Moderate	Early natural menopause	Fatal ischaemic heart disease	MA (4)		×
9	Muka 2016	Moderate	Age at menopause	Fatal stroke	MA (6)	38% very high	✓
	Gong 2015	Low	Early natural menopause	Fatal stroke	MA (5)		×

	Tao 2015	Moderate	Early Natural menopause	Fatal stroke	MA (5)		×
10	Grandi 2019	Moderate	Pre-eclampsia	Fatal CVD	MA (9)	30% very high	✓
	Pensee Wu 2017	Moderate	Pre-eclampsia	Fatal CVD	MA (4)		×
11	Grandi 2019	Moderate	Pre-eclampsia	Non-fatal coronary heart disease	MA (9)	5.6% slight	✓
	Pensee Wu 2017	Moderate	Pre-eclampsia	Non-fatal coronary heart disease	MA (10)		✓
12	Grandi 2019	Moderate	Pre-eclampsia	Non-fatal stroke	MA (9)	33% very high	✓
	Pensee Wu 2017	Moderate	Pre-eclampsia	Non-fatal stroke	No MA (7)		×
13	Grandi 2019	Moderate	Pre-eclampsia	Fatal stroke	No MA (3)	25% very high	×
	Pensee Wu 2017	Moderate	Pre-eclampsia	Fatal stroke	MA (2)		✓
14	Kramer 2019	Moderate	Gestational diabetes mellitus	Fatal and non-fatal CVD	MA (9)	25% very high	✓
	Grandi 2019	Moderate	Gestational diabetes mellitus	Fatal and non-fatal CVD	MA (8)		×
	Jing Li 2018	Moderate	Gestational diabetes mellitus	Fatal and non-fatal CVD	MA (7)		×
15	Grandi 2019	Moderate	Pre-term birth	Non-fatal CVD	MA (12)	23% very high	✓
	Pensee Wu 2018	Moderate	Pre-term birth	Non-fatal CVD	MA (8)		×
	Robbins 2014	Moderate	Pre-term birth	Non-fatal CVD	MA (2)		×
16	Grandi 2019	Moderate	Pre-term birth	Fatal CVD	MA (4)	28.6% very high	×
	Pense Wu 2019	Moderate	Pre-term birth	Fatal CVD	MA (5)		✓
17	Heida 2016	Moderate	Pre-term birth	Fatal and non-fatal stroke	MA (3)	25% very high	✓
	Robbins 2014	Moderate	Pre-term births	Fatal and non-fatal stroke	Narrative (2)		×
18	Heida 2016	Moderate	Pre-term birth	Fatal and non-fatal coronary heart disease	MA (3)	20% very high	✓
	Robbins 2014	Moderate	Pre-term births	Fatal and non-fatal coronary heart disease	Narrative (3)		×
19	Pense Wu2018	Moderate	Pre-term birth	Fatal coronary heart disease	MA (5)	11% High	✓
	Robbins 2014	Moderate	Pre-term birth	Fatal coronary heart disease	Narrative 5		×
20	Zhao 2016	Moderate	Polycystic ovary syndrome	Non-fatal CVD	MA (10)	37.5% High	✓
	Tehrani 2019	Low	Polycystic ovary syndrome	Non-fatal CVD	MA (9)		✓*

	Gilbert 2018	Moderate	Polycystic ovary syndrome	Non-fatal CVD	Narrative (2)		×

CVD = cardiovascular disease, MA = Meta-analysis.

*The Tehrani paper was retained because, although there was overlap, it provided further information we considered clinically relevant.

Appendix 9: Final list of studies included or excluded from the analysis

A. List of studies included in analysis

			Fertility-related reviews
1	Xu Chen [452]	2018	Age at menarche and risk of all cause and cardiovascular mortality: a systematic review and dose-response meta-analysis.
2	Prentice P [202]	2012	Pubertal timing and adult obesity and cardiometabolic risk in women and men: a systematic review and meta-analysis
3	Glisic M [191]	2018	Association between progestin-only contraceptive use and cardiometabolic outcomes: A systematic review and meta-analysis
4	Xu Z [190]	2018	Association between oral contraceptive and risk of haemorrhagic stroke: A meta- analysis of observational studies.
5	Xu Z [186]	2015	Current use of oral contraceptives and the risk of first-ever ischemic stroke: A meta-analysis of observational studies
6	Roach [195]	2015	Combined oral contraceptives: the risk of myocardial infarction and ischemic stroke
7	Horton [205]	2015	Combined hormonal contraceptive use among obese women and risk for cardiovascular events: A systematic review
8	Sheikh [193]	2016	Risk of Stroke Associated with Use of Oestrogen Containing Contraceptives in Women with Migraine: A Systematic Review
9	Tepper [203]	2016	Nonoral combined hormonal contraceptives and thromboembolism: a systematic review
10	Dragoman [204]	2015	Combined hormonal contraceptive use among women with known dyslipidaemias: a systematic review of critical safety outcomes
11	Curtis [208]	2006	Combined oral contraceptive use among women with hypertension: A systematic review.
12	Zhao L [185]	2016	Polycystic ovary syndrome (PCOS) and the risk of coronary heart disease (CHD): a meta-analysis.

13	Zhou Y [209]	2017	Association between polycystic ovary syndrome and the risk of stroke and all-cause mortality: insights from a meta-analysis
14	Tehrani [189]	2019	Cardiovascular events among reproductive and menopausal age women with polycystic ovary syndrome: a systematic review and meta-analysis
15	Muka T [197]	2016	Association of Age at Onset of Menopause and Time Since Onset of Menopause with Cardiovascular Outcomes, Intermediate Vascular Traits, and All-Cause Mortality: A Systematic Review and Meta-analysis
16	Muka T [221]	2016	Association of vasomotor symptoms and other menopausal symptoms with risk of cardiovascular disease: A systematic review
17	Roeters [220]	2016	Cardiovascular disease risk in women with premature ovarian insufficiency: A systematic review and meta-analysis
18	Tao X-Y [199]	2016	Effect of primary ovarian insufficiency and early natural menopause on mortality
19	Dayan [212]	2017	Cardiovascular risk following fertility therapy
20	Nguyen B [235]	2017	Breastfeeding and maternal cardiovascular risk factors and outcomes: A systematic review
B			**Adverse Pregnancy outcomes**
21	Oliver-Williams [222]	(2013)	Miscarriage and future maternal cardiovascular disease: a systematic review and meta-analysis
22	Brouwers [223]	2018	Recurrence of pre-eclampsia and risk of future hypertension and cardiovascular diseases
23	Wu P [200]	2017	Preeclampsia and Future Cardiovascular Health: A Systematic Review and Meta-Analysis.
24	Li J [182]	2018	Increased risk of cardiovascular disease in women with prior gestational diabetes: A systematic review and meta-analysis
25	Wu P [183]	2018	Preterm delivery and maternal cardiovascular disease future risk: A systematic review and meta-analysis
26	Heida KY [226]	2016	Cardiovascular disease risk in women with a history of spontaneous preterm delivery: A systematic review and meta-analysis
27	Robbins [184]	2014	History of preterm birth and subsequent cardiovascular disease: a systematic review
28	Haichen Lv, [213]	2015	Parity and Cardiovascular Disease Mortality: A Dose-Response Meta-Analysis of Cohort Studies
29	Wenzhen Li [214]	2018	Parity and risk of maternal cardiovascular disease: A dose–response meta-analysis of cohort studies

30	Kramer [201]	2019	Gestational diabetes and the risk of cardiovascular disease in women: a systematic review and meta-analysis.
31	Grandi [38]	2019	Cardiovascular Disease-Related Morbidity and Mortality in Women with a History of Pregnancy Complications Systematic Review and Meta-Analysis
			Combined (Fertility related and adverse pregnancy outcomes)
32	Bolijn R [211]	2017	Reproductive factors in relation to heart failure in women: A systematic review

B. List of contemporary reviews with overlapping associations excluded from analysis

33	Gong D [198]	2015	Early age at natural menopause and risk of cardiovascular and all-cause mortality- A meta-analysis of prospective observational Studies
34	Hopmans [188]	2015	Increased risk of type II diabetes mellitus and cardiovascular disease after gestational diabetes mellitus: a systematic review
35	Gilbert [187]	2018	Comorbidities and complications of polycystic ovary syndrome: An overview of systematic reviews.
36	Tepper NK [194]	2016	Safety of hormonal contraceptives among women with migraine: A systematic review
37	Peragallo [196]	2013	Risk of acute thromboembolic events with oral contraceptive use: a systematic review and meta-analysis.
38	Tepper NK [192]	2016	Progestin-only contraception and thromboembolism: A systematic review.
39	Charalampopolous [35]	2014	Age at menarche and risks of all-cause and cardiovascular death: a systematic review and meta-analysis.

Appendix 10: Newcastle Ottawa scale appraisal scores for newly published studies.

Study ID	Selection	Comparability	Exposure	Total Score
Kirkegaard 2018	✶✶✶✶	✶✶	✶✶✶	9 (high)
Peters 2016	✶✶✶	✶	✶✶	7 (medium)
Peters 2017	✶✶✶	✶	✶✶✶	7 (medium)
Jacobson 2018	✶✶	✶✶	✶✶✶	7 (medium)
Nguyen 2019	✶✶✶	✶✶	✶✶✶	8 (high)
Ranthe 2013 #	✶✶✶✶	✶	✶✶	7 (medium)
Daly 2018 ##	✶✶✶✶	✶	✶✶	7 (medium)
Rajaei 2019*	✶✶✶	✶	✶✶	6* (low)

Score based on Newcastle Ottawa scale for cohort studies. * = Newcastle Ottawa score for case-control study. # = newly published study on history of miscarriage and maternal risk of stroke, ## = newly published study on history of gestational diabetes mellitus and maternal risk of stroke.

Chapter 4 Supplemental tables

Supplemental Table S4.1. General characteristics of systematic reviews included in the umbrella review

Supplemental Table S4.2. Summary of main findings, existing guidelines and recommendations for clinical practice and research

Supplemental Table S4.3: Tabular presentation of findings: Meta-analysis

Supplemental Table S4.4. Tabular presentation of findings: Narrative syntheses

Supplemental Table S4.5: General study characteristic for studies evaluating the association between breastfeeding and maternal risk of cardiovascular disease

Supplemental Table S4.1. General characteristics of systematic reviews included in the umbrella review.

Author/Year	Systematic review objective	Reproductive Factor	Comparator	Population source (number of participants)	Outcome	Study designs (number of studies)	Quality Appraisal Tool	Funding source
Fertility-related factors								
Xu Chen 2018 [34]	To clarify the dose-response relationship between age at menarche and all-cause mortality and cardiovascular disease mortality	Menarche	Reference category	General (2,341,769)	Cardiovascular disease mortality; ischaemic heart disease mortality; stroke mortality	Cohort (12)	NOS	National Natural Science Foundation China
Prentice and Viner [202]	To examine whether pubertal timing is related to long-term cardiovascular morbidity and mortality	Menarche before age of 12 years	Menarche after 12 years	General (NP)	Cardiovascular disease morbidity	Cohort (6) Case control (4)	CEBM	None
Glisic 2018 [191]	To determine impact of progesterone only contraceptive use on cardiometabolic outcomes (venous thromboembolism, myocardial infarction, stroke)	Progestin-only contraceptive	Non-users of progesterone only contraceptives	General (62,088)	Myocardial infarction; stroke	Cohort (7) Case-control (10) Nested case-control (2)	NOS	None
Zhenlin Xu 2015 [186]	Evaluate risk of ischaemic stroke associated with first ever use of any oral contraceptive pills and describe influence of oestrogen dose, progesterone, and study characteristics	Any oral contraceptive pill	Ever and never users of any oral contraceptive pill	General (1,701,114)	Ischaemic stroke	Cohort (3) Case-control (15)	NOS	National Natural Science Foundation of China
Zhenlin Xu 2018 [190]	To estimate risk of haemorrhagic stroke among current users of any oral contraceptive pill and how risk is affected by study characteristics	Any oral contraceptive pill	Ever and never users of any oral contraceptive pill	General (1,701,114)	Haemorrhagic stroke (subarachnoid haemorrhage and intra-cranial haemorrhage)	Cohort (5) Case-control (10)	NOS	National Natural Science Foundation of China

Roach 2015 [195]	To estimate myocardial infarction and ischaemic stroke in users and non-users of diverse types, generations, and doses of hormonal contraceptives	Combined oral contraceptive	Ever and never users of combined oral contraceptive	General (NP)	Myocardial infarction; stroke	Cohort (1) Case-control (23)	ROBIS	None
Horton 2016 [205]	To evaluate whether combined hormonal contraceptive use modifies the risk of acute myocardial infarction, stroke, venous thromboembolism, central venous thrombosis, in obese women and evaluate evidence of a dose-response relationship between BMI and venous thromboembolism	Combined oral contraceptive use in obese women	Combined oral contraceptive use in normal weight women; obese women not on combined oral contraceptive	Obese women (NP)	Acute myocardial infarction; stroke	Cohort (1) Case-control (11) Pooled studies (3)	U.S. Preventive Services Task Force	None
Sheikh Hu 2016 [193]	To assess whether risk of stroke is associated with oestrogen dose and whether there is synergism between migraine and combined hormonal contraceptives	Oestrogen-containing contraceptives	Not on oestrogen-containing contraceptives	Migraineurs (NP)	Stroke	Cohort (1) Case-control (11) Mixed cohort and case-control (2) Cross-sectional (1)	NOS GRADE	International Headache Academy
Tepper 2016 [203]	Risk of venous thromboembolism and arterial thromboembolism among women using non-oral combined hormonal contraceptives compared to women using combined oral contraceptives	Non-oral combined hormonal contraceptives (combined hormonal patch, ring and injectables)	Levonorgestrel and nomegestrol containing combined oral contraceptives	General (NP)	Acute myocardial infarction; stroke	Cohort (4) Case-control (4)	U.S. Preventive Services Task Force	Department of Reproductive Health and Research, WHO
Dragoman 2015 [204]	To investigate whether combined hormonal contraceptives modify the risk of myocardial	Combined hormonal contraceptive pills, transdermal patches, vaginal rings and	Combined oral contraceptive use without dyslipidaemia	Women with dyslipidaemia (NP)	Acute myocardial infarction; cerebrovascular accident	Case-control (1) Cohort (1)	U.S. Preventive Services Task Force	Department of Reproductive Health and Research, WHO

	infarction, stroke, venous thromboembolism, pancreatitis among women with dyslipidaemia, and determine whether existing lipid abnormalities worsen with combined hormonal contraceptive use	injectables in dyslipidaemia patients						
Zhou 2017 [209]	To investigate the link between polycystic ovary syndrome and stroke, death from any cause and whether BMI might explain higher risk of stroke	Polycystic ovary syndrome	Women without polycystic ovary syndrome	General (237,647)	Stroke	Cohort (9)	NOS	None
Zhao 2016 [185]	Summarise evidence on the association between polycystic ovary syndrome and cardiovascular disease	Polycystic ovary syndrome	Women without polycystic ovary syndrome	General (104,392)	Cardiovascular disease; coronary heart disease	Cohort (5) Case-control (5)	NOS	None
Tehrani 2019 [189]	To investigate whether cardiovascular events are increased in women with polycystic ovary syndrome and explore difference in polycystic ovary syndrome events in reproductive age women compared to menopausal/aging women who had polycystic ovary syndrome during their younger ages	Polycystic ovary syndrome	Healthy women without polycystic ovary syndrome	General (NP)	Cardiovascular disease; cardiovascular mortality; coronary heart disease; stroke; heart failure	Cohort (12) Case-control (1) Cross-sectional (3)	NOS	National Institute for Medical Research Development (NIMAD)
Dayan 2017 [212]	Summarise data linking fertility therapy with subsequent cardiovascular disease	Fertility therapy, ovulation induction drugs, ovulation stimulation drugs, in vitro fertilisation,	Women without fertility therapy	General population (NP)	Coronary ischemia; cardiovascular death; cardiovascular hospitalisations; heart failure; myocardial	RCT (1) Cohort (2) Case-cohort (1)	ACROBAT-NRSI	Heart and Stroke Foundation of Canada Grant in Aid

		intra-uterine insemination			infarction; stroke and transient ischaemic attack			
Haichen Lv 2015 [213]	Quantitatively assess the association between parity and cardiovascular disease mortality by summarizing evidence from prospective studies	Ever Parity	Nulliparous	General (994,810)	Cardiovascular disease mortality	Cohort (10)	NOS	None
Wenzhen Li 2018 [214]	A meta-analysis of cohort studies to investigate the association between parity and cardiovascular disease risk	Ever parity	Nulliparous	General (3,089,929)	Cardiovascular disease morbidity	Cohort (10)	NOS	China Postdoctoral Science Foundation
Nguyen 2017 [215]	Examine association between breastfeeding and maternal cardiovascular disease risk factors and outcomes	Breastfeeding	Breastfeeding less than 7 months	General (NP)	Subclinical and clinical cardiovascular disease (prevalence, incidence, mortality); cardiovascular disease risk factors	RCT (1) Cohort (10) Cross-sectional (9)	An adapted 15-item checklist derived from checklists for the reporting of observational studies	None
Roeters van Lennep, 2014 [220]	To assess the relationship between premature ovarian insufficiency and risk of ischaemic heart disease, stroke and overall cardiovascular disease	Premature ovarian insufficiency	Women without premature ovarian insufficiency	General (190,588)	Ischaemic heart disease (fatal and non-fatal); stroke (fatal and non-fatal); total cardiovascular disease (fatal and non-fatal)	Cohort (10)	Downs and Black	Dutch Society of Medical Specialists
Tao 2015 [199]	To systematically evaluate the association of all-cause, cardiovascular disease and all cancer mortality in women with premature ovarian insufficiency and early natural menopause	Premature ovarian insufficiency (Menopause<40 yrs.) Early natural menopause (Menopause at 40-44 yrs.>)	Menopause at >45 years	General (NP)	Cardiovascular disease mortality; ischaemic heart disease mortality; stroke mortality	Cohort (7)	NOS	None

Muka 2016 [197]	To systematically review and meta-analyse studies evaluating age at onset of menopause and time since onset of menopause and cardiovascular disease risk	Early menopause	Menopause at age >45 years; menopause at age 50-54 years	General (342,284)	Ischaemic heart disease (fatal and non-fatal); stroke (fatal and non-fatal); cardiovascular disease (fatal and non-fatal)	Cohort (24) Case-control (2) Cross-sectional (6)	NOS	Metagenetics
Muka 2016 [221]	To investigate the association between menopausal symptoms and cardiovascular disease	Vasomotor symptoms (hot flushes and night sweats) and menopausal symptoms (depression, panic attack, insomnia)	Women without menopausal symptoms	General (213,976)	Cardiovascular disease, coronary heart disease, stroke	Cohort (10)	NOS	Metagenics Inc
Adverse pregnancy outcomes								
Oliver-Williams 2015 [222]	To confirm or refute the association between miscarriage and future cardiovascular disease	History of miscarriages; history of recurrent miscarriages	Women without miscarriages	General (NP)	Coronary heart disease; stroke	Cohort (5) Case-control (5)	NOS	Medical Research Council (MRC) PhD Studentship
Brouwers 2018 [223]	To evaluate all evidence on the risk of developing future hypertension and cardiovascular disease after multiple pregnancies complicated by pre-eclampsia compared with pre-eclampsia in a single pregnancy followed subsequently by a normal pregnancy	Recurrent pre-eclampsia	A single episode of pre-eclampsia followed by uneventful pregnancies	General (52,544)	Cerebrovascular accident; ischaemic heart disease. thromboembolism, atherosclerosis; heart failure; fatal cardiovascular disease; hypertension or cardiovascular disease hospitalisation as an outcome	Cohort (6)	NOS	None
Pensee Wu 2017 [200]	To systemically evaluate and quantify the relationship between pre-eclampsia and future cardiovascular disease	Pre-eclampsia	Women without pre-eclampsia	General (6.4 million)	Heart failure; coronary heart disease (fatal and non-fatal); cardiovascular disease (fatal and non- fatal); stroke (fatal and non-fatal)	Cohort (18) Cross-sectional (4)	NOS	North Staffordshire Heart Committee

