THE ASSOCIATION BETWEEN SMOKING, SMOKING CESSATION AND MENTAL HEALTH

by

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ABSTRACT

Introduction: Smoking is a major risk factor for development of serious disease and smoking cessation greatly reduces this risk. The association between smoking, smoking cessation and mental health however, is less clear-cut, therefore this thesis aimed to further investigate this association.

Methods: The first part of the thesis reports a systematic review and meta-analysis of longitudinal studies to determine the difference in change in mental health between quitters and continuing smokers. The second part of the thesis reports three prospective analyses of individual level-patient data from five trials for smoking reduction treatment. The first analysis examined the association between cessation and change in mental health using propensity score matching (PSM). The second analysis examined the association between cessation and risk of psychiatric disorder using PSM. The final analysis examined the association between change in mental health after quitting and odds of relapse.

Results and interpretations: Cessation was associated with improvements in mental health compared with continuing smoking; there was no association between cessation and risk of psychiatric disorder, and no association between change in mental health after cessation and future relapse. Results support the misattribution hypothesis, and have implications for future research, smoking cessation treatment and public health policy.

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LIST OF ABBREVIATIONS

Abbreviation	Term
5-HT	Serotonin
95% CI	95% confidence interval(s)
APMS	Adult Psychiatric Morbidity Survey
CO/ppm	Carbon monoxide/parts per million
CPD	Cigarettes per day
DOH	Department of Health
EMA	Ecological momentary assessments
FTND	Fagerström Test for Nicotine Dependence
GABA	Gamma-aminobutyric acid
HSE	Health Survey for England
M	Mean
MAO	Monoamine oxidaise
MAOI	Monoamine oxidaise inhibitor
MDD	Major depressive disorder
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare Products Regulatory Agency (MHRA)
nAChR	Nicotinic acetylcholine receptor
NOS	Newcastle-Ottawa Scale
NRT	Nicotine replacement therapy
ONS	Office for National Statistics
PET	Positron emission tomography
PSM	Propensity score matching
SD	Standard deviation
SE	Standard error
SMD	Standardised mean difference
SPECT	Single-photon emission computed tomography imaging
THIN	The Health Improvement Network

THESIS OUTLINE

This thesis examined the association between smoking, smoking cessation and mental health in light of current theories and evidence from various disciplines. The first chapter denotes the public health importance of the thesis and introduces the field by critically reviewing relevant literature. The subsequent chapters represent four independent studies on the theme of smoking cessation and mental health. The data presented in Chapter Two were derived from a systematic review of published studies. Chapters Four to Six were prospective analyses of individual level patient data from five randomised controlled trials of nicotine therapy for smoking reduction, which were provided by McNeil AB pharmaceutical company, as described in detail in Chapter Three.

All chapters were written according to the relevant reporting guidelines. Chapter Two followed PRISMA (Moher et al. 2009) and MOOSE reporting guidelines (Stroup et al. 2000), and Chapters Four to Six were written according to STROBE guidelines for reporting of observational studies (Von Elm et al. 2007). Reporting of propensity score matching (PSM) procedures in Chapters Four and Five followed criteria outlined by a review of PSM methods (Thoemmes and Kim 2011).

Chapter Two reports a systematic review and meta-analysis of longitudinal studies which measured change in mental health outcomes from baseline to follow-up (>6 weeks) in smokers who quit and smokers who continued smoking. Numerous sensitivity analyses were conducted to address within and between study heterogeneity. In this study there was a significant association between stopping smoking and improvements in anxiety, depression,

psychological quality of life, positive affect and stress at follow-up, compared with continuing to smoke. This finding was consistent in people from different clinical and general populations and the effect estimates were equal or greater than those of anti-depressant treatment for mood disorders. However, these findings were potentially susceptible to group membership bias and unmeasured confounding.

Chapter Three describes data from six randomized placebo-controlled trials provided by McNeil AB Pharmaceutical Company and these data were used for analysis in Chapters Four to Six. This chapter describes the application process, data extraction, cleaning and synthesis, and also provides descriptive information about participants, trials and treatment characteristics.

In Chapter Four, the risk of group membership bias to the association between cessation and mental health was addressed using propensity score matching (PSM). PSM is a method used to balance covariates predictive of propensity to achieve abstinence between exposure groups. If a balance between the groups is reached the matched sample can be analysed to produce causal estimates. Mental health was measured using the SF-36 and repeated point-prevalence smoking status was biologically-validated over a six month period. Linear regression modelling was used to compare change in mental health from baseline to 12 month follow-up between quitters and continuing smokers, and effect estimates derived from matched and unmatched samples were compared. Estimates from both samples were similar and suggested that cessation was associated with clinically meaningful improvements in mental health.

The analysis of mean mental health scores in Chapters Two and Four may have concealed the rare occurrence of psychiatric disorder. Therefore, Chapter Five estimated the risk of psychiatric diagnosis after quitting compared with continuing to smoke. Similar to Chapter Four, estimates were compared between the whole sample and from participants matched using PSM in aim of overcoming group membership bias and confounding. Psychiatric diagnosis was ascertained by coding trials' adverse event data according to MedDRA 16.1 terminology. In a small sample of quitters, there was no evidence of psychiatric events six months after achieving abstinence, whereas about 2% of those who continued smoking reported evidence of a psychiatric disorder during the same six month period. The difference was similar between matched and unmatched samples, although results were not significant. The results in this chapter were inconclusive and a larger study using similar methodology should be conducted.

One of the potential explanations for the findings in Chapters Two, Four and Five is that some people stop smoking, experience improved mental health and therefore remain abstinent; whereas some people quit smoking, experience worse mental health and therefore relapse back to smoking. Chapter Six examined this hypothesis using logistic regression modelling to determine if post-cessation change in mental health was associated with future relapse. This chapter found no significant association and the findings were discussed in relation to smokers reported reasons for relapse.

Chapter Seven discusses how the thesis adds to current knowledge and contextualises the knowledge-to-date according to Bradford Hill's criteria for inferring casual associations. Secondly, clinical and public health implications are discussed and suggestions for future

research are made. The chapter concludes with summary statement for the overall contribution of the thesis.

DEFINITIONS

Mental health — The World Health Organization (2005) defines mental health as:

> "A state of well-being in which every individual realizes his or her own potential, can cope with the normal stresses of life, can work productively and fruitfully, and is able to make a contribution to her or his community… health is a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity."

CHAPTER ONE

1. LITERATURE REVIEW: SMOKING, SMOKING CESSATION AND MENTAL HEALTH

1.1. Introduction to Chapter One

Chapter One introduces the importance of the thesis is by illustrating the global tobacco epidemic, physical health hazards of smoking and the public health importance of smoking cessation. The second part of the chapter highlights evidence showing that most smokers want to quit however continue smoking because they feel that smoking offers mental health benefits, moreover that this belief is widespread amongst health professionals and presents a barrier to smoking cessation treatment in both general and clinical populations. The chapter then examines the epidemiological association between smoking, quitting and mental health in light of three hypotheses which aim to explain the causal nature of the association, and critically evaluates evidence from different fields in relation to these hypotheses. The final section evaluates current areas of uncertainty and presents the aims of the thesis.

1.2. Prevalence of tobacco smoking worldwide and in the United Kingdom

The Tobacco Atlas (Eriksen et al., 2012) estimated that approximately 20% of the world's adult population smoked in 2012. In the UK rates are similar, the Office of National Statistics (ONS) estimated that approximately 10 million or 20% of the UK general population were current smokers in 2011, with a slight gender gap in prevalence (Figure 1.1) (Office for National Statistics, 2013). The Smoking Tool Kit Study offers the most up-to-date data for smoking rates in England, and shows that prevalence has dropped below 20% for the first time to 19.2% (West and Brown, 2014). Smoking prevalence has decreased dramatically since 1974 (Figure 1.1) (Office for National Statistics, 2013) due to the success of public health policies and development of cessation interventions (Department of Health, 2008). Of the remaining UK smoking population, it has been estimated that over two thirds would like to quit (Lader, 2009), and this estimate is similar across western nations, for example, in the US (Centres for Disease Control and Prevention, 2011). In 2009, 75% of smokers had reported a recent quit attempt (Lader, 2009; Zhou et al., 2009). However, most quit attempts are unsuccessful, in the UK about 92% of smokers who attempt to quit relapse within two years (Lader, 2009).

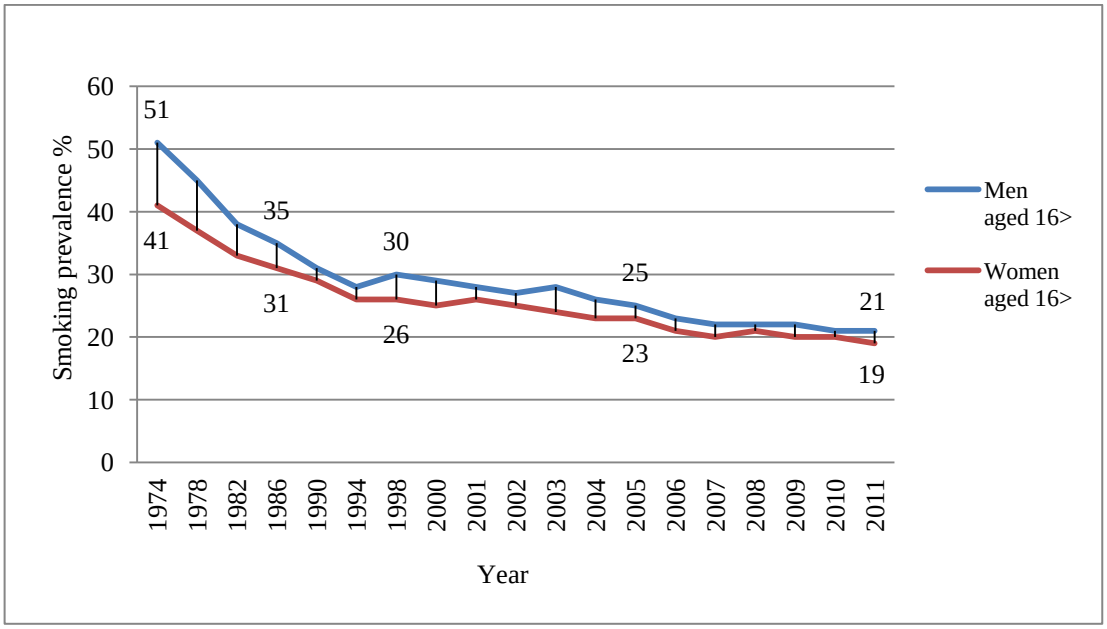

Figure 1.1 Changes in UK smoking prevalence by sex, between 1974 and 2011 (data from ONS)

1.3. Smoking, smoking cessation and physical health

Tobacco use continues to be the leading global cause of preventable death and has been described as a global epidemic (The World Health Organization, 2011). The association between tobacco smoking and hazards to physical health are well documented. In 2004 the Surgeon General of the United States' Centre for Disease Control and Prevention conducted a comprehensive literature review of the 'effects' of smoking in which evidence was collated from ecological, cross-sectional, cohort, case-control studies and intervention trials, and was peer reviewed by over 100 field experts. The report concluded there was sufficient evidence to infer a causal relationship between smoking and 10 different types of cancer, heart and respiratory diseases, and notably these diseases are amongst the top 10 most common causes of death in the UK (Cancer Research UK, 2013) (Office for National Statistics, 2011). In

2001 it was estimated that there were 2.3 million deaths worldwide from smoking related disease and that approximately every one in two long-term smokers will be killed by their addiction (Jha, 2009).

Two major longitudinal prospective cohort studies have aimed to determine the association between smoking and risk of morbidity and mortality. Pirie et al. (2013) conducted an analysis of data from 1.3 million women, over a 12 year period. The authors calculated 12 year relative risks for smokers versus never-smokers for all-cause mortality and death from specific disease with adjustment for demographic, geographic, and lifestyle factors. The results showed that current smokers had a greater relative risk (RR) compared with never-smokers for 30 different diseases including lung disease, RR=35.3 (95% CI: 29.2 to 42.5), lung cancer, 21.4 (19.7 to 23.2) and aortic aneurysm, 6.3 (5.2 to 7.7). In a study of data from 34,439 male doctors, Doll and colleagues (2004) aimed to determine the health hazards of smoking over 50 years. The researchers calculated the annual all-cause mortality rates per 1000 men in life-long smokers and non-smokers. The study found that life-long smokers aged 35 to 44 had a mortality rate 1.6 times greater than non-smokers, this mortality rate increased with age and peaked at 2.7 times greater for smokers aged 65 to 74 compared with non-smokers.

Several key studies have aimed to establish the physical health benefits of stopping smoking. The US Surgeon General (1990) compiled a report of available evidence from case-control studies, cross-sectional studies, and clinical trials which examined the association between smoking cessation and health outcomes. The report concluded that stopping smoking decreases the risk of many types of cancer, heart attack and stroke, and has significant health

benefits for pregnant women and their unborn child. The report concluded that smoking cessation has major and immediate health benefits at all ages, and these benefits occur for people with and without smoking-related disease.

Since the Surgeon General (1990) report, two major prospective longitudinal cohort studies have aimed to measure the health benefits of stopping smoking. Pirie et al. (2013) in a study referred to previously calculated the relative risk (RR) of all-cause mortality in later life, for ex-smokers compared with never-smokers. Results indicated that stopping before the age of 40 avoids more than 90% of excess mortality, and stopping smoking before the age of 30 avoids more than 97% of excess mortality. In the UK male doctors' study referred to above, Doll and colleagues (2004) calculated the annual all-cause mortality rates per 1000 men in life-long cigarette smokers and non-smokers over a 50 year period. Results showed that smokers who stopped before the age of 35 had similar survival rates as non-smokers, smokers who stopped at 40 gained about nine years of life expectancy, smokers who stopped at 50 gained about six years, and smokers who stopped at 60 were estimated to gain at least three years. The report concluded that the earlier one stops smoking the greater the reduction in the risk of mortality from smoking.

1.4. Reasons for continuing to smoke

As noted previously in section 1.2, most smokers want to stop smoking but are unsuccessful in doing so. Both qualitative and quantitative studies have investigated reasons why smokers continue to smoke. These studies have found that smokers consistently report that smoking

offers mental health benefits and that these benefits are an important reason for continuing. Studies involving interviews with smokers have identified that smokers report smoking relieves their emotional problems, feelings of depression and anxiety, stabilises mood, and can be used for relaxation and pleasure, as well as for relieving stress (Kerr et al., 2006; Lawn et al., 2002; Thompson et al., 2003). Smokers affirm that the emotional support gained from smoking is reinforcing and defers cessation, and these reports are consistent amongst smokers of all ages, in both heavy and light smokers, and in smokers with and without mental health disorders (Kerr et al., 2006; Lawn et al., 2002; Thompson et al., 2003).

The findings from qualitative research are supported by population surveys. Fidler et al. (2009) analysed survey data from over 2000 UK smokers and found about half of smokers reported smoking for enjoyment and stress-relief. Similarly, another study of over 2500 UK smokers (McEwen et al., 2008) found smokers ranked smoking "to cope with stress" above all other motives to smoke (i.e. for enjoyment). In a study conducted by Lerman and colleagues (1996) smokers with and without emotional difficulties reported smoking "to cope with unwanted emotion." A study of 2069 smokers (Ferguson et al., 2005) found that "smoking to cope" was significantly associated with lower cessation rates one year later, compared with other reasons for smoking, for example, smoking for pleasure, and similar studies have replicated these findings (McEwen et al., 2008). Finally, smokers report reduced confidence in their ability to refrain from smoking during times of stress (Ng and Jeffery, 2003), and "smoking to cope" has been found the only significant predictor of relapse across all socio-demographic groups (Pisinger et al., 2011).

1.5. Health professionals' beliefs about smoking

Health professionals' beliefs about patients' potential response to treatment influence whether or not they recommend the treatment in question (Lewis and Wilkinson, 2003; Vogt et al., 2005; Vogt et al., 2006). Health professionals have a major role in promoting and implementing smoking cessation treatments and their attitudes about the benefits of smoking and risks of cessation can influence the implementation of smoking cessation treatment in practice (Landman et al., 2007; Prochaska, 2011; Richards et al., 1996; Sargent et al., 2001).

Qualitative and quantitative studies have explored clinicians' attitudes towards promoting cessation in different health care settings. An international survey found that general practitioners perceived patients' stress levels as a major barrier to helping them stop smoking (Pipe et al., 2009), this is counter-intuitive given that a patient is more likely to experience life-changing illness from smoking rather than stress. Sarna and colleagues (2001) found that in secondary care settings oncology nurses believed that "cessation intervention may be harmful and increase stress" in patients with smoking-related cancer, this attitude is detrimental to patients' health as cessation has been found to improve the prognosis of smoking related cancer (Parsons et al., 2010).

In mental health settings, smoke-free hospital policies have been introduced to improve the health of psychiatric patients (Department of Health, 2008; 2010). However, views that smoking offers mental health benefits for psychiatric patients are widely-held (Mendelsohn and Montebello, 2013; Ratschen et al., 2009a). Qualitative studies have identified that many mental health clinicians believe smoking enhances the patient-clinician alliance, that cessation

may worsen their patients' condition and leave them socially isolated, and some clinicians feel that they are taking away one of their patients only pleasures in life (Campion et al., 2008; Johnson et al., 2010; McNally et al., 2006; Parker et al., 2012; Ratschen et al., 2009a; 2009b). These beliefs likely present barriers to smoking cessation treatment in patients with mental health problems (Parker et al., 2012) and likely contribute to the existence of health inequalities in smoking prevalence (discussed ahead in 1.8).

1.6. Neurobiology of tobacco's psychoactive effects

Tobacco smoke contains an estimated 4000 plus chemical components and some of which are psychoactive (Borgerding and Klus, 2005; Rose, 2006; Rose et al., 2010; Thielen et al., 2008; United States Environmental Protection Agency, 1992). Smokers report that smoking has psychoactive effects (e.g. stress-relieving or mood enhancing) and this belief is also upheld by health professionals. This section will examine the neurobiological evidence to determine the validity of any psychoactive effects from smoking tobacco.

Tobacco has two main neurological mechanisms which initiate and maintain addiction. Firstly, it produces rewarding or pleasant effects which reinforce smoking behaviour, for example euphoria and relaxation (Benowitz, 2010). Secondly, after chronic exposure to tobacco, abstinence leads to a withdrawal syndrome, in which the smoker seeks to avoid by continuing to smoke (Benowitz, 1999; 2010). Withdrawal symptoms from tobacco include anxiety, irritability, depressed mood, anger, impatience and restlessness (Hughes, 2007b), and

these begin to occur shortly after having smoked a cigarette (Jarvik et al., 2000). These mechanisms will be discussed in relation to tobacco's main psychoactive ingredients.

1.6.1. Effects of nicotine

Nicotine is the most researched component of tobacco smoke and is generally agreed to be the most addictive (Office on Smoking and Health and Office of the Surgeon General, 1998). When nicotine travels to the brain it binds to nicotinic acetylcholine receptors (nAChR) at the synaptic cleft (the gap between the neurons) and this opens the channel between the neurons, allowing entry of sodium or calcium in turn causing the release of neurotransmitters (jas-Bailador and Wonnacott, 2004). Tobacco use is associated with an up-regulation of binding to nAChR transmitters, and after chronic exposure to tobacco this up-regulation eventually results in a change to the neurotransmitter pathway (termed a neuroadaptation), leaving the person tolerant to the rewarding effects of nicotine (Benowitz, 2010; Wang and Sun, 2005). Thus, during periods of abstinence from tobacco withdrawal symptoms occur as the pathway is unable to function normally without a nicotine supply (Wang and Sun, 2005).

Results from studies in animals have shown a dose-response effect whereby increased nicotine exposure is correlated with higher concentration of nAChR density (Rowell and Li, 1997). Negative affect experienced during nicotine withdrawal appears to be mediated by nAChRs and is regulated by a number of neurotransmitter systems (Balfour, 2009; Fowler et al., 2003; Kenny and Markou, 2001; Rose, 2007). During withdrawal from tobacco, nicotinic receptors promote inhibition or release of numerous neurotransmitters which act on mood regulation. For example, corticotrophin is a neurotransmitter which is involved in stress

response. The corticotrophin-releasing factor receptor system is activated during withdrawal leading to an increase in levels of extra-hypothalamic corticotrophin, which in turn, is thought to heighten stress-levels during withdrawal (Benowitz, 1999; George et al., 2007). Serotonin (5-HT) is involved in mood regulation, and its release is thought to be reduced during tobacco withdrawal leading to feelings of depression and anxiety (Benwell and Balfour, 1979; Ridley and Balfour, 1997), and this is supported by evidence that anti-depressants targeting the re-uptake of serotonin during withdrawal reverse withdrawal-effects (Harrison et al., 2001). Gamma-aminobutyric acid (GABA) and glutamate systems are affected by nicotine use and are also involved in mood disturbances (Sanacora et al., 2012). The effect of tobacco on these systems is less well understood but it is thought that Glutamate and GABA release is selectively increased in certain brain sites and decreased in others, leading to an increase in anxious reactions during withdrawal (Kenny and Markou, 2001). In summary, the combination of withdrawal effects in multiple neurotransmitter explains the marked disruption in mood during times of withdrawal which last up to 30 days after cessation (Hughes, 2007b). Furthermore, there is a dose-response relationship between tobacco consumption and increases in neuroadaptations, which may elucidate severity of withdrawal symptoms in those who are more dependent (discussed ahead in section 1.7).

Compared with other addictive drugs, nicotine has weak reinforcing effects and these do not seem powerful enough to explain the intense addiction reported by smokers (Balfour, 2009). Moreover, some chemical components of tobacco smoke interact with nicotine to create effects whereas other chemical components act independently to nicotine (Borgerding and Klus, 2005; Rose, 2006; Rose et al, 2010; Thielen et al., 2008; United States Environmental Protection Agency, 1992).

1.6.1. Effects of tobacco on dopamine pathways

Dopamine is an important factor in the initiation and maintenance of tobacco addiction and is mediated by nicotinic pathways (Mansvelder and McGehee, 2002) and the MAO system (Mansvelder and McGehee, 2002). Dopamine is associated with feelings of pleasure and reward, and is involved in initiation and maintenance of many addictive drugs (Volkow et al., 2004). MAO inhibition through non-nicotinic pathways is thought to increase levels of dopamine inside the synapse (Dani and De Biasi, 2001; Nestler, 2005). Nicotine causes the release of dopamine in the mesolimbic area, the corpus striatum and the frontal cortex, in turn producing positive feelings. The dopaminergic neurons in the ventral tegmental area of the midbrain and the release of dopamine in the nucleus accumbens are particularly important as this pathway is involved in feelings of reward and pleasure (Dani and De Biasi, 2001; Nestler, 2005). Activation of these pathways and associated positive feelings have a role in initiation of nicotine addiction, however chronic exposure to tobacco leads to neuroadaptations in these pathways and the smoker will need to maintain nicotine levels to enable dopamine transmission (Benowitz, 2010). There is evidence that smoking-induced dopamine release is dose-dependent (Brody et al., 2010) and nicotine withdrawal is associated with significant increases in reward threshold, deficiencies in dopamine release and reduced reward (Benowitz 1999; Epping-Jordan et al., 1998). Thus evidence suggests that activation of dopamine pathways are likely to initiate addiction, possibly suggesting initial self-medication behaviours; however after chronic exposure to tobacco regular consumption is required to maintain optimal levels.

1.6.2. Effects of tobacco on the monoamine oxidaise system

Tobacco has been found to influence the monoamine oxidaise (MAO) system which is responsible for the metabolism of neurotransmitters associated with mood. Tobacco use is believed to inhibit monoamine subtypes (MAO-A and MAO-B), in turn reducing the breakdown of mood neurotransmitters such as, serotonin, norepinephrine, dopamine and phenethylamine. Inhibition of MAO-A and MAO-B reduces the breakdown of these neurotransmitters, therefore increasing their presence within the synapse and improving mood. For these reasons, tobacco has been compared to anti-depressants known as monoamine oxidaise inhibitors (MAOI)s (Berlin et al., 1995; Fowler et al., 2003; Norman et al., 1987). Smokers have been found to have low levels of MAO platelet activity and this is thought to be a result of chronic exposure to nicotine rather than a biological characteristic of smokers (Norman et al., 1987). Rose et al. (2001) found that the intensity of withdrawal symptoms was inversely related to platelet MAO levels activity, in that smokers with the lowest platelet MAO experienced the most intense withdrawal symptoms.

It has been suggested that those with poor mental health have a certain neurobiological disposition which makes them susceptible to tobacco addiction (Berg et al., 2013). People with high levels of MAO activity are at risk for mood disorders as MAO-A and MAO-B breakdown mood-related neurotransmitters and therefore decreasing their presence within the synapse and lowering mood (Meyer et al., 2006). Individuals with depression are more also likely to be dependent upon tobacco (section 1.7) and this may be due to the inhibitory effects of tobacco on MAO activity.

In sum, the effects of tobacco on the MAO system likely act independently from the nAChR system and provide anti-depressant effects on mood while simultaneously exacerbating tobacco withdrawal symptoms. It is possible that smokers with mood disorders are more susceptible to tobacco dependency because of these anti-depressant effects.

1.6.3. Reversibility of neuroadaptations

It is possible that neuroadaptations resulting from chronic tobacco use and associated mood effects return to normal functioning after cessation. Equally, it is also possible that chronic tobacco use is associated with permanent damage in neurotransmitter systems which in turn may cause 'offset effect(s)' in mood functioning following abstinence from tobacco. An offset effect is termed as a permanent worsening in mental health and is thought to occur as a result of sustained cessation (Hughes, 2007a; 2007c). There are a small number of studies which have examined the influence of cessation on neurotransmitter systems.

Mamede et al. (2007) investigated functioning in nicotinic receptor pathways after sustained cessation using SPECT imaging (single-photon emission computed tomography). The researchers compared functioning of non-smokers with smokers who had stopped at four hours, 10 and 21 days after continuous abstinence. Results indicated that the nicotinic receptor functioning of abstainers down-regulated to the level of non-smokers at three weeks after smoking cessation. This indicates that the up-regulation in the nicotinic receptor system associated with chronic exposure to tobacco may be a temporary neuroadaptation. Notably, these results coincide with the finding that self-reported withdrawal symptoms begin to

improve at around three to five weeks post-cessation (Hughes, 2007b). However, Mamede et al.'s (2007) study was limited as it was conducted in a small, all male sample.

Brody and colleagues (2010) aimed to determine whether treatment for smoking cessation induced change in intrasynaptic dopamine concentration in 43 smokers who attempted to quit. Each participant underwent positron emission tomography (PET) scanning sessions at pre-treatment and eight weeks post-treatment. In this study, five of the 11 quitters had one cigarette-free week at the time of the second scan, the remainder having quit earlier and remained abstinent; the quit group as a whole had a mean of 19.9 days abstinence. The results indicated that DA release was not significantly affected by reductions in daily smoking or cessation treatment. This suggests that helping smokers to stop does not alter intrasynaptic dopamine levels. However, a longer follow-up period or a larger sample may be required to determine significant changes.

There are few studies investigating the influence of cessation on neurological functional, and the available studies report mixed findings. There is some evidence to suggest that neuroadaptations in nicotinic pathways reverse, and the timeframe in which these changes occur coincides with self-reported reduction in tobacco withdrawal symptoms. However, studies which have assessed change in dopamine release following cessation treatment have not found any significant associations, though it is possible that a longer follow-up or larger sample is needed. Importantly, none of the available evidence can determine if neurotransmitter systems return to their previous state prior to tobacco use. It is possible that some systems return to previous functioning and others remain damaged after cessation.

1.7. Surveys of smoking, smoking cessation and mental health

Population surveys have examined the association between smoking and mental health. The Surgeon General (2004) collected evidence from a combination of sources (previously discussed in section 1.3) to investigate the mental health status of smokers. The review found 15 studies that compared mental health of smokers with non-smokers, some of whom had medical and mental health disorders. These studies consistently found that smokers reported worse mental health than non-smokers including; lower life-satisfaction, lower well-being, poorer mental health, more psychological symptoms and higher depression scores. The report also found there was some evidence of a dose-response relationship, in that higher consumption was linked to a worse psychological status. The report concluded there was "…direct evidence of the relationship of smoking to a diminished health status." This report highlights the association between smoking and poor mental health outcomes, however the direction of causation could not be established.

Cross-sectional studies in general populations have also examined the association between cessation and mental health. In a cross-sectional survey of approximately 250,000 smokers and quitters, McClave et al. (2009) found that stopping smoking was associated with reduced lifetime depression and anxiety compared with continuing smoking, OR=0.7 (95% CI: 0.6 to 0.8). Survey data from 7000 UK participants indicated that quitters reported greater life enjoyment, life satisfaction and happiness compared to smokers and never smokers (Shahab and West, 2012). Other analyses of survey data from over 60,000 participants found quitters had a slightly elevated odds of depression and anxiety, compared with never smokers, OR=1.13 (95% CI: 1.0 to 1.2) (Mykletun et al., 2008), however results also suggested that the

longer one remained abstinent the odds of depression and anxiety became significantly reduced. A European survey of over 10,000 smokers found that lower stress was not associated with cessation in men, OR=1.0 (95% CI: 0.7 to 1.4) or women, 0.9 (0.7 to 1.2), however better mood was associated with cessation in women, but not in men; and an increase in interest was significantly associated with cessation in men, but not in women (Van Loon et al., 2005).