Kramer 2019 [201]	Evaluate the impact of gestational diabetes on future incidence of cardiovascular disease.	Gestational diabetes	Women without gestational diabetes	General population (5,390,591)	Cardiovascular disease	Cohort (8) Case-control (1)	NOS	None
Jing Li 2018 [182]	To investigate the effect of diabetes mellitus on long-term cardiovascular disease risk	Gestational diabetes	Pregnant women without gestational diabetes	General (3,417,020)	Coronary artery disease; stroke	Cohort (7)	Moderate	Tianjin Medical University's Talent Recruitment Grant and the National 13th 5-Year's Plan Grant of China
Pensee Wu 2018 [183]	To systematically evaluate the evidence on the association between preterm births and future maternal risk of cardiovascular disease	Preterm birth	Pregnant women without preterm birth	General (5,813,682)	Cardiovascular disease; cardiovascular disease death; coronary heart disease; coronary heart disease death; stroke; stroke death	Cohort (15) Case-control (3) Cross-sectional (1)	NOS	North Staffordshire Heart Committee
Heida 2014 [226]	To summarise evidence on the association between history of spontaneous preterm delivery and risk of ischaemic heart disease, stroke, and cardiovascular disease	Preterm birth	Uncomplicated pregnancies	General (4,172,204)	Fatal and non-fatal ischaemic heart disease, stroke, and cardiovascular disease	Cohort (10)	NOS	Quality fund (SKMS) of the Netherlands Association of Medical Specialists
Robbins 2014 [184]	Summarise evidence on preterm birth and cardiovascular disease morbidity or mortality	Preterm birth	Uncomplicated pregnancies	General	Fatal and non-fatal cardiovascular disease, stroke, ischaemic heart disease, atherosclerosis	Cohort (8) Cross-sectional (1) Cohort-nested case-control (1)	Community Guide's methods	None
Bolijn 2016 [211]	To provide an overview of the current evidence on the association between reproductive factors and risk of heart failure	Parity; gravidity. age at menopause; preterm delivery and small for gestational age; gestational diabetes; polycystic ovary syndrome; hysterectomy; hypertensive disorders		General (NP)	Heart failure	RCT (1) Cohort (15) Case-control (2) Cross-sectional (3)	Quality assessment tools from the NHLBI and NIH	None

		of pregnancy; reproductive duration and age at first hormonal replacement therapy						
Grandi 2019 [38]	To determine an association between a broad array of pregnancy complications and cardiovascular disease	Hypertensive disorders of pregnancy; placental abruption; preterm birth; gestational diabetes; low birth weight; small for gestational age; stillbirth; miscarriage	Women without pregnancy complications	General (28,993,438)	Cardiovascular disease (coronary heart disease, cerebrovascular accident, myocardial infarction, coronary revascularisation, transient ischaemic attack, stroke); cardiovascular disease mortality.	Cohort (73) Case-control (11)	ROBINS-I	Personal funding

ACROBAT-NRSI A Cochrane Risk Of Bias Assessment Tool for Non-Randomised Studies of Interventions BMI = body mass index, CEBM = Centre for evidenced based medicine, GRADE = Grading of Recommendations, Assessment, Development and Evaluation, NHLBI = National Lung and Blood Institute, NIH = National Institute of Health, NP = not provided, NOS = Newcastle Ottawa Scale, RCT = randomised controlled trial, ROBINS-I = risk of bias in non-randomised studies – of interventions, ROBIS-I = risk of bias in systematic reviews, SKMS = Stichting Kwaliteitsgelden Medisch Specialisten (Quality Assurance Medical Specialists Foundation), WHO = World Health Organisation.

Supplemental Table S4.2: Summary of main findings, existing guidelines and recommendations for clinical practice and research

Reproductive factor	Systematic review ID (AMSTAR 2 rating)	Primary study design (number)	Outcome by fatality type: Effect size (95% CI)	Mention of female-specific risk factors in the current UK (NICE/RCOG/FSRH) guidelines	Umbrella review comments
Fertility-related factors					
Early menarche					
	Prentice and Viner 2012[202] (Moderate)	Cohort (5)	Non-fatal composite cardiovascular disease: HR 1.15 (1.02 to 1.28)	No mention as part of cardiovascular disease risk assessment in any guidelines.	**Conclusion:** Early age at menarche was associated with cardiovascular disease risk. **Recommendations:** (1) Recognition of early menarche as a risk enhancing factor for cardiovascular disease in cardiovascular disease prevention guidelines. (2) Periodic evaluation of cardiovascular disease risk factors among women history of early age at menarche
	Xu Chen 2018[34] (Moderate)	Cohort (6) Cohort (7) Cohort (6)	Fatal Composite cardiovascular disease: RR 0.99 (0.98 to1.01) Fatal ischaemic heart disease; RR 0.97 (0.95 to 0.99) Fatal stroke: RR 0.983 (0.954 to1.012)		
Hormonal contraceptives (oral)					
Oral contraceptive pills (includes either combined oral contraceptive or progesterone-only pills)	Zhenlin Xu 2015[186] (Moderate)	Cohort (3), Case-control (15)	Non-fatal ischaemic stroke: OR 2.47 (2.04 to 2.99)	***FSRH (UK):***[248]Recommends women to be advised that current combined oral contraceptive use is associated with increased risk of myocardial infarction and stroke. The risk may be magnified when combined oral contraceptives are used in women with additional cardiovascular disease risks. Based on an out of date meta-analysis, the guideline notes that combined hormonal contraceptive use is not associated with increased risk of haemorrhagic stroke.	**Conclusion:** Oral contraceptive pill use (combined oral contraceptives and progesterone-only contraceptives) compared to non-use was associated with increased risk of cardiovascular disease outcomes including haemorrhagic stroke. Progesterone-only contraceptive use was not associated with increased cardiovascular disease risk. Despite the increased risk in relative terms, the absolute risk for myocardial infarction (10.1/100000 person-years) and stroke (21/100000 person-years) among combined oral contraceptive users is low.[157] **Recommendations:** An update of current guidelines is needed to reflect recent evidence
	Zhenlin Xu 2018[190] (Moderate)	Cohort (5) Case-control (10)	Non-fatal haemorrhagic stroke: OR 1.39 (1.05 to 1.83)		
Combined oral contraceptive pills	Roach[195] 2015 (Moderate)	Case-control (11) Case-control (10)	Fatal and non-fatal myocardial infarction: RR 1.6 (1.3 to 1.9) Fatal and non-fatal ischaemic stroke: RR 1.7 (1.5 to 1.9)		
Progesterone only contraceptives	Glisic 2018[191] (Moderate)	Cohort (1) Case-control (4) Cohort (1)	Non-fatal myocardial infarction, oral route**:** (progesterone-only contraceptives): RR 0.98 (0.66 to 1.47)		

		Case-control (4)	Non-fatal stroke, oral formulation (progesterone-only contraceptives): RR 1.02 (0.72 to 1.44)		that links current combined oral contraceptive use to increased risk of haemorrhagic stroke. Caution in the use of combined oral contraceptives among women with sex-specific risk factors for cardiovascular disease.
Hormonal contraceptives (non-oral)					
Combined non-oral hormonal contraceptives (transdermal patch, vaginal and injectables)	Tepper 2016[203] (Low)	Cohort (1) Case-control (1) Cohort (1) Case-control (1)	Non-fatal myocardial infarction: OR 0.2 to OR 1.6; the null value of 1 crossed in all the included studies Non-fatal stroke: OR 0.8 to OR 1.2; the null value of 1 crossed in all the included studies	Evidence does not support an association between non-oral combined hormonal contraceptives and risk of myocardial infarction or stroke.	**Conclusion:** No association was found in the limited number of studies available **Recommendations (future research):** Studies investigating the association between non-oral hormonal contraceptive use and cardiovascular disease risk are sparse. Well-conducted observational studies are needed to investigate the cardiovascular safety of non-oral forms of hormonal contraceptives.
Progesterone only Contraceptives (injectable, and intra-uterine)	Glisic 2018[191] (Moderate)	Cohort (1) Case-control 2) Cohort (1) Case-control (2)	Non-fatal myocardial infarction, non-oral route (implants, injectable, intra-uterine): RR 1.10 (0.77 to 1.56) Non-fatal stroke, non-oral formulation (implants, injectable, intrauterine): RR 0.78 (0.60 to 1.00)		
Hormonal contraceptive use among women with co-existing illness					
Oestrogen containing contraceptives (Oral, patch and ring) use among women with migraine	Sheikh Hu 2016 [193] (Moderate)	Case-control (5) Mixed Cohort & Case-control (1)	Fatal and non-fatal ischaemic stroke: OR 2.08 to OR 16.9	***FSRH-UK MEC:***[453] Recommend caution in use of oestrogen-containing contraceptive pills among women with migraine, dyslipidaemia, obesity and hypertension as these are established risk factors for cardiovascular disease.	**Conclusion:** Combined oral contraceptive use among women with migraine, dyslipidaemia or hypertension compared to non-use among women without these conditions was associated with higher risks of cardiovascular disease. **Recommendations (future research):** (1) No evidence regarding the cardiovascular safety of non-oral forms of combined hormonal contraceptive use (patch, ring or injectables) in pre-existing conditions that predispose to cardiovascular disease risk were identified from the reviews. Well-conducted observational studies are needed to clarify their safety profile. (2) There was conflicting evidence on the association between combined hormonal contraceptive use in obese women compared to non-use in women of normal weight and the risk
Combined hormonal contraceptives (oral pills, transdermal patch, vaginal rings,) among women with dyslipidemia	Dragoman 2015[204] (Moderate)	Case-control (1) Cohort (1)	Non-fatal myocardial infarction: OR 25 (6 to 109) Non-fatal stroke: IRR 1.76 (1.51 to 2.06)		

Combined hormonal oral pills, transdermal patch, vaginal rings,) contraceptive use in obese women **Combined oral contraceptive use among women with hypertension**	Horton 2016[205] (Low) Curtis 2006[208] (Low)	Case-control (3) Case-control (3) Case-control (4) Case-control (8)	Non-fatal myocardial infarction: OR 0.88 to OR 5.1 Non-fatal stroke: OR 0.59 to OR 4.6 Non-fatal myocardial infarction: OR 6 to OR 68. All studies reported statistically significant results Non-fatal ischaemic stroke: OR 3.1 to OR 14.5. All studies reported statistically significant results		of cardiovascular disease outcomes. Well-designed observational studies are needed to clarify the cardiovascular disease risk posed by combined hormonal contraceptive use in obese women. (3) No evidence regarding the cardiovascular safety of progesterone-only contraceptive use among women with co-existing conditions that predispose to cardiovascular disease risk were identified. Well-conducted observational studies are needed to clarify their safety profile.
Polycystic ovary syndrome					
	Zhao 2016[185] (Moderate) Zhous 2017[209] (Moderate) Bolijn 2017[211] (Moderate) Tehrani 2019[189] (Low)	Cohort (5) Case-control (5) Cohort (2) Case-control (3) Cohort (9) Cross-sectional study (1) Cohort (6) Cross-sectional study (1) Cohort (1)	Non-fatal cardiovascular disease: OR 1.30 (1.09 to 1.56) Non-fatal ischaemic heart disease: OR 1.44 (1.13 to 1.84) Non-fatal stroke: OR 1.36 (1.09 to 1.7) Non-fatal heart failure: OR 3.24 (0.53 to 19.94) Non-fatal composite cardiovascular disease: HR 1.43 (1.27 to 1.61) in reproductive age polycystic ovary syndrome patients. Non-fatal composite cardiovascular disease: HR 1.03 (0.41 to 2.59) in	***NICE/RCOG:***[454] Recognises cardiovascular disease risk factors are more prevalent among women with polycystic ovary syndrome. Recommends for prospective studies to investigate the association between polycystic ovary syndrome and cardiovascular disease risk.	**Conclusion:** Polycystic ovary syndrome was associated with an increased risk of cardiovascular disease outcomes **Recommendation/future research:** (1) Inclusion of polycystic ovary syndrome as a risk enhancing factor for cardiovascular disease in current cardiovascular disease prevention guidelines**.** (2) Periodic assessment for cardiovascular disease risk factors among women with polycystic ovary syndrome. (3) No association was found between polycystic ovary syndrome and heart failure risk. Evidence was derived from a single cross-sectional with a small sample size leading to imprecise estimates. Well-designed observational studies are needed to investigate this association.

			menopausal age polycystic ovary syndrome patients		
Fertility therapy					
Fertility therapy (in-vitro fertilisation, intrauterine insemination)	Dayan 2017[212] (Moderate) Bolijn 2017[211] (Moderate)	Cohort (3) RCT (1) Cohort (2) Cohort (1)	Fatal and non-fatal cardiovascular disease: HR 0.91 (0.67 to 1.25) Fatal and non-fatal stroke: HR 1.25 (0.96 to 1.63) Fatal and non-fatal heart failure: HR 0.60 (0.30 to 1.22)	***NICE:***[455] Recommends providing patients with information on the long-term risks associated with fertility therapy. No mention of potential long-term cardiovascular disease risk.	**Conclusion:** Women on fertility therapy compared to those without fertility therapy were not at an increased risk of cardiovascular disease. **Recommendations (future research):** Evidence was derived from few observational studies resulting in imprecise estimates**.** Prospective cohort studies are needed to investigate the long-term cardiovascular disease risk associated with fertility therapy.
Parity					
	Wenzhen Li 2018[214] (Moderate) Haichen Lv 2015[213] (Moderate)	Cohort (9) Cohort (6)	Non-fatal and fatal cardiovascular disease: RR 1.14 (1.09 to 1.18) Fatal cardiovascular disease: RR 0.79 (0.60 to 1.06)	**NICE**:[456] No mention of long-term maternal cardiovascular disease risk and follow-up.	**Conclusion:** Higher parity compared to nulliparity was associated with morbidity but not mortality from cardiovascular disease. The dose-response analysis revealed a J-shaped association between parity and risk of cardiovascular disease outcomes with increasing parity linked to higher cardiovascular disease risk. **Recommendations:** (1) Update of cardiovascular disease prevention guideline to recognise multiparity risk as a risk-enhancing factor for cardiovascular disease. (2) Periodic evaluation of cardiovascular disease risk factors among women with high parity (>5).
Breastfeeding*					
	Nguyen 2017[215] (Moderate)	Cohort (9) Case-control (1)	Overall, ever breastfeeding and a longer lactation duration was associated with reduced risk of non-fatal and fatal cardiovascular disease outcomes.	NICE: No mention of cardiovascular benefits of breastfeeding.[456]	**Conclusion:** Breastfeeding and longer lactation duration is associated with decreased risk of cardiovascular disease. **Recommendations:** Breastfeeding information should be included within ante-natal clinics to advise women of the reduced risk.

Premature ovarian insufficiency					
	Roeters van Lennep 2014[220] (Moderate) Tao 2015[199] (Moderate)	Cohort (2) Cohort (7) Cohort (7) Cohort (7) Cohort (3) Cohort (4)	Fatal and non-fatal cardiovascular disease: HR 1.61 (1.22 to 2.12) Fatal and non-fatal ischaemic heart disease: HR 1.69 (1.29 to 2.21) Fatal and non-fatal stroke: HR 1.03 (0.88 to 1.99) Fatal cardiovascular disease: RR 1.24 (0.98 to 1.58) Fatal ischaemic heart disease: RR 1.48 (1.02 to 2.16) Fatal stroke: RR 1.00 (0.86 to 1.16)	***NICE:***[457] Recognises that women with premature ovarian insufficiency are potentially at increased risk of cardiovascular disease complications. Recommends future research to clarify the long-term effects of premature ovarian insufficiency on psychological and physical health including cardiovascular disease.	**Conclusion:** Premature ovarian insufficiency was associated with an increased risk of cardiovascular disease. **Recommendations:** (1) Update of current guideline to reflect current evidence on the association between premature ovarian insufficiency and cardiovascular disease risk. (2) Periodic evaluation for the presence of cardiovascular disease risk factors among women with premature ovarian insufficiency.
Menopause					
Early menopause (natural and surgical)	Muka 2016[197] (Moderate) Bolijn 2017[211] (Moderate)	Cohort (3) Cross-sectional study (2) Cohort (1) Cohort (4) Cross-sectional study (2) Cohort (5) Cohort (4) Cross-sectional study (2) Cohort (5) Cohort (2)	Fatal cardiovascular disease: RR 1.19 (1.08 to 1.31) Non-fatal cardiovascular disease: RR 1.56 (1.08 to 2.26) Fatal ischaemic heart disease: RR 1.11 (1.03 to 1.20) Non-fatal ischaemic heart disease: RR 1.50 (1.28 to 1.76) Fatal stroke: RR 0.99 (0.92 to 1.07) Non-fatal stroke: 1.23 (0.98 to 1.53) Non-fatal heart failure: HR 1.36 to HR 1.66	***NICE***:[457] No mention on long-term maternal cardiovascular disease risk and follow up.	**Conclusion**: Early menopause and menopausal symptoms were associated with increased cardiovascular disease risk. **Recommendations:** (1) Update of current guideline to reflect current evidence on the association between early menopause and menopausal symptoms and cardiovascular disease risk. (2) Periodic evaluation for the presence of cardiovascular disease risk factors among women with early menopause.
Early natural menopause	Tao 2015[199] (Moderate)	Cohort (9)	Fatal cardiovascular disease: RR 1.10 (0.91 to 1.13)		

		Cohort (4) Cohort (5)	Fatal ischaemic heart disease: RR 1.09 (1.00 to 1.18) Fatal stroke: RR 0.94 (0.86 to 1.03)		
Menopausal symptoms	Muka 2016[221] (Moderate)	Cohort (4) Cohort (7) Cohort (3)	Fatal and non-fatal cardiovascular disease: RR 1.29 (0.98 to 1.71) Fatal and non-fatal ischaemic heart disease: RR 1.18 (1.03 to 1.35) Fatal and non-fatal stroke: RR 1.08 (0.89 to 1.32)		
Adverse pregnancy outcomes					
Pregnancy loss					
Miscarriage	Oliver-Williams 2013[222] (Moderate) Grandi 2019[38] (Moderate)	Cohort (3) Case-control (5) Cohort (2) Case-control (1) Cohort (6) Case-control (1)	Fatal and non-fatal ischaemic heart disease: OR 1.45 (1.18 to 1.78) Fatal and non-fatal stroke: OR 1.11 (0.72 to 1.69) Fatal and non-fatal cardiovascular disease: OR 0.83 to 2.69	***NICE:*** No mention of long-term maternal cardiovascular disease risk.[458–460]	**Conclusion:** History of pregnancy loss (miscarriage and stillbirth) was associated with an increased risk of cardiovascular disease. **Recommendations:** (1) Pregnancy loss (miscarriage and stillbirths) should be included in relevant guidelines as risk enhancing factors for cardiovascular disease. (2) Periodic evaluation of cardiovascular disease risk factors among women history of pregnancy loss.
Recurrent Miscarriage	Oliver-Williams 2013[222] (Moderate)	Cohort (3) Case-control (4)	Fatal and non-fatal ischaemic heart disease: OR 1.99 (1.13 to 3.50)		
Stillbirth	Grandi 2019[38] (Moderate)	Cohort (4) Cohort (4)	Non-fatal composite cardiovascular disease: OR 1.49 (1.08 to 2.06) Fatal composite cardiovascular disease: OR 2.23 (1.90 to 2.62)		
Hypertensive disorders of pregnancy					
Pre-eclampsia	Grandi 2019[38] (Moderate)	Cohort(16) Cohort (6)	Non-fatal composite cardiovascular disease: OR 2.24 (1.72 to 2.93) for moderate pre-eclampsia Non-fatal composite cardiovascular disease: OR 2.74 (2.48 to 3.04) for severe pre-eclampsia	***NICE:***[461] Recognises that hypertensive disorders of pregnancy are associated with a 1.5-3-fold risk of cardiovascular disease outcomes. Women with hypertensive disorders of pregnancy should be advised on	**Conclusion:** Hypertensive disorders of pregnancy (pre-eclampsia and gestational hypertension) were associated with an increased risk of cardiovascular disease.

		Cohort (9) Cohort (9)	Fatal composite cardiovascular disease: OR 1.73 (1.46 to 2.06) Non-fatal cerebrovascular accident: OR 2.95 (1.10 to 7.90)	the increased cardiovascular disease risk. Recommends that such women should maintain a healthy lifestyle including avoiding smoking and maintaining an appropriate weight.	**Recommendation:** Periodic evaluation of cardiovascular disease risk factors among women with history of hypertensive disorders of pregnancy.
	Pensee Wu 2017[200]((Moderate)	Cohort (4) Cohort (4) Cohort (4)	Fatal ischaemic heart disease: RR 2.10 (1.25 to 3.51) Non-fatal stroke: OR 2.95 (1.10 to 7.90) Fatal stroke: RR 1.97 (0.80 to 4.88) Non-fatal heart failure: RR 4.19 (2.09 to 8.38)		
Recurrent pre-eclampsia	Brouwers 2018[223] (Moderate)	Cohort (2) Cohort (2) Cohort (3)	Non-fatal ischaemic heart disease: RR 2.40 (2.15 to 2.68) Non-fatal stroke: RR 1.69 (1.21 to 2.35) Non-fatal Heart failure: RR 2.88 (2.23 to 3.72)		
Gestational hypertension	Grandi 2019[38] (Moderate)	Cohort (9) Cohort (4)	Non-fatal cardiovascular disease: RR 1.67 (1.28 to 2.19) Non-fatal stroke: RR 1.83 (0.79 to 4.22)		
Gestational diabetes mellitus					
	Kramer 2019[201] (Moderate)	Cohort (8) Case-control (1)	Non-fatal and fatal cardiovascular disease: RR 1.98 (1.57 to 2.50)	***NICE:***[462] No mention of maternal cardiovascular disease risk assessment and long-term follow-up.	**Conclusion:** History of gestational diabetes mellitus was associated with an increased risk of cardiovascular disease. **Recommendations**: (1) Updating of current guidelines to include gestational diabetes as a risk enhancing factor for cardiovascular disease. (2) Periodic evaluation of cardiovascular disease risk factors among women with a history of gestational diabetes.
	Jing Li 2018[182] (Moderate)	Cohort (4) Cohort (2)	Non-fatal coronary artery disease: RR 2.09 (1.56 to 2.80) Non-fatal stroke: RR 1.25 (1.07 to 1.48)		
Placental abruption					
	Grandi 2019[38] (Moderate)	Cohort (7)	Fatal and non-fatal composite cardiovascular disease: OR 1.82 (1.42 to 2.33)	***RCOG:***[463] No mention of maternal cardiovascular disease risk assessment and long-term follow-up .	**Conclusion:** History of placental abruption was associated with an increased risk of cardiovascular disease.

					Recommendations: (1) Updating of guidelines to include placental abruption as a risk enhancing factor for cardiovascular disease. (2) Periodic evaluation of cardiovascular disease risk factors among women with a history of placental abruption.
Preterm birth					
Preterm birth	Grandi 2019[38] (Moderate) Pensee Wu 2018[183] (Moderate) Heida 2014 [226] (Moderate) **Recurrent preterm birth**	Cohort (12) Cohort (4) Cohort (4) Cross-sectional study (1) Cohort (4) Cohort (6) Cohort (2) Cohort (4) Cohort (3) Cohort (3) Robbins 2014[184] (Moderate) Cohort (2)	Non-fatal cardiovascular disease: OR 1.63 (1.39 to 1.93) Fatal cardiovascular disease: OR 1.93 (1.83 to 2.03) Non-fatal ischaemic heart disease: RR 1.49 (1.38 to 1.60) Fatal ischaemic heart disease: RR 2.11 (1.87 to 2.36) Non-fatal stroke RR 1.65 (1.51 to 1.79) Fatal stroke: RR 1.30 (0.94 to 1.80) Fatal- and non-fatal cardiovascular disease: HR 2.01 (1.52 to 2.65) Fatal and non-fatal ischaemic heart disease: HR 1.38 (1.22 to 1.57) Fatal and non-fatal stroke: HR 1.71 (1.53 to 1.91) Fatal and non-fatal composite cardiovascular disease: HR 1.4 to HR 1.8	***NICE***:[464] No mention of maternal cardiovascular disease risk assessment and long-term follow-up.	**Conclusion:** Maternal history of preterm birth was associated with later risk of cardiovascular disease **Recommendations**: (1) Updating of guidelines to include preterm birth as a risk enhancing factor for cardiovascular disease. (2) Periodic assessment of cardiovascular disease risk factors among women with a history of preterm births.
Low birth weight & small for gestational age					
	Grandi 2019[38] (Moderate)	Cohort (4)	Fatal and non-fatal composite cardiovascular disease: OR 1.29 (0.91 to 1.83)	***NICE***:[465] No mention of maternal cardiovascular disease risk assessment and long-term follow-up.	**Conclusion:** Maternal history of low birth weight and small for gestational age offspring was associated with increased cardiovascular disease risk.

	Grandi 2019[38] (Moderate)	Cohort (10)	Fatal and non-fatal composite cardiovascular disease: OR 1.09 to OR 3.50		**Recommendations:** (1) Updating of guidelines to include preterm birth as a risk enhancing factor for cardiovascular disease. (2) Periodic evaluation of cardiovascular disease risk factors among women with a history of small for gestational age offspring.

FSRH = Faculty of Sexual and Reproductive Health guidelines, FSRH-UK MEC = Faculty of Sexual and Reproductive Health guidelines, Faculty of Sexual and Reproductive Health, United Kingdom medical eligibility criteria, HR = hazard ratio, NICE = National Institute for Health and Care Excellence, OR = odds ratio, RCT = randomised controlled trial, RR = risk ratio, RCOG= Royal College of Obstetricians and Gynaecologists, * = updated systematic review

Supplemental Table S4.3. Tabular presentation of findings: Meta-analysis.

Reproductive factor	Study identity Author/Year	Outcome	Secondary Analysis	No of studies included	Participants	Evidence synthesis	I^2 statistic	Overall evidence of publication bias	AMSTAR 2 rating
Fertility-related factors									
Early age at menarche	Xu Chen 2018 [34]	Fatal ischaemic heart disease		7	NP	RR 0.969 (0.947-0.993)	44.9%	P = 0.573	Moderate
				6	NP	RR 0.983 (0.954-1.012)	58.1%	P = 0.881	
				6	NP	RR 0.993 (0.975-1.012)	53.1%	P = 0.091	
	Prentice and Viner [202]	Non-fatal CVD		5	126,083	HR 1.15 (1.02-1.28)	47%	None	Moderate
Combined oral contraceptive	Roach 2015 [195]	Fatal and non-fatal myocardial infarction		14	NP	RR 1.6 (1.3-1.9)	78.3%	Not assessed	
		Fatal and non-fatal stroke		13	NP	RR 1.7 (1.5 - 1.9)	78.3%		
		Fatal and non-fatal myocardial infarction and stroke	*Oestrogen dose*						
			20 µg	2	NP	RR 1.6 (1.4-1.8)	0.0%		
			30-40 µg	2	NP	RR 2.0 (1.4-3.0)	50.4%		
			>49 µg	2	NP	RR 2.4 (1.8-3.3)	29.6%		
		Fatal and non-fatal myocardial infarction and stroke	*Progestin generation*						
			1st	7	NP	RR 1.2 (0.8-1.9)	69.4%		
			2nd	8	NP	RR 1.1 (0.8-1.7)	82.0%		
			3rd	6	NP	RR 1.1 (0.7-1.7)	79.9%		
Oral contraceptive pills	Xu 2015 [186]	Non-fatal ischaemic stroke		18	NP	RR 2.47 (2.04-2.99)	77.5%	None	Moderate
			Oestrogen dose						
			20 µg	3	NP	OR 1.56 (1.36-1.79)	0.0%		
			30-40 µg	5	NP	OR 1.75 (1.61-1.89)	0.0%		

			<50 µg	11	NP	OR 1.97 (1.61-2.41)	68.4%		
			>50 µg	9	NP	OR 3.28 (2.49-4.32)	47.8%		
			Progesterone only pill	4	NP	OR 0.99 (0.71-1.37)	0.0%		
			Progestin combined with <50 µg oestrogen						
			1st	5	NP	OR 1.63 (0.97-2,75)	48.1%		
			2nd	5	NP	OR 2.17 (1.59 -2.97)	68.8%		
			3rd	5	NP	OR 2.01 (1.46-2.76)	65.4%		
			4th	5	NP	OR 1.52 (1.23-1.89)	0.0%		
			Progestin combined with all dose oestrogen						
			1st gen	8	NP	OR 2.71 (1.76-4.17)	50.4%		
			2nd gen	8	NP	OR 2.23 (1.88-2.98)	71.9%		
			Dyslipidaemia						
			Yes	5	NP	OR 2.24 (1.65-3.05)	74.8%		
			No	13	NP	OR 2.59 (2.08-3.24)	60.6%		
			Obesity						
			Yes (BMI >27.3)	3	NP	OR 1.78 (0.24-13.26)	87.0%		
			No (BMI <27.3)	3	NP	OR 2.03 (1.43-2.87)	6.2%		
			History of Migraine						
			Yes	6	NP	OR 6.33 (2.35-17.05)	80.6%		
			No	6	NP	OR 2.55 (1.10-5.91)	80.4%		
			Age						
			>35 years	6	NP	OR 3.08 (1.82-5.23)	56.4%		
			<35 years	6	NP	OR 1.82 (1.38-2.39)	0.0%%		
			Smoking						
			Current	7	NP	OR 4.90 (3.17-7.57)	42.3%		
			Non-current	7	NP	OR 2.59 (1.96-3.43)	12.5%		
			Blood pressure						
			Hypertensive	5	NP	OR 8.02 (5.53-11.64)	0.0%		
			Normotensive	5	NP	OR 2.73 (2.22-3.37)	5.3%		
	Xu 2018 [190]	Fatal and non-fatal haemorrhagic stroke		15	NP	OR 1.39 (1.05-1.83)	65.6%	None	Moderate
			Stroke subtype						
			Sub-arachnoid haemorrhage	10	NP	OR 1.60 (1.21-2.12)	41%		

			Intra-cranial haemorrhage	4	NP	OR 0.92 (0.33-2.54)	82.6%		
			Outcome						
			Morbidity	10	NP	OR 1.71 (1.82-2.29)	50.7%		
			Mortality	5	NP	OR 0.95 (0.59-1.50)	60.6%		
			Oestrogen dose						
			High	2	NP	OR 1.60 (1.12-2.27)	0.0%		
			Low	8	NP	OR 1.19 (0.86-1.66)	76.3%		
			Progestin						
			1st	3	NP	OR 0.91 (0.77-1.09)	0.0%		
			2nd	4	NP	OR 1.76 (1.25-2.48)	0.0%		
			3rd	4	NP	OR 1.70 (0.72-4.02)	-		
			Migraine						
			Ever	5	NP	OR 1.97 (1.19-3.27)	0.0%		
			Never	5	NP	OR 1.43 (0.84-2.43)	49.6%		
			Smokers						
			Current	6	NP	OR 4.52 (2.27-8.99)	80.8%		
			Non-current	5	NP	OR 1.35 (1.03-1.76	0.0%		
			Blood pressure						
			Hypertensive	5	NP	OR 6.02 (1.50-24.25	89.9%		
			Normotensive	3	NP	OR 1.37 (1.06-1.75)	0.0%		Moderate
Progesterone only pills	Glisic 2018 [191]	Non-fatal myocardial infarction		6	NP	RR 0.98 (0.66-1.47)	0%		
		Non- fatal stroke		6	NP	RR 1.02 (0.72-1.44	0%		
Polycystic ovary syndromme	Zhous 2017 [209]	Non-fatal stroke		8	28,977	OR 1.36 (1.09-1.7)	44.7%		Moderate
			BMI-adjusted						
			Yes	5		OR 1.24 (0.98-1.59)	32.2%		
			No	3		OR 2.2 (1.25-3.88)	42.4%		
			Polycystic ovary syndrome diagnosis						
			Definite	5		OR 1.84 (1.14-2.99)	18.2%		
			Possible	3		OR 1.25 (0.97-1.61)	65.7%		
			Mean age						
			>50 years	5		OR. 1.31(1.04-1.65)	21.4%		
			<50 years	3		OR 2.03 (0.93-4.43)	55.5%		

			Cohort type						
			Retrospective	4		OR 2.29(1.43-3.67)	27.5%		
			Prospective	4		OR 1.17(0.91-1.51)	0%		
			Sample size						
			<10,000	5		OR 1.56(0.81-2.99)	15.3%		
			>10000	3		OR 1.33 (1.09-1.69)	74.2%		
			Quality						
			Low	4		OR 1.36 (1.03-1.79	37.7%		
			High	4		OR 1.36 (0.94-1.97)	61.7%		
	Zhao 2016 [185]	Non-fatal CVD		10	104,392	OR 1.30 (1.09-1.56)	40%	None	Moderate
			Type of CVD						
			Non-fatal coronary heart disease	5	86,816	OR 1.44 (1.13-1.84)	59%		
			Non-fatal myocardial infarction	5	86,816	OR 1.01 (0.68-1.51)	0%		
	Tehrani 2019 [189]	Non-fatal CVD	*Age group of participants (Population based studies)*						Low
			Reproductive age group	12	NP	HR 1.429 (1.270-1.607)	73%		
			Menopausal age group	1	NP	HR 1.030 (0.410-2.588)	-		
Fertility Therapy	Dayan 2017 [212]	Fatal and non-fatal CVD		4	1,426,640	HR 0.91 (0.67-1.25)	36.6%	Not assessed	Moderate
Ever Parity versus Nulliparous (Ref)	Wenzhen Li 2018 [214]	Non-fatal CVD		13	3,089,929	RR 1.14 (1.09-1.18)	89.6%	None	Moderate
			CVD type						
			Coronary heart disease	7	NP	RR 1.14 (1.12-1.16)	51.1%		
			Ischaemic heart disease	2	NP	RR 1.23 (1.08-1.39)	0%		
			Stroke	4	NP	RR 1.08 (1.05-1.10)	0%		
			BMI adjusted						
			Yes	9	NP	RR 1.15 (1.10-1.21)	61.2%		
			No	4	NP	RR 1.11 (1.09-1.12)	64.1%		

			Hypertension adjusted						
			Yes	3	NP	RR 1.28 (1.16-1.42)	64.3%		
			No	10	NP	RR 1.11 (1.09-1.12)	51.1%		
			Smoking adjusted						
			Yes	9	NP	RR 1.15 (1.10-1.21)	61.2%		
			No	4	NP	RR 1.11 (1.09-1.12)	64.1%		
			Diabetes adjusted						
			Yes	9	NP	RR 1.15 (1.10-1.21)	61.2%		
			No	4	NP	RR 1.11 (1.09-1.12)	64.1%		
	Haichen Lv 2015 [213]	Fatal CVD		6	994,810	RR 0.79 (0.60-1.06)	90.9%	None	Moderate
Premature ovarian insufficiency	Roeters van Lennep, 2014 [220]	Fatal and non-fatal ischaemic heart disease		7	NP	HR 1.69 (1.29-2.21)	22%	Not assessed	Moderate
		Fatal and non-fatal stroke		7	NP	HR 1.03 (0.88-1.99)	0%		
		Fatal and non-fatal CVD		2	NP	HR 1.61 (1.22-2.12)	0%		
	Tao 2015 [199]	Fatal CVD		7	NP	RR 1.24(0.98-1.58)	0%		Moderate
		Fatal ischaemic heart disease		3	NP	RR 1.48(1.02-2.16)	0%		
		Fatal stroke		4	NP	RR 1.00 (0.86-1.16)	0%		
Early natural menopause	Tao 2015 [199]	Fatal CVD		9	NP	RR 1.10 (0.91-1.13)	29.4%		Moderate
		Fatal ischaemic heart disease		4	NP	RR 0.94 (0.86-1.03)	0%		
		Fatal stroke		5	NP	RR 1.31 (0.78-2.18)	77%		
Early menopause <45 years in comparison to women > 45 years	Muka 2016 [197]	Fatal CVD		5	65,653	RR 1.19 (1.08-1.31)	30%	None	Moderate
		Non-fatal coronary heart disease		5	50,125	RR 1.50 (1.28-1.76)	0%	None	
		Fatal coronary heart disease		6	130,284	RR 1.11 (1.03-1.20)	42%		
		Non-fatal stroke		5	49,246	RR 1.23 (0.98-1.53)	51%		
		Fatal stroke		6	143,833	RR 0.99 (0.92-1.07)	34%		

Onset of menopause at 45-49 years vs women > 50 years	Muka 2016 [197]	Fatal CVD		4	62,995	RR 0.99 (0.92-1.07)	0%	None	Moderate
		Non-fatal coronary heart disease		2	36,483	RR 1.12 (0.95-1.31)	0%		
		Non-fatal stroke		2	41,347	RR 0.95 (0.74-1.23)	0%		
		Fatal coronary heart disease		3	121,444	RR 0.98 (0.93-1.04)	0%		
		Fatal stroke		5	129,041	RR 1.03 (0.91-1.16)	0%		
Menopausal symptoms	Muka 2016 [221]	Fatal and non-fatal coronary heart disease		7		RR 1.14 (0.98-1.34)	79%		Moderate
		Fatal and non-fatal stroke		Single study	60,027	RR 1.14(0.82-1.59)	N/A	None	
			Type of menopausal symptom						
		Fatal and non-fatal coronary heart disease	Vasomotor symptoms	2	70,814	RR 1.28 (1.08-1.52)	0%		
		Fatal and non-fatal coronary heart disease	Non-vasomotor symptoms	5		RR 1.14 (0.98-1.34)	5%		
Adverse pregnancy outcomes									
Miscarriage	Oliver-Williams [222]	Fatal and non-fatal coronary heart disease		8	517,504	OR 1.45 (1.18-1.78)	28.2%	Inconclusive	Moderate
		Fatal and non-fatal stroke		6	NP	OR 1.11 (0.72-1.69)	62.5%	Not assessed	
Recurrent miscarriage		Fatal and non-fatal coronary heart disease		7	NP	OR 1.99 (1.13-3.50)	63.8%	Present; p=0.028	
Stillbirth	Grandi 2019 [38]	Non-fatal CVD		4	NP	OR 1.49 (1.08-2.06)	0%	Not assessed	Moderate
		Fatal CVD		4	1,528,862	OR 2.23 (1.90-2.62)	0%	Not assessed	

Pre-eclampsia	Pensee Wu 2018 [200]	Non-fatal heart failure		4	1,986,285	RR 4.19 (2.09-8.38)	71%	Not assessed	Moderate
		Fatal coronary heart disease		4	677,378	RR 2.10 (1.25-3.51)	89%	Not assessed	
		Fatal stroke		2	NP	RR 1.97 (0.80-4.88)	86%	Not assessed	
		CVD death							
			Follow up time						
			<1 year						
			1-10 years	1	NP	RR 2.30 (1.65-3.20)			
			>10 years	3	NP	RR 2.21 (1.73-2.81)			
	Grandi 2019 [38]	Non-fatal coronary heart disease		9	NP	OR 1.73 (1.46-2.06)	99%	Not assessed	Moderate
		Non-fatal cerebrovascular accident		9	NP	OR 1.73 (1.46-2.06)	60.6%	Not assessed	
			Severity						
			Moderate	16	NP	OR 2.24 (1.72-2.93)	95%	Not assessed	
			Severe	6	2,282,470	OR 2.74 (2.48-3.04)	0%	Not assessed	
Recurrent Pre-eclampsia	Brouwers 2018 [223]	Non-fatal coronary heart disease		2	69,012	RR 2.40 (2.15-2.68)	0 %	Not assessed	Moderate
		Non-fatal heart failure		3	61,757	RR 2.88 (2.23-3.72)	27%	Not assessed	
		cerebrovascular accident		2	9,585	RR 1.69 (1.21-2.35)	75%	Not assessed	
Gestational hypertension	Grandi 2019 [38]	Non-fatal cerebrovascular disease		4	61,757	RR 1.83 (0.79-4.22)	98.4%	Not assessed	Moderate
		Non-fatal CVD		9	3,204,633	RR 1.67 (1.28-2.19)	83.9%	Not assessed	
Gestational diabetes mellitus	Kramer 2019 [201]	Non-fatal and fatal CVD		9	5390591	RR 1.98 (1.57-2.50)	80.2%	Not assessed	Moderate
			Restricted to women who did not develop type 2 diabetes mellitus	5	2147236	RR 1.56 (1.04, 2.32)	98%	Not assessed	

	Jing Li 2018 [182]	Non-fatal coronary artery disease		4	3,079,357	RR 2.09 (1.56-2.80)	91.2%	None; p=0.43	Moderate
		Non-fatal stroke		2	1,516,323	RR 1.25 (1.07-1.48)	0%	None	
Placental Abruption	Grandi 2019 [38]	Fatal and non-fatal CVD		7	5,799,266	OR 1.82 (1.42-2.33	66%	Not assessed	Moderate
Preterm Birth	Pensee Wu 2017 [183]	Non-fatal coronary heart disease		4	2,411,083	RR 1.49 (1.38-1.60)	54%	Not assessed	Moderate
		Fatal coronary heart disease		5	1,459,690	RR 2.11 (1.87-2.36)	0%	Not assessed	
		Stroke		5	1,499,386	RR 1.65 (1.51-1.79)	0%	Not assessed	
		Fatal stroke		2	699030	RR 1.30 (0.94-1.80)	66%	Not assessed	
	Grandi 2019 [38]	Non-fatal CVD		12	NP	OR 1.63 (1.39-1.93)	91.1%	Not assessed	Moderate
		Fatal CVD		4	372,199	OR 1.93 (1.83-2.03)	0%	Not assessed	
	Heida 2014 [226]	Fatal and non-fatal ischaemic heart disease		3	1,936,178	HR 1.38 (1.22-1.57)	74%	Not assessed	Moderate
		Fatal and non-fatal stroke		4	1,173,705	HR 1.71 (1.53-1.91)	0	Not assessed	
		Fatal- and non-fatal CVD		4	2,462,165	HR 2.01 (1.52-2.65)	77%	Not assessed	
Low birth weight	Grandi 2019 [38]	Fatal and non-fatal CVD		4	2,445,956	OR 1.29 (0.91-1.83)	96.5%	Not assessed	Moderate
			Sensitivity analyses	3	NP	OR 1.46 (1.11-1.91)	80.2%	Not assessed	

BMI = body mass index, CVD = cardiovascular disease, HR = hazard ratio, OR = odds ratio, NP = not provided, RR = risk ratio.