In summary, according to various sources of cross-sectional data there is a strong association between smoking and poor mental health and some evidence for an association between quitting and better mental health. These studies however, do not determine if smoking is a risk factor in development of poor mental health, if having a poor mental health is a risk factor for continuing to smoke, or if a third common factor is involved in the development of both smoking and poor mental health.

1.8. Mental health inequalities in smoking prevalence

It is possible that results from general population surveys are influenced by an over-representation of smokers with mental health problems. The Royal College of Psychiatrists and Royal College of Physicians (2013) examined smoking and mental health data from three UK population surveys with a combined total of 2.5 million residents; The Health Survey for England (HSE) (The NHS Information Centre, 2011), The Health Improvement Network (THIN) (Epidemiology and Pharmacology Information Core, 2014), and the Adult Psychiatric Morbidity Survey (AMPS) (McManus et al., 2009). The report found that out of the 10

million UK smokers, approximately three million reported evidence of mental disorder, up to two million had been prescribed a psychoactive medication and a further one million had a longstanding mental illness.

The HSE (The NHS Information Centre, 2011) reported smoking prevalence in those with a long standing mental health disorder was 37% compared with 20% in the general population (Dunstan, 2012), and moreover that smoking prevalence in this subgroup has changed very little over the last 20 years compared with the decline observed in the general population (Figure 1.2). Similar findings have been replicated in the US (Cook et al., 2014). This population also smoke a disproportionate amount of the total cigarette consumption per annum. In 2010 it was estimated that about 33% of all cigarettes smoked in England were smoked by people with a mental health disorder (McManus et al., 2010; Royal College of Physicians and Royal College of Psychiatrists, 2013) and estimates are similar in the US and Australia (Access Economics, 2007; Lasser et al., 2000).

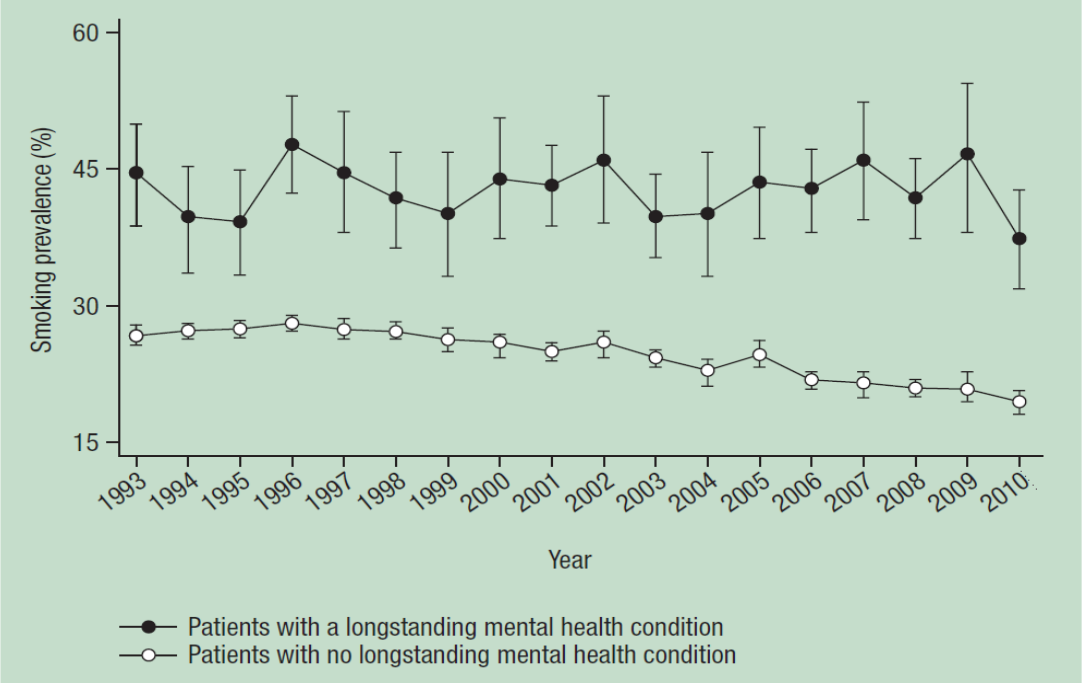

Figure 1.2 Changes in smoking prevalence between 1993 and 2010 in participants with or without longstanding mental health conditions (with 95% confidence intervals (CIs); data from the HSE)[1]

Data from APMS found that 34% of people with any common mental health disorder (e.g. depression, anxiety) were smokers, this survey also estimated that out of the 11% of adults in England to have consulted with a GP in the past year for a mental health or emotional complaint, one third of these were smokers and approximately half of the 0.7% of adults who attempted suicide in the last year were also smokers. Data from THIN indicated that out of the 4% of patients reporting one or more mental health diagnoses, 30% of these patients smoked. Data from these surveys suggested that rates of smoking ranged from 44.6% to 56% for those with a psychotic disorder, 31.4% to 39.8% for those with depression, and 31.1% of people with anxiety disorders (Royal College of Physicians and Royal College of Psychiatrists, 2013).

[1] Replicated with copyright permission granted from Royal College of Physicians in May 2014

Moreover, people with mental health disorders are more heavily dependent upon tobacco. In a longitudinal cohort study John et al. (2004) examined the association between nicotine dependency, daily cigarette consumption (cigarettes per day, CPD) and withdrawal symptoms, with odds of psychiatric disorder in a sample of 4000 European participants. They found significant dose-response relationships in that increasing consumption levels predicted greater odds of affective disorder, and greater nicotine dependency was associated with increased odds of both affective and anxiety disorders. Secondly, severity of withdrawal symptoms was associated with greater nicotine dependence, and there was a dose-response relationship between number of withdrawal symptoms and affective and anxiety disorders. Additionally, higher nicotine dependence was associated with increased odds of relapsing, OR=2.6 (95% CI: 1.2 to 5.3), and more severe withdrawal was associated with increased odds of relapse, 3.3 (1.5 to 7.4). However, for those who attempted cessation, having a psychiatric diagnosis was not associated with success of quit attempt. Similar findings have been noted elsewhere (Fergusson et al., 1996; Hitsman et al., 2003), however recent updates suggest smokers with a history of major depression are less likely to quit compared with smokers with no history of depression (Hitsman et al., 2013).

Although the mental health population has higher smoking rates compared with other groups, they are just as motivated to quit as general population smokers (Lasser et al., 2000). The ONS reported that 69% of smokers with a likely mental health problem stated that they wished to stop smoking (Coultard et al., 2002), other UK surveys have reported similar data (The NHS Information Centre, 2011), and estimates are similar in Australia and Canada (Addington et al., 1997; Stockings et al., 2013). Recent evidence suggests those with mental health disorders have a life expectancy of eight to 20 years shorter than the general

population, and much of this difference could be because of smoking (Chang et al., 2011; Chesney, Goodwin, and Fazel 2014). However, this population is less much likely to receive treatment for their smoking (Szatkowski and McNeill, 2013). As a result of these health inequalities, UK and US policy makers are currently targeting smoking in this population to reduce overall smoking prevalence (Hedden et al., 2012; Royal College of Physicians and Royal College of Psychiatrists, 2013).

1.9. Explanatory models for the association between smoking, cessation and mental health

The first part of this chapter has demonstrated that many smokers continue smoking because they feel that smoking offers mental health benefits. This notion is supported by some neurobiological evidence suggesting that tobacco may have some therapeutic properties, however most neurobiological evidence suggests smoking can lead to mood disturbances. Cross-sectional data indicates a strong association between smoking and poor mental health, and quitting and better mental health, moreover, the smoking population is over-represented by people with mental health disorders. However, from these studies, it is unknown if smoking is a risk factor in development of poor mental health, having poor mental health is a risk factor for smoking, or if a third common factor is involved the development of both smoking and mental illness. The next section will examine three opposing hypotheses which have attempted to explain the association between smoking and mental health.

1.9.1. The misattribution hypothesis

The misattribution hypothesis explains the association between smoking and poor mental health through the effects of the nicotine withdrawal cycle (Parrott, 1999; 1994; 2003). The model recognizes that chronic exposure to nicotine leads to periods of withdrawal which are characterized by restlessness, depressed mood, irritability and anxiety (Hughes, 2007b); and that these withdrawal effects are reliably relieved by smoking another cigarette (previously discussed in section 1.6). These psychological symptoms are also a hallmark of many mental health disorders. Accordingly, Parrot (1999; 1994; 2003) proposes that fluctuation in these symptoms and associated neuroadaptations (previously discussed in section 1.6) lead the smoker to have poor mental health. The hypothesis further suggests that after sustained cessation, withdrawal-induced negative affect dissipates and the smokers' mental health will improve. Moreover, the model suggests that smokers misattribute the ability of smoking to relieve withdrawal symptoms to its ability to relieve other negative emotional states (Benowitz, 1999; 2010; Parrott, 1999), thus, also explaining why smokers report therapeutic effects from smoking. This section discusses evidence from psychological neurobiological and prospective studies which form the basis of this hypothesis.

1.9.1.1. Experimental studies

Parrott (1994) examined self-rated feelings of stress and arousal, before and after each cigarette over a day of normal smoking in 105 smokers. He found that smokers reported high stress levels before smoking and low stress immediately after smoking, with stress developing in-between periods of smoking. The study concluded that smoking reliably relieves stress,

although there were individual differences in this 'effect'. Parrott and Garnham (1998) assessed mood outcomes in regular smokers, over-night deprived smokers and non-smokers, before and after a smoking/rest period. Smokers who were deprived overnight reported greater negative affect and stress before smoking compared with non-deprived smokers and non-smokers. After smoking, deprived smokers reported the greatest benefits from smoking, which reduced their negative mood to a similar level of non-deprived smokers, and non-smokers reported no significant changes in their mood after smoking. These findings suggest that smoking reverses the psychological symptoms of withdrawal, and has no effect on mood in non-smokers, studies with similar designs have replicated these findings (Adan and Sanchez-Turet, 2000; Herbert et al., 2001; Parrott and Kaye, 1999). Parrot (1999; 1995) argues smokers misattribute the ability of smoking to relieve these withdrawal symptoms to its ability to relieve stress and other negative emotion.

There are significant individual differences in the withdrawal effect. Parrott (1994) found the degree of change in negative affect was modulated by self-reported sedative effect of smoking, such that those who rated smoking as very relaxing displayed the greatest reduction in stress, and those who reported smoking as minimally relaxing reported little change in stress. Furthermore, withdrawal symptoms have been found more intense in heavier and more dependent smokers (Adan et al., 2004) and can vary over time, in that they normally peak during the first days of abstinence and remain for a few weeks (Hughes, 2007b). However, some symptoms such as depression may last longer for some individuals, and some have argued this may be a permanent effect of tobacco abstinence (Hughes, 2007a; 2007c). Thus, there is replicable evidence for the withdrawal cycle, however there are some individual differences between smokers in the severity of withdrawal effects.

1.9.1.2. Longitudinal cohort studies

The second part of the misattribution hypothesis suggests smoking can cause poor mental health. This notion can be explored through prospective longitudinal studies which have followed people's smoking and mental health over time.

Johnson et al. (2000) followed approximately 700 teenagers from the age of 16 to 22, to determine if uptake of smoking was associated with onset of anxiety disorder in later life. They found that heavy cigarette smoking during adolescence was associated with increased odds of anxiety disorder in adulthood, OR=5.5 (95% CI: 1.8 to 16.7), occurrence of anxiety disorder during adolescence was not associated with uptake of smoking during adulthood, and these findings were not altered by adjustment for covariates. In a similar study, Jamal and colleagues (2011) found that younger age of smoking onset was associated with shorter duration to onset of anxiety disorder. Wu and Anthony (1999) followed children over time and examined the association between smoking and onset of depression during the teenage years. Results indicated that smoking during early adolescence was associated with increased odds of depression in the teenage years. Another prospective longitudinal cohort found that those who began smoking at age 15 had an increased odds of any mental health disorder at 18 years, OR=2.8 (95% CI not reported) (McGee et al., 2000), however, after adjustment for environmental covariates and other substance use the association became weaker, 1.6 (95% CI not reported), suggesting that environmental factors contribute to the comorbidity of both smoking and mental health disorder.

Boden et al. (2010) prospectively analysed a longitudinal cohort study to assess the association between nicotine dependency and depressive symptoms in young adults. They followed over 1000 smokers' mental health from ages 18 to 25. Analyses were adjusted for genetic and environmental factors and time-dynamic covariates such as employment and drug use using structural equation modelling. This study found that time-varying environmental and genetic factors could not explain the longitudinal relationship between smoking and onset of depression. Furthermore, there was a strong relationship between dependency and depressive symptoms, such that those who were more dependent experienced more depressive symptoms. Other research has found a dose-response relationship in individuals with anxiety disorders, such that those who are heavier smokers have more symptoms of anxiety and depression, and have worse recovery outcomes (Jamal et al., 2012).

In contrast, an epidemiological study exploiting Mendelian randomisation examined the causal link between current smoking and current anxiety and depression (Bjorngaard et al., 2013). This study showed some evidence that the genetic variant associated with nicotine dependence was associated with anxiety in never and former smokers, but not in current smokers. If there was a causal link between smoking and mental disorder, one would expect the association to be prevalent in current smokers, therefore, as a whole the study did not support a causal link between smoking status and current mental health problems, arguing against the misattribution hypothesis. Whereas, other studies have found nicotine dependency and mental illness have a common genetic basis (previously discussed in section 1.9.3.2).

In sum, there is consistency between experimental and longitudinal studies. Experimental evidence shows that smoking reliably reverses negative affect in smokers and that longer

periods of abstinence are linked to worse withdrawal, and furthermore, non-smokers do not appear to display any mood benefits from smoking. Longitudinal data shows that smoking is related to onset of mental health disorder later on in life, which lends some support to the misattribution theory; although longitudinal data do not clarify whether poor mental health is the result of neuroadaptations. There is however, some evidence showing the reverse association (discussed in next section), and the possibility of a common cause threatens the strength of this unidirectional hypothesis. Importantly, these studies highlight the presence of individual differences, in that the most addicted smokers experience worse withdrawal and also seem to experience worse mental health later in life.

1.9.2. The self-medication hypothesis

The self-medication hypothesis was originally developed to help understand the aetiology and treatment of drug and alcohol addiction (Khantzian, 1974; 1975; 1978; 1997); and more recently this model has been adapted to explain the association between smoking and poor mental health (Khantzian, 1997). The hypothesis suggests that smokers use the chemical properties of tobacco to alleviate cognitive and emotional symptoms common in mental disorders. The model ascertains that people with mental health disorders are more likely to use tobacco for its therapeutic properties, and those with more severe disorders are more likely to be highly dependent. This model is supported by some neurobiological evidence suggesting that tobacco produces psychological effects independent of the withdrawal cycle and that these effects likely reinforce smoking behaviour (previously discussed in section 1.6). It is possible this model is mediated by neurobiological disposition (previously discussed in section 1.6) and social beliefs about smoking's therapeutic effects (previously discussed in

sections 1.4 and 1.5). To explore the self-medication model this section reviews evidence from experimental studies in humans and animals and from longitudinal cohorts.

1.9.2.1. Experimental evidence

Cognitive symptoms are common in many mental disorders therefore the model proposes that those with mental health disorders take up smoking to alleviate these symptoms in addition to other symptoms of their disorder. The effect of nicotine on cognitive performance has been examined in experimental studies of general population smokers and non-smokers. Foulds et al. (1996) conducted a placebo-controlled experimental study and compared cognitive performance between smokers and never smokers, before and after nicotine injection. Results demonstrated that nicotine enhanced attention, memory recall, verbal memory and reasoning performance in smokers, and attention and memory recall in never smokers. Smokers' enhanced performance was likely due to reversal of nicotine withdrawal (previously discussed in sections 1.6 and 1.9.1). In contrast the findings in never-smokers suggest there are some cognitive benefits from nicotine which may act independently from the withdrawal cycle. Similar studies have replicated the benefits of nicotine on memory and reaction times in both smokers and non-smokers, and have found dose-dependent improvements on memory tasks in both smokers and non-smokers (Ernst et al., 2001; Perkins et al., 1994). On the other hand, other experimental placebo-controlled studies have produced null findings suggesting there is no effect of smoking or nicotine on cognitive performance (Heishman et al., 1993; Petrie and Deary, 1989; Sakurai and Kanazawa, 2002).

Deficits in cognition function are a common characteristic of schizophrenia (and classed as a negative symptom), and it is thought that nicotine is especially therapeutic for people with this mental illness (Kumari and Postma, 2005). A review summarised experimental studies in humans and animals, which examined the effects of nicotine on nicotinic cholinergic systems involved in negative symptoms of schizophrenia (Levin et al., 2006). Animal studies showed consistent evidence that nicotine enhanced performance during memory, learning and attention tasks in animal models of schizophrenia. In seven studies assessing cognitive performance in people with schizophrenia, nicotine was found to improve performance on sensory gating, spatial information processing, attention and memory tasks, in two studies a null effect on memory performance was found. Similar evidence has been found in other disorders with cognitive deficits, such as ADHD (Gehricke et al., 2006; 2009). In sum, there is consistent evidence from experimental studies which support the self-medication model and suggest there may be a cognitive benefit from nicotine for people with certain mental disorders.

People with depression are thought to be more sensitive to cholinergic agonists (a chemical which binds to a receptor in turn activating a biological response) (Dagyé et al., 2011); therefore depressed individuals may be more responsive to nicotine's effects. In studies using animal models of depression rats exhibit a reversal of depressed behaviour after administration of nicotine compared with nicotine administration to non-depressed rats, whose behaviour shows no change and this therapeutic effect has been found to last up to 14 days in animals (Andreasen et al., 2011; Tizabi et al., 2010; Vieyra-Reyes et al., 2008). Several studies in humans have examined the effect of nicotine patches on depression symptoms in non-smokers with and without depression (Salin-Pascual et al., 1995; 1996;

1998). Results showed that nicotine patches relieved symptoms of depression over four days in non-smokers with major depression versus placebo, but had no mood effects in non-depressed participants. These findings have been replicated up to four weeks (McClernon et al. 2006). Thus, results from human and animal studies show that nicotine has therapeutic effects on symptoms independent of the withdrawal-cycle and these effects seem to be prominent in those with depression.

Cholinergic pathways are also impaired in anxiety disorders (Gray, 1982), it has been suggested that tobacco can produce anxiety-relieving effects during activation of the cholinergic system. In animal models of anxiety, some studies have reported a therapeutic effect of nicotine on anxiety, whereas other studies have reported nicotine exacerbates anxiety (Balfour et al., 1986; Irvine et al., 1999; Jonkman et al., 2008; Ouazana et al., 1999). File et al. (2000) found the effects of nicotine depended on location of administration, or on the type of animal model used, for example, nicotine may be more therapeutic in a generalised anxiety model compared with a social phobia model of anxiety. In summary, it is possible that nicotine may alleviate or worsen anxiety disorders however certain types of disorders may be more predisposed to these effects.

1.9.2.2. Longitudinal cohort studies

The self-medication hypothesis suggests people with mental health disorders are more susceptible to the effects of tobacco and evidence from neurobiological and experimental studies (previously discussed in sections 1.6 and 1.9.1.1 to 1.9.2.1) lend support to this. The hypothesis also suggests that smokers with poor mental health use smoking to alleviate

symptoms of their disorder. To further examine this notion, longitudinal studies can be used to determine if people with mental health disorders are more likely to begin smoking after onset of disease.

In a US cohort study Swendsen et al. (2010) followed 5000 participants aged 15 to 54, over 10 years to determine if having a mental disorder at baseline was associated with onset of smoking at follow-up. Results demonstrated that those with a mental disorder had an increased odds of smoking in later life; odds for major depression were, OR 1.4 (95% CI: 1.0 to 1.9), bipolar, 3.1 (1.9 to 5.1), phobias, 1.4 (1.0 to 1.9), any anxiety disorder, 1.5 (1.1 to 2.0), obsessive-compulsive disorder, 2.2 (1.4 to 3.4), ADHD, 1.8 (1.2 to 2.8), anti-social personality disorder, 2.0 (1.2 to 3.2).

Similarly, a meta-analysis of five longitudinal studies showed that people with ADHD were more likely to start smoking, compared to those without ADHD, RR=1.9 (95% CI: 1.3 to 2.3) (Royal College of Physicians and Royal College of Psychiatrists, 2013). However, analyses of ADHD subtypes demonstrated that hyperactivity–impulsivity was not associated with smoking initiation; and smoking initiation was only significantly increased in those with hyperactivity-inattention. As ADHD is characterised by cognitive deficits, it may be that those with the disorder smoke to alleviate these symptoms. Experimental evidence suggests tobacco offers cognitive benefits to those with schizophrenia, there are no prospective studies examining schizophrenia at baseline and later uptake of smoking. However, a systematic review of 42 cross-sectional studies showed there was a strong association between smoking and schizophrenia, OR=7.2 (95% CI: 6.1 to 8.3) (de Leon and Diaz, 2005).

Murphy and colleagues (2003) analysed data from a 40 year longitudinal cohort study and found subjects who became depressed during the study were more likely to start smoking, and there was no evidence for the reverse association. Escobedo et al, (1998) prospectively assessed the relationship between symptoms of depression and anxiety in early adolescence and uptake of smoking four years later. Results indicated that those who reported depressive symptoms at baseline were more likely to be smokers at follow-up, OR=1.3 (95% CI: 1.1 to 1.6). In contrast, another prospective study found that depressed mood during pre-teen years was not associated smoking initiation 20 months later (Polen et al., 2004), although the age of the sample may have been too young to predict smoking onset. Fergusson et al. (2003) found young people with major depression at baseline had elevated rates of smoking at multiple follow-ups during young adulthood, however those who smoked at baseline were also more likely to have depression in later years. Moreover the strength of these associations was greatly reduced after adjusting for factors associated with both smoking and depression, for example peer-group. Peer-group and other environmental factors have also been found associated with both smoking and mental health in other longitudinal studies (Killen et al., 1997; Patton et al., 1998). A similar pattern of results has been found for smoking and onset of anxiety disorders (Patton et al., 1998).

There is a clear link between mental health disorder and smoking in later life. These longitudinal associations, in combination with neurobiological and experimental evidence support the self-medication model. However, there is some evidence showing the reverse association, and the possibility of confounding from a common cause threatens the strength of this hypothesis.

1.9.3. The common cause hypothesis

Some research has found no significant association between smoking and mental health, or has identified confounding factors to be associated with both directions of the association. This suggests that the association between smoking and mental health may not be causal. It is possible that a third common factor which leads to both smoking and poor mental health may exist, the evidence exploring this hypothesis suggests that psychosocial, genetic or environmental factors may play a role in the development of co-morbid smoking and poor mental health.

1.9.3.1. Personality factors

Some personality traits may act as a shared vulnerability to both smoking and mental health problems. Neuroticism is characterized by anxiety, moodiness and worry (Goldberg, 1993; McCrae and Costa, 1987) and smokers consistently score higher on measures of neuroticism compared with never smokers (Spielberger and Jacobs, 1982; Terracciano and Costa, 2004). In a longitudinal cohort study Byrne and colleagues (1995) followed adolescents over 12 months and found that those who smoked at baseline and follow-up scored significantly higher on neuroticism compared with non-smokers. High neuroticism is also associated with poor psychological quality of life and with mood, neurotic and psychotic disorders (Graaf et al., 2000; Khan et al., 2005; Lahey, 2009; Weinstock and Whisman, 2006). Goodwin et al. (2002) found that neuroticism independently predicted the co-occurrence of smoking and panic attacks, but neuroticism did not predict either factor alone. Furthermore, there is some evidence that stopping smoking may be associated with reductions in neuroticism (Parrott,

1998). However, it is also possible that co-occurrence of smoking and mental disorder is a risk factor for the development of a neurotic personality. On the same note there are other personality traits which are related to mental illness such as low extraversion (Bienvenu et al., 2001; 2004) and conscientiousness (Terracciano and Costa, 2004), thus a multitude of traits may contribute to the co-occurrence, or vice-versa.

1.9.3.2. Common genetics and/or environment

Family studies have aimed to examine the co-occurrence of smoking and mental illness in probands (i.e. exposed participant, ascertained independently from their relatives) and their first degree relatives. If the association is strong across probands and their relatives this indicates a familial association. Family studies have shown that smoking and mental health disorder commonly co-occur in individuals within families, suggesting the contribution of shared environment or genetics and evidence is strong for depression, anxiety (Dierker et al., 2002; Swendsen and Merikangas, 2000), schizophrenia (Lyons et al., 2002) and ADHD (Rohde et al., 2004). However, these studies do not show the independent contribution of each factor to the association.

Studies in twins can be used to determine the contribution of genetics and environment on smoking behaviour and mental health (phenotypic characteristics). These studies typically compare phenotypic similarities between monozygotic twins who share 100% of the same genotype, with dizygotic twins who share 50% of the same genotype. One can assume substantial genetic contribution if monozygotic twins display similar traits or behaviours compared with dizygotic twins.

A cross-sectional study examined the association between smoking and depression in monozygotic and dizygotic twins discordant for depression history (Kendler et al., 1993). Co-twin analyses indicated that depression history did not significantly predict ever-smoking, and that smoking did not predict depression history. The best fit model indicated that common environment accounted for 27% of the variance in liability to smoking, but none for depression; and the association between co-morbid smoking and depression was highly correlated with genetic factors (r=0.56). This study suggests that common genes influence the association between depression and smoking, and results from similar twin studies support these findings (Edwards et al., 2011). Conversely, other twin studies have found that non-shared environment is dominant (McCaffery et al., 2003).

Research has examined if specific genes are associated with smoking and depression. Audrain-McGovern et al. (2004) analysed a longitudinal cohort study to determine if specific polymorphisms (in DRD2) were associated with smoking and depression in adolescents. Results showed there was a dose-response relationship between the number of DRD2-A1 alleles and depression symptoms, such that as number of alleles increased so did depression symptoms. Furthermore, there an association between the number of DRD2-A1 alleles and increased likelihood of progressing from at least 'one puff' at baseline to regular smoking two years later, OR=1.9 (95% CI: 1.2 to 2.9). However, this association became non-significant when adolescents who had not ever smoked "even a puff" were included in the model. Next the researchers investigated if depression moderated the association between DRD2-A1 alleles and smoking progression, and found that an increase of one standard deviation in depression symptoms almost doubled the effect of A1 alleles on smoking progression. The authors concluded that having at least one DRD2-A1 allele indicated a vulnerability to

depression, and that this genetic disposition to depression may have a synergistic effect on progression to smoking. Importantly, this model became non-significant when people who had never smoked were added, suggesting that perhaps smoking at least one-puff activates the DRD2 allele. Thus, smoking and depression share a common genetic pathway, however exposure to smoking may activate certain pathways.

Other studies have examined the impact of environment on smoking and depression and anxiety. Audrain-McGovern and colleagues (2009) prospectively analysed a longitudinal cohort study and measured adolescents' smoking behaviour and depression symptoms over four years. They found a bidirectional relationship such that depression symptoms during mid-adolescence predicted smoking progression in late adolescence, and smoking in mid-adolescence predicted depression in later adolescence. However, peer-group smoking mediated the association, such that more depression symptoms predicted an increase in the number of smoking peers, which in turn, predicted smoking progression. Other longitudinal cohort studies have similarly found peer group to be a mediating factor in the association between smoking and depression (Fergusson et al., 2003) and smoking and anxiety (Patton et al., 1998). These studies suggest that environmental factors influence the strength of the association.

Rates of smoking in people with schizophrenia are much higher than in other disorders (previously discussed in section 1.8), suggesting a stronger association in this disorder compared with other disorders or with the general population. People with schizophrenia have abnormal expression of certain genes which are implicated in both schizophrenia and nicotine dependence (Mexal et al., 2010; Riley et al., 2000). Lyons et al. (2002) conducted a co-twin

analysis of smoking behaviour in a sample of discordant twins (i.e. one with schizophrenia and the other without schizophrenia), versus a control group of twins (i.e. pairs without schizophrenia). They found that probands with schizophrenia had an increased odds of smoking, OR=2.6 (95% CI: 0.9 to 7.6), versus control twins without schizophrenia, and probands without schizophrenia also had an increased odds of smoking, 3.7 (1.1 to 12.3), versus control twins. The authors stated that smoking was influenced by familial vulnerability to schizophrenia. Alternatively, it is possible that family stresses associated with having a co-twin with schizophrenia might lead to adverse emotional consequences, in turn, increasing the risk of smoking. There are few twin studies in people with schizophrenia, however, the existing evidence suggests there is a genetic contribution to both smoking behaviour and the disorder.

There is a strong case for the contribution of a common cause to the co-occurrence of mental health problems and smoking. Personality traits are a possible risk factor, although the direction is uncertain. It appears that genetics may contribute more to the co-morbidity compared with environment; however there are some studies presenting null results or a strong environmental influence. Furthermore, it is possible that smoking 'one puff', activates certain genetic pathways which may dispose individuals to further smoking behaviour and/or mental health problems.

1.10. Smoking cessation and mental health

Each of the hypotheses discussed above have important implications for smokers, smoking cessation specialists and cessation interventions. The misattribution hypothesis suggests that after sustained cessation withdrawal induced negative affect will diminish and in turn smokers' mental health will improve. The self-medication hypothesis suggests that smoking alleviates symptoms of psychological distress, therefore after cessation the quitter will experience worse mental health. The common cause hypothesis suggests that quitting is unlikely to change mental health unless the true causal factors that maintain poor mental health also change. A literatures search using terms related to "mental health" "smoking" and "cessation" was conducted to find longitudinal studies and systematic reviews which have examined the influence of smoking cessation on mental health.

1.10.1. Longitudinal studies

The search strategy produced five longitudinal cohort studies which examined dichotomous mental health outcomes in smokers who stopped smoking compared to smokers who continued smoking. Three of these studies have not been reviewed elsewhere, two (Glassman et al., 2001; Tsoh et al., 2000) have been previously reviewed by both Hughes' (2007c) and Ragg et al. (2013) (as discussed ahead, in section 1.10.2).

Khaled et al. (2012) estimated the risk of major depression over nine years in 1184 self-reported heavy smokers who quit and 479 heavy smokers who continued smoking. Participants with a history of depression were excluded. They found that smokers were

significantly more likely to report onset of major depression compared with quitters, and this association remained significant after adjustment for common causes of both smoking and depression, including personality traits, family history of depression and stress, hazard ratio (HR)=3.3 (95% CI: 1.8 to 6.2). Secondly, the researchers categorised quitters according to the number of years they had been abstinent and compared risk of depression with those who continued smoking. Before and after adjustment for covariates there was a dose-response relationship between duration of abstinence and risk of depression; in that those who quit for longer periods showed less risk than those who had remained abstinent for shorter periods. For example, quitters who remained abstinent for one to five years showed a decreased risk, HR=0.5 (95% CI: 0.3 to 0.9) relative to smokers, and those who had remained abstinent for ≥21 years showed a five-fold protection against depression compared with continuing smokers, HR=0.2 (95% CI: 0.1 to 0.5). These findings suggest that quitting itself is protective, or that people who quit are more likely to have other protective traits than do people who continue smoking. However, this study was missing the depression status for one third of the participants and this may have introduced selection bias. It is also possible that reverse causality was operating, i.e. that improved mood facilitated quitting. Moreover, the largest threat to the association is bias arising through differences in participants' propensity to achieve abstinence, and in this analysis covariates associated with propensity to quit were not adjusted for, for example nicotine dependency, or receipt of smoking cessation treatment (Stead et al., 2012; Vangeli et al., 2011).

Sanchez-Villegas (2008) examined data from a cohort of university students who were followed-up every two years from 1999 to 2005. Data were analysed from 8556 participants who had no initial psychiatric diagnoses, and analyses were adjusted for major confounders

such as age, sex, marital status, and physical activity. Adjusted and unadjusted estimates were similar and indicated that those who were quit for more than 10 years were significantly less likely to report a new diagnosis of depression compared with those who continued smoking, adjusted HR=0.4 (95% CI 0.2 to 0.9), though outcome was not meticulously accessed. These data are similar to those reported above by Khaled et al. (2012), and this suggests there is some consistency in the association, and are further supported by studies showing that quitters are more likely to stop using anti-depressants after cessation, compared with continuing smokers (Shahab et al., 2014). However, interpretation of these studies remains inconclusive due to the possibility of reverse causation. Moreover, it is possible that there are systematic differences between quitters and continuing smokers, thus risk of bias through group membership cannot be ruled out.

Bolam et al. (2011) prospectively analysed data from an international general population cohort study. They examined whether or not cessation was associated with change in incidence of depression and anxiety nine months after stopping smoking. Smoking data were available for 1565 participants and 3% of these (N=42) reported being quit for six or more months. They reported no association between cessation and change in symptoms of depression or anxiety from baseline to nine months post-cessation, OR=1.0 (95% CI 0.4 to 2.6) and 1.1 (0.4 to 2.8), respectively. These data, however, were limited by the small number of people who maintained cessation, compared to those who continued smoking. Importantly, there was some evidence that those with poor mental health at baseline were more likely to drop-out by follow-up.

Tsoh et al. (2000) conducted a secondary analysis of two randomised controlled trials of smoking cessation treatment which included participants with and without a history of major depression. One trial was of nortriptyline (medication for cessation), plus cognitive behavioural therapy for smoking cessation (Hall et al., 1998), and the second trial was of nicotine replacement therapy (NRT), plus mood management for smoking cessation (Hall et al., 1996). At follow-up Tsoh et al. (2000) reported the incidence rate for major depression was 14.7% amongst quitters, and 13.4% amongst smokers. The depression rate for quitters was higher, however logistic regression models adjusted for depression history indicated that stopping smoking was no longer associated with onset of depressive episodes, OR=1.3 (95% CI: 0.6 to 2.6). In a similar study Glassman et al. (2001) conducted a secondary prospective analysis of RCT data in which participants with depression history were excluded. One hundred participants were randomised to receive sertraline (medication for cessation) or placebo for 11 weeks and were followed-up at six months, at follow-up 34 participants continued smoking and 6% of these had symptoms of major depression, compared with 42 participants who had quit by follow-up, of whom 31% reported major depression. Before and after adjustment for receipt of smoking treatment, quitting smoking was associated with an increased risk of depression compared with those who continued smoking, OR=7.2 (95% CI: 1.5 to 34.5). However, one must account for differential loss to follow-up between groups, 39% of smokers were lost to follow-up and their depression status was undetermined and only 5% of quitters were lost to follow-up. These studies indicate that quitting may be associated with increased risk of depression, and reverse causality may be less likely to arise in these studies as everyone attempted to quit and depression was measured shortly before the quit attempt and at follow-up, therefore cessation was less likely to be contingent on mood.

Though ultimately, interpretation of these studies' results is not straightforward due to confounding and attrition bias.

In sum, studies which have estimated the risk of disorder in people who stopped smoking compared with those who continued smoking present mixed results. Two studies were from general population cohorts. One study assessed change in risk, by measuring mental health before and after people stopped, compared with those who continued and found no association (Bolam et al., 2011), whereas another cohort study indicated a decreased risk at follow-up for quitters (Sanchez-Villegas et al., 2008). Two studies which excluded people with a history of depression were dissimilar. One of these reported that cessation was associated with increased risk of depression, although loss to follow-up was an issue here (Glassman et al., 2001). Whereas the other study reported that stopping smoking was associated with a decreased risk in depression, however the association was weaker for smokers more recently quit (Khaled et al., 2012). In all of these studies attrition was a problem, with one study displaying evidence that depressed participants may have been more likely to drop-out (Bolam et al., 2011), and in many population cohorts ascertainment of outcome was not strong. Overall, these studies are also at risk of unmeasured confounding and direction of causation is questionable, especially in population cohort studies. Moreover, the largest threat to the association is bias arising through participants' propensity to achieve abstinence. If bias through group membership occurs comparison of the groups is likely unjustified (Grimes and Schulz, 2002; Rosenbaum and Rubin, 1984). Covariates associated with propensity to quit (e.g. nicotine dependency) were rarely adjusted for in these studies therefore one cannot be sure if group membership was an issue. In conclusion, the results from these studies are uncertain.

1.10.2. Systematic reviews

The search strategy produced three systematic reviews which have examined the association between smoking cessation and mental health.

Hughes (2007c) conducted a review of seven cessation intervention studies of medication versus placebo for cessation and aimed to determine the onset of depression after cessation in those with depression history. All included studies excluded people with current major depression and reported cases of depression among subjects during follow-ups ranging from two to 12 months, however only one study statistically tested the association. Across the studies the incidence of major depression among smokers who tried to quit was 0% to 14%, those with a past history of major depression who tried to quit the rate was 3% to 25%, and among successful quitters the rate was 1% to 31%. In every trial the depression rate was highest in the quit group compared to the whole study cohort. Hughes (2007a; 2007c) argued the results supported self-medication hypothesis (Khantzian, 1997), or alternatively that depression after cessation may have been caused by long-term use of tobacco (previously discussed in section 1.6). Hughes (2007c) review could not provide a formal estimate for onset of major depression as comparison groups were not available. Importantly, in this review Hughes (2007c) highlighted the possibility that smokers and quitters may be inherently different, therefore any formal comparison would at risk of bias.

Banham and Gilbody (2010) systematically reviewed eight RCTs of smoking cessation interventions in people with severe mental illness (i.e. psychoses, bipolar disorder). All trials measured mental health outcomes during the intervention period with follow-ups ranging

from two to 24 months. Two studies measured anxiety, one of these found the intervention group significantly improved and the other reported no significant difference between trial arms. Eight studies measured depression, one reported a significant improvement in the intervention arm, and seven reported non-significant differences between trial arms. Three trials reported an improvement in psychotic symptoms in the treatment arm, and five reported no change. Furthermore, there were minimal psychiatric adverse events; only in one trial two participants had suicidal ideation, however the arm in which these occurred was not reported. These data were analysed by treatment group rather than by comparing data between people who quit or continued smoking, therefore do not directly estimate the effect of cessation on mental health. However, importantly this review did not find any evidence to suggest that helping people to stop smoking causes harm to mental health.

A systematic review aimed to investigate the impact of smoking cessation on schizophrenia and major depression (Ragg et al., 2013). The authors reviewed incidence and mean change data from RCTs of treatment for smoking, and cohort studies conducted in people with diagnoses of depression or psychotic-disorders. The clinical trials of smoking cessation treatment for people with psychosis were previously reviewed by Banham and Gilbody (2010). Six studies examined the impact of cessation in people with depression. Three of these studies reported change scores and two studies reported only descriptive data for quitters; none of these reported cessation was linked to psychological harm. One study, however found that those who quit had an increased risk of depression (Glassman et al., (2001) reviewed above). In sum, results from this review were mixed and there was significant heterogeneity between study design and summary statistics, therefore a formal estimate could not be calculated.

These reviews reported varied findings. Hughes (2007c) concluded there was evidence that those with depression history are at risk of depression after cessation. Banham and Gilbody (2010) found that helping people with severe mental illness to quit was not associated with psychological harm. Ragg et al. (2013) reported that cessation was not harmful to the mental health of people with psychotic illnesses, but for people with depression there was mixed evidence. Thus, based on these reviews the "effect" of smoking cessation on mental health is inconclusive.

1.11. Chapter summary and aim of thesis

This literature review has highlighted that smoking is major risk factor in the development of fatal or life-changing disease and by stopping smoking one can avoid the majority of this risk. However, the association between smoking, smoking cessation and mental health is less clear-cut. Most smokers want to quit but fail and report the mental health benefits of smoking are a major reason to continue. However, survey data indicates that smokers have poor mental health compared with non-smokers and furthermore that the smoking population is over-represented by people with mental health disorders. The belief that smoking has psychological benefits is also upheld by many health professionals, and in many cases this presents a serious barrier to cessation interventions in both general and clinical populations. Approximately one third of the smoking population show evidence of a mental health disorder; moreover, people with mental health disorders have a life expectancy of eight to 20 years shorter than the general population and much of this difference could be because of smoking (Chang et al., 2011; Chesney et al., 2013; 2014). However, evidence for mental health benefits from tobacco is not clear and the impact of quitting smoking on mental health is also uncertain. If this

association was clarified, and smoking cessation was found to offer mental health benefits, this could be used to motivate smokers to stop, empower smokers with confidence in their ability to control unwanted emotion, educate health professionals, and potentially used to inform public health policies.

The reviewed literature provides important information, however as discussed throughout this chapter these data are limited in various ways. Firstly, no systematic review has directly estimated change in mental health in quitters compared with continuing smokers. Secondly, no systematic review has examined change in mental health after cessation in those without diagnosed mental disorders. Overall, the vast majority of the reviewed studies are at risk of group membership bias and unmeasured confounding. Therefore, this thesis aims to:

1) Conduct a systematic review and meta-analysis of longitudinal studies to compare change in mental health between quitters and continuing smokers from general, psychiatric and other clinical populations, and to compare effect estimates between populations based upon their clinical characteristics. These data are presented in Chapter Two.
2) Conduct an analysis of individual level patient data to further examine the impact of group membership bias and confounding in the association between stopping smoking and mental health. Propensity score matching (PSM) will be used to create a matched sample of quitters and continuing smokers based upon characteristics which predict their propensity to achieve abstinence. Chapters Four and Five will use this method to examine a) change in mental health in quitters compared with those who continued

smoking and b) onset of psychiatric disorder after stopping smoking compared with those who continued smoking.

3) It is possible some people who quit experience worse mental health therefore relapse back to smoking, while quitters who experience mental health benefits continue to be abstinent. This hypothesis will be tested in Chapter Six, via an analysis of individual level patient data.

CHAPTER TWO

2. CHANGE IN MENTAL HEALTH AFTER SMOKING CESSATION: A SYSTEMATIC REVIEW AND META-ANALYSIS

2.1. Introduction to Chapter Two

In this chapter I present a systematic review and meta-analysis of longitudinal studies that reported the difference in change in mental health outcomes from baseline to follow-up between smokers who quit and smokers who continued smoking. The findings from this chapter were published in BMJ in February 2014 (Appendix 1):

> Taylor, G., McNeill, A. and Girling, A. et al. (2014). Change in mental health after smoking cessation: systematic review and meta-analysis. **BMJ,** 348 (g1151).

This chapter has been slightly edited to avoid repetition from Chapter One, and includes a supplementary analysis not included in the published version.

2.2. Background

Although smokers believe that smoking offers mental health benefits, there is a strong association between smoking and poor mental health (discussed previously in sections 1.7 to

1.8). Three broad explanations have been proposed to explain these associations: smoking and poor mental health might have common causes (discussed previously in section 1.9); people with poor mental health smoke to regulate feelings such as low mood and anxiety (Khantzian, 1997); or smoking might cause or exacerbate mental health problems (Parrott, 1999). Whatever the cause, the association between smoking and poor mental health warrants attention. Smokers might be less likely to stop if they believe their mental health will suffer, and some health professionals are reluctant to intervene with subgroups of smokers because they believe that this might be detrimental to their mental health (Johnson et al., 2010; McNally et al., 2006; Ratschen et al., 2009a).

2.2.1. Study aims and hypotheses

In this study the aim was to conduct a systematic review and meta-analysis of longitudinal data to examine the difference in change in mental health between people who stopped smoking and people who continued to smoke. I hypothesized that smokers who quit would experience an improvement in mental health because they would no longer experience multiple episodes of negative affect induced by withdrawal.

2.3. Methods

2.3.1. Eligibility criteria

A broad eligibility criterion was used to capture all potentially relevant data and then sensitivity and subgroup analyses were conducted to investigate clinical and methodological heterogeneity. Eligibility was decided on based on the following criteria:

Population — Studies of smokers in the general population or any that had selected smokers from populations defined by the presence of a clinical diagnosis;

Exposure — Studies that reported data on those who had continued smoking and those who had quit smoking during the study period;

Outcome — Any study that had measured mental health immediately before quitting and at least six weeks after quitting;

Language — No exclusions were made based on language;

Study design — Only longitudinal studies (that is, randomised controlled trials and cohort studies).

When data on change in mental health were available from different follow-ups within a single study the longest was used. Any type of measure of mental health was included (i.e.

self-report and clinician scored). Only studies that provided sufficient data to calculate the standardised mean difference (SMD) and its variance in change in mental health score from baseline to follow-up between quitters and continuing smokers were included. The standardised mean difference is the difference in change in mental health between baseline and follow-up divided by the standard deviation (SD) of the change. It is used to overcome the issue that depression, for example, can be measured by different questionnaires with different scoring systems. The questionnaires all measure depression but the different scoring means that they cannot be combined by using a simple mean. A SMD of 1 represents a difference in change in depression score of 1 SD. About 4 SD encompasses 95% of the population (Higgins and Green, 2011).

2.3.2. Information sources and searches

The following databases were searched for studies: Web of Science, Cochrane Central Register of Controlled Trials, Medline, Embase, and PsycINFO for studies published from inception to April 2012, a combination of text words and indexed terms related to "mental health," "smoking cessation," and "smoking reduction" were used (Appendix 2). Study authors were contacted to obtain relevant missing data. Reference lists of included studies were also searched. All non-English language studies were translated.

2.3.3. Study selection

The aim was to maximise sensitivity by including studies in initial screens even if data directly relevant to the study question were not presented in the abstract. One researcher (GT)

screened titles of retrieved studies for eligibility. The abstracts of eligible titles were screened twice for inclusion (GT, NL, PA). The researchers met after independently screening abstracts to discuss inclusion/exclusion of each article. If there were disagreements, two researchers obtained and read the full text article (GT, PA, AG, AM).

2.3.4. Data collection process

Two researchers piloted the data extraction form, and appropriate changes were then made (GT, AM). The same two researchers independently extracted data from each paper and agreed on final data extraction in the case of disagreement (GT, AM). The corresponding authors of studies were contacted for additional data when necessary. Studies were excluded only if data on the change in mental health and its variance could not be obtained.

2.3.5. Data items

The following data items were recorded:

Participants — Tobacco dependence and number of cigarettes smoked a day (CPD), age, sex, and motivation to quit, all at baseline.

Exposure — Classification and biological-validation of abstinence from tobacco.

Comparator — The same data items were extracted for continuing smokers.

Outcomes — Data on the change in mental health between baseline and follow-up. When such data were not available, relevant data were extracted to calculate this (see Appendix 3 for formulas). To categorise mental health outcomes each measure's key reference and questionnaire was examined to determine what it was designed to measure. The change in mental health unadjusted for confounding, and estimates which had been adjusted for confounding using multivariable techniques were extracted.

Other items — Additional data were extracted to investigate clinical and methodological heterogeneity within and across studies (see sensitivity analyses for justification and methods). These items included study design, study quality score (Newcastle-Ottawa scale) (Wells et al., 2010), evidence of outcome reporting bias, follow-up length, covariates adjusted for, mental health management used in the intervention, and number of participants analysed at baseline and follow-up.

2.3.6. Statistical methods

2.3.6.1. Data extraction

The summary measure was the SMD in change in mental health from baseline to follow-up between continuing smokers and people who managed to stop. Some studies reported either the difference in change or the standardised difference in change between continuing smokers and quitters, and hence data extraction of the effect estimate was straightforward. In some cases studies presented the mean change for each group and therefore permitted calculation of the differences. In other cases, studies reported the mean at baseline and at follow-up for each

group. The change and its variance was calculated using a standard formula (Follmann et al., 1992), imputing a correlation coefficient taken from one of the largest studies included in the review (formula reported in Appendix 3). In all cases, the variance was also extracted. If the variance was not presented it was calculated from P values, confidence intervals, or F values following standard formula as recommended by the Cochrane Collaboration (Higgins and Green, 2011).

2.3.6.2. Meta-analysis method

A generic inverse variance random effects model was used to pool the SMD between change in mental health in quitters and continuing smokers from baseline to follow-up. A random effects model was used as it incorporates heterogeneity both within and between studies. Statistical heterogeneity was assessed with Chi^2 and I^2 tests. The meta-analyses and sensitivity and subgroup analyses were all conducted using Review Manager 5.

Studies' effect estimates (SMD) were pooled by using the following outcome categories: anxiety, depression, mixed anxiety and depression, positive affect, psychological quality of life, and stress. The SMD was calculated because the scales used to measure each outcome varied within category. This is standard practice for meta-analyses as outlined within the Cochrane Collaboration Handbook of Systematic Reviews and Meta-Analyses (Albrecht et al., 2000) and as used in other high quality meta-analyses of continuous mental health outcomes (Bower et al., 2013; Hunot et al., 2007; Smith et al., 2010).

Studies with different follow-up periods were combined. Each study's longest follow-up period was used, as suggested by the Cochrane Collaboration. Heterogeneity between studies' follow-up length was accounted for by use of a random effects model. This is standard practice as outlined by the Cochrane Collaboration (Higgins and Green, 2011), and as used in other high-quality meta-analyses of continuous mental health, with varying follow-up periods (Bower et al., 2013; Hunot et al., 2007; Smith et al., 2010).

If studies provided sufficient data the standardised average mean change in mental health outcomes was calculated for quitters and smokers (formula presented in Appendix 3). These data were plotted for descriptive purposes only.

2.3.7. Quality assessment

The quality of the evidence in each study on the association of change in smoking status with change in mental health was assessed using the Newcastle-Ottawa quality scale (Wells et al., 2010), adapted for this study (Appendix 4), this assesses the quality of evidence based on the selection of the comparison groups, the comparability of the groups, and the quality of the measurement of exposure and outcome. The adapted scale rated studies from 0 to 5, and studies with a rating of 3 or lower were deemed as at higher risk of bias.

2.3.8. Assessment of publication and outcome reporting bias

Funnel plots were examined for evidence of asymmetry and Egger tests were conducted for evidence of small study bias using STATA 13 (Egger et al., 1997).

In some studies, data on change in mental health were presented incidentally and the aim was to report on other data. In others, the aim of the report was to present data on change in mental health, therefore the decision to publish might have been contingent on the results. The effect estimates were compared between studies in which mental health was the primary outcome and those in which it was not to assess if there was evidence of publication bias.

When studies had relevant data on change in mental health but did not report sufficient data for meta-analysis, attempt to estimate the direction of association to and compare this with included studies was made, as this could indicate reporting bias.

2.3.9. Sensitivity analyses and assessment of risk of bias within and across studies

Multiple sensitivity analyses were conducted to examine if the pooled effect estimate was influenced by including studies in which the risk of bias was greater or was influenced by characteristics of the study design or population. Either subgroup analyses were performed or studies presenting a risk of bias were removed and the pooled estimates were compared with and without the excluded studies.

2.3.9.1. Adjustment for covariates

It is possible that change in mental health could be confounded by other differences between continuing smokers and quitters. To account for this, some studies adjusted their data for covariates thought to be associated with change in smoking status or mental health. A

subgroup analysis was conducted to compare the effect estimate between studies that presented adjusted and unadjusted data.

2.3.9.2. Loss to follow-up

Some studies reported on change in mental health only in participants who were followed up, thus eliminating from the analysis those who were lost to follow-up. Other studies reported data on all participants who were present at baseline and the smaller number present at follow-up; it may be that people with poor mental health at baseline are more likely to drop out of studies (e.g. Bolam et al., 2011), thus possibly creating spurious changes in mental health through loss to follow-up. The convention in smoking cessation studies is to regard participants who are lost to follow-up as smokers, so loss to follow-up selectively affects the continuing smoker group. Whether or not studies reported data from a different number of participants at baseline and follow-up was recorded.

2.3.9.3. Ascertainment of smoking status

Some studies might misclassify exposure by using point-prevalence smoking abstinence. This could include participants who had been abstinent for only a week in the group were classed as having been abstinent for at least six weeks, though most smokers who are point prevalent abstinent for a week may have been abstinent for longer (Hughes et al., 2003; 2010). Recently abstinent smokers are likely to experience withdrawal symptoms including low mood (Hughes, 2007b). Thus, whether studies used a measure of prolonged or continuous abstinence (when misclassification could not have occurred) was recorded or if they used a

point-prevalence measure of abstinence. Likewise, particularly in smoking cessation trials, there is a danger that participants claim abstinence when this is not the case; therefore it best practice to biologically-validate smoking status (Hughes et al., 2003). Accordingly, whether or not self-reported abstinence was biologically-validated was recorded.

2.3.9.4. Motivation to quit

The hypothesis was that cessation improved mental health, but the outcome measure was the difference in change in mental health between those who stopped smoking and those who continued. It could be that such a difference would be evident if those who continued smoking had a worsening in mental health rather than those who stopped experiencing an improvement. Trying and failing to quit could worsen mental health, and some studies in the review derived data from smoking cessation trials. In these trials, all continuing smokers had tried but failed to achieve abstinence, and this disappointment could lead to worse mental health. In population cohorts, however, many continuing smokers would not have tried to achieve abstinence and therefore not have experienced this failure. Therefore studies were classified as selected or not selected by motivation to quit. Populations in which participants were not selected by motivation to quit were less likely to create this spurious difference between quitters and continuing smokers.

2.3.9.5. Psychotherapeutic component within cessation intervention

Having a psychotherapeutic intervention can improve mental health. Some smoking cessation interventions include mood management. Successful quitters often attend smoking cessation

clinics, while relapsers cease attending, meaning that one group might have had more counselling than the other. Trial protocols and the main report for smoking cessation intervention trials in which counselling had taken place were searched - to assess whether mood management was part of the intervention.

2.3.10. Additional analyses

2.3.10.1. Clinical population comparison

The studies included in the review enrolled the general population, pregnant women, or patients who were postoperative, had a chronic physical condition, a psychiatric condition, or chronic psychiatric or physical conditions. Effect estimates were compared between these populations to determine whether there was evidence of a difference in size or direction.

2.3.10.2. Study design

The hypothesis was that stopping smoking improved mental health but any association between cessation and improved mood could be caused by reverse causation—that is, that improved mood caused successful cessation. The studies in this review fell into two groups: those recruiting a general population of smokers and those in which all participants were enrolled in smoking cessation trials. In trials, all participants attempted to quit, furthermore, in these studies mental health was assessed shortly before quit attempt (baseline), and six weeks or more after; therefore any detected change in mental health occurred after achieving abstinence. If improved mental health led to cessation, change in mood would have occurred

before the trials baseline assessment and therefore would not have been detected by change scores. Thus, secondary analyses from trials exclude the possibility that improved mood led to cessation.

2.3.10.3. Length of follow-up

Studies were examined for evidence of a difference in effect estimates between studies in which change in mental health was assessed from six weeks to six months or more than six months after baseline.

2.4. Results

2.4.1. Study selection

The database and reference list searches resulted in 13,050 references. After initial screening 219 full text articles were accessed for eligibility, of which 166 were excluded before data extraction (references and reasons for exclusion are presented in Appendix 5) Twenty seven were then excluded during data extraction (references and reasons for exclusion are presented in Appendix 6), 15 of which provided sufficient descriptions to include in a narrative synthesis of the direction and/or significance of change in mental health (Appendix 7). Twenty-six studies were included in the meta-analyses and for six of these studies authors supplied additional data (Appendix 8). See Figure 2.1 for flow of records.

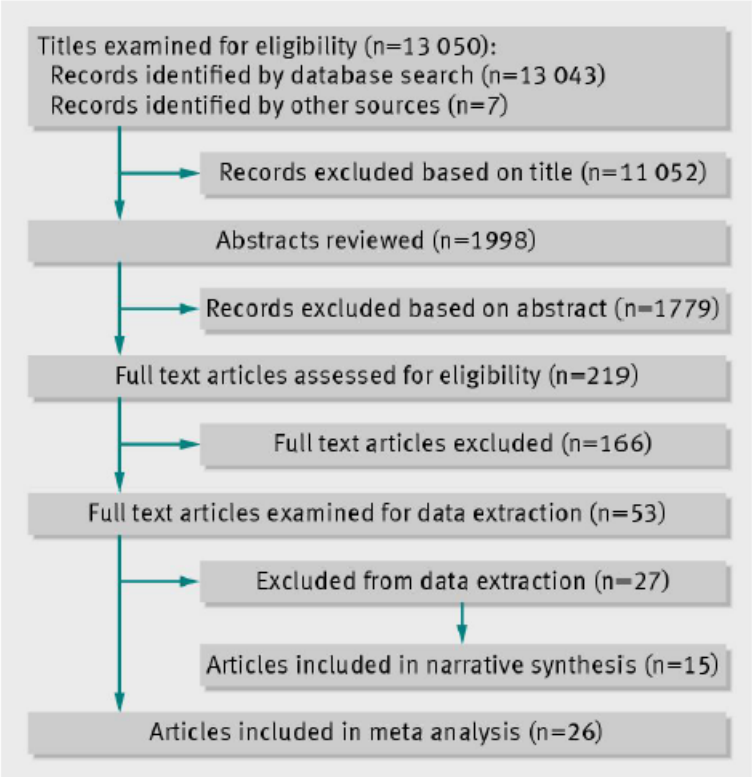

Figure 2.1 Flow and identification of studies to include in review of change in mental health after smoking cessation

2.4.2. Outcome categories

The included studies examined six different measures of mental health: anxiety, depression, mixed anxiety and depression, positive affect, psychological quality of life, and stress (Table 2.1).

2.4.3. Extraction

Several studies presented data on more than one outcome. Sixteen effect estimates were calculated from groups' mean mental health scores, which were reported at both baseline and follow-up. Seven were calculated from studies that presented each groups' mean change in

mental health score from baseline to follow-up. Two were calculated from a non-standardised difference in change. Three were extracted from other types of effect estimates.