Supplemental Table S4.4. Tabular presentation of findings: Narrative syntheses.

Reproductive factor	Author Year	Outcome	No of participants	Narrative summary Effect estimate (95% CI)	Reviewer's conclusions	Overall AMSTAR 2 rating for Review
Fertility-related factors						
Combined oral contraceptive use in obese women	Horton 2016 [205]	Non- fatal myocardial infarction	2,432	Tanis et al.[206] BMI <27.3 kg/m^2 not on combined oral contraceptive: Ref BMI <27.3 kg/m^2 on combined oral contraceptive: OR 2.4 (1.6-3.5) BMI ≥27.3 kg/m^2 not on combined oral contraceptive: OR 3.4 (2.2-5.3) BMI ≥27.3 kg/m^2 on combined oral contraceptive: OR 5.1 (2.7-9.6) Sidney et al.[466] BMI ≥27.3 kg/m^2 not on combined oral contraceptive: Ref BMI ≥27.3 kg/m^2 on combined oral contraceptive: OR 0.88 (0.33-2.36)	Evidence that combined hormonal contraceptive use modifies risk of myocardial infarction among obese women is inconclusive.	Low
		Non-fatal stroke	2,683	Kemmerman et al.[467] BMI <27.3 kg/m^2 no combined oral contraceptive: Ref BMI <27.3 kg/m^2 on combined oral contraceptive: OR 2.2 (1.5-3.0) BMI ≥ 27.3 kg/m^2 no combined oral contraceptive: OR 1.2 (0.7-2.2) BMI ≥27.3 kg/m^2 on combined oral contraceptive: OR 4.6 (2.4-8.9) Schwartz et al.,[430] BMI ≥ 27.3 kg/m^2 no combined oral contraceptive: Ref BMI ≥27.3 kg/m^2 on combined oral contraceptive: ischemic stroke pooled OR 0.59 (0.16-2.12); haemorrhagic stroke pooled OR 1.06 (0.35-3.21)	Evidence that combined hormonal contraceptive use modifies risk of stroke among obese women is inconclusive.	

Oestrogen-containing contraceptives use among women with migraine	Sheikh Hu 2016 [193]	Stroke	NP	Oestrogen contraceptives in migraine OR provided by 6 studies, point estimates ranged from 2.08-16.9. Studies were small and 95% CIs wide. Migraine with aura and on combined oral contraceptive Champaloux[468] Compared to neither migraine nor contraceptive use: OR 6.1 (3.1-12.1) for migraine with aura on combined oral contraceptive; OR 1.8 (1.1-2.9) for migraine without aura on combined oral contraceptive	An increased risk of stroke among women with migraine and on oestrogen contraceptives. Studies on stroke risk among women with migraine with aura are required.	Moderate
Combined non-oral hormonal contraceptives	Tepper 2016 [203]	Myocardial infarction stroke		Jick et al.[469] Acute myocardial infarction crude IRR 0.2 (0.004-1.7) Stroke crude IRR 1.2 (0.41-3.4) Dore et al [470] Acute myocardial infarction OR 1.6 (0.4-6.5) Ischaemic stroke OR 0.8 (0.2-4.5)	No increased risk of arteriothrombotic events (myocardial infarction and stroke) was observed among women using the patch compared to those using norgestimate combined oral contraceptives.	Moderate
Combined Hormonal contraceptives among women with dyslipidaemia	Dragoman 2015 [204]	Myocardial infarction Cerebrovascular accident	820,910	Tanis et al [206] Risk of myocardial infarction: Combined oral contraceptive non-use and hypercholesterolemia: OR 3.3 (1.6-6.8) Combined oral contraceptive use and hypercholesterolemia: OR 24.7 (5.6-108.5) Gronich et al.[207] Risk of cerebrovascular accident: Combined oral contraceptive non-use and hypercholesterolemia: Ref Combined oral contraceptive use and hypercholesterolemia: crude IRR 1.76 (1.51-2.06)	Evidence from observational studies of low quality suggests that myocardial infarction risk may be increased among combined oral contraceptive users with dyslipidaemia. In the unadjusted estimates combined oral contraceptive use among women with dyslipidaemia linked to an increased risk of stroke.	Moderate
Combined oral contraceptive use among women with hypertension	Curtis 2006 [208]	Myocardial infarction	3,523	Croft and Hannaford[471] No hypertension/no oral contraceptive use: Ref No hypertension/oral contraceptive use: OR 2.0 (1.1-3.9) Hypertension/no oral contraceptive use: OR 5.4 (2.6-11.2) Hypertension/oral contraceptive use: OR 7.7 (1.2-49.2)	Hypertensive users on oral contraceptive are at higher risk of myocardial infarction compared to normotensive non-oral contraceptive users.	Low

				Tanis et al [206] No hypertension/no oral contraceptive use: Ref No hypertension/oral contraceptive use: OR 2.1 (1.5-3.1) Hypertension/no oral contraceptive use: OR 5.1 (2.9-8.8) Hypertension/oral contraceptive use: OR 6.1 (3.1-12.1) D'Avanzo[472] Never use of oral contaceptive normotensive: Ref Hypertensive and oral contraceptive use: OR 28.4 (6.7-120.1) WHO developing countries[473] No hypertension/no oral contraceptive: Ref No hypertension/oral contraceptive use: OR 3.66 (1.81-7.39) Hypertension/no oral contraceptive use: OR, 9.52 (4.90-18.5) Hypertension/oral contraceptive use: OR 15.3 (3.27-71.6) WHO European countries[473] No hypertension/no oral contraceptive: Ref No hypertension/oral contraceptive use OR 3.85 (1.88-7.89) Hypertension/no oral contraceptive: OR 5.43 (2.39-12.4) Hypertension/oral contraceptive use: OR 68.1 (6.18-751)		
	Curtis 2006 [208]	Stroke	NP	Collaborative group [474] Hypertension/oral contraceptive use: Borderline hypertension: OR 5.2 (2.3-12.0) Moderate hypertension: OR 8.9 (3.5-22.8) Severe hypertension: OR 13.6 (4.8-38.6) Lidegaard et al:[475–477] OR for hypertension 3.1 ($p<0.001$) OR for combined oral contraceptive 1.8 (1.1-2.9) WHO Developing countries[473] No hypertension/no oral contraceptive: Ref	Hypertensive users on oral contraceptive are at higher risk of stroke compared to normotensive non-oral contraceptive users.	Low

				No hypertension/oral contraceptive use: OR 2.73 (1.97-3.77) Hypertension/no oral contraceptive use: OR 7.70 (5.36-11) Hypertension/oral contraceptive use: OR 14.5 (5.36-39.0) WHO European countries[473] Hypertension/no oral contraceptive use: Ref No hypertension/oral contraceptive use: OR 2.71 (1.47-4.99) Hypertension/no oral contraceptive use: OR 4.59 (2.39-8.82) Hypertension/oral contraceptive use: OR 10.7 (2.04-56.6) Heinemann et al.[478] No hypertension/no oral contraceptive use: Ref Hypertension/oral contraceptive use: OR 3.92 (2.24-6.97) Hypertension/no oral contraceptive use: OR 9.6 (3.25-30.57) Hypertension/oral contraceptive use: OR 3.07 (0.85-11.05) Lidegaard et al 2002 [479] 30-40 μg of ethinyl estradiol combined oral contraceptive use OR 1.6 (1.3-2.0) Hypertension OR 5.0 (3.3-7.4) Kemmeren et al [467] No hypertension/no oral contraceptive use: Ref No hypertension/no oral contraceptive: OR 2.7(1.8-4.0) Hypertension/no oral contraceptive use: OR 6.8 (3.7-12.2) Hypertension/oral contraceptive use: OR 7.6 (3.5-26.3) Siritho et al. [480] Oral contraceptive use: OR 1.76 (0.86-3.61) OR for hypertension: 2.18 (1.22-3.91) Nightingale and Farmer[481] Oral contraceptive use: OR 2.30 (1.15-4.59)		

				OR for hypertension: 4.61 (2.71-7.84)		
Polycystic ovary syndrome	Bolijn 2017 [211]	Heart Failure	308	Cheang et al.[210] A cross-sectional study; did not find an increased risk of heart failure among women with polycystic ovary syndrome: OR 3.24 (0.53–19.94). The number of heart failure cases was small (n=5).	The number of heart failure events was small (n=5). Evidence was derived from a study of low methodological quality. Longitudinal studies of high quality recommended.	Moderate
Breastfeeding	Nguyen 2017 [215]	Non-fatal CVD	229,007	Stuebe et al.[216] Outcome: Self-reported myocardial infarction Exposure: Lifetime duration of breastfeeding in months No breastfeeding: Ref >11–23 months: HR 0.93 (0.8-1.07) >23 months: HR 0.77 (0.62-0.94) Schwarz et al.[217] Outcome: Self-reported incidence of CVD Exposure: lactation duration in months Never breastfed: Ref 1–6 months: HR 1.03 (0.98, 1.08) 7–12 months: HR 0.97 (0.90, 1.04) 13–23 months: HR 0.98 (0.91-1.05) >24 months: HR 0.93 (0.85-1.02)	Lifetime duration of breastfeeding >23 months linked to lower incidence of CVD.	Moderate
Breastfeeding	Nguyen 2017 [215]	Fatal CVD	281,383	Gallagher et al.[218] Lactation duration, never (Ref) versus ever, in months: Ischaemic heart disease mortality: <6 months: HR 0.70 (0.42-1.16) 7–12 months: HR 0.50 (0.33-0.76) 13–24 months: HR 0.67 (0.46-0.97) 25–36 months: HR 0.53 (0.36-0.79) 37–48 months: HR 0.71 (0.48-1.06) >49 months: HR 0.78 (0.53-1.14) Ischaemic stroke: <6 months: HR 1.02 (0.63-1.66) 7–12 months: HR 1.05 (0.72-1.54) 13–months: HR 0.90 (0.62-1.31) 25–36 months: HR 1.15 (0.79-1.67)	Evidence suggests breastfeeding linked to lower mortality from ischaemic heart disease. No association was observed between lactation duration and mortality from ischaemic or hemorrhagic stroke.	Moderate

				37–48 months: HR 1.21 (0.83-1.77) >49 months: HR 1.20 (0.84-1.72) Hemorrhagic stroke: <6 months: HR 0.84 (0.63-1.12) 7–12 months: HR 0.98 (0.79-1.22) 13–months: HR 1.01 (0.82-1.24) 25–36 months: HR 0.88 (0.71-1.09) 37–48 months: HR 1.02 (0.82-1.28) >49 months: HR 1.05 (0.84-1.30) Natland et al.[219] In Women <65 years Ever lactated: Ref Nulliparous: HR 0.41 (0.16-1.04) Never lactated: HR 2.86 (1.51-5.39) In women over >65 years Ever lactated: Ref Nulliparous: HR 1.20 (1.0-1.44) Never lactated: HR 1.11 (0.77-1.69)	Norwegian women aged <65 years and who never breastfeed were at a three-fold higher risk of mortality from CVD. No linear relationship was noted. Instead, evidence of a U-shaped association was observed between categories of lactation duration.	
Early natural menopause	Bolijn 2017 [211]	Non-fatal heart failure	25,230	Ebong et al.[482] Self-report of early menopause (<45 years): HR 1.66 (1.01-2.73) Rahman et al.[483] Age at menopause: 50–54 years: Ref 40–45 years: HR 1.36 (1.16-1.60) 46–49 years: HR 1.13 (1.02-1.26) ≥55 years: HR 1.03 (0.93-1.14)	Two studies of good methodological quality suggested that early menopause is associated with heart failure risk.	Moderate
Adverse pregnancy outcomes						
Miscarriage	Grandi 2019 [38]	Fatal and non-fatal CVD		The effect estimates for 6 cohort studies [227,229,484–487] ranged from 0.91–2.69, while 1 case-control study[488] reported effect estimates of 0.83-1.17.	The definition of miscarriage was different across studies. The effect estimates varied across studies with some suggesting increased risk	Moderate

					while others suggesting no risk.	
Gestational diabetes	Bolijn 2017 [211]	Non-fatal Heart failure	853,558	Freibet et al.[224] HR 0.7 (0.3-1.9) Savitz et al.[225] OR 1.5 (1.0-2.2)	Gestational diabetes was not associated with heart failure. Further research needed to clarify the association.	Moderate
Recurrent Preterm birth	Robbins 2014 [184]	Fatal and non-fatal CVD		Catov et al.[55] CVD HR 1.4 (1.2-1.6) Ischaemic heart disease HR 1.8(1.4-2.3) Stroke HR 1.8 (1.4-2.2) CVD death HR 2.1 (1.2-3.7) Lykke et al.[489] Ischaemic heart disease death HR 1.4 (1.0-1.8)		Moderate
Recurrent preterm birth	Bolijn [211]	Heart failure	1,322,615	Freibert et al.[224] No association between preterm delivery and heart failure risk; OR not provided. Lykke et al.[489] Any preterm delivery was associated with heart failure risk; OR not provided.		Moderate
Small for gestational age	Grandi 2019 [38]	Fatal and non-fatal CVD	4,113,820	Effects estimates of ten studies ranged from 1.09-3.50.	Due to heterogeneity in exposure definition pooling was not possible. Overall small for gestational age was associated with an increased risk of CVD.	Moderate

BMI = body mass index, CVD = cardiovascular disease, HR = hazard ratio, IRR = incidence rate ratio, NP = not provided, OR = odds ratio, Ref = Reference, WHO = World Health Organisation.

Supplemental Table S4.5. General study characteristic for studies evaluating the association between breastfeeding and maternal risk of cardiovascular disease.

Study ID/ (Setting)	Objective	Study design	Exposure/ comparator	Outcome	Effect size (95% CI)	Covariates	NOS quality
Stuebe 2009 [216] (USA)	Evaluate the association between lactation duration and maternal incident myocardial infarction	Prospective cohort Study (1986-2002) of 89326 parous women in the Nurses' health study	Cumulative lactation duration versus never breastfeeding	Non-fatal Myocardial infarction	Never breastfed: Ref >0-3 months: HR 1.01 (0.91-1.11) >3-6 months: HR 1 (0.88-1.14) >6-11 months: HR 1.02 (0.88-1.18) >11-23 months: HR 0.93 (0.8-1.07) >23 months: HR 0.77 (0.62-0.94)	Age, parity, history of stillbirth, BMI at age 18, birth weight of subject, parental history of myocardial infarction before age 60, diet quintile, physical activity, smoking, menopausal status, and use of aspirin, alcohol, multivitamins, and postmenopausal hormones	High
Schwarz 2009 [217] (USA)	To evaluate the dose-response relationship between the cumulative number of months women lactated and postmenopausal risk factors for cardiovascular disease	Cohort study of 139,681 postmenopausal women with > 1 live birth.	Lactation duration in months versus never breastfed.	Non-fatal composite CVD	Never breastfed: Ref 1-6 months: HR 1.03 (0.98-1.08) 7-12 months: HR 0.97 (0.90-1.04) 13-23 months: HR 0.98 (0.91-1.05) >24 months: HR 0.93 (0.85-1.02)	Age, race, parity, age at menopause, education, income, family history (of diabetes mellitus, myocardial infarction or stroke), physical activity, energy, cholesterol, fat, fibre, and sodium intakes, tobacco history, hormone replacement therapy use, aspirin use, multivitamin use.	High
Gallagher 2011 [218] (China)	Examine the association between a wide range of reproductive factors and CVD	A cohort (1989-2000) of 259,494 non-smoking female textile workers	Breastfeeding duration in months versus parous women who never breastfed	Fatal coronary heart disease	Never (with live birth): Ref <6 months: HR 0.70 (0.42-1.16) 7-12 months: HR 0.50 (0.33-0.76) 13- 24 months: HR 0.67 (0.46-0.97) 25-36 months: HR 0.53 (0.36-0.79) 37-48 months: HR 0.71 (0.48-1.06)	Age, number of live births	Medium

		in Shanghai, China		Fatal ischaemic stroke Fatal haemorrhagic stroke	≥49 months: HR 0.78 (0.53-1.14) Never (with live birth): Ref <6 months: HR 1.02 (0.63-1.66) 7-12 months: HR 1.05 (0.72-1.54) 13- 24 months: HR 0.90 (0.62-1.31) 25-36 months: HR 1.15 (0.79-1.67) 37-48 months: HR 1.21 (0.83-1.77) ≥49 months: HR 1.20 (0.84-1.72) Never (with live birth): Ref <6 months: HR 0.84 (0.63-1.12) 7-12 months: HR 0.98 (0.79-1.22) 13-24 months: HR 1.01 (0.82-1.24) 25-36 months: HR 0.88 (0.71-1.09) 37-48 months: HR 1.02 (0.82-1.28) >49 months: HR 1.05 (0.84-1.30)		
Natland Fagerhaug 2013 [219] (Norway)	To investigate the association between lifetime lactation duration and cardiovascular disease mortality	A prospective cohort (1995-2010) of 21,889 women aged 30 to 85 years		Fatal composite CVD	Younger women (under 65 years) Ever lactated: Ref Never lactated: HR 2.86 (1.51-5.39) Nulliparous: HR 0.41 (0.16-1.04) Older women (over 65 years) Ever lactated: Ref Never lactated: HR 1.11 (0.77-1.69) Nulliparous: HR 1.20 (1.00-1.44)	Age, smoking status, physical activity, education, marital status and parity	High
Nguyen* 2019 [235] (New South wales Australia)	Examine the association between breastfeeding and CVD hospitalisation and death	Cohort study (2006-2014) of 100864 middle-aged (≥45 years) and parous women	Self-reported breastfeeding, never versus ever and average breastfeeding duration per child	Non-fatal composite CVD Fatal CVD Non-fatal CVD	Breastfeeding history Parous never breastfed: Ref Parous ever breastfed: HR 0.86 (0.78-0.96) Parous never breastfed: Ref Parous ever breastfed: HR 0.66 (0.49-0.89) Average duration of breastfeeding per child Never breastfed: Ref >0-6 months: HR 0.86 (0.78-0.96) >6-12 months: HR 0.85(0.75-0.97) >12 months: HR 0.89 (0.71-1.12)	age, country of birth, educational level, marital status, area-level socio-economic status, BMI, smoking status, alcohol intake, physical activity multivitamin use, omega 3 or fish oil use, use of aspirin, oral contraceptive use, mother's age for first child, mother's age for last child, family history of CVD, family history of	High

				Fatal CVD	Never breastfed: Ref >0-6 months: HR 0.69 (0.51-0.94) >6-12 months: HR 0.59 (0.41-0.84) > 12 months: HR 0.67 (0.28-1.57)	hypertension, family history of diabetes mellitus, self-reported hypertension/recent treatment for hypertension, and self-reported diabetes mellitus/recent treatment for diabetes mellitus	
Rajaei* 2019 (Stanford-USA) [236]	To evaluate the association between lactation duration and risk of developing non-fatal coronary artery disease	Hospital case-control study of 643 nulliparous and multiparous women aged 40-65 years	Exposure divided into two categories 1.Single longest duration of breastfeeding of all-live births 2. Total lifetime duration of breastfeeding	Non-fatal Coronary artery disease	<u>1.Single highest ever duration of breastfeeding across all live births</u> Never child/pregnant: Ref 1+ child, never breastfed: OR 1.79 (0.81-3.94) 1–4 months: OR 2.78 (1.43–5.39) 5–9 months: OR 1.04 (0.5–2.15) 10–18 months: OR 1.22 (0.63–2.37) 19+ months: OR 1.72 (0.69–4.26) Child and never breastfed: Ref 1-4 months: OR 1.57 (0.63-3.92) 5-9 months: OR 0.53 (0.2-1.39) 10- 18 months: OR 0.71 (0.29-1.76) ≥19 months: OR 0.89 (0.29-2.76) 1-4 months: Ref 5-9 months: OR 0.33 (0.14-0.8) 10-18 months: OR 0.47 (0.21-1.06) ≥19 months: OR 0.57 (0.2-1.65) <u>2.Total (summed over all live births) lifetime duration of breastfeeding</u> Never child/pregnant: Ref 1+ child; never breastfed: OR 1.78 (0.81-3.9) 0–7 months: OR 2.16 (1.14-4.09) 8–15.5 months: OR 1.7 (0.85-3.41) 16–26 months: OR 1.03 (0.47-2.26) 26.5+ months: OR 1.24 (0.57-2.7) Never breastfed: Ref	Adjusted for age, race, BMI, tobacco use, hypertension, systolic blood pressure, hyperlipidaemia, total cholesterol, HDL, triglycerides, and diabetes.	Low

					0-7 months: OR 1.18 (0.48 -2.86) 8-15.5 months: OR 0.88 (0.35-2.25) 16-26 months: OR 0.59 (0.21-1.63) 26.5 months: OR 0.71 (0.26-1.93) 0-7 months: Ref 8-15.5 months: OR 0.78 (0.34 -1.76) 16-26 months: OR 0.45 (0.17-1.16) ≥26.5 months: OR 0.62 (0.26-1.15)		
Jacobson* 2018 [237] USA	To assess the association between breastfeeding and risk of stroke and whether the association differs by ethnicity and race	Cohort study (1993-2010) 80191 parous women from the women's health observational study.	Never breastfeeding (< 1month) versus Ever-breastfeeding	Non-fatal Stroke	Ever Breastfed No: Ref Yes: HR 0.77 (0.70-0.84) Duration of breastfeeding Never: Ref 1-6 months: HR 0.81 (0.74-0.90) 7-12 months: HR 0.75 (0.66-0.85) ≥13 months: HR 0.74 (0.65-0.83)	Adjusted for age, regional centre, extension study inclusion, race/ethnicity, education, parity, age at menarche, family history, exercise at baseline, Healthy Eating Index at baseline, smoking history, body mass index at baseline, and multivitamin use at baseline.	Medium
Kirkegaard* 2018 [238] Denmark	To examine how any, partial, and full breastfeeding duration were associated with maternal risk of hypertension and CVD and how pre-pregnancy BMI and waist circumference influenced the association	Cohort study (1996–2002) of 63260 women with live-born singleton infants	Breastfeeding for less than 4 months vs breastfeeding for > 4months	Non-fatal CVD	Cardiovascular disease risk (18 months- 15 years postpartum): Pre-pregnancy normal/ underweight: < 4 months: Ref 4-10 months: HR 0.68 (0.58-0.80) >10 months: HR 0.61 (0.52-0.73) Pre-pregnancy overweight/ obese: <4 months: Ref 4-10 months: HR 0.79 (0.64-0.98) >10 months: 0.88 (0.71-1.10) Cardiovascular disease risk (7 years- 15 years postpartum): <4 months: Ref 4-10 months: HR 0.77 (0.63-0.94) >10 months: HR 0.77 (0.62-0.96)	Adjusted for age, pre-pregnancy BMI, alcohol intake before the index pregnancy, socio-occupational status, dietary intake, physical activity, smoking, preterm birth, preeclampsia and diabetes during the index pregnancy and parity at 18 months postpartum.	High
Peters 2017* [240] China	To examine the long-term CVD effects of breastfeeding	Cohort study (2004-2016) of 289 573 Chinese women	Ever breastfeeding compared to never breastfeeding	Non-fatal CVD	Lifetime lactation duration of breastfeeding among parous women Never: HR 1.00 (0.95-1.06) >0-12 months: HR 0.96 (0.93-0.99) 12-24 months: HR 0.97 (0.95-0.99)	Analyses are stratified by age at risk and study area, and adjusted for level of attained education, household income, smoking	Medium

	among Asian (Chinese) women)	aged 30-79 years at baseline	among parous women		24-36 months: HR 0.96 (0.94-0.98) 36-48 months: HR 0.92 (0.89-0.94) >48 months: HR 0.91 (0.88-0.93)	status, alcohol use, systolic blood pressure, history of hypertension, physical activity, body mass index, and history of diabetes.	
				Fatal CVD	Never: 1.00 (0.77 -1.29) >0-12 months: 0.88 (0.74-1.04) 12-24 months: 0.98 (0.87-1.09) 24-36 months: 0.93 (0.85-1.02) 36-48 months: 0.81 (0.74-0.89) >48 months: 0.86 (0.79-0.92)		
				Non-fatal coronary heart disease	Never: HR 1.00 (0.92-1.09) >0-12 months: HR 0.93 (0.89-0.99) 12-24 months: HR 0.92 (0.89-0.96) 24-36 months: HR 0.86 (0.83-0.89) 36-48 months: HR 0.86 (0.82-0.90) >48 months: HR 0.82 (0.79-0.86)		
				Non-fatal stroke	Outcome stroke Never: HR 1.00 (0.93-1.08) >0-12 months: HR 0.93 (0.89-0.97) 12-24 months: HR 0.93 (0.90-0.96) 24-36 months: HR 0.91 (0.88-0.94) 36-48 months: HR 0.86 (0.82-0.89) >48 months: HR 0.85 (0.82-0.89)		
Peters 2016* [239] European cohort	To assess the association between breastfeeding and risk of incident coronary heart disease	Cohort 8044 parous women	Ever breastfeeding compared to never breastfeeding	Non-fatal coronary heart disease	<u>Exposure lifetime duration of breastfeeding among parous women</u> Never breastfed: HR 1.00 (0.75-1.34) 0-3 months: HR 0.73 (0.60-0.89) 3-6 months: HR 0.68 (0.56- 0.83) 6-12 months: HR 0.69 (0.55 -0.87) 12-23 months: HR 0.63 (0.51-0.76) >23 months: HR 0.62 (0.45 -0.86)	Age at study entry and centre; attained education, smoking status, number of live born children (for breastfeeding analyses only); high blood pressure, HDL cholesterol, total cholesterol, history of diabetes mellitus, and BMI.	Medium

BMI = body mass index, CVD = Cardiovascular disease, HDL = high density lipoprotein, HR = hazard ratio, OR = odds ratio, Ref = reference. * Newly published observational studies

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Chapter 5 Supplemental tables and figures.

Tables

Table S5.1: Endometriosis diagnostic Read codes.

Table S5.2: Incidence rate endometriosis 1998-2017.

Table S5.3: Prevalence of endometriosis 1998-2017.

Table S5.4: Incidence of endometriosis by age categories.

Table S5.5: Incidence of endometriosis by Townsend deprivation quintiles.

Table S5.6: Incidence rates and hazard ratios for secondary cardiovascular outcomes.

Table S5.7: Sensitivity analysis.

Table S5.8: Sensitivity analysis

Figures

Figure S5.1: Cumulative hazard of secondary cardiovascular outcomes.

Figure S5.2: Forest plot hazard ratio and 95% confidence interval for sensitivity analyses.

Figure S5.3: Forest plot showing summary results of studies investigating the association between endometriosis and cardiometabolic outcomes including all-cause mortality.

Table S5.1 Endometriosis Read codes.

Code	Description
K504.00	Endometriosis of the rectovaginal septum and vagina
K50y300	Endometriosis of the vulva
K502.00	Endometriosis of the fallopian tube
K504000	Endometriosis of the rectovaginal septum
K504100	Endometriosis of the vagina
K50yz00	Other endometriosis NOS
Kyu9000	[X]Other endometriosis
BBL1.11	[M]Stromal endometriosis
K504z00	Endometriosis of the rectovaginal septum and vagina NOS
7E0D800	Laparoscopic laser destruction of endometriosis
K500z00	Endometriosis of uterus NOS
K50..11	Adenomyosis
K500111	Adenomyosis of endometrium
K50z.00	Endometriosis NOS
K501.00	Endometriosis of ovary
K505.00	Endometriosis of the intestine
K505000	Endometriosis of the appendix
K503.00	Endometriosis of the pelvic peritoneum
K505200	Endometriosis of the rectum
K505100	Endometriosis of the colon
K503000	Endometriosis of the broad ligament
K503100	Endometriosis of the pouch of Douglas
K503200	Endometriosis of the parametrium
K503300	Endometriosis of the round ligament
K505z00	Endometriosis of the intestine NOS
K503z00	Endometriosis of the pelvic peritoneum NOS
K500200	Endometriosis of cervix
K500100	Endometriosis of myometrium
K50..00	Endometriosis
K500000	Internal endometriosis
K50y.00	Other endometriosis
K500.00	Endometriosis of uterus
K501.11	Chocolate cyst of ovary
K50y000	Endometriosis of the bladder
K50y100	Endometriosis of the lung
K506.00	Endometriosis in scar of skin
K50y200	Endometriosis of the umbilicus

The relevant codes lists were generated through a rigorous process that involved the following key steps:

(i) creation of a comprehensive list of search terms;

(ii) a search of the Read code dictionary for relevant codes using the list of search terms;

(iii) (iii) a search of additional relevant codes lists from online Read code repositories, [100] or from the main text or supplemental information of published studies;[311]

(iv) Rating each code in the code list for relevance and deciding on the final list by consulting clinical experts (general practitioners and consultant specialists).

Table S5.2: Incidence rate of endometriosis among women aged 16-50 years: 1998-2017

Year	No of incidence cases	Person years	Incidence rate/ 10,000
1998	229	186904.66	12.25
1999	330	262491.69	12.57
2000	509	337256.13	15.09
2001	676	482917.09	14.00
2002	845	607814.94	13.90
2003	1001	723785.63	13.83
2004	1087	771969.13	14.08
2005	1082	847411.81	12.77
2006	1100	896963.81	12.26
2007	1087	929600.38	11.69
2008	1148	982025.69	11.69
2009	1322	1028990.00	12.85
2010	1265	1021759.90	12.38
2011	1206	1024680.60	11.77
2012	1276	1052251.60	12.13
2013	1188	1025639.10	11.58
2014	1098	953400.44	11.52
2015	968	839514.25	11.53
2016	899	718630.75	12.51
2017	734	637498.75	11.51

Table S5.3: Prevalence of endometriosis among women aged 16-50 years: 1998-2017

Year	No of patients with endometriosis	Population	Prevalence
1998	1845	154206	119.65
1999	3186	244289	130.42
2000	4088	305015	134.03
2001	6528	460013	141.91
2002	8207	557004	147.34
2003	10557	693844	152.15
2004	12206	764783	159.60
2005	13736	819678	167.58
2006	15720	903610	173.97
2007	16925	940257	180.00
2008	17868	973353	183.57
2009	19553	1042491	187.56
2010	20290	1055709	192.19
2011	20348	1045728	194.58
2012	20923	1058996	197.57
2013	21407	1078603	198.47
2014	20209	1006526	200.78
2015	18905	930093	203.26
2016	15687	775377	202.31
2017	14032	697137	201.28

Table S5.4: Incidence of endometriosis by age categories

Age categories	No of incidence cases	Person years	Incidence rate/ 10,000
< 18 years	1690	2391641.50	7.07
18-25 years	4121	3126002.80	13.18
26- 30 years	4268	2656961.30	16.06
31-35 years	4375	2906039.80	15.05
36-40 years	3082	2471991.50	12.47
41-45 years	1413	1530377.40	9.23
46-50 years	250	411093.19	6.08

Table S5.5: Incidence of endometriosis among women aged 16-50 years by Townsend deprivation quintiles

Townsend quintile of deprivation	No of incidence cases	Person years	Incidence rate / 10,000
1	4379	3141551.00	13.94
2	3526	2725893.30	12.94
3	3584	2898900.30	12.36
4	3088	2647855.30	11.66
5	2034	1949721.00	10.43

Table S5.6: Incidence rates and hazard ratios for secondary cardiovascular outcomes

	Arrhythmia		**Hypertension**		**Mortality**	
	Endometriosis	Unexposed	Endometriosis	Unexposed	Endometriosis	Unexposed
Population	55712	222635	54323	216799	53330	212938
Events, n (%)	329 (0.59)	890 (0.40)	2350 (4.33)	7563 (3.49)	310 (0.6)	1730 (0.8)
Person-years	358334.4	1237956	336325.8	1160001.2	343676.2	1181546
Crude incidence rate/1000 person years	0.92	0.72	6.99	6.52	0.90	1.46
Age at outcome, median (IQR)	40.2 (33.5-45.2)	41.5 (37.1-46.3)	42.0 (37.5-46.2)	42.5 (38.0-46.3)	42.3 (36.9-46.7)	42.5 (37.9-48.6)
Crude HR (95% CI)	1.26 (1.11-1.44)		1.06 (1.01-1.11)		0.61 (0.54-0.69)	
P-value	0.001		0.016		<0.001	
Model 1	1.32 (1.16-1.49)		1.12 (1.07-1.17)		0.65 (0.58- 0.74)	
P-value	<0.001		<0.001		<0.001	
Model 2 Adjusted HR (95% CI)	1.26 (1.11-1.43)		1.12 (1.07- 1.17)		0.66 (0.59-0.74)	
P-value	0.001		0.001		<0.001	

Abbreviations: CVD = composite cardiovascular disease, IHD = ischaemic heart disease, IQR= Inter-quartile range, HR = hazard ratio.

Model 1 adjusted for: age, Townsend deprivation quintiles, BMI, smoking status, lipid-lowering medication, alcohol use, hypertension (except for hypertension outcome), and diabetes mellitus.

Model 2 adjusted for covariates in model 1 plus: connective tissue disorders, migraine, contraceptive use, parity status, PCOS.

Table S5.7: Incidence rates and hazard ratios for cardiometabolic outcomes (sensitivity analyses) by cohort group

	Excluding PID		**Excluding hysterectomy/ oophorectomy**		**Excluding adverse pregnancy outcomes (APOs)**		**Incident case analysis**	
	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed
Population	50228	216022	47461	215589	48217	215589	19125	76020
Events, n (%)	484 (0.96)	1582 (0.73)	499 (1.03)	1477 (0.69)	499 (1.03)	1422 (0.66)	123 (0.64)	346 (0.46)
Person-years	317615.3	1190817	292989.9	1181849	311959.2	1096189	111204.4	356245.6
Crude incidence rate/ 1000 person years	0.81	0.68	1.22	1.24	1.60	1.30	1.11	0.97
Age at outcome median (IQR)	42.6 (37.5-46.8)	43.4 (39.0-47.0)	42.6 (37.5-46.8)	43.4 (39.1-47.1)	42.6 (37.5-46.8)	43.4 (39.1-47.1)	40.7 (35.4-45.5)	41.6 (37.34 -46.05)
Crude HR (95% CI)	1.13 (1.02-1.26)		0.97 (0.87-1.09) p= 0.663		1.21 (1.09-1.34)		1.09 (0.89-1.34)	
P- value	0.016		0.663		< 0.001		0.393	
Adjusted HR 95% CI								
Model 1	1.24 (1.12-1.38)		1.18 (1.06- 1.34)		1.34 (1.21- 1.48)		1.22 (1.00- 1.50)	
P-value	<0.001		0.004		<0.001		0.056	
Model 2	1.22 (1.10-1.35)		1.17 (1.04- 1.31)		1.30 (1.18- 1.45)		1.21 (0.98-1.49)	
P-value	< 0.001		0.010		<0.001		0.074	

Footnotes: CVD = cardiovascular disease, PID = pelvic inflammatory disease, composite APO's = Adverse pregnancy outcomes. Adverse pregnancy outcomes include a composite of**;** miscarriage, stillbirths, gestational diabetes mellitus, preeclampsia, premature delivery, placental abruption

Model 1 adjusted for: age, Townsend deprivation quintiles, BMI, smoking status, lipid-lowering drug medication, alcohol use, hypertension, and diabetes mellitus.

Model 2 adjusted for covariates in model 1 plus: Charlson's connective tissue disorders, migraine, contraceptive use, parity status, PCOS.

Table S5.8: Incidence rates and hazard ratios for cardiometabolic outcomes (sensitivity analyses) by cohort group

	Polycystic ovary syndrome		**Excluding current prescription for GnRH agonist**	
	Exposed	Unexposed	Exposed	Unexposed
Population	52516	217366	53361	222283
Events, n (%)	552	1648	552	1669
Person-years	341017	1210880	341646	1231793
Crude incidence rate/ 1000 person years	1.62	1.36	1.62	1.35
Age at outcome median (IQR)	42.6 (37.5-47.8)	43.4 (39.1- 47.1)	42.6 (37.5-46.8)	43.4 (39.1- 47.1)
Crude HR (95% CI)	1.17 (1.06-1.29)		1.17 (1.07-1.29)	
P- value	0.002		0.001	
Adjusted HR 95% CI				
Model 1	1.28 (1.16-1.41)		1.28 (1.16-1.41)	
P-value	<0.001		<0.001	
Model 2	1.25 (1.13 - 1.38)		1.25 (1.14-1.38)	
P-value	<0.001		<0.001	

Model 1 adjusted for: age, Townsend deprivation quintiles, BMI, smoking status, lipid-lowering drug medication, alcohol use, hypertension, and diabetes mellitus.

Model 2 adjusted for covariates in model 1 plus: Charlson's connective tissue disorders, migraine, contraceptive use, parity status, PCOS

*Model 2 excludes PCOS in the adjustment.