Table 2.1 Included study and population characteristics

Outcome category	First author, and year of publication	Study design	Outcome measure(s)	Follow-up(s)	Population	Percentage male	Mean (SD) age
Anxiety	Becona, 2002	Secondary analysis of cessation intervention	State Trait Anxiety Inventory (state anxiety subscale)	12 months	General	53%	37.3
	Dawkins, 2009	Randomized experimental trial	Hospital Anxiety and Depression Scale (anxiety subscale)	3 months	General	47%	68.9
	McDermott, 2013 (in submission during search)	Secondary analysis of cessation intervention	State Trait Anxiety Inventory-6	6 months	General	45%	Abstainers 51.5, smokers 47.7
	Solomon, 2006	Cohort	Brief Symptom Inventory (anxiety subscale)	7 weeks	Pregnant	0%	24.3
Depression	Berlin, 2010	Secondary analysis of cessation intervention	The Hamilton Rating Scale for Depression	11 weeks	Psychiatric	37%	44.5
	Blalock, 2008	Secondary analysis of cessation intervention	Beck Depression Inventory	3 months	Psychiatric	19%	48
	Busch, 2011	Secondary analysis of cessation intervention	Centre for Epidemiologic Studies Depression Scale	6 and12 months	General	10%	32.9
	Dawkins, 2009	Randomized experimental trial	Hospital Anxiety and Depression Scale (depression subscale)	3 months	General	47%	68.9
	Kahler, 2002	Secondary analysis of cessation intervention	Beck Depression Inventory	6 and 12 months	Psychiatric	41%	45.1

	Kahler, 2011	Secondary analysis of cessation intervention	Centre for Epidemiologic Studies Depression Scale	26 months	General	55%	41.5
	Kinnunen, 2006	Cohort	Minnesota Multi-phasic Personality Inventory 2 (depression subscale)	5 years	General	100%	42
	Munafo, 2008	Cohort	Edinburgh Postnatal Depression Scale	4 months, 3 years	Pregnant	0%	29
	Solomon, 2006	Cohort	Brief Symptom Inventory (depression subscale)	7 weeks	Pregnant	0%	24.3
	Vasquez, 1999	Secondary analysis of cessation intervention	Beck Depression Inventory	12 months	General	35%	34.9 (9.4)
Mixed anxiety and depression	Blalock, 2008	Secondary analysis of cessation intervention	Positive and Negative Affect Schedule (negative affect subscale)	3 months	Psychiatric	19%	48
	Chassin, 2002	Cohort	Negative affect scale (non-standardised)	6 years	General	48%	27.0
	Kahler, 2009	Secondary analysis of cessation intervention	Multidimensional Personality Questionnaire (stress reaction subscale)	6 months	General	57·6%	40.9 (12.7)
	Mino, 2000	Cohort	General Health Questionnaire-30	6 and 12 months	General	100%	Abstainers 33.3, smokers 36.1
	Steinberg, 2011	Cohort	Kessler Psychological Distress Scale	6 months	Chronic physical and/or psychiatric condition	47%	Median 40 to 64
Positive affect	Blalock, 2008	Secondary analysis of	Positive and Negative Affect Schedule	3 months	Psychiatric	19%	48

		cessation intervention	(positive affect subscale)				
	Croghan, 2005	Cohort	Short Form Health Survey-36 (energy and vitality subscale)	12 months	General	52%	Abstainers 52.8 (11.2), smokers 54.6 (15.6)
	Mitra, 2004	Cohort	Short Form Health Survey-36 (energy and vitality subscale)	3 to 4 years	Chronic physical and/or psychiatric condition	42%	43.8 (13.3)
Psychological quality of life	Balduyck, 2011	Cohort	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (emotional functioning subscale)	6 and12 months	Post-surgical	71%	59.3
	Croghan, 2005	Cohort	Short Form Health Survey-36 (mental health composite)	12 months	General	52%	Abstainers 52.8 (11.2), smokers 54.6 (15.6)
	Longmore, 2007	Cohort	Short Form Health Survey-12 (mental health composite)	12 months	Chronic physical conditions	Not reported	18+
	McFall, 2006	Secondary analysis of cessation intervention	Short Form Health Survey-36 (mental health composite)	2 months	Psychiatric	91.6%	52.1 (6.8)
	Mitra, 2004	Cohort	Short Form Health Survey-36 (mental health subscale)	3 to 4 years	Chronic physical and/or psychiatric condition	42%	43.8 (13.3)
	Quist-Paulsen, 2006	Secondary analysis of cessation intervention	Cardiac Arrhythmia Suppression Trial Inventory (mental health subscale)	12 months	Chronic physical conditions	73%	56.5
	Sarna, 2008	Cohort	Short Form Health Survey-36 (mental	8 to 9	General	0%	Range 29 to 71

			health composite)	years			
	Stewart, 1995	Secondary analysis of cessation intervention	Short Form Health Survey-36 (mental health subscale)	6 months	General	58%	40.6
Stress	Chassin, 2002	Cohort	Stress (non-standardised composite)	6 years	General	48%	27.0
	Hajek, 2010	Secondary analysis of cessation intervention	Non-standardised measurement of perceived stress	12 months	Chronic physical conditions	77%	56.0
	Manning, 2005	Secondary analysis of cessation intervention	Perceived Stress Scale-14	6 months	General	31%	44.4
Beck's Depression Inventory (Beck et al., 1988), Brief Symptom Inventory (Derogatis, 1993), Cardiac Arrhythmia Suppression Trial Inventory (Wiklund et al., 1992), Centre For Epidemiological Studies Depression Scale (Ross and Mirowsky, 1984), European Organization For Research And Treatment Of Cancer Quality Of Life Questionnaire (The European Organization for Research and Treatment of Cancer, 2001), Edinburgh Postnatal Depression Scale (Cox et al., 1987), Fagerström Test For Nicotine Dependence (Fagerström et al., 1990), General Health Questionnaire – 30 Item Form (Japanese Version) (Nakagawa and Daibo, 1985), Kessler Psychological Distress Scale (Kessler et al., 2002), Hospital Anxiety And Depression Scales (Zigmond and Snaith, 1983), Hamilton Depression Inventory (Hamilton, 1960), Minnesota Multi-Phasic Personality Inventory (Butcher, 1989) , Multidimensional Personality Questionnaire (Tellegen, 1982), Positive And Negative Affect Scales (Watson et al., 1988), Perceived Stress Scale – 14 Item Form (Cohen et al., 1983), Short Form Health Survey-36 (Ware et al., 1993) (Ware, 1993), State Trait Anxiety Inventory – 6 Item Form (Marteau and Bekker, 1992) , State Trait Anxiety Inventory (Spielberger et al., 1983).						

2.4.4. Study characteristics

Eleven of the studies were cohort studies, 14 were secondary analyses of cessation interventions, and one was a randomised trial. Study enrolment included the general population (14 studies), populations living with a chronic physical condition (three), pregnant women (two), postoperative patients (one), people with either a chronic physical and/or psychiatric condition (two), and people with psychiatric conditions (four). The median age was 44, and on average 48% were male. On average, participants smoked 20 cigarettes a day and scored 5.4 on the Fagerström test for nicotine dependence (FTND), indicating moderate dependence. The median length of follow-up was six months (Table 2.2).

In 11 studies, abstinence was measured as continuous abstinence from a point soon after baseline assessment, and in 18 studies abstinence was biologically-validated. In seven studies participants received a psychological intervention as part of the cessation intervention. In 17 studies participants were motivated to quit (Table 2.3).

2.4.5. Study quality

Twenty studies had high quality scores on the Newcastle-Ottawa scale, and five had medium to low scores; for one study there was insufficient information to determine a score (conference abstract) (Table 2.3).

Table 2.2 Characteristics of populations' tobacco use and cessation intervention

First author, year of publication	Behavioural support and medication	Baseline FTND scores M (SD)	Difference between groups P-value for FTND	Baseline cigarettes per day (CPD) M (SD)	Difference between groups P-value for CPD
Balduyck, 2011	No behavioural support. No mood management.	Not measured	Not reported	Abstainers (smoking pack-years (SD)) 36.6 (17.3), smokers 41.3 (16.9)	Not reported
Becona, 2002	Six weekly behavioural support sessions. No mood management.	Cohort 5.4 (2.4)	Not reported	Cohort 26.4 (10.4)	Not reported
Berlin, 2010	Sertraline plus behavioural support or placebo sertraline plus behavioural support. Participants received mood management counselling.	Abstainers 6.6 (2.8), smokers 6.7 (2.4)	P=0.88	Abstainers 23.3 (8.6), smokers 26.0 (10.6)	P=0.27
Blalock, 2008	Behavioural support and mood management counselling	Abstainers 3.9 (1.5), smokers 5.6 (2.4)	P>0·05 (non-significant)	Abstainers 23.1 (7.0), smokers 23.5 (5.3)	P>0.05 (non-significant)
Busch, 2011	Some participants received standard support and some received mood management. Participants who reported readiness to quit were provided nicotine replacement therapy (NRT) (patches).	Cohort 4.6 (1.4)	Not reported	Cohort 15.1 (8.6)	Not reported
Chassin, 2002	No behavioural support provided. No mood management	Not measured	Not reported	Abstainers median 10 to 14, smokers median 10 to 14	P=0.68
Croghan, 2005	Behavioural support, mood management, and/or pharmacological support.	Not measured	Not reported	Cohort median 20 to 39	Not reported
Dawkins, 2009	No behavioural support but received financial incentive for maintaining smoking or abstinence status as allocated. No mood management.	Abstainers 4.6 (1.7), smokers 5.29 (1.81)	P=0.11	Smokers 18.5 (6.3)	P=0·68

Hajek, 2010	Single brief support. No mood management.	75.3% of the cohort smoked within 30 minutes of waking.	Not reported	Cohort 21 (13)	Not reported
Kahler, 2002	Some participants received standard smoking cessation treatment (ST) and some received ST plus cognitive behavioural therapy.	Cohort 6.4 (1.8)	Not reported	Cohort 27.3 (11.3)	Not reported
Kahler, 2009	Behavioural support, NRT and mood management plus brief alcohol intervention.	Cohort 5.0 (2.0)	Not reported	Cohort 22.0 (10.9)	Not reported
Kahler, 2011	Counselling plus NRT (nicotine patch) or counselling plus NRT (patch) plus brief alcohol intervention. No mood management.	Cohort 5.0 (2.2)	Not reported	Cohort 21.3 (9.4)	Not reported
Kinnunen, 2006	No behavioural support. No mood management	Not reported	Not reported	Not reported	Not reported
Longmore, 2007	No behavioural support. No mood management.	Not reported	Not reported	Not reported	Not reported
Manning, 2005	Eight weekly sessions of motivational interviewing. No mood management.	Not measured	Not reported	Cohort 17.1 (8.5)	Not reported
McDermott, 2013 (in submission during search)	Seven weekly behavioural support sessions. No mood management.	Abstainers 4.8 (2.0), smokers 5.7 (2.2)	P<0.01	Abstainers 18.7 (7.8), smokers 21.0 (8.9)	P<0.01
McFall, 2006	Behavioural, pharmacological and mood management.	Cohort 6.2 (2.2)	Not reported	Cohort 26.0 (14.5)	Not reported
Mino, 2000	No behavioural support. No mood management.	Not measured	Not reported	Abstainers 15.7 (10.1), Smokers 20.0 (8.4)	Not reported
Mitra, 2004	No behavioural support. No mood management.	Not measured	Not reported	Not reported	Not reported

Munafo, 2008	No behavioural support. No mood management.	Not reported	Not reported	Not reported	Not reported
Quist-Paulsen, 2006	Behavioural support with no mood management, plus NRT.	Not measured	Not reported	Abstainers 14.0 (6.0), smokers 16.0 (7.0)	P=0·42
Sarna, 2008	No behavioural support. No mood management.	Not measured	Not reported	Cohort 16.8 (10.3)	Not reported
Solomon, 2006	Abstinence-monitoring schedule plus TAU. Participants were allocated to receive a financial incentive after successful biologically-validation or to receive a financial incentive independent of smoking status. No mood management.	Not measured	Not reported	Abstainers 9.7 (6.0), smokers 22.4 (9.6)	P< 0·01
Steinberg, 2011	Behavioural support, no mood management. Plus combination pharmacotherapy of NRT and or bupropion or varenicline	Not measured	Not reported	Cohort 19.0 (SD not reported)	Not reported
Stewart, 1995	Self-help booklet with no mood management described plus NRT (gum) and a financial incentive.	Not measured	Not reported	Cohort 19.7 (11.1)	Not reported
Vasquez, 1999	Multi component behavioural treatment. No mood management.	Cohort 4.8 (2.3)	Not reported	Cohort 24.6 (8.9)	Not reported

Table 2.3 Study characteristics that may present a risk of bias

First author, year of publication	Publication status	Measurement of abstinence	Bio-validation of smoking status	Newcastle-Ottawa Scale score (Range 0 to 5, 0=low)	Same N of participants at baseline and follow-up?	Motivated to quit?	Psychotherapeutic component in cessation intervention?	Statistical adjustment for covariates	Any evidence of outcome reporting bias?	Was publication based on change in mental health?
Balduyck, 2011	Published and unpublished	Point-prevalence	Not bio-validated	4	Different	Not selected by motivation to quit	Did not receive mood management	No adjustment	No	No
Becona, 2002	Published	Point-prevalence	Bio-validated	5	Same	Motivated to quit	Did not receive mood management	No adjustment	No	Yes
Berlin, 2010	Published	Continuous	Not bio-validated	5	Same	Motivated to quit	Received mood management	Adjusted for treatment group (placebo or sertraline)	No	Yes
Blalock, 2008	Published and unpublished	Continuous	Bio-validated	5	Same	Motivated to quit	Received mood management	Unadjusted and adjusted data. Adjusted for baseline CO, baseline, withdrawal measure score and treatment group.	No	Yes
Busch, 2011	Published	Point-prevalence	Bio-validated	4	Different	Not selected by motivation	Received mood management	No adjustment	No	Yes

						to quit				
Chassin, 2002	Published and unpublished	Continuous	Not bio-validated	3	Same	Not selected by motivation to quit	Did not receive mood management	No adjustment	No	Yes
Croghan, 2005	Published	Continuous	Not bio-validated	3	Same	Motivated to quit	Received mood management	Adjusted for age and sex reference norms (US)	No	No
Dawkins, 2009	Published and unpublished	Continuous	Bio-validated	4	Same	Not selected by motivation to quit	Did not receive mood management	No adjustment	No	Yes
Hajek, 2010	Published	Continuous	Bio-validated	4	Same	Motivated to quit	Did not receive mood management	No adjustment	No	Yes
Kahler, 2002	Published	Continuous	Bio-validated	5	Different	Motivated to quit	Received mood management	Adjusted for baseline (session 1) BDI scores	No	Yes
Kahler, 2009	Published	Continuous	Bio-validated	4	Different	Motivated to quit	Received mood management	No adjustment	No	No
Kahler, 2011	Published and unpublished	Point-prevalence	Bio-validated	5	Different	Motivated to quit	Did not receive mood management	Unadjusted and adjusted data. Adjusted for treatment condition, MDD history, gender, and FTND	No	Yes
Kinnunen,	Published	Continuous	Not bio-	4	Different	Not selected	Did not receive	MMPI-2 scores were	No	Yes

2006			validated			by motivation to quit	mood management	adjusted for age reference norms		
Longmore, 2007	Published (conference abstract)	Not reported	Not reported	Not reported	Different	Not selected by motivation to quit	Did not receive mood management	Adjusted for "demographic, clinical, and socioeconomic factors and baseline health status" but no further details.	No	Yes
Manning, 2005	Published	Point-prevalence	Bio-validated	4	Different	Motivated to quit	Did not receive mood management	No adjustment	No	Yes
McDermott, 2013 (in submission during search)	Published	Continuous	Bio-validated	4	Same	Motivated to quit	Did not receive mood management	Adjusted for age, nicotine dependence and cigarette consumption	No	Yes
McFall, 2006	Published	Point-prevalence	Bio-validated	5	Different	Motivated to quit	Received mood management	No adjustment	Yes	No
Mino, 2000	Published data	Point-prevalence	Does not report assessment of smoking status validation	4	Different	Not selected by motivation to quit	Did not receive mood management	No adjustment	No	Yes
Mitra, 2004	Published	Point-	Not bio-	2	Same	Not selected	Did not receive	Adjusted for gender,	No	No

	data	prevalence	validated			by motivation to quit	mood management	ethnicity, years of education, age at baseline, numbers of domains in which respondents were dependent in activities of daily living.		
Munafo, 2008	Published data	Point-prevalence	Non bio-validated	3	Different	Not selected by motivation to quit	Did not receive mood management	No adjustment	No	Yes
Quist-Paulsen, 2006	Published data	Point-prevalence	Bio-validated	5	Same	Motivated to quit	Did not receive mood management	No adjustment	No	No
Sarna, 2008	Published data	Point-prevalence	Non bio-validated	3	Different	Not selected by motivation to quit	Did not receive mood management	Adjusted for age, BMI, living alone, co-morbidity and BL SF-36 scores	No	Yes
Solomon, 2006	Published data	Point-prevalence	Bio-validated	4	Same	Motivated to quit	Did not receive mood management	No adjustment	No	Yes
Steinberg, 2011	Published and unpublished data	Point-prevalence	Bio-validated	4	Same	Motivated to quit	Did not receive mood management	No adjustment	No	Yes
Stewart, 1995	Published data	Point-prevalence	Bio-validated	4	Same	Motivated to quit	Did not receive mood management	Adjusted for age, gender ethnicity, education,	No	Yes

								employment status, marital status, number of choric conditions, number of cigarettes consumed at enrolment, nicotine dependency, nicotine gum intervention.		
Vasquez, 1999	Published data	Continuous	Bio-validated	5	Same	Motivated to quit	Did not receive mood management	No adjustment	No	Yes

2.4.6. Results of meta-analyses

If studies reported change data separately for quitters and continuing smokers (i.e. rather than difference in change between groups) these data were used to calculate each groups' standardised average mean change in scores, for each outcome. On average, smokers who quit showed an improvement from baseline to follow-up, and those who continued smoking showed small change, if any, in mental health outcomes (Figure 2.2).

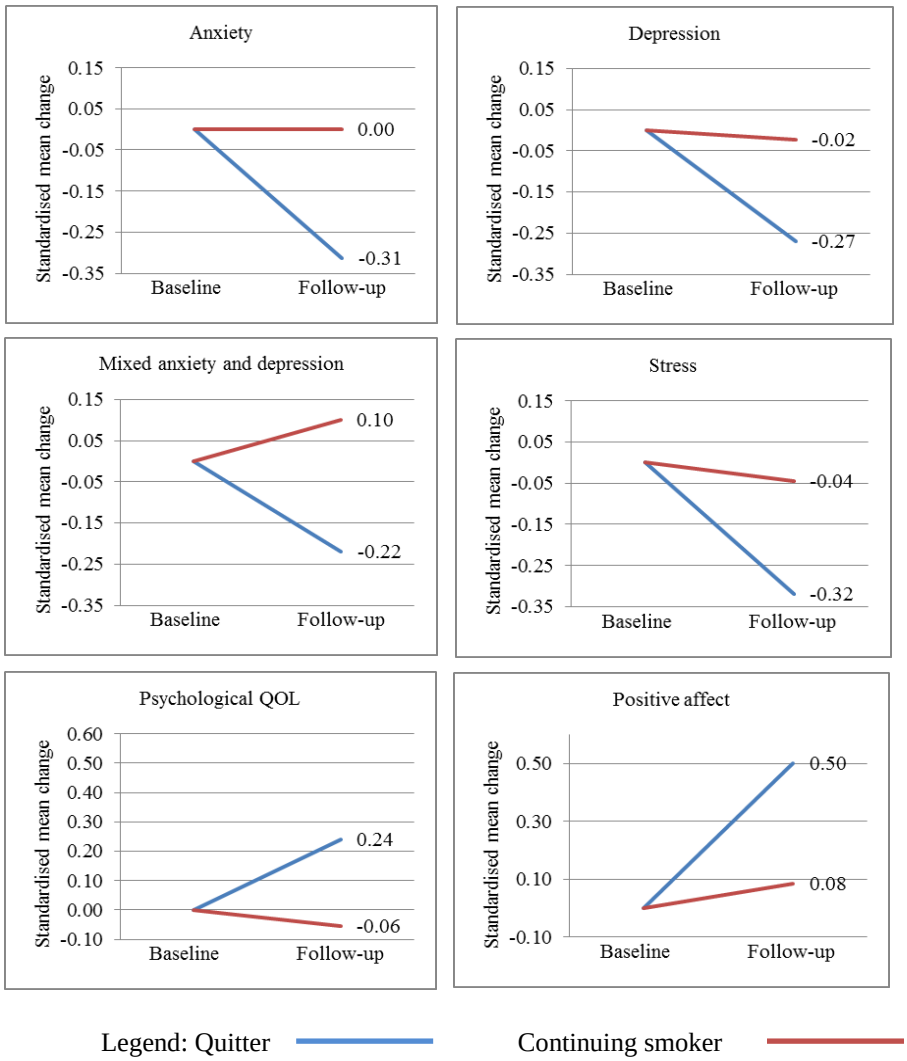

Figure 2.2 Groups' standardised average mean change in mental health outcomes

2.4.6.1. Anxiety

Four studies reported change in anxiety from baseline to follow-up, with follow-ups ranging from seven weeks to 12 months (median six months). On average, quitters' anxiety scores improved and continuing smokers did not display change from baseline to follow-up (Figure 2.2). The difference in change was significant ((standardised mean difference) (SMD) –0.37, 95% CI: –0.70 to –0.03; P=0.03). There was substantial statistical heterogeneity between studies (I^2=71%) (Higgins and Green, 2011) (Figure 2.3).

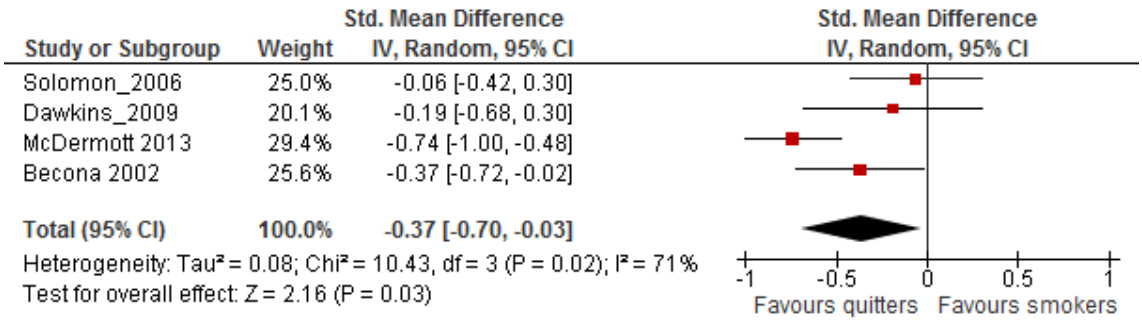

Figure 2.3 Difference between change in anxiety from baseline to longest follow-up in people who stopped smoking or continued to smoke

2.4.6.2. Mixed anxiety and depression

Five studies reported change in mixed anxiety and depression from baseline to follow-up, with follow-up ranging from three months to six years (median six months). On average, quitters displayed an improvement in symptoms, and continuing smokers showed a slight worsening in symptoms from baseline to follow-up (Figure 2.2). The difference in change was significant (SMD –0.31, 95% CI: –0.47 to –0.14; P<0.001; I^2=0%) (Figure 2.4).

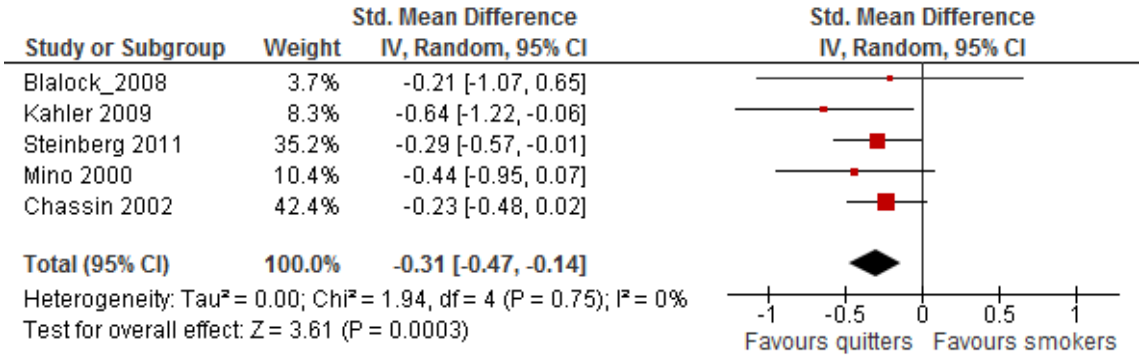

Figure 2.4 Difference between change in mixed anxiety and depression from baseline to longest follow-up in people who stopped smoking or continued to smoke

2.4.6.3. Depression

Ten studies reported change in depression from baseline to follow-up, with follow-up ranging from 11 weeks to five years (median 12 months). On average, quitters showed an improvement in depressive symptoms, and continuing smokers slightly improved from baseline to follow-up (Figure 2.2**Error! Reference source not found.**). The improvement as significantly larger in the quit group (SMD –0.25, 95% CI: –0.37 to –0.12; P<0.001; I^2=30%) (Figure 2.5).

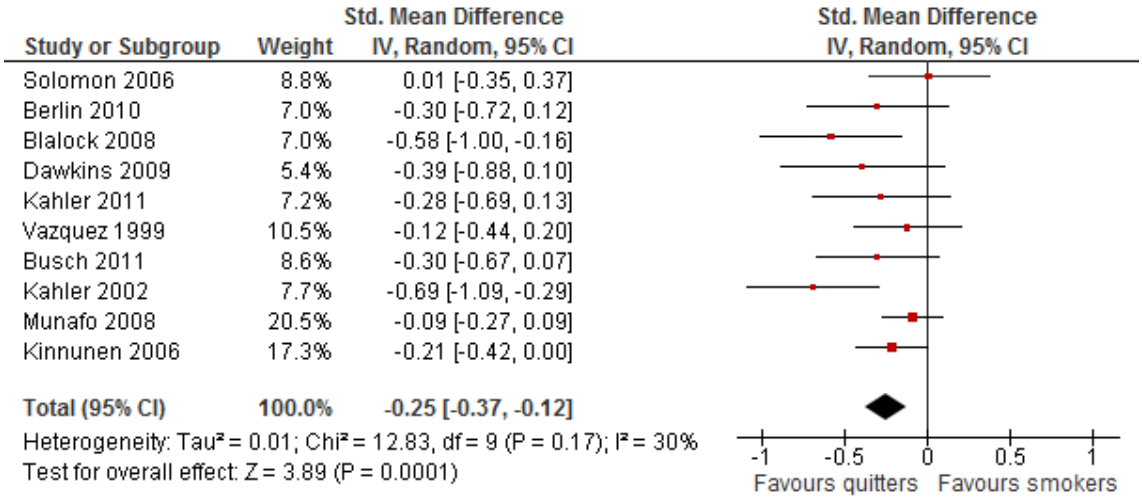

Figure 2.5 Difference between change in depression from baseline to longest follow-up in people who stopped smoking or continued to smoke

2.4.6.4. Stress

Three studies reported change in stress from baseline to follow-up, with follow-up ranging from six months to six years (median 12 months). On average, quitters displayed an improvement in stress and continuing smokers showed a slight improvement (Figure 2.2). The improvement was significantly greater in the quit group (SMD –0.27, 95% CI –0.40 to –0.13; P<0.001) from baseline to follow-up (I^2=0%) Figure 2.6.

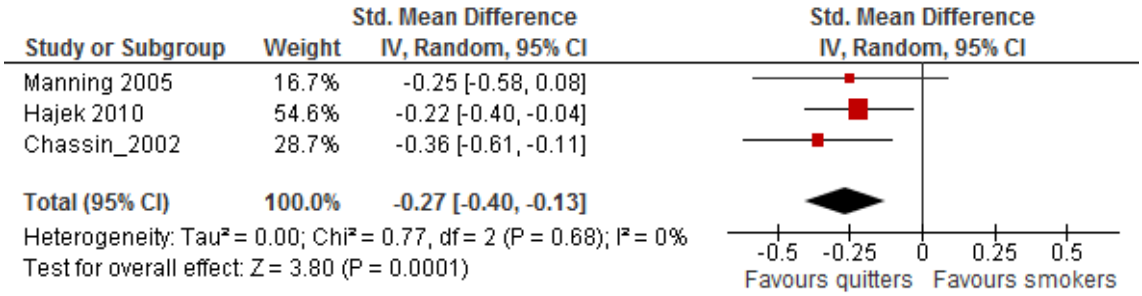

Figure 2.6 Difference between change in stress from baseline to longest follow-up in people who stopped smoking or continued to smoke

2.4.6.5. Psychological quality of life

Eight studies reported change in psychological quality of life from baseline to follow-up, with follow-ups ranging from two months to nine years (median 12 months). On average, quitters displayed a significant improvement in psychological quality of life from baseline to follow-up and continuing smokers showed a slight worsening (Figure 2.2). The difference in change was significant (SMD 0.22, 95% CI: 0.09 to 0.36; P<0.001). There was moderate statistical heterogeneity between studies (I^2=63%) (Higgins and Green, 2011) (Figure 2.7).

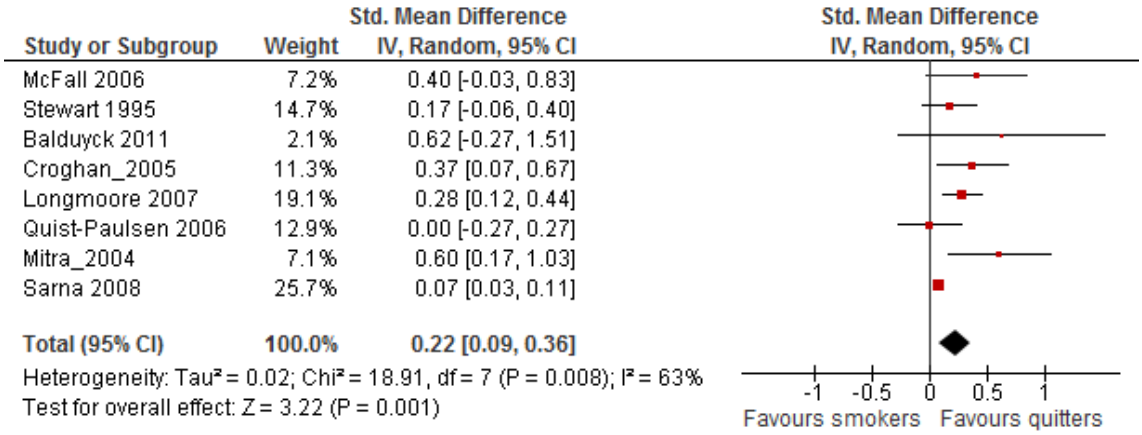

Figure 2.7 Difference between change in psychological quality of life from baseline to longest follow-up in people who stopped smoking or continued to smoke

2.4.6.6. Positive affect

Three studies reported change in positive affect from baseline to follow-up, with follow-ups ranging from three months to four years (median 12 months). On average, quitters showed an improvement in positive affect, and continuing smoker's scores slightly increased from baseline to follow-up (Figure 2.2). The difference in change was significant (SMD 0.40, 95% CI: 0.09 to 0.71; P=0.01; I^2=49%) (Figure 2.8).

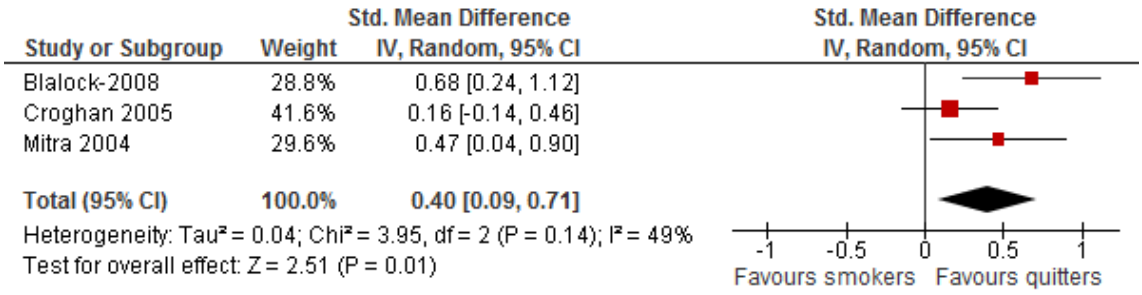

Figure 2.8 Difference between change in positive affect from baseline to longest follow-up in people who stopped smoking or continued to smoke

2.4.7. Sensitivity and subgroup analyses

Numerous sensitivity and subgroup analyses were conducted to investigate clinical and methodological heterogeneity and to investigate risk of bias within and across studies (results reported in Appendix 9).

2.4.7.1. Study quality

Removal of studies with medium to low scores on the Newcastle-Ottawa Scale did not greatly change the summary estimates (Appendix 9).

2.4.7.2. Publication and outcome reporting bias

There were sufficient studies to create funnel plots for anxiety, depression, mixed anxiety and depression, and psychological quality of life. The plots were symmetrical for depression, anxiety, and mixed anxiety and depression and asymmetrical for psychological quality of life (Appendix 9). Egger tests indicated that small studies measuring psychological quality of life provided larger effect estimates than studies with larger samples (P=0.017). Seven out of eight of the pooled studies, however, had sample sizes ranging from 34 to 323. Thus, the result of the Egger test was likely influenced by the only large study (Sarna, 2008), which analysed data from 11,809 participants, and accounted for 25.7% of the pooled effect estimate. There was no evidence of small study bias for studies that measured anxiety (P=0.184), depression (P=0.064), mixed anxiety and depression (P=0.307), positive affect (P=0.179), or stress (P=0.705).

In 20 of the 26 studies, the main aim was to report on change in mental health and the decision to publish could have been contingent on the strength or significance of the finding (Table 2.3). The main aim of the six other studies was to report on other outcomes, and they reported only psychological quality of life and positive affect. Subgroup analysis showed no evidence of a difference in effect between studies that did not primarily report on change in mental health and those that did so for psychological quality of life (P=0.19) and positive affect (P=0.14). One of the 26 studies showed evidence of multiple testing and selectively reported the only significant result (Table 2.3).

Results of narrative synthesis — Fifteen studies were excluded because there were insufficient data to extract an effect size or its variance, despite contact with the authors (Appendix 9). Nine of the 15 studies reported on the significance of the difference in change between quitters and continuing smokers: three reported no significant difference, five favoured quitters, and one study showed a difference favouring continuing smoking. Of the nine studies, seven reported that mental health improved in quitters, one showed no change, and one showed a worsening in mental health for quitters. Five of nine studies reported information on change in mental health for continuing smokers, three studies reported that mental health had worsened at follow-up and two reported that it had improved.

2.4.7.3. Adjustment for covariates

Two studies supplying estimates for three outcomes (anxiety, depression, and positive affect) provided effect sizes of the difference in change in mental health both unadjusted and adjusted for confounders. The confounders included demographics, information pertaining to

tobacco consumption, and/or treatment allocation. Comparison of these estimates indicated that adjustment did not greatly change the results (Table 2.4)

Summary effect estimates from studies that supplied only unadjusted effect estimates were compared with studies that supplied only adjusted effect estimates. Studies adjusted for several potential confounders (Table 2.5). For anxiety one study adjusted for covariates, for depression four studies adjusted for covariates, for psychological quality of life five studies adjusted for covariates, for positive affect two studies adjusted for covariates, and for stress and mixed anxiety and depression no studies adjusted for covariates. The effect sizes were similar for studies that did and did not adjust for covariates for all outcomes except anxiety. Studies that adjusted for covariates showed a significantly larger difference between quitters and smokers than those that did not adjust.

Table 2.4 Comparison of unadjusted and adjusted estimates from studies in which both were presented				
Study	**Covariates adjusted for**	**Outcome (measure)**	**Standardised mean difference (95% CI)**	
			Unadjusted estimate	**Adjusted estimate**
Blalock (2008)	Baseline CO expiration, baseline nicotine withdrawal score, treatment group allocation	Beck's depression inventory	–0.54 (–1.42 to 0.34)	–0.58 (–1.00 to –0.16)
		Positive and negative affect schedule (positive affect subscale)	0.59 (–0.29 to 1.47)	0.68 (0.24 to 1.12)
McDermott (2012)	Age, nicotine dependence, and daily cigarette consumption	State trait anxiety inventory-6	–0.62 (–0.88 to –0.36)	–0.74 (–1.00 to –0.48)

Table 2.5 Subgroup analysis with comparison of effect estimates between studies that did and did not adjust for covariates

Outcome	Standardised mean difference (95% CI)			Test for subgroup differences
	Original estimate	Adjusted estimate	Unadjusted estimate	
Anxiety*	–0.37 (–0.70 to –0.03) (4 studies)	–0.74 (–1.00 to –0.48) (1 study)	–0.34 (–0.61 to –0.07) (4 studies)	χ^2=4.40, P=0.04
Depression	–0.25 (–0.37 to –0.12) (10 studies)	–0.41 (–0·65 to –0·17) (4 studies)	–0.15 (–0.27 to –0.03) (7 studies)	χ^2=3.49, P=0.062
Mixed anxiety and depression	–0.31 (–0.47 to –0.14) (5 studies)	No data	–0.31 (–0.47 to –0.14) (5 studies)	Not applicable
Positive affect	0.40 (0.09 to 0.71) (3 studies)	0.28 (–0.02 to 0.57) (2 studies)	0.68 (0.24 to 1.12) (1 study)	χ^2=2.22, P=0.14
Psychological quality of life	0.22 (0.09 to 0.36) (8 studies)	0.24 (0.07 to 0.40) (5 studies)	0.22 (–0.13 to 0.57) (3 studies)	χ^2=0.01, P=0.92
Stress	–0.27 (–0.40 to –0.13) (3 studies)	No data	–0.27 (–0.40 to –0.13) (3 studies)	Not applicable

*Please note that for anxiety and depression some studies provided both adjusted and unadjusted estimates, therefore these were compared within the corresponding subgroup analysis.

2.4.7.4. Loss to follow-up

Twelve of the 26 studies reported means at baseline on a larger number than contributed to the mean at follow-up. Removal of these 12 did not greatly change the effect estimates (Appendix 9).

2.4.7.5. Ascertainment of smoking status

Eleven studies did not report continuous abstinence, classification of smoking status was not clear in four studies, and eight did not biochemically confirm abstinence, exclusion of these did not change the results (Appendix 9).

2.4.7.6. Motivation to quit

In a subgroup analysis, effect estimates from 16 studies in which participants were all attempting to quit were compared with the 10 studies in which participants were not selected by motivation to quit. There was no evidence of subgroup differences (Appendix 9), suggesting that deterioration in mental health as a reaction to failing to quit was an unlikely cause of the difference between quitters and continuing smokers.

2.4.7.7. Psychotherapeutic component within cessation intervention

Seven studies included a psychotherapeutic element in the cessation intervention to help participants manage symptoms of anxiety or low mood. Removal of these studies did not greatly change the summary estimate (Appendix 9).

2.4.8. Additional analyses

2.4.8.1. Comparison of clinical population

Fourteen studies enrolled smokers from the general population, four enrolled patients with psychiatric disorders, three enrolled patients with chronic physical conditions, two enrolled patients with either psychiatric or physical conditions, two enrolled pregnant women, and one enrolled patients after surgery. Test for subgroup differences for change in depression was significant due to the small effect found in pregnant women –0.07 (95% CI: –0.23 to 0.09) compared to the other populations where estimates ranged between –0.23 (95% CI: –0.37 to –0.09) and –0.53 (95% CI: –0.77 to –0.29) (Table 2.6). There was no evidence of subgroup differences for any other outcome.

Populations with psychiatric disorders were especially of interest, and data from this population were available on change in depression, mixed anxiety and depression, and positive affect. The effect estimates for this subgroup compared with the general population were –0.39 (95% CI: –0.63 to –0.14) versus –0.30 (–0.48 to –0.12) for depression; –0.21 (–1.07 to 0.65) versus –0.32 (–0.53 to –0.11) for mixed anxiety and depression; 0.40 (–0.03

to 0.83) versus 0.15 (–0.01 to 0.30) for psychological quality of life; and 0.68 (0.24 to 1.12) versus 0.16 (–0.14 to 0.46) for positive affect.

Table 2.6 Subgroup analysis with comparison of effect estimates between different clinical populations		
Outcome and population	**Effect estimate standardised mean difference (95% CI)**	**Test for subgroup differences**
Anxiety		
Overall	–0.37 (–0.70 to –0.03)	—
General (3 studies)	–0.48 (–0.81 to –0.15)	χ^2=2.77, P=0.10
Pregnant (1 study)	–0.06 (–0.42 to 0.30)	
Depression		
Overall	–0.25 (–0.37 to –0.12)	
General (5 studies)	–0.23 (–0.37 to –0.09)	χ^2=9.74, P=0.008
Psychiatric condition (3 studies)	–0.53 (–0.77 to –0.29)	
Pregnant (2 studies)	–0.07 (–0.23 to 0.09)	
Mixed anxiety and depression		
Overall	–0.31 (–0.47 to –0.14)	—
General (3 studies)	–0.32 (–0.53 to –0.11)	χ^2=0.08, P=0.96

Psychiatric condition (1 study)	–0.21 (–1.07 to 0.65)	
Chronic physical and/or psychiatric condition (1 study)	–0.29 (–0.57 to –0.01)	
Psychological quality of life		
Overall	0.22 (0.09 to 0.36)	—
General (3 studies)	0.15 (–0.01 to 0.30)	χ^2=5.25, P=0.25
Psychiatric condition (1 study)	0.40 (–0.03 to 0.83)	
Chronic physical and/or psychiatric condition (1 study)	0.60 (0.17 to 1.03)	
Chronic physical condition (1 study)	0.16 (–0.11 to 0.43)	
Postoperative (1 study)	0.62 (–0.27 to 1.51)	
Positive affect		
Overall	0.40 (0.09 to 0.71)	—
Chronic physical and/or psychiatric condition (1 study)	0.47 (0.04 to 0.90)	χ^2=3.95, P=0.11
General (1 study)	0.16 (–0.14 to 0.46)	
Psychiatric condition (1 study)	0.68 (0.24 to 1.12)	

Stress		
Overall	–0.27 (–0.40 to –0.13)	—
General (2 studies)	–0.32 (–0.52 to –0.12)	χ^2=0.51, P=0·48
Chronic physical condition (1 study)	–0.22 (–0.40 to –0.04)	

2.4.8.2. Study design

Eleven studies were cohort studies, 14 were secondary analyses of cessation interventions, and one was a randomised trial. There was no evidence of subgroup differences between these study designs (Appendix 9).

2.4.8.3. Length of follow-up

The effect sizes were similar for studies that assessed mental health between six weeks and six months and those with follow-ups longer than six months (Appendix 9). Studies were ordered according to follow-up length in forest plots (Figure 2.2 to 2.8) which indicated no clear chronological pattern in effect estimates.

2.5. Discussion

There was consistent evidence that stopping smoking is associated with improvements in depression, anxiety, stress, psychological quality of life, and positive affect compared with continuing to smoke. The strength of association was similar for both the general population and clinical populations, including those with mental health disorders. There was no evidence that methodological heterogeneity or short comings explained these associations nor was there substantial evidence of publication bias.

2.5.1. Limitations, strengths and potential sources of bias

The strengths of this study lay in the broad search terms that were used to retrieve literature, including hand searching to avoid missing available literature and also checking reference lists of included studies. Authors of studies were contacted and data were calculated from papers in which, in many cases, these data were not provided in a directly usable form.

In most included studies, the quality of measurement of exposure status—smoking—was adequate. Nearly half of the studies reported prolonged or continuous abstinence that was biologically-validated; this removed the threat of misclassification of exposure. Sensitivity analysis showed no evidence that studies that assessed smoking in other ways could have altered the results. Inclusion of such studies would, in general, underestimate the true strength of the association. Likewise, assessment of outcome was good, with participants completing validated self-reported mental health questionnaires before they stopped smoking and at follow-up. Assessors were, in that sense, blind to exposure status, and no study was set up primarily to investigate change in mental health on cessation.

Confounding is usually a major threat to the validity of most associations based on observational data. However, adjustment for potential confounders, which were mostly factors associated with propensity to achieve cessation, had only small effects in the studies that reported such data. The data within each study were robust and the association was unlikely to arise through bias.

The validity of the review rests on whether the search retrieved appropriate literature. This study aimed to retrieve a large number of cohort studies that might have contained data, even when this was not readily apparent. Doing so, several studies were uncovered that would have been missed if the search was confined to studies that seemed to be about smoking cessation and mental health. In all cases, the data were derived from secondary analyses of studies investigating other hypotheses (for example, secondary analyses of cessation interventions, population cohorts). It could be that authors of similar studies analysed data in the same way but found no association so may have chosen not to publish those data. One example of this was located when a study reported quantitative data only for the significant (and presumably stronger) association and did not report other non-significant associations. Other studies that reported on the association but not completely enough to assess quantitatively, however, seemed to give similar results to those in which the data were more clearly presented. Overall, there was little evidence of publication bias, but this cannot be excluded.

2.5.2. Possible interpretations

Data in this study are valid and there are three possible explanations for the association. The first is that smoking cessation causes the improvement in mental health, the second is that improving mental health causes cessation, and the third is that a common factor explains both improved mental health and cessation. Observational data can never prove causality, but almost all that is known about the harms of smoking and the benefits of cessation derive from observational studies, as randomised trials to examine this have insurmountable ethical and practical difficulties, i.e. one cannot randomise people to smoke or quit.

Could a common factor explain both cessation and improved mental health? This supposes that a single factor—such as positive life events—can cause people to attempt or achieve cessation and improve mental health. There is no evidence that positive life events or any other single mechanism are associated with both cessation and improved mental health. In addition, mental health outcomes were assessed anywhere from seven weeks to nine years after baseline, and it seems implausible that such mechanisms are associated with positive mental health changes during this entire period.

An obvious explanation for the association is that improvements in mental health prompt people to attempt cessation and that this explains the association. This is contradicted by these data, however. Over half the studies were secondary analyses of randomised trials. In these studies everyone attempted cessation and therefore the decision to quit was not contingent on change in mental health. Importantly, those who did achieve abstinence in these trials, any detected change in mental health would have occurred after cessation rather than before cessation (previously discussed in section 2.3.10.2). Subgroup analyses that split data by whether they were derived from such trials or from population cohorts, showed no evidence of a difference in the effect estimates between the study types. These data support the notion that cessation improves mood. However, it may be possible success of the quit attempt was dependent upon change in mood.

In some, but not all, of the studies the change in mental health in quitters and continuing smokers could be calculated, rather than just the difference in the change as presented in the meta-analyses. In these studies, the average mean change was calculated separately for each group. These data indicated little change in mental health from baseline to follow-up in

continuing smokers, while smokers who quit showed reductions in adverse mental health symptoms and improvements in positive affect and quality of life. In support of these data, one of the studies in the review was a trial in which participants were randomised to continue smoking or quit. Obviously adherence to this instruction was not absolute, but analysis of these data by trial arm showed a modest benefit of cessation compared with continuing to smoke. The trial was not powered to detect this difference and it was not significant, but it does provide further evidence to support the notion that stopping smoking leads to improvements in mental health.

Data from a systematic review of randomised trials also supports the notion that cessation improves mental health. Banham and Gilbody systematically reviewed eight trials of smoking cessation interventions in people with severe mental illnesses (Banham and Gilbody, 2010). All trials that assessed psychological function typically used several scales at multiple times. Most showed no difference between active and control groups, but the two studies that reported significant differences favoured the intervention groups (study details previously discussed in section 1.10.2). Another study reported after this review randomised people with serious mental illness to cessation support or usual care. It showed that cessation support reduced readmissions for worsening mental illness (Prochaska et al., 2013). These data do not directly estimate the effect of cessation on mental health because most people who were randomised to the intervention did not quit. But these findings, in people with serious mental illness, support the findings in our review that psychological outcomes improve on cessation.

2.5.3. Possible mechanisms

The hypothesis that cessation improves mood is supported by a plausible biological mechanism. As discussed previously (section 1.6), chronic tobacco smoking is associated with neuroadaptations in nicotinic pathways in the brain. Neuroadaptations in these pathways are associated with occurrence of depressed mood, agitation, and anxiety shortly after a cigarette is smoked (Benowitz, 1999; 2010; Mansvelder and McGehee, 2002; Wang and Sun, 2005). This is known as the withdrawal cycle and is marked by fluctuations in a smoker's psychological state throughout the day (Benowitz, 1999; 2010) and could worsen mental health (Parrott, 1999). A study reported that the neurological functioning of quitters returned to the same level as non-smokers by three weeks after cessation (Mamede et al., 2007), consistent with reports that withdrawal symptoms abate after a few weeks (Hughes, 2007b). The misattribution hypothesis is that smokers attribute these symptoms as arising from stress or poor mental health and conclude from the ability of cigarettes to ameliorate these symptoms that cigarettes improve mental health.

Not all data, however, support this causal interpretation. An epidemiological study exploiting Mendelian randomisation examined the causal link between current smoking and current anxiety and depression (Bjorngaard et al., 2013). This study showed some evidence that the genetic variant was associated with anxiety in never and former smokers; however as a whole the study did not support a causal link between smoking status and current mental health problems. These data argue against the misattribution hypothesis, whereby periods of psychological changes related to withdrawal from smoking are eliminated by neurological adaptation to permanent deprivation of nicotine.

2.5.4. Clinical implications

If the associations observed in this review are causal then the effect size is clinically important. Fournier and colleagues (2010) meta-analysed trials of selective serotonin reuptake inhibitors and estimated the effect size. For mild to moderate depression the effect estimates ranged from –0.17 to –0.11; this is lower than the effect size for smoking cessation. A meta-analysis of 34 randomised controlled trials assessed the effect of anti-depressants on generalised anxiety disorder (National Institute for Health and Clinical Excellence, 2011). These effect estimates ranged from –0.23 (–0.43 to –0.13) to –0.50 (–0.77 to –0.23); this is similar to smoking cessation at –0.37. This result is particularly important in view of the current findings in patients with psychiatric disorders. There was no evidence that the effect size differed between population subgroups based on clinical diagnosis, and the effect on depression, psychological quality of life, and positive affect was significant in people who had mental disorders. These data should reassure doctors treating patients with mental illness that cessation is unlikely to exacerbate their symptoms and might indeed be therapeutic.

2.6. Conclusion

Whether or not smoking cessation directly causes the observed improvement in mental health, there are direct clinical implications. Smokers can be reassured that stopping smoking is associated with mental health benefits. This could also overcome barriers that clinicians have toward intervening with smokers with mental health problems. Furthermore, challenging the

widely held assumption that smoking has mental health benefits could motivate smokers to stop.

2.7. Chapter summary

This chapter reported a systematic review and meta-analysis of longitudinal studies comparing the difference in change between those who quit and continued smoking. Meta-analyses of 26 studies found consistent evidence showing smoking cessation was associated with improvements in mental health outcomes. The size of the effect was equal or greater to anti-depressant treatment. Within and between study heterogeneity was explored through multiple sensitivity analyses and found that risk of confounding to the association was low.

CHAPTER THREE

3. INTRODUCTION TO THE MCNEIL TRIAL ANALYSES

3.1. Introduction to Chapter Three

In this chapter I introduce a dataset obtained for the analyses presented in Chapters Four to Six. The data were provided by McNeil pharmaceutical company and contains individual-level patient data from six placebo-controlled randomised trials of nicotine replacement therapy (NRT) for smoking reduction. This chapter describes the data application process, methods used to prepare these data for analysis, and presents descriptive information about the trials and about ascertainment of exposures and outcomes used in the subsequent chapters.

3.2. Background to the McNeil trials

The data supplied for the analyses presented in Chapters Four to Six were provided by McNeil AB, which is incorporated in Sweden and is part of Johnson and Johnson, a global healthcare company. McNeil AB conducts research, develops and produces medicines for self-care which can be purchased without prescription. In 1978 (known then as Pharmacia AB) McNeil AB launched NICORETTE, a brand of NRT used to treat nicotine dependence. NICORETTE is now available in seven variants which are currently available in over 70 countries (McNeil AB, 2014). McNeil conducted a series of double-blind randomized

placebo-controlled trials of NICORETTE NRT for smoking reduction during 1997 and 2003. The individual patient data from these trials was provided for use in this thesis.

3.3. Application process

Ideally, trials of smoking cessation treatment would have been analysed to examine the aims of the thesis, however, due to unforeseen circumstances and time restraints the data described in this chapter were opportunistically selected. These data were obtained in a four stage process. Firstly, the trials' protocols were examined to determine if the data were useable for the proposed analyses (study protocol presented in Appendix 11) and to ensure the trials were compatible for a merged longitudinal analysis. Each trial's protocol was examined to ensure that key variables were assessed using the same measures and that there was consistency across trials' follow-up points, inclusion/exclusion criteria and data collection processes. Secondly, a detailed request for the dataset was sent, which involved writing a summary of the proposed analyses and a detailed data request describing which variables were required for the analyses. Finally, a data-sharing agreement was arranged between McNeil AB and the universities involved in the analyses. To ensure these data arrived on time for use in this thesis, I was directly involved in managing and pursing academics and contracts' administrators.

3.4. Downloading, checking and combining data

Please see Appendix 12 for methods used to download, clean and combine data.

Table 3.1 Variables recorded within each trial and their characteristics

		Trial 1	Trial 2	Trial 3	Trial 4	Trial 5	*Trial 6 (excluded)*[1]
Demographic	Age	Continuous					
	Sex	Binary					
Treatment	Treatment allocation	Binary (Placebo or Active)					
Nicotine dependency	Fagerström Tolerance Questionnaire	Continuous scale 1-10 (8> high dependence)					
Intention to quit	How motivated are you to quit smoking?	Not recorded	Continuous 10 CM VAS* (10= maximum motivation)	Not recorded	Not recorded	Not recorded	*Not recorded*
	Do you intend to quit smoking completely in the next month?	Not recorded	Not recorded	Not recorded	Not recorded	Not recorded	*Not recorded*
	Rate the likelihood that you will quit smoking in the next 6 months	Not recorded	Not recorded	Continuous 10 CM VAS (10= maximum motivation)	Continuous 10 CM VAS (10= maximum motivation)	Continuous 10 CM VAS (10= maximum motivation)	*Not recorded*
	How much would you say you want to stop smoking	Categorical (not at all, a little, somewhat, a lot)	Not recorded	Not recorded	Not recorded	Not recorded	*Not recorded*
	How much does a part of you want to go on smoking?	Categorical (not at all, a little, somewhat, a	Not recorded	Not recorded	Not recorded	Not recorded	*Not recorded*

		lot)					
	Rate the likelihood that you will not be smoking in one year.	Not recorded	Not recorded	Continuous 10 CM VAS (10= maximum likelihood)	Continuous 10 CM VAS (10= maximum likelihood)	Continuous 10 CM VAS (10= maximum likelihood)	*Not recorded*
Intention to reduce	What is your personal goal in terms of cigarettes per day?	Continuous	Not recorded	Not recorded	Not recorded	Not recorded	*Not recorded*
	How motivated are you to reduce your smoking from current level?	Not recorded	Continuous 10 CM VAS (10= maximum motivation)	Not recorded	Not recorded	Not recorded	*Not recorded*
	Rate the likelihood that you will make a serious attempt to reduce your smoking during the next month.	Not recorded	Not recorded	Continuous 10 CM VAS (10= maximum likelihood)	Continuous 10 CM VAS (10= maximum likelihood)	Continuous 10 CM VAS (10= maximum likelihood)	*Not recorded*
	Rate the likelihood that you will reduce smoking by 50%.	Not recorded	Not recorded	Continuous 10 CM VAS (10= maximum likelihood)	Continuous 10 CM VAS (10= maximum likelihood)	Continuous 10 CM VAS (10= maximum likelihood)	*Not recorded*
	Rate the likelihood that one year from now, be smoking at least 50% less than what you are smoking now.	Not recorded	Not recorded	Continuous 10 CM VAS (10= maximum likelihood)	Continuous 10 CM VAS (10= maximum likelihood)	Continuous 10 CM VAS (10= maximum likelihood)	*Not recorded*
	How do you intend to change your smoking in the next month?	Not recorded	Not recorded	Not recorded	Categorical (stay quit, start smoking again,	Categorical (stay quit, start smoking again,	*Categorical (stay quit, start smoking again,*

					quit, reduce from current level, keep current level, increase from current level)	quit, reduce from current level, keep current level, increase from current level)	*quit, reduce from current level, keep current level, increase from current level)*
Smoking history	How old were you when you started smoking regularly	Continuous					*Not recorded*
	Longest period without smoking	Categorical (<1 week, 1week-1month, >1month-3 months, >3 months)					
	Times tried to quit smoking	Categorical never (once, 2 to 5 times, 6 to 10 times, more than 10 times)					
	How long time was the last time you tried to stop?	Categorical (0-6 months, >6-12months, >12 months)					
Mental health	SF-36 emotional well-being subscale	Continuous 0-100 (100=better health)					Not recorded
Smoking status	Co/ppm reading	Expired CO parts per million					
	How many cigarettes do you smoke a day as an average?	Continuous					
	Have you stopped smoking?	Binary (yes, no)					
Relief from craving questionnaire	Rate the feeling pepped up effects from your last cigarette	Categorical (not at all, mild, moderate, strong, very strong)					*Not recorded*
	Rate the calming effects from your last cigarette.	Categorical (not at all, mild, moderate, strong, very strong)					*Not recorded*
	What best applies to you experience from your latest	Categorical (very unpleasant, somewhat unpleasant, neutral, somewhat pleasant, very pleasant)					*Not recorded*

	cigarette?						
	Rate the frequency of urges to smoke.	Not recorded	Continuous VAS 10=max effect	Continuous VAS 10=max effect	Continuous VAS 10=max effect	Continuous VAS 10=max effect	*Not recorded*
	Rate the strengths of urges to smoke.	Not recorded	Continuous VAS 10=max effect	Continuous VAS 10=max effect	Continuous VAS 10=max effect	Continuous VAS 10=max effect	*Not recorded*
	Rate the satisfaction from smoking.	Not recorded	Continuous VAS 10=max effect	Continuous VAS 10=max effect	Continuous VAS 10=max effect	Continuous VAS 10=max effect	*Not recorded*
	Rate the unpleasant symptoms from your last cigarette	Categorical (not at all, mild, moderate, strong, very strong)	Not recorded	Not recorded	Not recorded	Not recorded	*Not recorded*
Adverse events	Description/code	Brief description and World Health Organization code	Brief description and World Health Organization code	Brief description and World Health Organization code	Brief description and World Health Organization code	Brief description and MedDRA 5.1 code	*Brief description and MedDRA 5.1 code*
	Start date	Day/month/year					

*VAS= visual analogue scale

[1]Reason for exclusion explained in section 3.5.2

Please note: to ensure participant anonymity McNeil pharmaceutical could not supply education, income, ethnicity and marital status data.

3.5. About the trials

3.5.1. Study design

Data were originally collected during randomised controlled trials (RCT), with multiple follow-ups over a two year period (see Table 3.2 for follow-up points). The original reports of the five double-blind placebo-controlled RCTs of NRT for smoking reduction have been previously reported or published (Batra et al., 2005; Bolliger et al., 2000; Haustein, 2001; Rennard et al., 2006; Wennike et al., 2003). Smoking reduction is a harm-reduction approach to nicotine dependence, in which smokers aim to reduce their daily cigarette consumption. These trials were aimed at people who have found it hard to quit previously, those who wanted to cut-down to quit, or those who wanted to permanently reduce their smoking (Table 3.2).