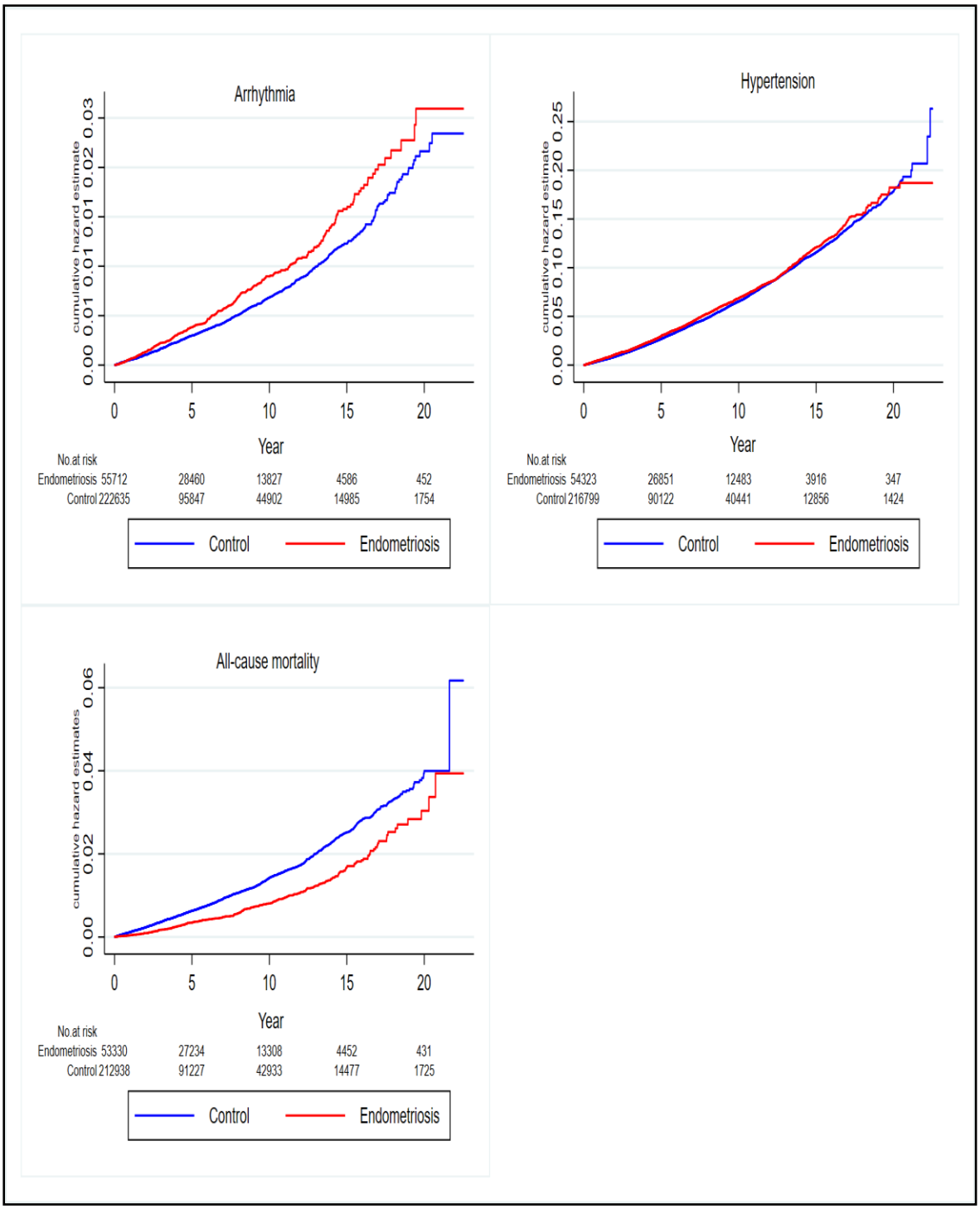

Figure S5.1: **Cumulative hazard of secondary cardiovascular outcomes among women with endometriosis (exposed) and those without endometriosis (unexposed/control).**

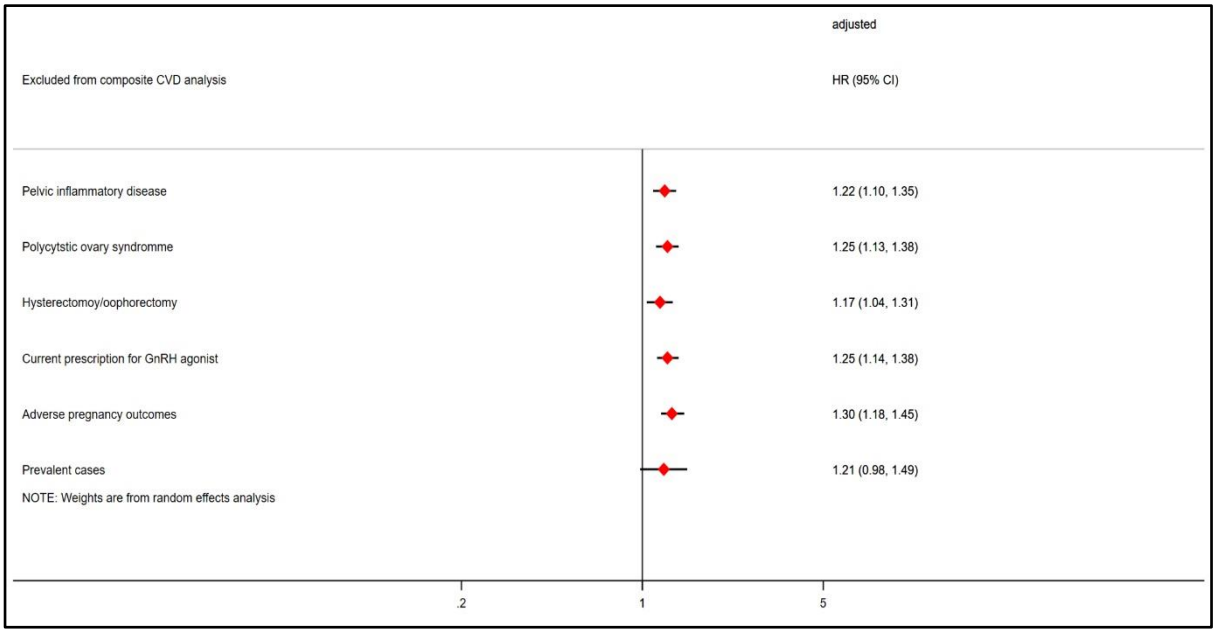

Figure S5.2: Forest plot showing the fully adjusted effect estimates and corresponding 95% confidence intervals of composite cardiovascular disease outcomes after exclusion of women with history of: pelvic inflammatory disease; polycystic ovary syndrome; hysterectomy or oophorectomy; current prescription for gonadotropin (GnRH) hormone agonist; adverse pregnancy outcomes; and prevalent cases of endometriosis and their corresponding controls. Adverse pregnancy outcomes included a composite of: miscarriage, stillbirths, gestational diabetes mellitus, preeclampsia, premature delivery, placental abruption.

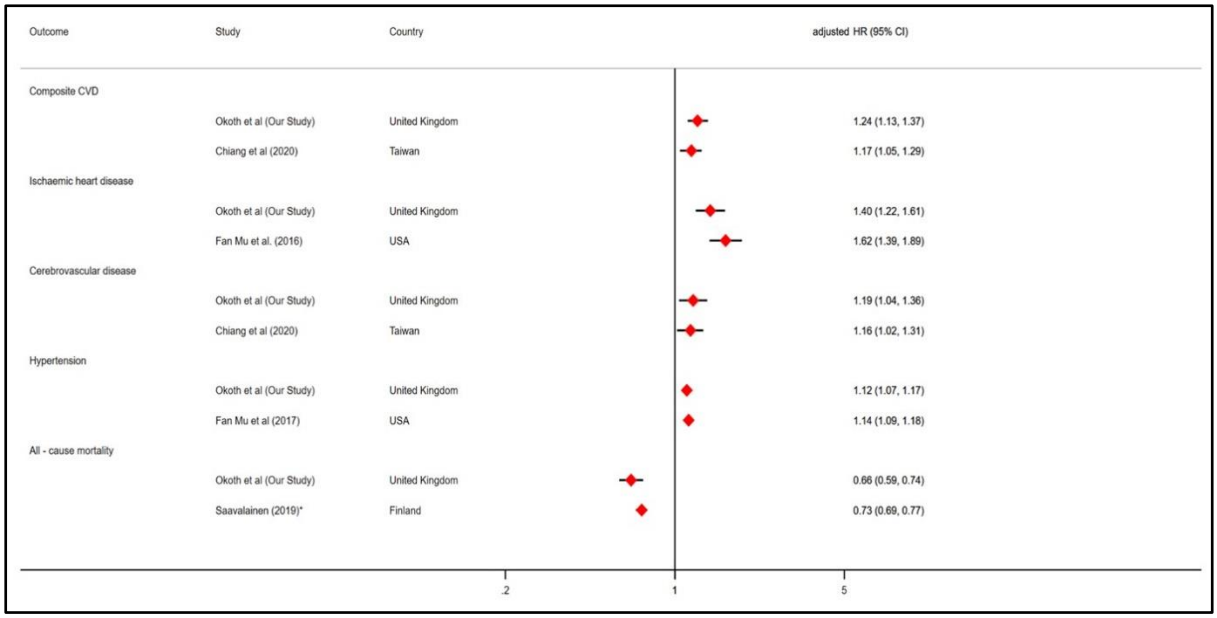

Figure S5.3: Forest plot showing a summary of studies investigating the association between endometriosis and various cardiometabolic outcomes. Effect estimates for the study by Saavalainen et al are rate ratio and 95% confidence interval.

Chapter 6 Supplemental tables and figures

Supplemental Tables

Table S6.1: Incidence rate of pelvic inflammatory disease among women aged 16-50 years: 1998 -2017.

Table S6.2: Prevalence of pelvic inflammatory disease among women aged 16-50 years: 1998-2017

Table S6.3: Incidence of pelvic inflammatory disease by age categories

Table S6.4: Incidence of PID among women aged 16-50 years by Townsend deprivation quintiles.

Table S6.5: (Sensitivity analyses): Incidence rates and hazard ratios for composite cardiovascular disease (CVD) and CVD subtypes for women with a history of PID compared to controls.

Table S6.6: (Sensitivity analyses): Incidence rates and hazard ratios for hypertension and type 2 diabetes mellitus for women with a history of pelvic inflammatory disease (PID) compared to controls.

Supplemental Figures

Figure S6.1: Study participant flow chart.

Table S6.1: **Incidence rate of pelvic inflammatory disease among women aged 16-50 years: 1998 -2017**

Year	No. of incident cases	Person-years	Incidence rate/10,000 person-years
1998	596	183887.5	32.4
1999	720	257534.3	28.0
2000	839	331807.8	25.3
2001	1089	480284.6	22.7
2002	1356	602413.4	22.5
2003	1564	723199.5	21.6
2004	1531	777968.6	19.7
2005	1489	850801.9	17.5
2006	1318	900047.6	14.6
2007	1179	933595	12.6
2008	1119	988257.1	11.3
2009	1193	1035927.7	11.5
2010	1187	1030002.1	11.5
2011	1049	1034079.8	10.1
2012	1070	1065746	10.0
2013	970	1041861.9	9.3
2014	842	970712.1	8.7
2015	721	859902.1	8.4
2016	614	741442.6	8.3
2017	526	665698.1	7.9

Table S6.2: **Prevalence of pelvic inflammatory disease among women aged 16-50 years: 1998-2017**

Year	No. of patients with PID	Population	Prevalence/10,000 population
1998	6210	156630	396.5
1999	9480	246598	384.4
2000	11889	306733	387.6
2001	17287	467696	369.6
2002	20442	563755	362.6
2003	24931	704436	353.9
2004	27388	785251	348.8
2005	29077	840414	346.0
2006	32189	922729	348.9
2007	32967	958980	343.8
2008	33399	994539	335.8
2009	34462	1063695	324.0
2010	33973	1076777	315.5
2011	32851	1066644	308.0
2012	32185	1082059	297.4
2013	31413	1104362	284.4
2014	28576	1031610	277.0
2015	25977	956722	271.5
2016	20220	801646	252.2
2017	17216	726315	237.0

Table S6.3: Incidence of pelvic inflammatory disease by age categories

Age categories	No. of incident cases	Person-years	Incidence rate/10,000 person-years
16-19 years	5664	3007871.8	18.8
20-24 years	3976	2081580.1	19.1
25-29 years	4041	2579121.8	15.7
30-34 years	3684	2932162.5	12.6
35-39 years	2475	2649987	9.3
40-44 years	1196	1769741.3	6.8
45-50 years	321	644913.5	5.0

Table S6.4: **Incidence of PID among women aged 16-50 years by Townsend deprivation quintiles.**

Townsend quintile of deprivation	No. of incident cases	Person-years	Incidence rate/10,000 person-years
1 (least deprived)	3465	3107992.5	11.2
2	3258	2684137	12.1
3	3980	2840628	14.0
4	4217	2576176.3	16.4
5 (most deprived)	3489	1891168.3	18.5

Table S6.5 (Sensitivity analyses): Incidence rates and hazard ratios for composite cardiovascular disease (CVD) and CVD subtypes for women with a history of PID compared to controls

	Composite CVD		Ischaemic Heart Disease		Cerebrovascular disease		Heart failure	
	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed
Population	14966	51933	15062	52235	15074	52319	15130	52498
Events, n (%)	150	409	72	187	80	210	20	100
Person-years	91,859.8	290,272.0	92,729.8	292,862.3	92,859.4	293,478.5	93,402.0	294,966.5
Crude incidence rate/1000 person years	1.6	1.4	0.8	0.6	0.9	0.7	0.2	0.3
Crude HR (95% CI)	1.14 (0.94-1.37)		1.19 (0.91-1.57)		1.18 (0.91-1.53)		0.61 (0.38- 0.99)	
P-value	0.183		0.204		0.210		0.047	
Adjusted HR (95% CI)	1.13 (0.93-1.36)		1.20 (0.91-1.58)		1.18 (0.91-1.53)		0.64 (0.40-1.04)	
P-value	0.213		0.197		0.220		0.072	

CVD = composite CVD, HR= Hazard ratio.

Model adjusted for age, Townsend deprivation quintiles, BMI, smoking status, lipid-lowering medication (current users, with a record of a prescription within 60 days prior to index date), diabetes mellitus hypertension contraceptive use (current users, defined as those prescribed combined oral contraceptive pills within the last 365 days prior to cohort entry) and reproductive conditions (premature delivery, miscarriage, stillbirths, gestational diabetes mellitus, polycystic ovary syndrome, pre-eclampsia, endometriosis).

Table S6.6 (Sensitivity analyses): Incidence rates and hazard ratios for hypertension and type 2 diabetes mellitus for women with a history of pelvic inflammatory disease (PID) compared to controls.

	Hypertension		Type 2 diabetes mellitus	
	Exposed	Unexposed	Exposed	Unexposed
Population	14,438	50,292	14,906	5,1817
Events, n (%)	523	1495	239	568
Person-years	86,714.4	274,668.3	91,325.9	289,203.5
Crude incidence rate/1000 person years	6.0	5.4	2.6	2.0
Crude HR (95% CI)	1.09 (0.99- 1.21)		1.31 (1.12-1.52)	
P-value	0.078		0.001	
Adjusted HR (95% CI)	1.11 (1.00-1.23)		1.26 (1.08-1.47)	
P-value	0.046		0.003	

CVD = composite CVD, HR= hazard ratio.

Model adjusted for age, Townsend deprivation quintiles, BMI, smoking status, lipid-lowering medication premature delivery, miscarriage, stillbirths, gestational diabetes mellitus, polycystic ovary syndrome, pre-eclampsia, endometriosis.

* = Model adjusted for diabetes mellitus, # = Model adjusted for hypertension

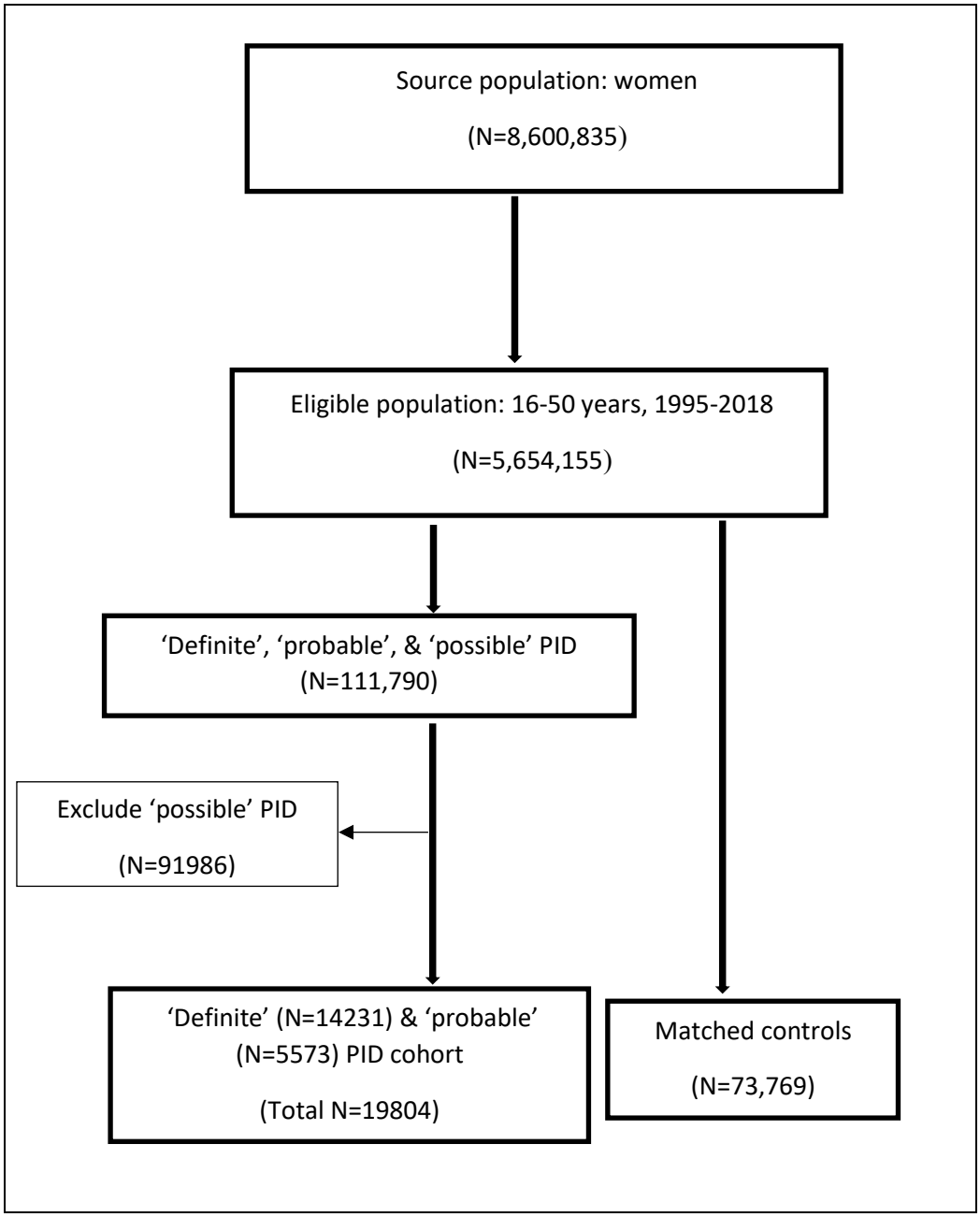

Figure S6.1: **Study participant flow chart.**

Classifications 'Definite', 'probable' and 'possible' based on French et al.

French CE, Hughes G, Nicholson A, Yung M, Ross JD, Williams T, et al. Estimation of the Rate of Pelvic Inflammatory Disease Diagnoses: Trends in England, 2000–2008. Sex Transm Dis. 2011 Mar;38(3):158–62.

Chapter 7 Supplemental tables and figures.

Tables

Table S7.1: Classification of menstrual cycle characteristics

Table S7.2: Diagnostic Read codes for menstrual cycle regularity and menstrual cycle frequency.

Table S7.3: Incidence rates and hazard ratios of cardiometabolic outcomes

Table S7.4: Sensitivity analyses menstrual cycle regularity and composite CVD analyses (excluding women with amenorrhoea, polycystic ovary syndrome, endometriosis, current hormonal contraceptive use, uterine fibroids)

Table S7.5: Incidence rates and hazard ratio for cardiometabolic outcomes (sensitivity analyses excluding polycystic ovarian syndrome, endometriosis, and fibroids as covariates from adjusted Cox proportional hazard model)

Table S7.6: Sensitivity analyses menstrual cycle frequency and composite CVD (excluding women with amenorrhoea, polycystic ovary syndrome, endometriosis, current hormonal contraceptive use, uterine fibroids)

Table S7.7: Incidence rates and hazard ratios for cardiometabolic outcomes among women with frequent (short) menstrual cycles and infrequent (Long) menstrual cycle.

Table S7.8: Summary of selected existing literature examining the association between menstrual characteristics and cardiometabolic outcomes

Figures

Figure S7.1 Study participants flow chart.