3.5.2. Trials' variables

Table 3.1 presents the variables which were recorded within each trial. To protect participants' anonymity McNeil did not provide ethnicity, education or income data. Most variables were recorded consistently across trials, some trials' recorded a few variables differently from one another (i.e. one trial recorded variables as continuous, where as another trial recorded the same variable as dichotomous), and some trials' did not record the same variables as other trials'. For the analyses presented in Chapters Four to Six the following data were required to ascertain outcome, exposure and confounding: Age, sex, nicotine

dependency, treatment received, smoking status, SF-36, adverse events. Other variables such as smoking behaviour and history, and intention to quit were also were relevant (discussed in section 4.3.4). Trial 6 was excluded from all analyses because the study did not record participants' SF-36 scores.

3.5.3. Trials' measurement of smoking and mental health

Smoking status — Participants' self-reported, seven-day point-prevalence smoking status was recorded at every follow-up throughout the trials' study periods (See Table 2.1 for follow-up points). Self-reported smoking was biologically validated using expired carbon monoxide (CO) readings of ≥10 parts per million (ppm), and self-reported cessation was biologically validated at CO/ppm <10.

Mental health — The RAND-36/SF-36 is a short form self-report questionnaire designed to detect changes in physical and mental health status. This study used the "emotional wellbeing" subscale to assess mental health. Scores range from 0 to 100. Scores of ≤38 indicate presence of mental health problem (Hays et al.,1993; 1998).

Adverse events — During each trial's duration, newly occurring psychiatric symptoms were recorded at each visit during assessment of potential adverse events. Research staff recorded a brief description of the event or symptoms and coded the symptoms according to terms provided by a regulated dictionary (see Table 3.1).

3.5.4. Settings

These trials were conducted between 1997 and 2003 and each trial lasted about two years, on average. The trials were conducted in medical centres within each trial's home country. Baseline and follow-up data were collected at both common and different time points (Table 3.2).

3.5.5. Interventions

Each trial used a slightly different multi-component intervention for smoking reduction (Table 3.2). NRT was prescribed to help smokers reduce their daily cigarette consumption (CPD) and the trials differed in the dose and delivery of NRT (i.e. gum or inhaler). Participants were randomised to receive either active or placebo treatment. Both active and placebo groups received behavioural advice to reduce their cigarette consumption, with no mood management advice. In each trial, participants were asked to reduce their CPD as much as possible, there were no agreed reduction goals (e.g. reduce 50% of baseline intake), however participants were advised about possible ways to achieve this, such as; increased interval between cigarettes, longer time to first cigarette in the morning and removal of habitual cigarettes. Smoking cessation was recommended as the ultimate goal, but was not mandatory. The trials reported a moderate effect of NRT on smoking reduction (Batra et al., 2005; Bolliger et al., 2000; Haustein, 2001; Rennard et al., 2006; Wennike et al., 2003).

3.5.6. Ethics and data protection

Each trial received ethical approval from the appropriate bodies within the country it was conducted. For the analyses presented in the thesis all data were anonymized, were accessible only by the named authors and were kept on encrypted computers. To ensure participant anonymity, data pertaining to ethnicity, education, income and marital status could not be provided.

Table 3.2 Trial and population characteristics

Population	Setting	Age M(SD)	FTND M(SD)	% Male	Year (enrolment to final follow-up)	Number enrolled after screening	Treatment	Control treatment	Comparison treatment	Follow-up periods (weeks)	Where biological data were analysed	Data collected by
Trial 1 Switzerland												
General	Hospital outpatient clinic	46.0 (10.5)	5.5 (2.1)	47.5 %	1997 to 1999	400	10mg nicotine oral inhaler plus behavioural advice to reduce smoking at each visit. Participants did not receive advice to quit.	Placebo inhaler	N/a	Baseline, 1, 2, 6, 13, 18, 26, 52, 78, 104	Bio-analytical research corporation Ghent Belgium Laboratories	Study nurse
Trial 2 Denmark												
General	Hospital outpatient clinic	43.8 (10.0)	6.4 (1.8)	37.7 %	1999 to 2001	411	2 or 4 mg nicotine gum for up to 12 months plus moderate behavioural smoking reduction information at each visit. Participants did not	Placebo gum	N/a	Baseline, 2, 10, 18, 26,	Pharmacia AB, Consumer	Study nurse

							receive advice to quit.			39, 52, 104	Healthcare, Helsingborg, Sweden.	
Trial 3 Australia												
General	Hospital outpatient clinic	43.6 (11.1)	6.5 (2.0)	45.4 %	1999 to 2001	436	2 or 4 mg nicotine gum plus advice to reduce smoking for up to 12 months plus behavioural smoking reduction information at each visit. Participants did not receive advice to quit.	Placebo gum	N/a	Baseline, 2, 6, 10, 18, 26, 39, 52, 65	Pharmacia, Consumer Healthcare, Helsingborg	Study nurse
Trial 4 US												
General	Hospital outpatient clinic	45.0 (12.2)	6.5 (2.0)	44.9 %	1999 to 2000	434	10mg nicotine inhaler plus some advice to reduce smoking. Participants did not receive advice to quit.	Placebo inhaler	N/a	Baseline, 2, 6, 10, 18, 26, 39, 52, 65	Pharmacia, Consumer Healthcare in Helsingborg	Investigator and study nurse
Trial 5 Germany												

General	Hospital outpatient clinic	41.3 (9.4)	5.5 (1.9)	50.1 %	2000 to 2001	385	4mg nicotine gum plus advice to reduce smoking gradually. Participants did not receive advice to quit.	Placebo gum	10mg nicotine oral inhaler plus advice to reduce quickly, and to quit smoking within four weeks	Baseline , 2, 6, 10, 18, 26, 39, 52	Not reported	Study nurse
***Trial 6 Switzerland (excluded from analyses)*[1]**												
General	*Hospital outpatient clinic*	*42.6 (10.1)*	*5.8 (1.9)*	*41.6 %*	*2001 to 2003*	*364*	*4mg nicotine gum plus behavioural advice to reduce smoking at each appointment. Participants did not receive advice to quit.*	*Placebo gum*	*N/a*	*Baseline , 2, 6, 10, 18, 26, 39, 52*	*Phizer Helsingborg Sweden; Exhaled air CO was measured by use of a Bedfont Smokerlyzer .*	*Study nurse*

[1]Excluded as missing mental health outcome data (SF-36)
Fagerström Test of Nicotine Dependency (FTND)

3.5.7. Participants

The trials recruited adult smokers from the general population via newspaper advertisements and those enrolled did not receive any financial incentives for their participation. After screening for eligibility criteria (described ahead in Table 3.3), each trial enrolled between 350 and 450 smokers and these participants were followed-up several times over a period of one to two years. Participants were similar in age, sex and nicotine dependency (FTND); mean age range across trials was 41.3 to 46.1 years; 37.7% to 50.1% were male; and the nicotine dependency scores ranged from 5.5 to 6.5. Further participant characteristics are described in Table 3.2.

3.5.8. Inclusion and exclusion criteria

Each trial had similar inclusion (listed ahead) and exclusion criteria (reported in Table 3.3). There was some variation between trials' terminology used to describe inclusion criteria, however in essence, each trial aimed to recruit the same type of participants. Each trial included participants aged 18 and older, who smoked daily for at least three years and participants were biologically-validated as smoking. All participants wanted to reduce their smoking, were prepared to adhere to the trial protocol and provided informed consent.

Participants were excluded from the McNeil trials if they:

- Were currently using NRT, or partaking in a behavioural or pharmacological smoking cessation/reduction program;

- Were using any other nicotine containing products;
- Had unstable angina pectoris or myocardial infarction within three months before enrolment;
- Were pregnant, breastfeeding, or intended to be pregnant;
- Were under psychiatric care or taking medication which might interfere with the study;
- Had an alcohol or drug problem which may interfere with the study;
- Intended to quit smoking in the next month;
- Had any medical conditions deemed inappropriate for study entry by the responsible physician (US);
- Were living in a household where more than one member desired to participate in the study (US).

Table 3.3 Trials' inclusion criteria

Inclusion category	Inclusion criterion	Trial ID and country					
		Trial 1 Denmark	**Trial 2 Switzerland**	**Trial 3 Australia**	**Trial 4 US**	**Trial 5 Germany**	***Trial 6 Switzerland (excluded)***
Age	Aged 18 or older						
Cigarettes per day (CPD)	Smoked ≥ 15 CPD						
	Smoked at least ≥ 20 CPD						
Bio-verification	CO/ppm reading of 15 or more						
	CO/ppm reading of 10 or more						
Time as smoker	Had smoked for at least three years						
Attempt to stop smoking	Had failed a quit-attempt at least once in the last 12 months						
	Had failed a quit-attempt at least once in the last 24 months						
	Had failed a quit attempt at least once in the last 24 months, but not failed in the six months before the start of the trial						
Want to reduce smoking	Wanted to reduce their smoking with assistance of NRT						
	Want to reduce smoking at baseline						
	Likely to make an attempt to reduce smoking						
	Accept use of NRT for an extended period of time						
Adhere to protocol	Prepared to adhere to the trial protocol						
Informed consent	Willing to provide signed informed consent						
Understanding of trial	Able to understand the trial's objectives						

procedures	Possess the ability to read write and speak English		

Blue shading: Inclusion criteria required for entry to trial

[1]Trial 6 was excluded as it was missing mental health outcome data (SF-36)

3.5.9. Participant attrition

Table 3.4 presents the number of participants who provided smoking status data at each follow-up. The attrition rates from baseline to final follow-up ranged from 35% to 61%. Overall, the risk of attrition bias is high, although these attrition rates are similar to other RCTs of NRT for smoking interventions (Stead et al., 2012).

Table 3.4 Number of participants in each trial providing smoking status data

Trial ID	**After screening**	**6 month follow-up**	**1 year**	**% lost at final follow-up**
Trial 1	400	304	331	23%
Trial 2	411	189	175	57%
Trial 3	436	202	207	53%
Trial 4	434	232	171	61%
Trial 5	385	196	213	47%
Trial 6 (excluded)	*362*	*213*	*219*	*39%*
TOTAL (N=5)	**2066**	**1123**	**1097**	**47%**

3.6. Risk of bias across trials

Each prospective observational analysis presented in Chapters Four to Six will include a different set of exposure, outcome and cofounding variables; therefore each analysis (Chapters Four to Six) will be separately assessed for risk of bias using the Newcastle-Ottawa Scale (Wells et al., 2010).

3.7. Chapter summary

Five McNeil trials were conducted according to strict protocols and had consistent inclusion and exclusion criteria. Data required to ascertain exposure, outcome and confounding variables for the prospective analyses in the thesis were measured in the same manner across trials. Trial 6 was excluded as it was missing mental health outcome data. Any differences between the way in which variables were recorded will be addressed within the subsequent chapters, where applicable.

CHAPTER FOUR

4. THE ASSOCIATION BETWEEN SMOKING CESSATION AND CHANGE IN MENTAL HEALTH: A COMPARISON OF REGRESSION MODELLING AND PROPENSITY SCORE MATCHING

4.1. Introduction to Chapter Four

The results in Chapter Two showed that stopping smoking was associated with improvements in mental health, critics however countered that selection bias or unmeasured confounders were possible explanations of the findings (Sanderson et al., 2014). Thus in this chapter I will address these possibilities by conducting a prospective analysis of the McNeil trials data to examine the association between smoking cessation and change in mental health and compare estimates derived from regression modelling with those derived from propensity score matching. Although propensity score matching reduces the sample size and leads to greater imprecision, it offers more potential for controlling group membership bias and confounding. This chapter has been summarised and is currently under peer review for publication in the British Journal of Psychiatry (please see Appendix 13).

4.2. Background

As discussed previously (section 1.4) many smokers continue smoking because they believe smoking offers mental health benefits. However, this is not consistent with data presented in Chapter Two, in which a systematic review and meta-analysis found consistent evidence that sustained smoking cessation was associated with improved mental health compared with continuing to smoke (Taylor et al., 2014). This evidence supports the misattribution hypothesis (previously discussed in section 1.9.2), such that after sustained cessation the ex-smoker no longer experiences withdrawal-induced negative affect, thus leading to improvements in mental health compared with continuing to smoke. However, the study was of observational data and has been criticized for being susceptible to bias through unmeasured confounding or predisposition to group membership (Sanderson et al., 2014).

Ideally a randomised study would be used to determine if the association is a true cause-effect relationship. One of the studies in the review was a trial where participants were randomised to continue or to quit smoking (Dawkins et al., 2009) and results showed a modest benefit of cessation on mental health compared with continuing to smoke. However, allocating people to continue to smoke or remain abstinent is problematic, because some people will choose to stop regardless of allocation, while other cannot achieve abstinence. For example, in the study reported by Dawkins and colleagues (2009) only 31% of participants allocated to abstinence could achieve this, while 18% of the continue-smoking arm chose to stop smoking. Thus, selection to exposure group is a major threat to the validity of data reported in Chapter Two.

4.2.1. Multivariate regression versus propensity score matching modelling

Regression modelling is a common way to account for confounding in observational analyses, and aims to weaken the impact of confounding by adjusting for observed covariates. However, there are some downfalls to use of regression modelling in the context of smoking cessation and mental health. By use of "adjustment" the model is corrected based on the covariates' association with both exposure (quitting or continuing smoking) and outcome (change in mental health), thus adjustment makes assumptions about the linearity between the exposure and outcome variables. During assessment of smoking status and mental health this method of analysis may not be the most useful, as selection bias to exposure group is very probable (as discussed above in section 4.2).

Alternatively, propensity score matching (PSM) can be used to account for confounding in observational analyses. PSM involves matching individuals within a sample based upon characteristics which predict their propensity to belong to the exposure group. Accordingly, in this study, a propensity score is defined as a smokers conditional probability (odds) of quitting versus continuing smoking, given the observed confounders (Rosenbaum and Rubin, 1984). The use of PSM addresses some weaknesses indentified in regression models. Firstly, propensity scores predict exposure selection, without consideration of the outcome, thus, by balancing observed confounders between groups, the effect of selection bias can be reduced. Secondly, to predict exposure selection one can test a multitude of covariates for statistical importance therefore optimizing the matching criteria. Furthermore, one can examine the overlap of groups' propensity scores, to ensure that adequate matching is conducted within a common region. If there is sufficient overlap between groups' propensity scores, one can

estimate the average treatment effect, which incorporates the possibility of unknown confounding (Rosenbaum and Rubin, 1984).

Critics discount the validity of PSM compared with randomisation to control for unknown confounding (Freemantle et al., 2013). However, as noted above, in the case of smoking cessation and mental health, there is evidence that no randomised design is satisfactory or feasible because participants cannot conform to their allocated smoking status. In the case of PSM analyses, sensitivity of the association to unmeasured confounders can be estimated (Rosenbaum and Rubin, 1984) by comparing adjusted regression models between matched and unmatched samples, and this can be used to interpret the validity of the results (Stürmer et al., 2005), regression modelling alone cannot provide this information. PSM has been also criticised for confounding by indication, which commonly occurs when treatment and outcome are influenced by the expectation of prognosis (Viswanathan et al., 2014). This usually takes place when the participant is judged as less likely to respond to treatment due to an underlying condition. Thus, in this case confounding by indication may occur if a health professional does not recommend cessation treatment to a certain patient, because the professional feels cessation would not be appropriate in the patients' circumstances. Confounding by indication cannot be eliminated by PSM. However, in this analysis, participants were included and excluded based upon the same criteria, rather by than the judgment of a health professional, and furthermore participants were aiming to reduce cigarette consumption rather than quit. Therefore, confounding by indication is unlikely to be an issue in this study.

4.2.2. Study aims and hypotheses

To determine if there have been any studies which have used PSM to investigate the association between smoking cessation and mental health a literature search was conducted using a combination of search terms "cessation", "propensity score matching", "mental health". This search did not generate any studies which investigated the association between smoking cessation and change in mental health using PSM.

If improved mental health observed in quitters compared with continuing smokers presented in Chapter Two was influenced by group membership bias or other unmeasured confounding, effect estimates derived from PSM, in theory, should produce different results to estimates derived from regression modelling alone.

This study aimed to:

1. Estimate the strength of the association between cessation and change in mental health using an adjusted regression model;
2. Match quitters and continuing smokers on their conditional probability of achieving abstinence, using observed baseline variables;
3. Compare regression coefficients derived from the matched sample with those derived from the whole (unmatched sample).

4.3. Methods

4.3.1. Study design and setting

A prospective analysis of individual-level patient data derived from five RCTs of nicotine replacement therapy (NRT) for smoking reduction. These data were provided by McNeil pharmaceutical company as described in Chapter Three; and the trials were conducted separately in North America, Europe and Australia by research teams selected by McNeil pharmaceutical company.

4.3.2. Participants and study size

All participants were recruited via newspaper advertisements from the general population and were aged ≥18 years. Participants were included in the trials if they were daily smokers for at least three years, had biologically-validated smoking status at baseline and were motivated to reduce their smoking. Participants were followed up at multiple time points over a two year period. See Chapter Three for further details.

After screening for eligibility criteria there were 2066 participants enrolled in the trials. At baseline 2059 participants provided smoking status information. Nine-hundred-and-thirty-seven participants provided data at baseline, and six and 12 month follow-ups, of these, 757 completed carbon monoxide (CO) tests; 68 participants were validated as quit at both follow-ups (CO/parts per million (CO/ppm) <10) and 589 as smokers at both follow-ups (CO/ppm ≥10).

4.3.3. Aim 1: Determine the association between smoking cessation and change in mental health in the whole sample (unmatched)

Linear regression modelling was used to determine the difference in mental health at follow-up, with adjustment for baseline values, between smokers who quit and smokers who continued, this model was repeated with adjustment for covariates (Table 4.1). Variables were ascertained as described in the following sections ahead.

Table 4.1 Adjusted and unadjusted linear regression model for the whole (unmatched sample)

Predictor	Outcome	Adjustment
Smoking status	Mental health (SF-36) at 12 month follow-up	Baseline mental health
Smoking status	Mental health (SF-36) at 12 month follow-up	Baseline mental health, treatment status, FTND, Trial ID, sex and age

4.3.3.1. Exposure

Exposure was self-reported and biologically-validated, repeated point-prevalence (seven-day) smoking status at both six and 12 months. Quitters were biologically validated as quit (CO/ppm <10) at both time-points and smokers were biologically validated as smoking (CO/ppm ≥10) at both time-points (see Figure 4.1). Those who reported quit, but failed biological-validation were excluded, and those who reported smoking but failed biological-validation were also excluded from the analysis.

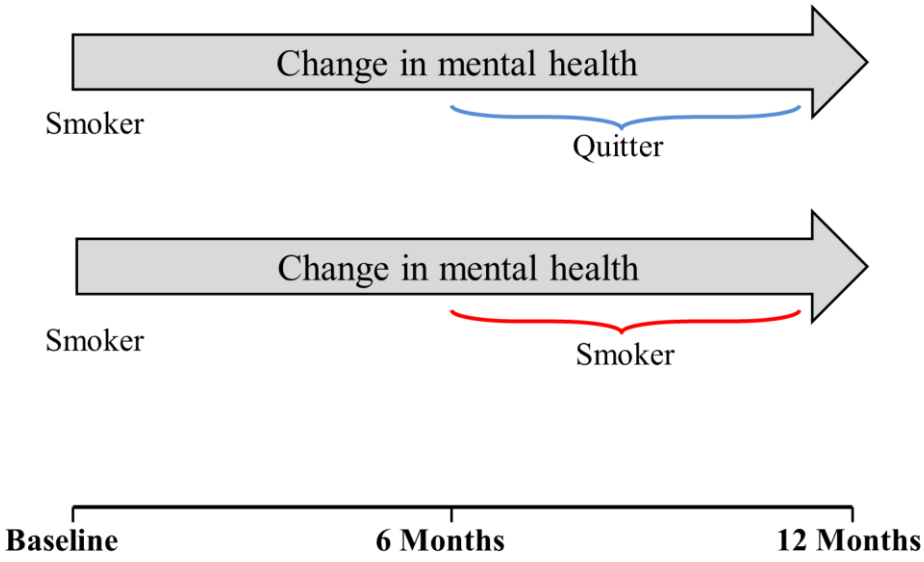

Figure 4.1 Timeframe for measurement of exposure and outcome variables

4.3.3.2. Outcome

Mental health was self-reported and measured using the RAND 36 item health survey 1.0. This scale is also known as the SF-36; however the RAND-36 uses slightly different scoring algorithms The RAND-36/SF-36 is a short form self-report questionnaire designed to detect changes in physical and mental health status. This study used the "emotional wellbeing" subscale to assess mental health. Scores range from 0 to 100 and a score of ≤38 indicates presence of a mental health problem (Hays et al., 1993; 1998). In the general population the subscale's mean and standard deviation are 70.4 (22.0). A minimally important difference on the emotional wellbeing subscale can be determined by effect size (standardised mean difference) between 0.09 and 0.28 equivalent to 2.0 to 6.2 points difference on the scale (Hays and Morales, 2001).

Outcome was change in mental health at 12 month follow-up, with adjustment for baseline values (Figure 4.1). Participants mean change scores were not used to measure change in mental health from baseline to follow-up, because of regression to the mean when using within-person, repeated measures data. Regression to the mean occurs when extreme measurements tend to be followed by measurements which are closer to the group mean (Barnett et al., 2005). Therefore, use of mean change scores can exaggerate extreme effects and compromise statistical precision. For these reasons, Vickers et al. (2001) suggest when using a regression model to compare change in a continuous outcome between two groups, follow-up scores should be adjusted for baseline values.

4.3.3.3. Confounding variables

The adjusted regression model (conducted using the whole sample) included nicotine dependency (FTND), treatment allocation (placebo or active), Trial ID, sex and age as covariates.

4.3.4. Aim 2: Match participants on propensity scores

A propensity score was calculated for each participant representing the conditional probability (odds) of quitting smoking (versus continuing to smoke), and was developed using observed baseline covariates found to predict repeated point-prevalence smoking status. PSM intended to balance the distribution of demographic, psychological and behavioural covariates between the groups (Rosenbaum and Rubin, 1983).

The McNeil trials were conducted in different countries, and this could introduce systematic differences between the participants if trial was not a matching criterion. In addition, while the measurement of some variables was consistent across trials, other measures differed by trial. Therefore to account for systematic differences between trials and to include as many baseline covariates as possible in the matching procedure, participants were matched within trials (see Appendix 1 for variables). The matching procedure is described in detail below.

4.3.4.1. Step 1: Determine which baseline covariates should contribute towards propensity scores

The following two methods were used to determine which covariates should be used to develop propensity scores.

Literature search — A literature search was conducted to find systematic reviews of characteristics which predict cessation success. A combination of the following search terms were used "cessation" "quit" "predict$" "success" "associa$" "characteristic$" "variable" "covariate". The search produced two major reviews[2]. Vangeli and colleagues (2011) systematically reviewed 17 prospective studies of adults, which aimed to examine predictors of achieving cessation. The review found that only nicotine dependency consistently predicted cessation success across studies. A review by the Cochrane group (Stead et al., 2012) pooled results from 111 RCTs comparing NRT with placebo/non-NRT control, and the results indicated that NRT increases success of quitting by 50% to 70%. Accordingly, nicotine

[2] Another review by Hitsman et al (2013) identified that depression history predicted failed cessation; however participants' depression history data were not available for these analyses.

dependence scores (FTND) (Fagerström et al., 1990) and NRT treatment status (active or placebo) were forced into propensity score models.

Logistic regression model — To determine which baseline variables predicted repeated point-prevalence smoking status, behavioural, psychological and demographic baseline covariates (Table 3.1 presents a detailed list of covariates) were entered into a forward stepwise logistic regression model, after forced entry of FNTD scores and treatment status. $P<0.10$ was used to determine entry into the model.

4.3.4.2. Step 2: Calculate participants' propensity scores

PSMATCH2 command in STATA 13 was used to calculate propensity scores (Leuven and Sianesi, 2003). Participants' propensity scores were estimated using a logistic regression (Rosenbaum and Rubin, 1984) in which smoking status was the outcome variable and baseline covariates (as identified during Step 1) were entered as the predictors. The estimated propensity score was the participants' predicted probability (odds) of achieving abstinence derived from the fitted regression model.

Participants' propensity scores were matched using 1:1 nearest neighbour matching, with no replacements, and matching was conducted within the common support region (see Step 3 ahead for further details about the common support region). Thus each participant in the quit group was matched to a single participant in the continuing smoker group with the closest estimated propensity score. Nearest neighbour 1:1 matching uses a greedy algorithm which sorts the observations in the quit group by their estimated propensity score, then matches each

observation sequentially to an observation in the continuing smoker group that has the closest propensity score, within the common support. Once a participant was matched, they were not re-entered into the algorithm.

4.3.4.3. Step 3: Model adequacy checks

The main PSM model was checked for adequacy using the following checks as recommended by Thoemmes and Kim (2011):

Checking covariate balance before and after matching — The propensity score model was checked to ensure that a balance of means and variances was achieved for covariates after matching (Thoemmes and Kim, 2011). The standardised differences were examined and T-tests were conducted to analyse distribution of covariates between groups, before and after matching.

The standardised % bias before and after matching was calculated to assess bias reduction. The standardised percent bias is the percent difference of the sample means in the quitters and continuing smokers (whole or matched sample), as a percentage of the square root of the average of the sample variances in each group. The achieved percentage of reduction in bias (Rosenbaum and Rubin, 1985) was calculated. After matching bias should be between 5% (Rosenbaum and Rubin, 1985) and 10% (Heinze and Juni, 2011) to determine an adequate model.

Common support — Matching was restricted within the common support region. The common support region is defined as the area in which the groups' propensity score distributions are commonly observed. If the overlap between the distributions is broad, this allows for causal estimates over the full range of propensity scores in the sample (King and Zeng, 2005). However, small common support regions restrict the estimation of a causal effect and can result in bias by changing the observed population (King and Zeng, 2005). This can be examined diagrammatically; plots of Kernel density estimations of groups' propensity scores were examined by group, before and after matching as recommended by Thoemmes and Kim (2012). Kernel density estimation is a non-parametric method of estimating the probability density function of a continuous variable.

4.3.5. Aim 3: Determine the association between smoking cessation and mental health in the matched sample

4.3.5.1. Linear regression modelling in the matched sample

Linear regression modelling was conducted in the matched sample to examine the association between smoking cessation and mental health. Exposure and outcome were ascertained in the same manner as discussed in sections 4.3.3.1 and 4.3.3.2, adjustment for confounding is discussed ahead. Linear regression modelling compared follow-up mental health scores between groups, with adjustment for baseline values (Table 4.2).

Confounding — Using the matched sample, the linear regression model was only adjusted for age and sex. The model was not adjusted for FTND and treatment allocation, because these

covariates were forced into propensity scores, nor was the model adjusted for Trial ID, as participants were matched within trials to account any systematic differences between trials.

Table 4.2 Linear regressions models conducted in matched sample

Predictor	Outcome	Adjustment
Smoking status	Change in mental health	Baseline mental health, sex, age

4.3.5.2. Main PSM model and sensitivity analyses

The trials measured key baseline variables consistently; however each trial also measured some variables in different ways. Therefore participants were a) matched within trials using all relevant variables (see Appendix 1 for variables), and in another model participants were b) matched across trials using variables which were measured consistently. Matching was repeated within or across trials, with and without common support restrictions, and regression coefficients were compared between the sensitivity models (See Table 4.3 for analysis breakdown).

Table 4.3 Analysis breakdown: PSM analyses and linear regressions conducted after matching

Primary or sensitivity analysis	Matching within or across trials	Within/without common support restrictions	Predictor	Outcome	Covariates
Primary	Within trials	Within common support	Smoking status	Mental health (SF-36)	Baseline mental health, sex, age
Sensitivity	Within trials	Without common support	Smoking status	Mental health (SF-36)	Baseline mental health, sex, age
	Across trials	Without common support	Smoking status	Mental health (SF-36)	Baseline mental health, Trial ID, sex, age
	Across trials	Within common support	Smoking status	Mental health (SF-36)	Baseline mental health, Trial ID, sex, age

The primary analysis is indicated by blue text

4.3.6. Clinically important change

A minimally clinically important difference on the SF-36 emotional well-being subscale is determined by an effect size (SMD) of 0.09 to 0.28 (Hays and Morales, 2001). To determine if the association between smoking cessation and mental health was a clinically important change the SMD was calculated using Cohen's *d* (Cohen, 1988). Cohen's *d* was calculated before and after matching, whereby the mean follow-up mental health score for smokers (x_2) was subtracted from that of quitters (x_1), and this difference was divided by the cohort's standard deviation (McGough and Faraone, 2009):

$$d = \frac{x_1 - x_2}{s}$$

4.3.7. Missing data

If participants were missing any relevant data they were excluded from the analysis. The number of participants excluded for missing outcome data are reported in the results.

4.3.8. Risk of bias

An adapted version of the Newcastle-Ottawa Scale was used to assess risk of bias in observational studies (Appendix 4). The measure rates studies on a scale of 1 to 5: 1 indicates a high risk of bias and 5 indicates a low risk of bias.

4.3.9. Ethics and data protection

Please see Chapter Three for details pertaining to ethics and data protection.

4.4. Results

4.4.1. Participants in the whole (unmatched) sample

In the whole sample 68 participants were biologically validated as quit at both six and 12 month follow-up, and 589 as smokers at both six and 12 month follow-up. Three smokers and one quitter were excluded due to missing baseline mental health scores. Twenty-six smokers were missing mental health data at 12 month follow-up and no quitters were missing mental health outcome data at follow-up. Smokers excluded for missing follow-up data had a M (SD) baseline SF-36 mental health score 74.0 (15.7), this was similar to the mean baseline score of included smokers 71.2 (17.5) and those excluded were psychologically healthy (scores of ≤38 indicate health problem (Hays et al., 1998)). After exclusion for missing mental health data, 67 participants were biologically validated as repeated point prevalence quitters and 560 biologically validated as repeated point prevalence smokers.

Table 4.4 Baseline characteristics of whole sample

	Smokers (N=560)	**Quitters (N=67)**	**Test of significance**	**P-value**
Age, M (SD)	45.6 (10.6)	46.2 (10.2)	T = –0.52	0.607
Sex, % male (N)	48% (258)	52% (35)	$Chi^2 = 0.42$	0.515
FTND, M(SD)	6.2 (1.9)	5.3 (2.5)	T = 3.42	0.0007
SF-36 Mental health, M (SD)	71.2 (17.5)	74.8 (13.6)	T = –1.64	0.101
Treatment status, % received active (N)	50% (280)	72% (48)	$Chi^2 = 11.42$	0.001

Table 4.4 displays baseline characteristics for smokers and quitters in the whole sample. There were significant baseline differences between the groups' FTND scores, and the proportion who received active treatment, there were no differences between groups' age, sex or baseline mental health.

4.4.2. Aim 1: Determine the association between smoking cessation and change in mental health in the whole (unmatched) sample

The first aim was to determine the difference in change in mental health from baseline to 12 month follow-up between smokers and quitters in the whole sample. Both groups showed an improvement in SF-36 mental health scores, and the improvement was greater in the quit group 4.90 (95% CI: 1.14 to 8.65) compared with continuing smokers 0.98 (-0.43 to 2.39) (Figure 4.2). SF-36 mental health outcome scores were compared between groups with adjustment for baseline mental health, and the mean difference was significant, 5.48 (95% CI: 1.62 to 9.35; $P<0.001$). After adjusting for FTND scores, trial ID, sex, age and treatment status the adjusted mean difference between groups remained significant, 4.50 (3.56 to 8.50; $P= 0.025$).

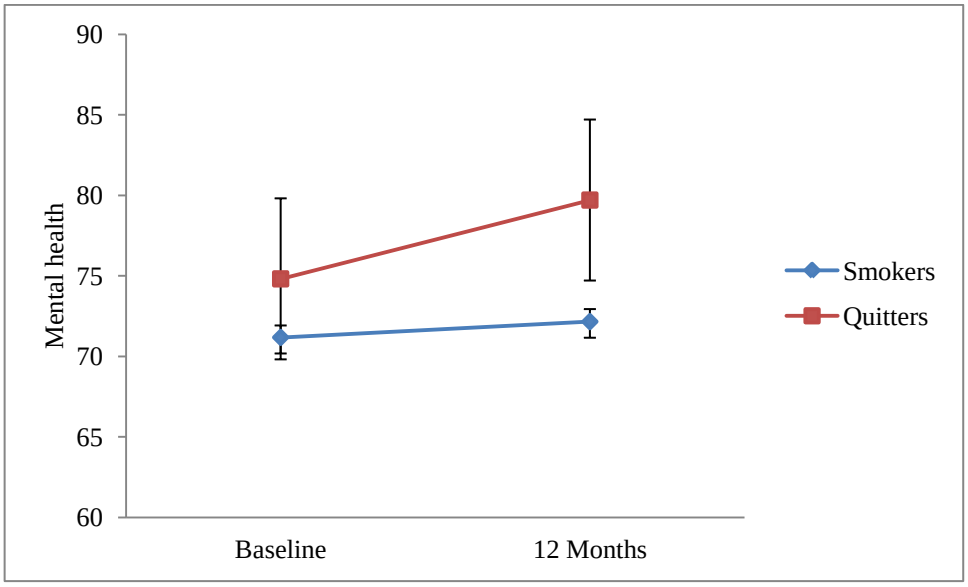

Figure 4.2 Means and standard errors: unmatched groups' change in mental health over time

4.4.3. Aim 2: Match participants on propensity scores

The first objective of the PSM procedure was to determine which covariates should be used to develop propensity scores. Covariates were selected based upon their association with smoking status, within each trial, after forced entry of FTND and treatment status. Table 4.5 presents odds ratios and 95% CIs for covariates which predicted cessation at the P<0.10 significance level. In the main PSM model the following baseline covariates were included in the propensity scores: FTND scores, NRT treatment status, age started smoking, report of calming effects from smoking, report of unpleasant symptoms from smoking, length of time to last cessation attempt, experience from last cigarette, longest period without smoking, SF-36 mental health (one trial) (Table 4.5).

Table 4.5 Main PSM model: Odds ratios and 95% CI for baseline predictors of smoking status at six and 12 month follow-up

Trial ID	Covariate	OR (quit=1)	95% CI	P-value
1	FTND (high score = more dependent)	0.52	0.36 to 0.74	<0.001
	NRT treatment (active=1)	0.41	0.09 to 1.86	0.25
	Age started smoking	1.38	1.18 to 1.62	<0.001
	Calming effect from smoking (high score = maximum effect)	2.15	1.15 to 4.00	0.016
	Number of unpleasant symptoms from smoking (more symptoms = higher score)	2.17	1.12 to 4.20	0.021
	Time to last cessation attempt	3.74	0.85 to 16.38	0.80
2	FTND (high score = more dependent)	0.87	0.59 to 1.27	0.460
	NRT treatment (active=1)	11.65	1.38 to 98.17	0.024
	Pleasant experience from last cigarette (high rating = maximum enjoyment)	2.36	1.0 to 5.41	0.043
3	FTND (high score = more dependent)	0.98	0.74 to 1.30	0.907
	NRT treatment (active=1)	3.06	0.77 to 12.14	0.112
	Longest period without smoking	1.87	1.07 to 3.26	0.028
4	FTND (high score = more dependent)	0.80	0.55 to 1.16	0.241

	NRT treatment (active=1)	2.91	0.50 to 16.79	0.232
5	FTND (high score = more dependent)	0.85	0.62 to 1.16	0.316
	NRT treatment (active=1)	6.07	1.75 to 21.05	0.004
	Pleasant experience from last cigarette (high rating = maximum enjoyment)	0.43	0.24 to 0.77	0.005
	SF-36 mental health (high score=better mental health)	1.05	1.01 to 1.09	0.021
	Age started smoking	0.77	0.59 to 1.00	0.046
	Age	1.07	1.00 to 1.15	0.043

4.4.3.1. Variables used to develop propensity scores in sensitivity models

Slightly different covariates contributed towards propensity scores in sensitivity models where participants were matched across trials. Table 4.6 displays a summary of the covariates used to develop propensity scores during matching across trials; the odds and 95% CIs for the association between these variables and propensity to quit are reported in Appendix 15. The covariates were similar to the main model, and baseline mental health did not predict smoking status in sensitivity models where participants were matched across trials.

Table 4.6 Which covariates are important predictors of smoking status in sensitivity models

	Kept in model at P<0.1 level	**Forced into regression**
Across Trials	Demographic, Intention to quit/reduce, Smoking history, CPD, Relief from smoking questionnaire	FTND, treatment status
Within Trials	Same as main analysis	

4.4.3.2. Main model adequacy checks

The main PSM model matched participants within each trial therefore adequacy checks were conducted within trials.

Checking covariate balance before and after matching — Means of variables entered into propensity scores were compared between groups, and were examined before and after

matching (presented in Appendix 16). In all cases, variables which were significantly imbalanced before matching became balanced after matching (Heinze and Juni, 2011; Rosenbaum and Rubin, 1985). No variables became significantly imbalanced after matching. The percent difference in bias between groups before and after matching was also examined (Appendix 16). In Trial 1, after matching, three (out of six) variables were adequately matched; in Trial 4, zero (out of two) variables were adequately matched; in Trial 5, three (out of six) variables were adequately matched. In Trials 2 and 3, after matching all variables were adequately matched (six out of six). In sum, matching led to a ≥90% reduction in bias for 13/20 variables. Please see Appendix 16 for further details.

Common support — The distribution of smokers' and quitters' propensity scores before matching were examined for a common support region (overlap in score distributions). Figure 4.3 shows the common support region was not large, but the overlap was sufficient for matching within common region. Figure 4.4 displays that smokers and quitters were predominately matched within a common region.

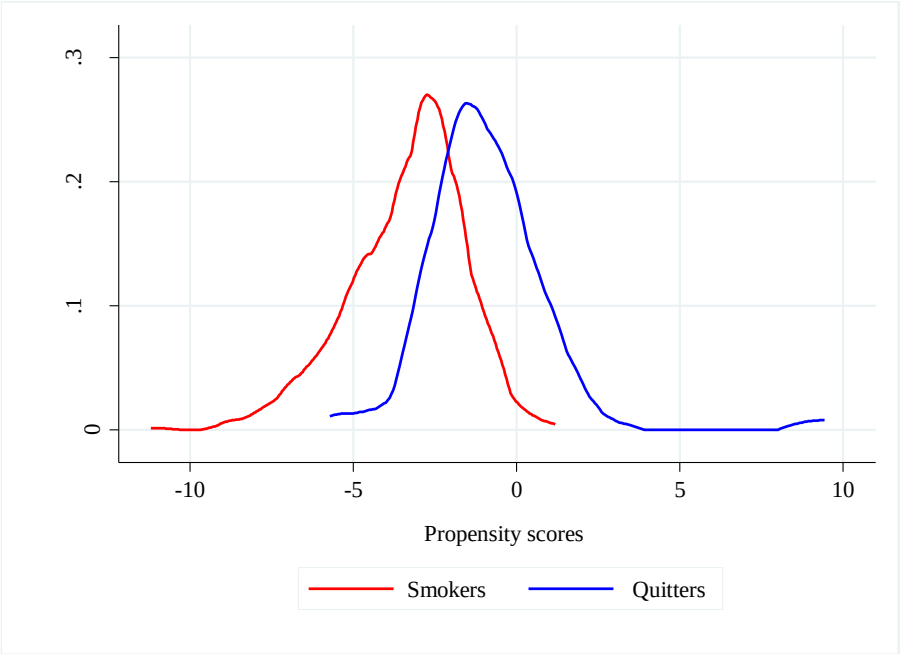

Figure 4.3 Overlay of Kernel density distributions of quitters' and smokers' propensity scores in the whole sample

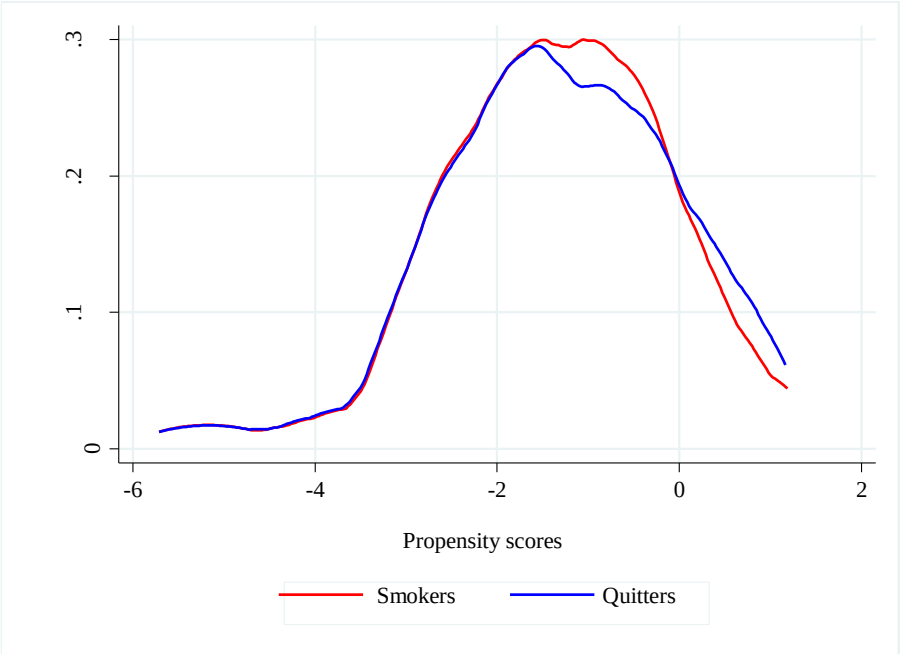

Figure 4.4 Overlay of Kernel density distributions of quitters' and smokers' propensity scores in matched sample

4.4.4. Aim 3: Compare the association between smoking cessation and mental health between matched and unmatched samples

4.4.4.1. Participants after PSM

The PSM model included 67 biologically validated continuous quitters who were matched to 67 smokers with similar propensity scores. Sixteen participants (12%), eight per matched sample, were lost as they did not fall within the common support. Those who were excluded for this reason had similar baseline mental health scores to those included, M (SD)s for excluded smokers were 77.0 (14.6) and 73.5 (16.4) for excluded quitters; FTND scores of excluded smokers were 4.0 (2.4) and 3.4 (1.9) for excluded quitters. Six excluded smokers and seven excluded quitters received active NRT. Thus, baseline data for those excluded due to common support restrictions were similar to baseline data of those included.

Table 4.7 Matched participants' baseline characteristics

Characteristic	**Smokers (N=59) M (SD)**	**Quitters (N=59) M (SD)**	**Test of significance**	**P-value**
Age	48.3 (10.4)	45.8 (9.0)	T=1.44	0.152
Sex (% male)	46%	53%	Chi^2= 0.54	0.461
FTND	5.6 (2.1)	5.6 (2.4)	T=0.04	0.968
SF-36 Mental health	77.5 (15.1)	75.0 (13.3)	T=0.95	0.340
Treatment status (% received active)	29%	31%	Chi^2=0.04	0.840

Table 4.7 displays baseline characteristics for smokers and quitters matched within the common support. In the whole sample there were significant differences between the groups' FTND scores and the number of people receiving active treatment (Table 4.4). After matching a balance between groups' baseline characteristics was reached.

4.4.4.2. Regression analysis after PSM

In the main PSM model participants were matched within trials and common support restrictions were used. Quitters showed an improvement in SF-36 mental health scores (mean change) 4.54 (95% CI: 0.35 to 8.74) and smokers displayed a slight worsening in mental health scores –0.23 (–4.75 to 4.34) (Figure 4.5). After adjustment for baseline mental health, age and sex the difference in outcome scores was not significant (B=3.37; 95% CI: –2.15 to 8.90; P=0.229). Similar to the adjusted mean difference in the unmatched sample (section 4.4.2), the change remained in favour of the quit group, but the estimate was no longer precise.

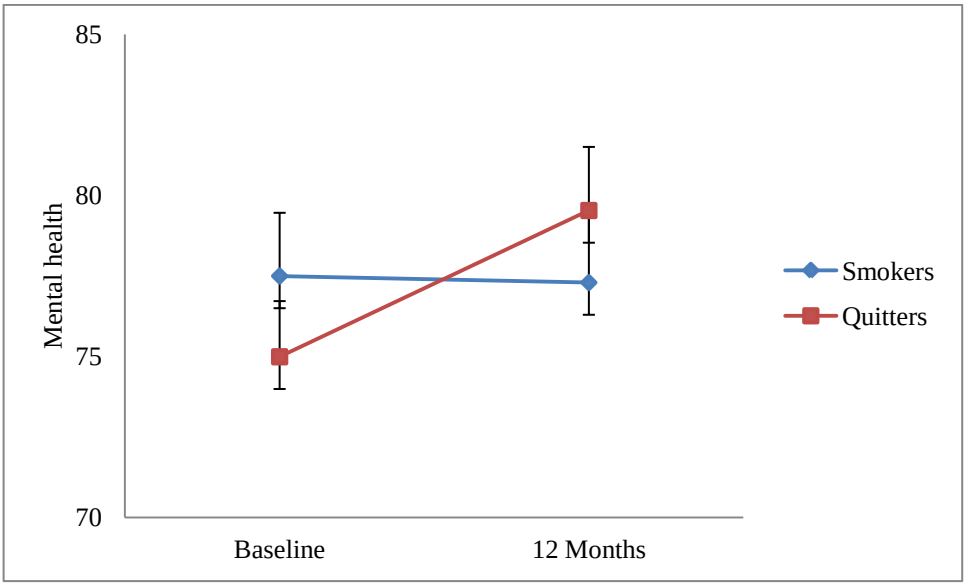

Figure4.5 Means and standard errors: matched groups' change in mental health over time

4.4.4.3. Main model and sensitivity models

Three additional PSM models (described in detail in Table 4.3) were conducted based on different methodological decisions, these included matching participants across trials, and matching without common support restriction. The association between stopping smoking and change in mental health was examined in these sensitivity models after adjustment for age, sex, baseline mental health and Trial ID, where applicable (Appendix 17). In each sensitivity model smokers and quitters presented balanced baseline mental health scores. At follow-up smokers' mean scores indicated either a slight improvement or slight worsening, and in all analyses quitters showed a moderate improvement in mental health. The adjusted mean differences (95% CI), ranged from, 3.97 (–1.00 to 8.93) to 3.55 (–1.29 to 8.40) (Appendix 17), suggesting the association observed was not influenced by any methodological decisions made.

4.4.5. Minimal clinically important difference

As described above, a minimally important difference on the SF-36 mental health subscale is indicated by an effect size (SMD) of 0.09 to 0.28 (Hays and Morales, 2001). The standardised effect size was *d*=0.42 (95% CI: 0.16 to 0.67) in the whole sample, after matching the effect estimate declined and became imprecise 0.14 (–0.22 to 0.50).

4.4.6. Risk of bias

The study's risk of bias was assessed using the Newcastle-Ottawa Scale, and scored 4/5, indicating a low risk of bias. The study lost one point because of high loss to follow-up (Appendix 18).

4.5. Discussion

4.5.1. Summary of key results

Regression modelling showed evidence that smoking cessation was associated with improved mental health compared with continuing smoking and this finding was not altered by adjustment for confounding. Propensity score matching offers potential to control group membership bias, as well as confounding. Using this technique a good match between smokers that continued smoking and those that stopped smoking was achieved. Doing so, the regression coefficient for the difference between smokers and quitters was similar to that achieved by regression methods alone, but it was no longer significant.

Comparison of the two statistical approaches shows that the regression analysis in the whole sample was more powerful, however there was more potential for bias. The regression analysis after matching participants on their propensity scores was less powerful, however there was less potential bias. The effect estimates were similar from both analyses giving confidence that the significant effect seen in the unmatched sample was less likely to be due to confounding.

4.5.2. Limitations, strengths and potential sources of bias

PSM is a valuable tool for causal inference in observational research, however it has its limitations and these will be addressed in relation to this study. Firstly, PSM is argued to balance unobserved confounding between groups (Rosenbaum and Rubin, 1983a; 1983b), however one cannot be completely certain this has been achieved, limiting inferences drawn from these findings. Secondly, there was a moderately sized common support region, and this somewhat restricts estimation of a causal effect, and may introduce bias by changing the observed population (King and Zeng, 2005). However, only 12% of quitters were lost, and those excluded did not differ on baseline characteristics compared with the remainder of the sample, and moreover estimates derived from models using common support restrictions were similar to those derived from models with no common support restrictions.

The size of the cohort was an obvious issue in this study as it gives rise to considerable imprecision. The largest analysis in the unmatched sample included 67 quitters, and the final matched analysis included 59 in each group, and this was not large enough to produce statistically significant evidence of a clinically important difference.

To ensure patient anonymity, demographic characteristics such as ethnicity, social class and education could not be used in analyses. These demographics are possible predictors of change in smoking status, however a recent systematic review did not find consistent evidence to support this (Vangeli et al., 2011). In support of this, adjustment for potential confounders such as age, sex and Trial ID (which accounts for country of participant), had only a small effect on the regression model. Importantly, the strongest predictor of mental health at follow-up is mental health at baseline (Asendorpf, 1992; Burns et al., 2014) and these analyses measured mental health change, within individuals using adjustment for baseline values. However, confounding via interactions between covariates may be a possibility.

There was significant loss to follow-up in the McNeil trials, although these rates were similar to other trials of NRT (Stead et al., 2012). The association between mental health and drop out is not clear and may bias the association. Studies in depressed individuals have found that worse baseline mental health was associated with dropout at follow-up (Bolam et al., 2011; Munoz et al., 1997), whereas another study found no association (Borrelli et al., 2002). Bias would only occur, however, if drop out differed by exposure group, which is not necessarily implied by drop out being associated with change in mental health.

4.5.3. Strengths of study

The strengths of this observational study lay in its ascertainment of exposure and outcome. Stringent criteria for assessment of exposure were adopted, therefore in this study there was a minimal chance of misclassification. Participants were biologically validated as either quit or smoking, at both follow-up periods. These are highly accepted evidence-based cut-off criteria (Hughes et al., 2003; West et al., 2005), and repeated point-prevalence is likely to produce results similar to those from a continuously abstinent group (Hughes et al., 2003; 2010), therefore exposure misclassification is unlikely to be an issue. The outcome mental health was measured using the RAND-36/SF-36 "emotional well-being subscale". This measure of mental health is psychometrically sound in general and clinical populations, is highly validated and sensitive to change (Hays et al., 1998; Hays and Morales, 2001). Secondly, risk of bias was assessed using a tool purposefully modified to rate studies which investigate the association between smoking cessation and mental health; the study's rating suggests a low risk of bias to the association.

Sensitivity analyses were examined to address heterogeneity in these data and bias from methodological decisions made. The association was examined after matching participants across and within trials, and after matching participants with and without common support restrictions. The association at its weakest, remained favourable for quitters.

4.5.4. Interpretation

As was the case in Chapter Two, there are three possible explanations for the association. The first is that smoking cessation improves mental health; the second is that improving mental health leads to cessation; and the third is that a common factor caused both improved mental health and cessation.

The third explanation, the common cause, would require that the common factor would have had to occur within the first six months of follow-up, be common across cultures (Europe, US and Australia), and have persisting effects on mental health that could be observed at the 12 month follow-up. There is no evidence that positive life events, for example, are associated with sustained cessation. The possibility of a single event leading to both cessation and improved mental health seems less plausible, particularly considering the evidence presented in Chapter Two, where improved mental health was seen nine years after cessation.

There is a plethora of data which support the notion that cessation improves mental health. Firstly, data in Chapter Two display consistencies in this association and through sensitivity analyses weaken reverse causation and confounding (Appendix 9). Furthermore, this notion is supported by a study in which participants were randomised to quit or continue smoking, which showed a modest benefit of cessation (Dawkins et al., 2009). Thus there is adequate evidence to support the notion that stopping smoking may likely lead to improvements in mental health. However, these trials were of people who wanted to reduce their smoking rather than quit smoking, thus these participants were not selected based on their desire to

stop. It is possible that mood improved from baseline to six months, which then initiated a cessation attempt[3]. Therefore, reverse causation is possible in this analysis.

4.5.5. Biological explanation

The notion that stopping smoking improves mental health is supported by a biological model (previously discussed in section 1.6). Chronic tobacco smoking is associated with neuroadaptations in nicotinic pathways in the brain (Benowitz, 1999; 2010; Mansvelder and McGehee, 2002; Wang and Sun, 2005), these changes induce a withdrawal cycle, and are marked by fluctuations in a smoker's psychological state throughout the day (Benowitz, 1999; 2010) and could worsen mental health (Parrott, 1999). It has been found that the neurological functioning of quitters returns to the same level as non-smokers at three weeks after cessation (Mamede et al., 2007), which is consistent with reports that psychological withdrawal symptoms subside after a few weeks (Hughes, 2007b). It is possible that smokers assume that because smoking alleviates these feelings, that smoking a cigarette has improved their mental health when in fact it was smoking that caused these problems.

4.5.6. Clinical implications

If the association is causal, then this study shows that the 'effect' of cessation on mental health is likely clinically important, although after reduction in sample size after PSM this estimate became imprecise, somewhat smaller, and of borderline clinical significance. These data should be used in conjunction with other observational studies and should reassure health

[3] This hypothesis could not be tested due to missing mental health data at six month follow-up.

care professionals and smokers that smoking cessation is not likely to cause psychological harm.

4.6. Conclusion

Overall, this study suggests that the association between smoking cessation and improved mental health was not altered by matching smokers and quitters on their propensity to achieve abstinence, therefore results derived from regression modelling alone are unlikely to be influenced by disposition to group membership or confounding. This study is in agreement with other data which suggest that cessation may lead to improved mental health, and is supported by a plausible biological pathway.

4.7. Chapter summary

The findings in Chapter Two may have been biased by group membership and unmeasured confounding. Therefore in this chapter the association between cessation and mental health was assessed using PSM to control for these biases and produce causal effect estimates. Estimates derived from PSM and regression modelling produced similar estimates compared to regression modelling alone, suggesting the findings were associated with cessation, rather than arising through other bias.

CHAPTER FIVE

5. ASSESSING THE ASSOCIATION BETWEEN SMOKING CESSATION AND ONSET OF PSYCHIATRIC DISORDER, USING PROPENSITY SCORE MATCHING

5.1. Introduction to Chapter Five

It has been suggested that after cessation some quitters' may experience psychiatric disorder as a result of cessation. If this hypothesis is true, analysis of means, as reported in Chapters Two and Four may have concealed the uncommon occurrence of psychiatric disorder. Therefore, this Chapter reports a secondary analysis of the McNeil trials, in which the association between smoking cessation and onset of psychiatric disorder is assessed by comparing risk-difference estimates between smokers and quitters, before and after using propensity score matching (PSM) techniques.

5.2. Background

It has been suggested that some psychological withdrawal symptoms from tobacco may display a permanent deterioration after cessation, known as an offset effect (Hughes, 2007a) (previously discussed in sections 1.6.3, 1.9.2 and 1.10.2). If an offset effect occurs, the level of symptom is abnormal and permanent. For example, if a quitter experiences an offset effect,

this would mean that become depressed as a result of cessation. Hughes (2007c) argues that there are two interpretations of the offset effect. Firstly, the person's mental health may have been poor before they began to use tobacco, and that tobacco use improved the symptoms of their disorder; this notion is supported by the self-medication hypothesis (Khantzian, 1997) (previously discussed in section 1.9.2). Another explanation is that the onset of disorder after cessation results from neuropsychological damage caused by chronic tobacco use (previously discussed in section 1.6).

Chapters Two and Four examined the difference in change in mental health between people who quit and people who continued smoking, these chapters displayed that stopping smoking was associated with improvements in mental health outcomes, and that continuing smoking was associated with little change (Figures 2.2, 4.2, and 4.5). If there were uncommon occurrences of psychiatric disorder, analysis of group means may have not revealed this (McCaffery and Elliott, 2008).

Three reviews (Banham and Gilbody, 2010; Hughes, 2007c; Ragg et al., 2013) and three other studies not reviewed elsewhere (Bolam et al., 2011; Sanchez-Villegas et al., 2008; Khaled et al., 2012) have examined risk of depression or anxiety after cessation, or other psychiatric symptoms (all reviews and studies previously discussed in detail in section 1.10). In summary, the findings from these reviews and studies are mixed, some suggest that cessation was not associated with risk of depression, anxiety or other disorders in psychiatric or general populations (Banham and Gilbody, 2010; Bolam et al., 2011); one review reports cessation was linked to increased risk of depression in smokers with depression history (Hughes, 2007c); another review suggests cessation was associated with a possible risk of depression in

those with depression history (Ragg et al., 2013), whereas other studies report cessation was associated with decreased risk of depression in the general population (Khaled et al., 2012; Sanchez-Villegas et al., 2008). In most of these studies attrition was a problem, with one study showing some evidence that depressed people were more likely to drop-out (Bolam et al., 2011) and in population cohort studies ascertainment of outcome was not strong. Another major problem within these studies is the risk of group membership bias, which is a likely source bias in observational studies of quitters and smokers, but also in randomised designs (as previously discussed in sections 1.10, 2.5 and 4.2.1).

5.2.1. Study aims

No previous study has used propensity score matching (PSM) to address group membership bias when investigating the association between cessation and risk of psychiatric disorder (as assessed by literature review reported in section 4.2). Therefore in this chapter the association between smoking cessation and risk of psychiatric disorder was assessed by comparing risk estimates derived from the whole sample with estimates derived from a sample matched on their propensity to achieve abstinence. This study aimed to:

1) Determine the risk of psychiatric disorder onset during a six month period after cessation compared with continuing smoking during the same period;
2) Calculate propensity scores for quitters and continuing smokers using observed baseline covariates;
3) Recalculate the risk difference in the matched sample.

5.3. Methods

5.3.1. Study design

A prospective observational analysis of individual level patient data derived from the McNeil trials (see Chapter Three for further trial details).

5.3.2. Setting

The trials' settings have been previously reported in sections 3.5 and 4.3.1 to 4.3.2.

5.3.3. Participants and study size

Participant characteristics have been previously reported in sections 3.5 and 4.3.2. After screening there were 2066 participants enrolled in the trials. At baseline 2059 participants provided smoking status information, of these, 937 participants provided smoking data at both six and 12 month follow-ups. Sixty eight participants were biologically-validated as repeated point-prevalence (seven day) quitters (carbon monoxide/parts per million (CO/ppm <10) and 589 as repeated point-prevalence smokers (CO/ppm ≥10).