Figure S7.2: Interaction between (A) irregular menstrual cycles and (B) frequent or infrequent menstrual cycles and lifestyle factors (Body mass index, smoking, and alcohol use

Table S7.1: **Classification of menstrual characteristics.**

Menstrual characteristic	**Description**	**Normal limits (5^{th} to 95^{th} percentile)**
Frequency of menses	Frequent	< 24 days
	Normal	24-38 days
	Infrequent	>38 days
Regularity of menses (cycle to cycle variation over 12 months)	Absent	No
	Regular	Variation +2 to 20 days
	Irregular	Variation greater than 20 days
Duration of flow	Prolonged	>8.0 days
	Normal	4.5—8.0 days
	Shortened	< 4.5 days
Volume of blood loss per months	Heavy	>80 millilitres
	Normal	5—80 millilitres
	Light	5 < millilitres

Table S7.2: **Read codes for cycle irregularity and cycle frequency.**

The relevant diagnostic and other health related code lists were generated through a careful process that involves the following sequential steps; (i) Development of a comprehensive list of search terms, (ii) A search of the Read code dictionary for relevant codes using the list of search terms, (iii) A search of additional relevant codes lists from online Read code repositories, or supplemental information of published studies, (iv) Rating each code in the code list for relevance and deciding on the final list by consulting clinical experts (general practitioners and consultant specialists)

READ CODE	DESCRIPTION	Classification
1571	H/O: amenorrhoea	Regularity of menses
K590.00	Absence of menstruation	Regularity of menses
K590.11	Amenorrhoea	Regularity of menses
K590000	Primary amenorrhoea	Regularity of menses
K590z00	Amenorrhoea NOS	Regularity of menses
K594.00	Irregular menstrual cycle	Regularity of menses
K594z00	Irregular menstrual cycle NOS	Regularity of menses
K598.00	Menometrorrhagia	Regularity of menses
K59y.11	Metropathia haemorrhagica	Regularity of menses
Kyu9C00	[X]Other specified irregular menstruation	Regularity of menses
1572	H/O: polymenorrhoea	Frequency of menses
K591.00	Scanty or infrequent menstruation	Frequency of menses
K591.11	Infrequent menstruation	Frequency of menses
K591100	Oligomenorrhoea	Frequency of menses
K591200	Primary oligomenorrhoea	Frequency of menses
K591z00	Scanty or infrequent menstruation NOS	Frequency of menses
K592.00	Excessive or frequent menstruation	Frequency of menses
K592.11	Frequent menses	Frequency of menses
K592100	Polymenorrhoea	Frequency of menses
K592111	Epimenorrhoea	Frequency of menses
K592z00	Excessive or frequent menstruation NOS	Frequency of menses

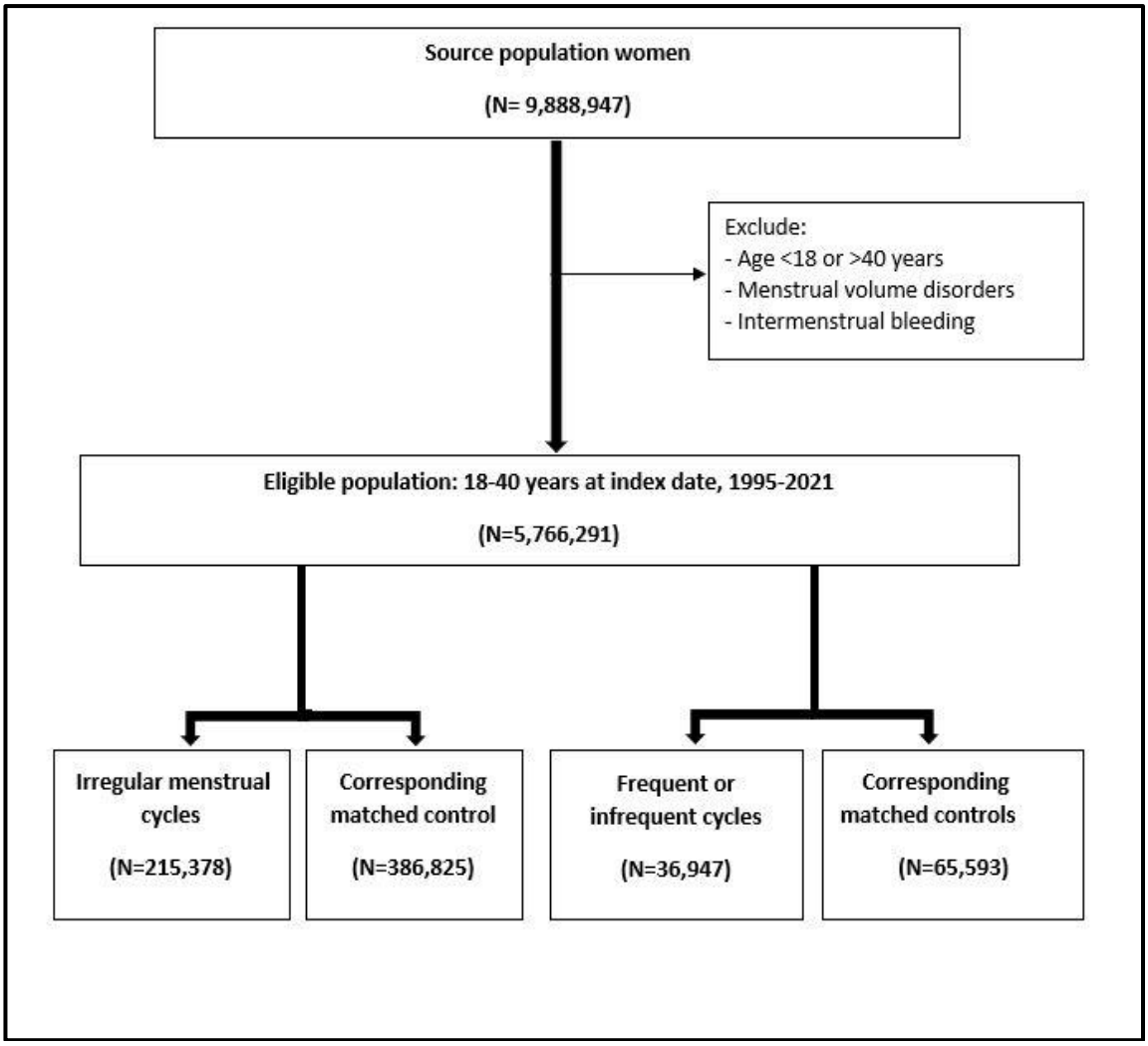

Figure S7.1: **Study participant flow chart.**

Table S7.3: Incidence rates and hazard ratio for cardiometabolic outcomes

	Menstrual cycle regularity		Menstrual cycle frequency	
	Irregular (exposed)	**Regular (Unexposed)**	**Frequent/Infrequent (exposed)**	**Normal (unexposed)**
Composite CVD				
Population	214,915	386,261	36,873	65,484
Events, n (%)	896 (0.42%)	1056 (0.27%)	205 (0.56%)	202 (0.31%)
Person-years	1339541	2121954	248301.2	377644.7
Crude incident rate/1000 years	0.67	0.50	0.83	0.53
Age at outcome Median (IQR)	43.1 (37.4-47.8)	42.7 (37.6-47.8)	43.2 (38.5 – 48.5)	43.5 (37.4 -48.2)
Crude HR (95% CI)	1.26 (1.15-1.38)		1.46 (1.20-1.78)	
P-value	< 0.001		<0.001	
Adjusted HR (95% CI)	1.08 (1.00-1.19)		1.24 (1.02-1.52)	
P-value	0.062		0.031	
IHD				
Population	215,259	386,702	36,933	65,571
Events, n (%)	342 (0.16%)	353 (0.09%)	77 (0.21%)	76 (0.12%)
Person-years	1344052	2127601	249369.3	378907.9
Crude incident rate/1000 years	0.24	0.17	0.30	0.20
Age at outcome Median (IQR)	44.0 (40.1-48.4)	44.6 (40.3-49.8)	45.1 (40.5-49.2)	45.8 (40.9-51.0)
Crude HR (95% CI)	1.43 (1.23-1.66)		1.44 (1.05-1.97)	
P-value	< 0.001		0.025	
Adjusted HR (95% CI)	1.18 (1.01-1.37)		1.13 (0.81-1.57)	
P-value	0.033		0.464	
Cerebrovascular disease				
Population	215,071	386,446	36,897	65,520
Events, n (%)	494 (0.22%)	620 (0.16%)	124 (0.34%)	111 (0.17%)
Person-years	1342726	2125102	248888	378288
Crude incident rate/1000 years	0.37	0.29	0.50	0.29
Age at outcome Median (IQR)	42.5 (35.8-47.2)	42 (36.1-47.3)	43.2 (38.5-48.6)	42.7 (35.3-47.6)
Crude HR (95% CI)	1.19 (1.06- 1.34)		1.62(1.26-2.00)	
P-value	0.004		< 0.001	

Adjusted HR (95% CI)	1.04 (0.92-1.17)		1.43 (1.10-1.87)	
P-value	0.508		0.007	
Heart failure				
Population	215,332	386,749	36,935	65,579
Events, n (%)	139 (0.06%)	138 (0.04%)	23 (0.06%)	30 (0.05%)
Person-years	1346027	2129232	249715	379180
Crude incident rate/1000 years	0.1	0.06	0.09	0.08
Age at outcome Median (IQR)	44.4 (37.9 - 49)	41.5 (36.7-46.9)	45.2 (35.4-48.9)	39.9 (33.6-45.7)
Crude HR (95% CI)	1.48 (1.17-1.87)		1.10 (0.64-1.90)	
P-value	0.001		0.723	
Adjusted HR (95% CI)	1.30 (1.02-1.65)		0.99 (0.57-1.75)	
P-value	0.033		0.985	
Hypertension				
Population	212,747	383,644	36,476	65,031
Events, n (%)	4529 (2.13%)	5788 (1.51%)	1060 (2.91%)	1109 (1.71%)
Person-years	1300272	2076051	239680	369126
Crude incident rate/1000 years	3.48	2.79	4.42	3.00
Age at outcome Median (IQR)	41.6 (36.4-46.2)	41.8 (36.8-46.6)	42 (37.3 - 47)	43 (37.7- 47.8)
Crude HR (95% CI)	1.19 (1.14 - 1.24)		1.41 (1.30-1.54)	
P-value	< 0.001		<0.001	
Adjusted HR (95% CI)	1.07 (1.03-1.11)*		1.31 (1.21-1.43) *	
P-value	0.001		<0.001	
Diabetes mellitus				
Population	213,480	384,466	36,613	65,201
Events, n (%)	2412 (1.13%)	2215 (0.58%)	582 (1.59%)	383 (0.59%)
Person-years	1322940	2106721	244548.3	375211.8
Crude incident rate/1000 years	1.82	1.05	2.38	1.02
Age at outcome Median (IQR)	40.6 (34.8-45.3)	41.3 (36.1-46.2)	40.5 (34.3-46.2)	42.8 (38.3-47.1)
Crude HR (95% CI)	1.66 (1.56-1.75)		2.25(1.96-2.53)	
P-value	< 0.001		<0.001	
Adjusted HR (95% CI)	1.37 (1.29-1.45) #		1.74 (1.52-1.98) #	
P-value	<0.001		<0.001	

Adjusted for age, Townsend quintile of deprivation, body mass index, smoking, lipid medication, Alcohol status, hypertension, diabetes mellitus, current use of combined oral contraceptive, connective tissue disorders, migraine, polycystic ovary syndrome, gestational diabetes mellitus (types 1 and 2), pre-eclampsia, pre-term birth, pelvic inflammatory disease, endometriosis, fibroids.

*= Adjusted for all above except hypertension

#= Adjusted for all above except diabetes mellitus

Table S7.4: Incidence rates and hazard ratios for composite CVD (Sensitivity analyses for menstrual cycle regularity)

Composite CVD	Amenorrhoea		Polycystic ovary syndrome		Endometriosis	
	Exposed	**Unexposed**	**Exposed**	**Unexposed**	**Exposed**	**Unexposed**
Population	87,208	386,261	202970	379839	212568	382545
Events, n (%)	304 (0.35%)	1056	847	1036	879	1031
Person-years	489801	2121954	1279818	2091715	1323378	2099435
Crude incident rate/1000 years	0.62	0.50	0.67	0.50	0.66	0.49
Age at outcome Median (IQR)	43.2 (38.5-48.5)	43.5 (37.4-48.2)	43.3 (37.4-48.0)	42.7 (37.4-47.8)	43.1 (37.4-47.9)	42.7 (37.6-47.8)
Crude HR (95% CI)	1.27 (1.12-1.45)		1.25 (1.14-1.37)		1.27 (1.16-1.39)	
P-value	<0.001		<0.001		<0.001	
Adjusted HR (95% CI)	1.09 (0.96-1.24)		1.09 (0.99-1.19)		1.09 (0.99-1.20)	
P-value	0.173		0.080		0.068	

Adjusted for age, Townsend quintile of deprivation, body mass index, smoking, lipid medication, Alcohol status, hypertension, diabetes mellitus, current use of combined oral contraceptive, connective tissue disorders, migraine, polycystic ovary syndrome, gestational diabetes mellitus, pre-eclampsia, pre-term birth, pelvic inflammatory disease, endometriosis, fibroids.

Composite CVD	Current contraceptive use		Fibroids	
	Exposed	**Unexposed**	**Exposed**	**Unexposed**
Population	149170	282064	214219	384998
Events, n (%)	712 (0.48%)	889 (0.32%)	890 (0.42%)	1047 (0.27%)
Person-years	916037	1514532	1335370	2114492
Crude incident rate/1000 years	0.78	0.58	0.67	0.50
Age at outcome Median (IQR)	43.7 (38.1-48.3)	42.9 (38.1-48.2)	43.2 (37.4-47.9)	42.7 (37.6-47.7)
Crude HR (95% CI)	1.24 (1.12-1.36)		1.26 (1.15-1.38)	
P-value	< 0.001		<0.001	
Adjusted HR (95% CI)	1.03 (0.94-1.15)		1.09 (0.99-1.19)	
P-value	0.445		0.067	

Adjusted for age, Townsend quintile of deprivation, body mass index, smoking, lipid medication, Alcohol status, hypertension, diabetes mellitus, current use of combined oral contraceptive, connective tissue disorders, migraine, polycystic ovary syndrome, gestational diabetes mellitus, pre-eclampsia, pre-term birth, pelvic inflammatory disease, endometriosis, fibroids.

Table S7.5: Incidence rates and hazard ratio for cardiometabolic outcomes (sensitivity analyses excluding polycystic ovarian syndrome, endometriosis, and fibroids as covariates from the adjusted model)

	Menstrual cycle regularity		Menstrual cycle frequency	
	Irregular (exposed)	Regular (Unexposed)	Frequent/Infrequent (exposed)	Normal (unexposed)
Composite CVD				
Population	214,915	386,261	36,873	65,484
Events, n (%)	896 (0.42%)	1056 (0.27%)	205 (0.56%)	202 (0.31%)
Person-years	1339541	2121954	248301.2	377644.7
Crude incident rate/1000 years	0.67	0.50	0.83	0.53
Age at outcome Median (IQR)	43.1 (37.4-47.8)	42.7 (37.6-47.8)	43.2 (38.5 – 48.5)	43.5 (37.4 -48.2)
Crude HR (95% CI)	1.26 (1.15-1.38)		1.46 (1.20-1.78)	
P-value	< 0.001		<0.001	
Adjusted HR (95% CI)	1.09 (1.00-1.20)		1.28 (1.05-1.55)	
P-value	0.052		0.016	
IHD				
Population	215,259	386,702	36,933	65,571
Events, n (%)	342 (0.16%)	353 (0.09%)	77 (0.21%)	76 (0.12%)
Person-years	1344052	2127601	249369.3	378907.9
Crude incident rate/1000 years	0.24	0.17	0.30	0.20
Age at outcome Median (IQR)	44.0 (40.1-48.4)	44.6 (40.3-49.8)	45.1 (40.5-49.2)	45.8 (40.9-51.0)
Crude HR (95% CI)	1.43 (1.23-1.66)		1.44 (1.05-1.97)	
P-value	< 0.001		0.025	
Adjusted HR (95% CI)	1.18 (1.02-1.37)		1.14 (0.82-1.57)	
P-value	0.029		0.443	
Cerebrovascular disease				
Population	215,071	386,446	36,897	65,520
Events, n (%)	494 (0.22%)	620 (0.16%)	124 (0.34%)	111 (0.17%)
Person-years	1342726	2125102	248888	378288
Crude incident rate/1000 years	0.37	0.29	0.50	0.29
Age at outcome Median (IQR)	42.5 (35.8-47.2)	42 (36.1-47.3)	43.2 (38.5-48.6)	42.7 (35.3-47.6)
Crude HR (95% CI)	1.19 (1.06- 1.34)		1.62(1.26-2.00)	
P-value	0.004		< 0.001	

Adjusted HR (95% CI)	1.04 (0.93-1.18)		1.48 (1.14-1.92)	
P-value	0.480		0.003	
Heart failure				
Population	215,332	386,749	36,935	65,579
Events, n (%)	139 (0.06%)	138 (0.04%)	23 (0.06%)	30 (0.05%)
Person-years	1346027	2129232	249715	379180
Crude incident rate/1000 years	0.1	0.06	0.09	0.08
Age at outcome Median (IQR)	44.4 (37.9 - 49)	41.5 (36.7-46.9)	45.2 (35.4-48.9)	39.9 (33.6-45.7)
Crude HR (95% CI)	1.48 (1.17-1.87)		1.10 (0.64-1.90)	
P-value	0.001		0.723	
Adjusted HR (95% CI)	1.30 (1.03-1.65)		1.03 (0.59-1.79)	
P-value	0.029		0.910	
Hypertension				
Population	212,747	383,644	36,476	65,031
Events, n (%)	4529 (2.13%)	5788 (1.51%)	1060 (2.91%)	1109 (1.71%)
Person-years	1300272	2076051	239680	369126
Crude incident rate/1000 years	3.48	2.79	4.42	3.00
Age at outcome Median (IQR)	41.6 (36.4-46.2)	41.8 (36.8-46.6)	42 (37.3 - 47)	43 (37.7- 47.8)
Crude HR (95% CI)	1.19 (1.14 - 1.24)		1.41 (1.30-1.54)	
P-value	< 0.001		<0.001	
Adjusted HR (95% CI)	1.08 (1.04-1.12)*		1.33 (1.22-1.45) *	
P-value	p<0.001		<0.001	
Diabetes mellitus				
Population	213,480	384,466	36,613	65,201
Events, n (%)	2412 (1.13%)	2215 (0.58%)	582 (1.59%)	383 (0.59%)
Person-years	1322940	2106721	244548.3	375211.8
Crude incident rate/1000 years	1.82	1.05	2.38	1.02
Age at outcome Median (IQR)	40.6 (34.8-45.3)	41.3 (36.1-46.2)	40.5 (34.3-46.2)	42.8 (38.3-47.1)
Crude HR (95% CI)	1.66 (1.56-1.75)		2.25(1.96-2.53)	
P-value	< 0.001		<0.001	
Adjusted HR (95% CI)	1.41 (1.33-1.50)#		1.84 (1.61-2.10) #	
P-value	<0.001		<0.001	

Adjusted for age, Townsend quintile of deprivation, body mass index, smoking, lipid medication, Alcohol status, hypertension, diabetes mellitus, current use of combined oral contraceptive, connective tissue disorders, migraine, gestational diabetes mellitus (types 1 and 2), pre-eclampsia, pre-term birth, pelvic inflammatory disease.

*= Adjusted for all above except hypertension

#= Adjusted for all above except diabetes mellitus

Table S7.6: Incidence rates and hazard ratios for composite CVD (Sensitivity analyses for menstrual cycle frequency)

Composite CVD	Amenorrhoea		Polycystic ovary syndrome		Endometriosis	
	Exposed	**Unexposed**	**Exposed**	**Unexposed**	**Exposed**	**Unexposed**
Population	31,096	65,484	33125	64469	36457	64848
Events, n (%)	153 (0.49%)	202 (0.31%)	182 (0.55%)	199 (0.31%)	201 (0.55%)	199 (0.31%)
Person-years	198450.6	377644.7	228639.5	372663.2	245064.4	373542.3
Crude incident rate/1000 years	0.77	0.53	0.80	0.53	0.82	0.53
Age at outcome Median (IQR)	43.4 (38.2-49.0)	43.5 (37.4-48.2)	43.1 (38.5-48.0)	43.5 (37.7-48.2)	43.2 (38.5-48.5)	43.3 (37.3-48.2)
Crude HR (95% CI)	1.41 (1.14-1.74)		1.40 (1.14-1.72)		1.46 (1.20-1.78)	
P-value	0.001		0.001		<0.001	
Adjusted HR (95% CI)	1.18 (0.95-1.47)		1.23 (1.01-1.51)		1.24 (1.02-1.52)	
P-value	0.130		0.043		0.035	

Adjusted for age, Townsend quintile of deprivation, body mass index, smoking, lipid medication, Alcohol status, hypertension, diabetes mellitus, current use of combined oral contraceptive, connective tissue disorders, migraine, polycystic ovary syndrome, gestational diabetes mellitus, pre-eclampsia, pre-term birth, pelvic inflammatory disease, endometriosis, fibroids.

Composite CVD	**Current contraceptive use**		**Fibroids**	
	Exposed	**Unexposed**	**Exposed**	**Unexposed**
Population	26620	48155	36729	65274
Events, n (%)	165 (0.62%)	172 (0.36%)	204 (0.56%)	199 (0.30%)
Person-years	177420.8	273834.2	247286.2	376280.8
Crude incident rate/1000 years	0.93	0.63	0.83	0.53
Age at outcome Median (IQR)	43.4 (39.3-48.9)	43.7 (38.3-48.4)	43.2 (38.5-48.5)	43.5 (37.3-48.4)
Crude HR (95% CI)	1.40 (1.13-1.74)		1.48(1.21-1.80)	
P-value	0.002		<0.001	
Adjusted HR (95% CI)	1.14 (0.91-1.42)		1.26 (1.03-1.54)	
P-value	0.259		0.025	

Adjusted for age, Townsend quintile of deprivation, body mass index, smoking, lipid medication, Alcohol status, hypertension, diabetes mellitus, current use of combined oral contraceptive, connective tissue disorders, migraine, polycystic ovary syndrome, gestational diabetes mellitus, pre-eclampsia, pre-term birth, pelvic inflammatory disease, endometriosis, fibroids.

Table S7.7: Incidence rates and hazard ratios for cardiometabolic outcomes (Sensitivity analyses for frequent and infrequent cycles separately)

	Menstrual cycle frequency (short)		Menstrual cycle frequency (Long)	
	Frequent (exposed)	**Normal (Unexposed)**	**Infrequent (exposed)**	**Normal (unexposed)**
Composite CVD				
Population	16063	27976	20810	37508
Events, n (%)	125	107	80	95
Person-years	122864.1	183737.4	125,437.1.	193,907.3
Crude incident rate/1000 years	1.0	0.6	0.7	0.5
Age at outcome Median (IQR)	44.3 (39.2-49.3)	44.4 (39.4-49.9)	41.8 (37.7-46.6)	42.5 (34.7-46.2)
Crude HR (95% CI)	1.66 (1.28-2.15)		1.24 (0.92-1.67)	
P-value	<0.001		0.161	
Adjusted HR (95% CI)	1.42 (1.09-1.85)		1.06 (0.78-1.45)	
P-value	0.009		0.704	
IHD				
Population	16094	28021	20839	37550
Events, n (%)	46	46	31	30
Person-years	123541.7	184410.1	125, 827.6	194497.8
Crude incident rate/1000 years	0.4	0.2	0.2	0.2
Age at outcome Median (IQR)	45.9 (41.1-49.8)	47.8 (42.6-51.4)	43.0 (39.1-47.8)	45.0 (39.1-48.1)
Crude HR (95% CI)	1.41 (0.93-2.12)		1.48 (0.89-2.44)	
P-value	0.102		0.127	
Adjusted HR (95% CI)	1.13 (0.74- 1.72)		1.16 (0.68- 1.97)	
P-value	0.570		0.582	
Cerebrovascular disease				
Population	16079	27996	20818	37524
Events, n (%)	82	55	42	56
Person-years	123258.6	184112.6	125629.7	194174.9
Crude incident rate/1000 years	0.7	0.3	0.3	0.3
Age at outcome Median (IQR)	43.5 (38.5-49.3)	43.3 (39.3-49.6)	41.7 (38.6- 46.2)	41.6 (33.5-46.2)
Crude HR (95% CI)	2.12 (1.51- 2.99)		1.12 (0.75-1.67)	
P-value	<0.001		0.583	

Adjusted HR (95% CI)	1.88 (1.33-2.67)		1.01 (0.66-1.53)	
P-value	<0.001		0.980	
Heart failure				
Population	16094	28023	20841	37556
Events, n (%)	11	16	12	14
Person-years	123761.3	184559.3	125953.5	194620.9
Crude incident rate/1000 years	0.1	0.1	0.1	0.1
Age at outcome Median (IQR)	47.6 (41.3-49.8)	38.6 (33.9-48.9)	39.7 (33.7-46.6)	40.7 (31.9-45.5)
Crude HR (95% CI)	0.97 (0.45-2.09)		1.27 (0.58-2.74)	
P-value	0.935		0.550	
Adjusted HR (95% CI)	0.93 (0.42- 2.06)		1.13 (0.50-2.54)	
P-value	0.858		0.770	
Hypertension				
Population	15868	27732	20608	37299
Events, n (%)	589	620	471	489
Person-years	118078.5	178641	121601.2	190485.1
Crude incident rate/1000 years	5.0	3.5	3.9	2.6
Age at outcome Median (IQR)	43.0 (38.4-47.8)	43.4 (39.0-48.4)	40.7 (36.7-45.3)	42.2 (36.0-46.8)
Crude HR (95% CI)	1.38 (1.23-1.55)		1.44 (1.27-1.64)	
P-value	P<0.001		P<0.001	
Adjusted HR (95% CI)	1.37 (1.22-1.54)		1.24 (1.08-1.41)	
P-value	<0.001		0.002	
Diabetes mellitus				
Population	15979	27860	20634	37341
Events, n (%)	239	214	343	169
Person-years	121590.4	182497.1	122957.8	192714.7
Crude incident rate/1000 years	2.0	1.2	2.8	0.9
Age at outcome Median (IQR)	41.4 (34.6-47.8)	43.2 (39.1-47.2)	39.8 (34.3-45.1)	42.0 (37.8-46.6)
Crude HR (95% CI)	1.60 (1.33-1.92)		3.04 (2.53-3.65)	
P-value	<0.001		<0.001	
Adjusted HR (95% CI)	1.37 (1.13-1.65)		2.24 (1.85-2.72)	
P-value	<0.001		<0.001	

Adjusted for age, Townsend quintile of deprivation, body mass index, smoking, lipid medication, Alcohol status, hypertension, diabetes mellitus, current use of combined oral contraceptive, connective tissue disorders, migraine, polycystic ovary syndrome, gestational diabetes mellitus (types 1 and 2), pre-eclampsia, pre-term birth, pelvic inflammatory disease, endometriosis, fibroids.

*= Adjusted for all above except hypertension

#= Adjusted for all above except diabetes mellitus

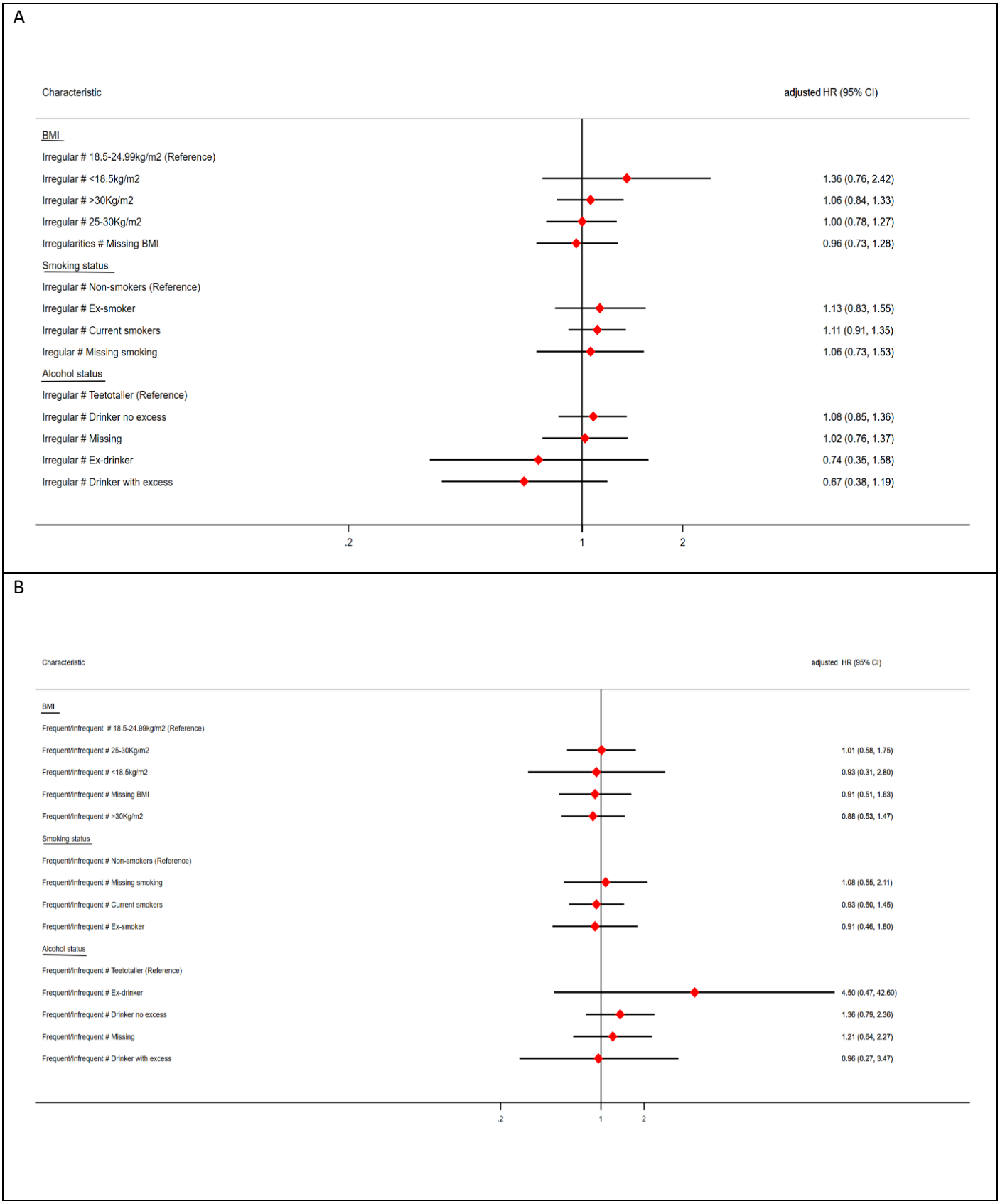

Figure S7.2: Interaction between (A) irregular menstrual cycles and (B) frequent or infrequent menstrual cycles and lifestyle factors (Body mass index, smoking, and alcohol use).

Table S7.8: Summary of selected existing literature examining the association between menstrual characteristics and cardiometabolic outcomes.

Author year	Objective	Study design & population	Exposure	Confounder adjustment	Outcome & results (Multivariable analyses)
Iliodromiti & Nelson.[366] 2017 UK	To assess whether irregular menstrual cycles are associated with CVD events (morbidity and mortality)	Prospective cohort UK biobank 40,896 Non menopausal women aged 50 years and below	Menstrual cycle regularity reported as irregular cycles or cycles longer than 34 days (N= 8835) versus regular cycles (N=32061)	Adjusted for multiple confounders (not provided)	*Irregular menstrual cycles* Fatal and non-fatal CVD events HR 1.05 (95% CI, 0.91-1.20) Fatal and non-fatal IHD events HR 0.88(95% CI, 0.58-1.34) Fatal and non-fatal cerebrovascular events HR 0.85 (95% CI, 0.47 to 1.51)
Wang et al.[353] 2022 USA	To investigate whether menstrual cycle characteristics across the reproductive lifespan are associated with CVD. How strongly do hypercholesterolemia, chronic hypertension mediate the association	Prospective cohort study. (Nurses' Health Study II) 80 630 female Nurses from the US Follow-up 1993-2017 Menstrual cycle characteristics (regularity and length reported for ages 14-17 years and 18-22 years at enrolment 1989 and in 1993 at ages 29-46 years	Menstrual cycle regularity Very regular (3-4 days before or after expected) Regular (within 5-7 days) Usually, irregular Always irregular No periods Menstrual cycle length < 12 days 21-25 days 26-31 days 32-39 days 40-50 days >50 days or too irregular to estimate	Age, race & ethnicity, age at menarche, parental history of CVD BMI, time-varying menopausal status and hormone usage, hormone therapy use, parity, regular aspirin use, physical activity, smoking status, Alternative Healthy Eating Index diet	Fatal and Non-fatal composite CVD (MI, revascularisation, CABG, PCI, and stroke) **Cycle regularity (Fully adjusted model 2)** *14-17 years:* Always irregular or no period (HR 1.15; 95% CI, 0.99-1.34) Usually irregular (HR 1.05; 0.99-1.34) *18-22 years:* Always irregular or no period (HR 1.36; 95% CI, 1.06-1.75) Usually irregular: (HR 1.08; 95% CI 0.85-1.37) *29-46 years:* Always irregular or no period (HR 1.40; 95% CI, 1.14-1.71) Usually irregular: (HR 1.26; 95% CI ,1.06-1.49) **Cycle length (Fully adjusted model 2)** 18-22 years: ≥ 40 days or too irregular (HR 1.44; 95% CI, 1.13-1.34) 32-39 days: (HR 1.06; 95 CI, 0.86-1.31) 29-46 years: ≥ 40 days or too irregular (HR 1.30; 95% CI, 1.09-1.57) 32-39 days: (HR 1.05; 95% CI 0.89-1.24)
Wang et al.[352] 2020 USA	To determine whether irregular or prolonged menstrual cycles are associated with all-cause and cause-specific premature mortality (70 years of age).	Prospective cohort study. (Nurses' Health Study II) 79505 female Nurses from the US Follow-up 1993-2017 Menstrual cycle characteristics (regularity and length reported for ages 14-17 years and 18-22 years at enrolment 1989 and in 1993 at ages 29-46 years	Menstrual cycle regularity Very regular (3-4 days before or after expected) Regular (within 5-7 days) Usually, irregular Always irregular No periods Menstrual cycle length < 12 days 21-25 days 26-31 days 32-39 days 40-50 days >50 days or too irregular to estimate	Age, menopausal status, age at menarche, race, family history of myocardial infarction, stroke, diabetes, baseline hypertension, cholesterol levels, parity, alcohol consumption, BMI, physical activity, smoking status, alternative health eating index.	Premature (< 70 years) CVD **Cycle regularity (Fully adjusted model 2)** *14-17 years:* Irregular or no period (HR 1.11; 95% CI, 0.76-1.61) *18-22 years:* Irregular or no period (HR 1.24; 95% CI, 0.70-2.18) *29-46 years:* Irregular or no period (HR 1.59; 95% CI, 1.04-2.45) **Cycle length (Fully adjusted model 2)** 18-22 years: ≥ 32 days or too irregular (HR 1.16; 95% CI, 0.67-2.04) 29-46 years: ≥ 32 days or too irregular (HR 1.46; 95% CI, 0.99-2.16)
Wang et al.[367] 2020 USA	To examine the association between menstrual cycle characteristics and risk of type 2 diabetes mellitus	Prospective cohort (Nurses Health II) study 75,546 premenopausal US female nurses aged 29-46 years at baseline.	Menstrual cycle irregularity reported as regular (within 5-7 days of expected period), usually irregular, always irregular, no period.	Age, age at menarche, ethnicity, family history of diabetes, menopausal status, menopausal hormone use, parity, household income, oral contraceptive use, alcohol consumption,	Outcome Type 2 diabetes mellitus **Irregular menstrual cycles (Fully adjusted model 2)** 14-17 years Always irregular or no period: (HR 1.32; 95%CI, 1.22-1.44) Usually irregular: (HR 1.15; 95% CI 1.05-1.25)

		Menstrual cycle characteristics (regularity and length reported for ages 14-17 years and 18-22 years at enrolment 1989 and in 1993 at ages 29-46 years	Menstrual cycle length defined as usual (< 21 days), 21-25 days, 26-31 days, 32-39 days, 40-50 days, > 50 days or too irregular to estimate	BMI, physical activity, smoking status, and Alternative Healthy Eating Index diet quality score (quintiles)	Ages18-22 years Always irregular or no period (HR 1.41 95%CI, 1.23-1.62) Usually irregular (HR 1.22; 95% CI, 1.07-1.39) Ages 29-46 years Always irregular or no period (HR1.66 95%CI, 1.49-1. 84) Usually irregular (HR 1.35; 95% CI 1.23-1.48) **Cycle length (Fully adjusted model 2)** Ages 18-22 years >40 days: (HR 1.37; 95% CI 1.19-1.57) 32-39 days: (HR 1.18; 95% CI 1.06-1.33) Ages 29-46 >40 days: (HR 1.50; 95% CI 1.36-1.65) 32-39 days: (HR 1.37; 95% CI 1.36-1.65)
Solomon et al.[41] 2002 USA	To evaluate the risk of CHD and stroke associated with history of irregular menstrual cycles	Prospective cohort study (Nurses Health II) study. 82,349 female nurses from the USA aged 25-35 years at baseline Follow-up from 1982-1996	Menstrual cycle regularity reported via questionnaire as very regular, usually regular, very irregular	age, BMI, cigarette smoking, menopausal status, HRT use, parental history of MI, parity alcohol use, aspirin use, multivitamin, use of vitamin E supplements, physical activity level, history of oral contraceptive use.	*Very irregular menstrual cycle* Composite CVD fatal and non-fatal aRR 1.46 (95% CI, 1.23–1.74) Fatal and non-fatal CHD aRR 1.53 (95% CI, 1.24–1.90) Non-fatal CHD aRR 1.38 (95% CI, 1.06-1.80) Fatal CHD aRR 1.88 (95% CI, 1.32-2.67) Overall (fatal and non-fatal) stroke aRR, 1.30; 95% CI (0.97–1.74) *Usually, irregular* Composite CVD aRR 1.17(95% CI, 1.03-1.33) Total CHD aRR 1.22 (95% CI, 1.04–1.44) Non-fatal aRR 1.27 (95% CI, 1.05–1.54) Fatal CHD aRR 1.11 (95% CI, 0.82–1.50) *Usually, regular* Total CHD aRR 1.11 (95% CI,0.82–1.50) Non-fatal CHD aRR 0.96 (95% CI, 0.82–1.12) Fatal CHD aRR 1.12 (95% CI, 0.90–1.40)
Kiconco et al.[368] 2021 Australia	To evaluate risk of heart disease and diabetes mellitus in women with irregular menstrual cycles compared to those with regular menstrual cycles.	Longitudinal cohort study of 13714 women aged 45-50 years at baseline	Menstrual cycle irregularity (N=1048) and regular menstrual cycle (N= 12135)	age, country of birth, education level, occupation, marital status, alcohol consumption, physical activity, oral contraceptive pill use use, hormonal replace therapy use, and body mass index	*Irregular menstrual cycles* Heart disease (myocardial infarction and angina) HR 1.20 (95% CI, 1.01-1.43) Diabetes mellitus HR 1.17 (95% CI, 1.00-1.38)
Gast et al.[398] 2010 Netherlands	To examine whether long and irregular cycles are associated with future risk of type 2 DM and CHD	Prospective cohort study (The Netherlands Prospect and MORGEN cohort) 23,571 women aged 30-40 years at baseline.	Menstrual cycle characteristics defined as irregular, regularly short (<26 days), regularly normal (27 -29 days), regularly long (30 days) Cycle length was defined as long (≥ 30 days) or short (≤ 26 days)	Age, BMI waist–hip ratio, physical activity, smoking, education level, ever use of OCs, HT, oophorectomy, and menopausal status,	*Irregular menstrual cycles* Coronary Heart disease HR 1.28 (95% CI, 1.05-1.56) Type 2 diabetes mellitus HR 1.21 (95% CI 0.96- 1.54)

Dovom et al.[372] 2016 Iran	To evaluate the association between history of irregular menstrual cycles and metabolic disorders	Prospective cohort (Tehran lipid and glucose study) of 2128 Iranian women aged 18-49 years at baseline Duration of follow-up: 15 years	Menstrual cycle regularity reported as regular as regular versus irregular	age, BMI, parity, FBS, BS-2hr, family history of diabetes mellitus, menstrual status for Diabetes mellitus	*Irregular menstrual cycles* Diabetes mellitus: HR 1.73 (95% CI, 1.14-2.64) Hypertension: HR 1.26(95% CI, 0.89-1.80)
Solomon et al.[383] 2001 USA	To evaluate the risk of type 2 diabetes mellitus in women with long or irregular menstrual cycles	Prospective cohort study. 101, 073 women aged 18-22 years at baseline Duration of follow-up: 8 years	Menstrual cycle characteristics regularity reported as very regular (within 3 days), regular, usually irregular, always irregular, no period Menstrual cycle length reported as <21 days, 21-25 days, 26-31 days, 32-39 days, 40-50 days, >50 days, or too irregular to estimate)	Age, time period, BMI, smoking, family history of diabetes mellitus, physical activity level, and duration of oral contraceptive use.	*Irregular menstrual cycles or no period* Usual cycle length in days. 26-31 days: RR 1.0 (Reference) < 21 days: RR 1.50 (0.70-3.19) 21-25 days: RR 1.18 (0.87-1.58) 32-39 days: RR 1.03 (0.79-1.33) >= 40 days or highly irregular: RR 2.08 (1.61-2.66)