5.3.4. Variables

5.3.4.1. Exposure

Exposure was self-reported and biologically-validated, repeated point-prevalence (seven-day) smoking status at both six to 12 months. Groups were biologically-validated as quit (CO/ppm <10) or smoking (CO/ppm ≥10). Those who failed biological-validation were not included in this analysis.

5.3.4.2. Outcome

Outcome was onset of psychiatric disorder between six and 12 month follow-up points, during which time repeated point-prevalence cessation or continued smoking was self-reported and biologically-validated (Figure 5.1).

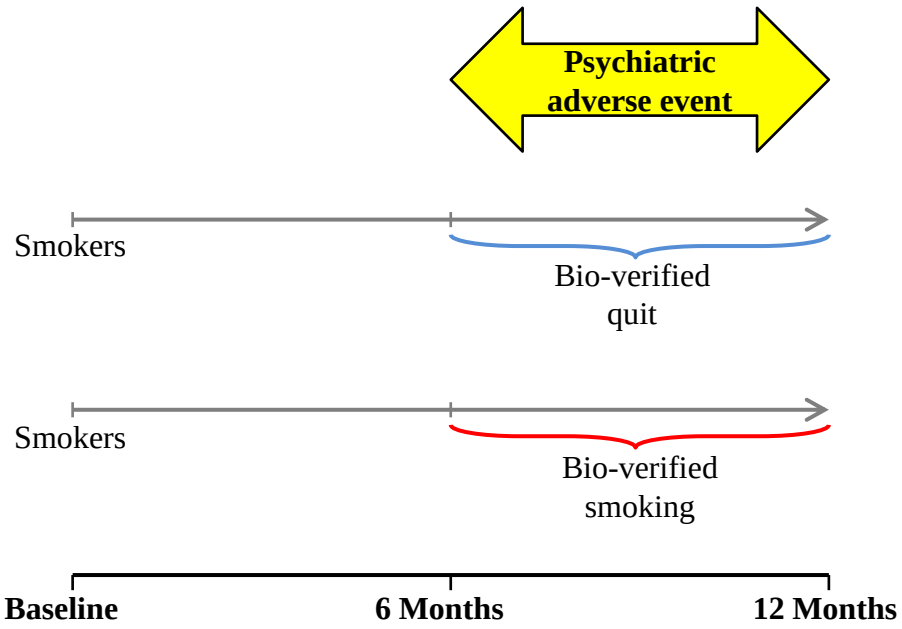

Figure 5.1 Timeframe for measurement of exposure and outcome variables

Psychiatric disorder was ascertained by coding each trial's adverse event data according to the MedDRA database (version 16.1) (Medical Dictionary for Regulatory Activities, 2013). MedDRA is an internationally used set of terms relating to medical conditions and was purposely designed to assist clinicians and researchers communicate medical information, including adverse event data. The trials' adverse event data comprised of brief descriptions and key terms recorded by trial researchers (previously discussed in section 3.5). Each adverse event key term was entered into the MedDRA 16.1 online database to determine its classification according to the 'Lowest Level Term' (i.e. symptom). Adverse events were considered to be psychiatric if the 'Lowest Level Term' mapped on to the classification of 'Psychiatric Disorder'. The corresponding 'High Group Level Term' (e.g. 'mood disorders') was recorded to determine the type of disorder. There were no cases where a 'Lowest Level Term' could be classed under two different psychiatric disorders. If the 'Lowest Level Term'

fell under two ‘System Organ Classes’ (i.e. Psychiatric conditions) PA and GT read the adverse event description in detail to decide if the event was likely to be psychiatric-related or otherwise. Any remaining key terms which did not meet ‘Psychiatric Disorder’ criteria were coded as ‘No psychiatric disorder.’ GT and PA were blinded to participants’ smoking status.

5.3.5. Risk of bias

An adapted version of the Newcastle-Ottawa Scale was used to assess risk of bias in observational studies (Appendix 4). The measure rates studies on a scale of 1 to 5: 1 indicates a high risk of bias and 5 indicates a low risk of bias.

5.3.6. Statistical methods

5.3.6.1. Calculation of difference before and after PSM

To assess the association between smoking cessation and onset of psychiatric disorder, the risk of psychiatric disorder was compared between quitters and continuing smokers, by calculating Pearson’s Chi^2 and the risk-difference in the whole (unmatched) sample. To see if the association was altered by use of PSM McNemar’s Chi^2 and risk difference were calculated after matching participants on their propensity scores.

5.3.6.2. Propensity score matching procedure

Matching participants on their propensity to quit aims to balance the distribution of demographic, psychological and behavioural characteristics between quitters and continuing smokers (Rosenbaum and Rubin, 1984). The PSM procedure and methods were previously described in detail in section 4.3.4. Each participant's propensity score was developed using covariates which were identified as important predictors of achieving abstinence (previously reported in section 4.3.4.2). The analyses described in this Chapter used the same PSM models as described in Chapter Four.

5.3.6.3. Primary model and sensitivity analyses

To determine if the results were influenced by heterogeneity between trials measurement of variables or by methodological decisions made, three additional PSM models were developed (outlined in Table 4.3). In these models, participants were matched either within or across trials, and models were repeated with and without common support restrictions (previously discussed in section 4.3.5.2), estimates derived from these sensitivity models were compared with those derived from the main PSM model.

5.3.6.4. Adequacy checks

All methods used to determine model adequacy were previously reported in section 4.3.4.3.

5.3.6.5. Missing data

If participants were missing data they were excluded from the analysis. The number of participants excluded for missing data and corresponding missing information is reported in the results.

5.3.6.6. Post-hoc power

To determine the study's achieved power at the $p<0.05$ significance level a post-hoc power calculation was made using a standard formula (e.g. Rosner, 2011).

5.3.7. Ethics and data protection

Please see Chapter Three for details pertaining to ethics and data protection.

5.4. Results

5.4.1. Participants in the whole (unmatched) sample

The study included 68 participants biologically validated as repeated point-prevalence (seven day) quitters and 589 as repeated point-prevalence smokers. No smokers or quitters were missing outcome data. Table 5.1 displays baseline characteristics for smokers and quitters,

there were significant differences between the groups' nicotine dependency scores (FTND) and the proportion receiving active nicotine replacement treatment (NRT).

Table 5.1 Baseline characteristics of whole sample

Characteristic	Smokers (N=589)	Quitters (N=68)	Test of significance	P-value
Age	45.6 (10.6)	46.2 (10.2)	T = –0.52	0.607
Sex, % male (N)	48% (283)	52% (35)	Chi^2= 0.42	0.515
FTND	6.2 (1.9)	5.3 (2.5)	T = 3.42**	0.0007
SF-36 Mental health	71.2 (17.5)	74.8 (13.6)	T = -1.64	0.101
Treatment status, % received active (N)	50% (295)	72% (49)	Chi^2=11.42**	0.001

Table 5.2 shows that quitters did not report any incidences of psychiatric disorder between six and 12 month follow-ups. In the smoking group, there were seven cases of depressed mood disorders and disturbances, and three cases of anxiety disorders and symptoms between six and 12 month follow-ups. There were no cases of any other type of disorder (e.g. schizophrenia) during this six month period.

Table 5.2 Frequency of onset of psychiatric disorder during biologically-validated smoking or quit period		
MedDRA 16.1 High level group term	**Smokers (N=589)**	**Quitters (N=68)**
No psychiatric disorder	579	68
Anxiety disorders and symptoms	3	0
Changes in physical activity	0	0
Depressed mood disorders and disturbances	7	0
Manic and bipolar mood disorders and disturbances	0	0
Mood disorders and disturbances not elsewhere classified	0	0
Personality disorders and disturbances in behaviour	0	0
Psychiatric disorders not elsewhere classified	0	0
Schizophrenia and other psychotic disorders	0	0
Sleep disorders and disturbances	0	0
Somatoform and factitious disorders	0	0
Suicidal and self-injurious behaviours not elsewhere classified	0	0

5.4.2. Pearson's Chi^2 and risk difference in whole (unmatched sample)

Pearson's Chi^2 and risk difference were calculated to determine the difference in risk of onset of psychiatric disorder, between continuing smokers and quitters. Ten (1.7%) smokers and zero quitters reported evidence of a psychiatric disorder between six and 12 month follow-up, the risk difference between groups was not significant, -0.017, P=0.28 (Table 5.3). The confidence intervals for this estimate were unreliable as they do not take in to account zero variability in risk in the quit group.

Table 5.3 Risk difference of onset of psychiatric disorder during biologically-validated smoking or quit period in the whole sample		
	Smokers (N=589)	**Quitters (N=68)**
No psychiatric disorder reported	579	68
Psychiatric disorder reported	10	0
Risk	0.017	0
Risk difference (95% CI)	-0.017 (-0.03 to -0.01)*	
Pearson Chi^2	1.17	
P-value	0.28	
* The confidence interval is unreliable as it does not take in to account zero variability in risk in the quit group.		

5.4.3. Propensity score matching results

Matching variables and model adequacy were previously reported in section 4.4.3.

5.4.4. Participants after PSM

The PSM analysis included 68 repeated point-prevalence quitters, who were matched to 68 smokers with similar propensity scores. Sixteen participants, eight per group could not be matched within the common support. Quitters who were excluded for this reason presented similar baseline characteristics to included quitters (Table 5.4); the mean (SD) mental health score (SF-36) of excluded quitters was 71.4 (15.2), mean FTND score was 3.9 (2.0) and all received active NRT. Smokers who were excluded for this reason also had similar baseline characteristics compared with included smokers (Table 5.4); the mean (SD) mental health score for excluded smokers was 77.0 (14.6); Mean FTND scores was 4.1 (2.4), and 6 excluded smokers received active NRT.

Table 5.4 displays baseline characteristics for smokers and quitters matched within the common support. Before PSM there were significant differences between the groups' FTND scores and the proportion of people receiving of active treatment (Table 5.1), after matching, groups' baseline characteristics became balanced.

Table 5.4 Baseline characteristics in matched sample

Characteristic	**Smokers (N=60) M(SD)**	**Quitters (N=60) M(SD)**	**Test of significance**	**P-value**
Age	48.0 (10.7)	46.0 (8.8)	T = 1.11	0.2674
Sex, % male (N)	48% (29)	53% (32)	$Chi^2 = 0.30$	0.584
FTND	5.5 (2.2)	5.5 (2.5)	T = 0.12	0.9073
SF-36 Mental health	76.9 (15.1)	75.2 (13.4)	T = 0.63	0.5244
Treatment status, % received active (N)	73% (44)	68% (41)	$Chi^2 = 0.36$	0.547

5.4.5. McNemar's Chi^2 and difference after PSM

McNemar's Chi^2 and risk difference were calculated to determine the difference in risk of psychiatric disorder between six and 12 month follow-ups, between matched groups. In the matched sample, one smoker (1.7%) (depressed mood disorder) and no quitters reported evidence of a psychiatric disorder during this period. The risk difference between matched groups was not significant, -0.017, P = 1.0 (Table 5.5), and the results were very similar to

those calculated from the whole sample (Table 5.3). The confidence intervals for this effect were unreliable as they do not take in to account zero variability in risk in the quit group.

Table 5.5 Risk difference of onset of psychiatric disorder during biologically-validated smoking or quit period in the matched sample

	Smokers (N=60)	**Quitters (N=60)**
No psychiatric report	59	60
Psychiatric AE report	1	0
Risk difference (95% CI)	-0.017 (-0.07 to 0.03)*	
McNemar's Chi^2	1.00	
P-value	1.00	
* The confidence interval is unreliable as it does not take in to account zero variability in risk in the quit group.		

5.4.6. Model adequacy checks

Model adequacy checks were previously reported and discussed in section 4.4.3.2.

5.4.7. Sensitivity analyses

Matching participants across trials resulted in zero psychiatric diagnoses between six and 12 month follow-up in both groups, therefore differences could not be calculated. Matching participants within trials resulted in a maximum of three diagnoses (all depressed mood disorders) in the continuing smoker group, and none in the quit group. Sensitivity analyses

displayed that the estimates were all non-significant and ranged from -0.017 to -0.030 indicating a slightly elevated risk for continuing smokers (Appendix 19).

5.4.8. Risk of bias

Risk of bias was assessed using the Newcastle-Ottawa Scale and this study received 4/5 stars indicating a low risk of bias (Appendix 20). The study lost one point because of high attrition.

5.4.9. Post-hoc power

This study achieved 0.5% power to detect significant differences at the $p<0.05$ level. Therefore a sample size of 3076 per arm would be required to detect a difference of 1.5% to 2.5% between exposure groups, with 80% power.

5.5. Discussion

In this study of smokers from the general population, no one who stopped smoking reported onset of psychiatric disorder six months following cessation. By contrast, several people who continued to smoke did so, resulting in an estimate of a higher risk in continuing smokers compared with quitters, this estimate was not altered by use of PSM within-trials. However, the results in this study were inconclusive and the study was not adequately powered to detect statistical significance.

The findings of this study were not likely to be influenced by methodological decisions, as assessed during sensitivity analyses. Our primary model matched participants within trials to increase the number of characteristics that were matched, including variables that would be difficult to adjust for in regression models, such as country. Our model also used common-support restrictions to ensure that participants' propensity scores fell within the same distributions. Most importantly this model matched participants on emotional-wellbeing where it was found to predict group membership. This model was least susceptible to bias and was therefore used as the primary model.

However, in sensitivity analyses where participants were matched across trials this resulted in zero psychiatric diagnoses in both quitters and smokers between six and 12 month follow-up, this is likely to be the result of inadequate sample size required to detect a true incidence of psychiatric disorder. Furthermore, the results of these sensitivity analyses were influenced by matching participants on fewer covariates, and by matching participants across trials participants from different countries were matched with one another, therefore it is likely groups' were not adequately matched.

5.5.1. Limitations, strengths and potential sources of bias

As this study used the same matched sample as in Chapter Four, the issues surrounding the use of PSM were the same in this chapter and have been previously discussed in section 4.5. Briefly, PSM can theoretically account for unmeasured bias (Rosenbaum and Rubin, 1983a; 1983b), but one cannot be completely sure. The area outside the common region was large (Figure 4.3) and this may have restricted estimation of a causal effect and in bias by changing

the observed population (King and Zeng, 2005). However, only 12% of quitters were lost due to common support restrictions and those excluded did not differ on baseline characteristics compared with the remainder of the sample.

The size of the cohort was an issue in this study. In the whole sample there were only 68 quitters, and the matched sample only had 60 participants per group, thus this study was underpowered and was likely too small to detect a dichotomous outcome such as psychiatric disorder (McCaffrey and Elliott, 2008). Accordingly, the lack of report of disorder in the quit group was an artefact of the small sample. It is possible that the incidence of psychiatric disorder is very rare for quitters; however a larger sample would be needed to determine this.

As discussed in the previous chapter (section 4.5.2), due to patient confidentiality certain demographic data, such as ethnicity, social class and education were not supplied, and therefore participants were not matched on these characteristics. However, a recent systematic review did not find consistent evidence to suggest that demographic characteristics were associated with cessation (Vangeli et al., 2011). Therefore it is unlikely that exclusion of these characteristics influenced the association greatly, although interactions between covariates may be possible.

This study adopted stringent criteria for assessment of exposure which limits misclassification of smoking status (previously discussed in section 4.3.3.1). The outcome of psychiatric disorder was ascertained from trial reports of patients symptoms, and these were coded according to the MedRA database (Medical Dictionary for Regulatory Activities, 2013). The MedRA database is a standardised tool designed to guide categorisation of trial adverse

events. This study used this tool to code pre-existing event descriptions by researchers originally involved in the treatment trials; this may have introduced bias, although as those researchers were blinded to the hypotheses of this analysis, it is hard to see a mechanism for such bias. Furthermore, overall risk of bias in this study was low according to the NOS and sensitivity analyses produced similar results. Finally, as no quitters reported a psychiatric disorder a regression model could not be fitted to compare adjusted and unadjusted models. Importantly though, the largest risk to this association was group membership bias (Dawkins et al., 2009; Hughes, 2007c), which can be greatly accounted for by nicotine dependency and receipt of treatment (Stead et al., 2012, Vangeli et al., 2011), this study was able to account for these factors and other confounding through PSM, and the study's findings were not altered by matching participants on these characteristics.

5.5.2. Interpretation of findings

Although data presented in this study are inconclusive, they are supported by other studies which report smokers have an increased risk of mood disorder compared with quitters (Khaled et al., 2012). Cautiously, it may be concluded that cessation reduced the incidence of disorder, and this is supported by a recent study reporting that after cessation quitters were more likely to stop anti-depressant treatment (Shahab et al., 2014). The misattribution hypothesis recognises that chronic exposure to nicotine leads to periods of low mood and anxiety (previously discussed in sections 1.6.1 and 1.9.1). These psychological symptoms are also a hallmark of many mood disorders, thus Parrot (1999; 2003) proposes that after sustained cessation, the smokers' mental health will return to a more desired state and risk of disorder will be reduced (previously discussed in section 1.9.1). This model is supported by

longitudinal data, neurobiological evidence and experimental neurological functional imaging studies (previously discussed in sections 1.6 and 2.5.3). Although this model appears to support the findings in this study, one cannot be certain, and a study with a larger sample should investigate this in the future. Importantly, it is equally possible that the incidence of psychiatric disorder in the continuing smoking group could be a consequence of partaking in a reduction study. In the original trials all participants attempted to reduce their smoking, and it may be that reducing daily smoking, or failing to do so induces periods of depression or anxiety. This is an area for future research.

5.6. Conclusion

The results from this study were inconclusive and the study design should be replicated in a larger sample.

5.7. Chapter summary

In Chapters Two and Four the use of means to examine the association between mental health and smoking cessation may have concealed evidence of psychiatric disorder, therefore the onset of psychiatric disorder after quitting compared with continuing smoking was examined using PSM and risk difference methodology. Results showed no one who stopped smoking reported onset of psychiatric disorder six months following cessation, whereas several people who continued to smoke did so, resulting in an estimate of a higher risk in continuing smokers

compared with quitters, although this was not significant. Due to lack of variability in the quit group the results in this chapter were inconclusive and should be replicated in a larger study.

CHAPTER SIX

6. DOES WORSE MENTAL HEALTH AFTER SMOKING CESSATION PREDICT RELAPSE?

6.1. Introduction to Chapter Six

It is possible that some quitters experience improved mental health after smoking cessation and therefore remain abstinent, whereas, other quitters may experience worse mental health after cessation, and therefore be more likely to relapse. If this hypothesis is true, it may explain the association between smoking cessation and mental health reported in Chapters Two and Four. To test this hypothesis, in Chapter Six I present a prospective analysis of the McNeil trials to examine the association between change in mental health and risk of relapse.

6.2. Background

Chapters Two and Four report a strong association between stopping smoking and improved mental health. Hughes (2007c) suggests that some smokers experience a permanent worsening in mental health after cessation, resulting from either chronic exposure to tobacco or from abstinence of tobacco's therapeutic properties, and as a result, are at risk of relapse (previously discussed in sections 1.6, 1.9.2 and 1.10.2). This hypothesis, if true, could explain the findings in Chapters Two and Four.

A literature review was conducted to determine if any previous studies have examined this association. A series of terms related to “smoking” “relapse” and “mental health” were used to search “MEDLINE”, “PsycINFO” and “PsycARTICLES” “EMBASE”. The search strategy produced 1520 articles, the titles and abstracts were examined narrowing these articles down to 52 relevant articles. Examination of the full-texts resulted in two systematic reviews of predictors of relapse, however neither presented relevant data (Hitsman et al., 2013; Vangeli et al., 2011), and three studies which investigated the association between change in mental health (after the withdrawal period) and relapse (Gruder et al., 2013; Manning et al., 2005; Yong et al., 2010).

Yong et al. (2010) prospectively examined the association between emotional experiences after quitting and odds of relapsing versus remaining abstinent over a four year period. After cessation, participants were asked to rate questions such as, “Since you quit, has your ability to calm down when you feel stressed or upset improved, gotten worse or stayed the same?” Results indicated that the perception of worsened emotional control after cessation was associated with increased odds of relapse at follow-up, OR (95% CI), 1.6 (1.3 to 2.1); these results are supported by other studies in which smokers report the mental health benefits of smoking deter them from achieving abstinence (previously discussed in section 1.4). However, in Yong et al.’s study (2010) mental health was not assessed using a validated tool, and the data were based on participants’ recollections of events, both of these study features may introduce bias (Coughlin, 1990; Hassan, 2006; Wood et al., 2007). Ideally, to measure an accurate account of mental health during the transition from smoker to quitter, scores would be recorded using a validated measure at a time of regular smoking and then compared to a time after cessation.

Gruder et al. (2013) prospectively examined change in depression scores from baseline, when participants were smoking, to two year follow-up, when participants had either relapsed or quit. Results indicated that change in depression scores was not associated with odds of relapse versus remaining abstinent, OR=0.9 (95% CI 0.7 to 1.4). In a similar study, Manning et al. (2005) analysed data from a cessation treatment trial to determine if change in stress from baseline (before quitting) to six month follow-up was associated with relapse at six month follow-up. Analyses indicated that there was no association between change in stress scores and odds of relapse at follow-up, 1.0 (0.9 to 1.1). Both studies reported no association between change in mental health outcomes and relapse. However, in these studies final mental health score was measured after relapse had occurred, thus the data do not clearly assess whether change in mental health contributed to relapse.

Therefore, to assess the association I conducted a prospective analysis using logistic regression modelling to determine if change in mental health during the cessation period was associated with odds of relapsing versus remaining abstinent at a later follow-up.

6.3. Methods

6.3.1. Study design

A prospective observational study of individual level patient data derived from the McNeil trials (trials' characteristics previously discussed in Chapter Three).

6.3.2. Participants and study size

Seven-hundred-and-forty-one participants provided smoking data at both four and 12 month follow-ups. At four month follow-up 107 participants were biologically-validated as quit, of these, 80 participants provided sufficient data at 12 month follow-up to determine their relapse status.

6.3.3. Variables

6.3.3.1. Exposure

Exposure was defined as change in mental health score from when the person was a smoker, at baseline, to after they had reported biologically-validated, seven day, point-prevalence cessation at four month follow-up. Mental health scores were measured using the "emotional wellbeing" subscale from the RAND-36/SF-36 item health survey 1.0. Scores range from 0 to 100 and scores of ≤38 indicates presence of a mental health problem. In the general population the subscale's mean and standard deviation are 70.38 (21.97) (Hays et al., 1993; 1998). Further information about the scale has been previously reported in section 4.3.3.2.

6.3.3.2. Outcome

The outcome was biologically-validated, self-reported point-prevalence (seven-day) smoking status at four and 12 months. Relapse was defined as biologically-validated (carbon monoxide/parts per million (CO/ppm) <10) point-prevalence abstinence at four months

follow-up, and return to smoking at 12 months follow-up. Repeated point-prevalence cessation was defined as biologically-validated (CO/ppm <10) self-reported cessation at both four and 12 month follow-up. Those whose carbon monoxide did not confirm either smoking or quitting at four or 12 month follow-ups were not included in the analysis. Quitters who did not provide smoking status data at 12 months were excluded from the analysis. See Figure 6.1 for visualization of measurement of exposure and outcome.

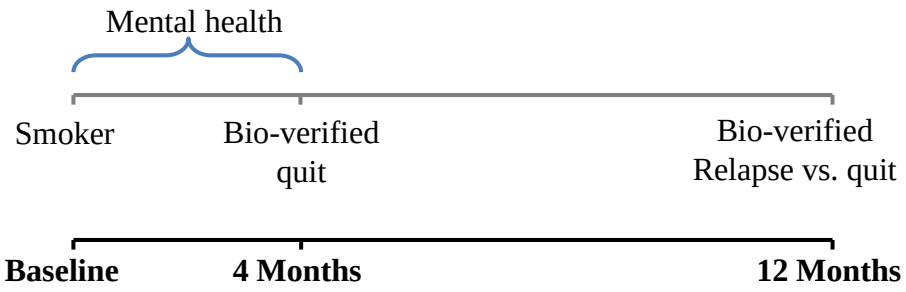

Figure 6.1 Timeframe for measurement of exposure and outcome variables

6.3.3.3. Confounding variables

The following variables were entered into the adjusted logistic regression model: nicotine dependency, as measured using the Fagerström Test of Nicotine Dependence (FTND) (Fagerström et al., 1990) and NRT treatment status (placebo or active) (Stead et al., 2012), sex, age and baseline mental health score (SF-36) (Asendorpf, 1992; Barnett et al., 2005; Niaura et al., 2001).

6.3.4. Statistical methods

Individual level patent data from five trials of NRT for smoking reduction were pooled according to methods described previously in Chapter Three. Logistic regression modelling was used to assess the association between change in mental health and relapse. Exposure was change in mental health from baseline (pre-cessation) to four month follow-up (time point of biologically-validated abstinence). The outcome variable was biologically-validated relapse (coded as 1) or repeated point-prevalence abstinence (coded as 0). The regression model was repeated with and without adjustment for FTND score, NRT treatment status, baseline mental health (SF-36), sex and age.

6.3.5. Sensitivity analysis

Ideally change scores would have been calculated for participants who had remained abstinent for six weeks minimum to ensure they were no longer experiencing psychological withdrawal symptoms from tobacco abstinence (Hughes, 2007b). To address the issue that those who reported point-prevalence cessation at four month follow-up may have been recently quit, a sensitivity analysis was conducted to include participants who had likely been quit for at least six weeks up to the four month follow-up[4].

The analysis included quitters who reported point-prevalence cessation (biologically-validated) at both 10 week and four month follow-ups. It is likely these quitters were

[4] NB. This analysis was not used as the main analysis because there were limited data available due to differences between trials' follow-up points.

continuously abstinent over this six week period (Hughes et al., 2003; 2010); the logistic regression model described in section 6.3.5 was repeated using this group of quitters.

6.3.6. Missing data

Participants with any missing data were excluded from the analysis. The number of participants excluded for missing outcome data and their characteristics are presented in the results.

6.3.7. Risk of bias

An adapted version of the Newcastle-Ottawa Scale was used to assess risk of bias in observational studies (Appendix 4). The measure rates studies on a scale of 1 to 5: 1 indicates a high risk of bias and 5 indicates a low risk of bias.

6.3.8. Ethics and data protection

See Chapter Three for further information pertaining to ethics and data protection.

6.4. Results

6.4.1. Participants

One-hundred-and-seven participants were biologically-validated as quit at four months, of these 80 reported smoking status at 12 months. Twenty-seven did not provide smoking data at 12 months and were excluded from the analysis; these participants were on average psychologically healthy, according to the SF-36 (Hays et al., 1998), with a mean (M) and standard deviation (SD) of 71.7 (21.2). Of the 80 participants reporting outcome data at four and 12 months, two quitters were excluded for missing mental health data. The baseline score for the quitter missing data at follow-up was 56, and the follow-up score of the quitter missing data at baseline was 82, neither scores indicate poor mental health (Hays et al., 1993). After excluding for missing data, the analysis included 17 quitters classified as relapsed at 12 month follow-up, and 61 as quit at 12 month follow-up

6.4.2. Characteristics of quitters and relapsers

Baseline characteristics of quitters and relapsers are presented in Table 6.1. T-tests indicated that groups were not significantly different in age, sex, nicotine dependency (FTND), baseline mental health (SF-36) or receipt of active NRT.

Table 6.1 Baseline characteristics of relapsers and quitters				
Characteristic	**Quitter (N=61)**	**Relapser (N=17)**	**Test of significance**	**P-value**
Age, M (SD)	46.9 (9.6)	45.3 (11.9)	T = 0.55	0.58
Sex, % male (N)	49% (30)	71% (12)	Chi^2= 2.45	0.12
FTND, M (SD)	5.5 (2.4)	5.6 (1.5)	T = - 0.25	0.803
SF-36 Mental health, M (SD)	74.5 (14.7)	69.6 (18.0)	T = 1.18	0.24
Treatment status, % received active (N)	72% (44)	71% (12)	Chi^2=0.02	0.901

6.4.3. Unadjusted logistic regression analysis

Twenty-one percent (n=17) of those who reported cessation at four months, reported relapse at 12 month follow-up. The mean change and SD in mental health scores from baseline to four month follow-up for repeated point-prevalence quitters was 2.22 (14.77), and the mean change in mental health scores for quitters who had reported relapse at 12 month follow-up was 3.05 (17.64).

The unadjusted model indicated that change in mental health was not associated with odds of relapsing, compared with staying quit, odds ratio and 95% confidence intervals (OR; 95% CI) were 1.00 (0.97 to 1.04), P=0.84. After adjustment for baseline mental health, FTND scores, NRT status, age and sex, the association remained non-significant, 0.99 (0.95 to 1.03), P=0.58 (Table 6.2).

Table 6.2 Adjusted logistic regression model		
Variable	**OR (95% CI) (relapse=1)**	**P-value**
Change in mental health (baseline to follow-up)	0.99 (0.95 to 1.03)	0.58
Baseline mental health	0.97 (0.93 to 1.01)	0.19
Treatment status (1=active)	1.00 (0.28 to 3.61)	0.99
FTND	1.02 (0.79 to 1.32)	0.86
Sex (female)	0.39 (0.12 to 1.28)	0.12
Age	0.99 (0.93 to 1.05)	0.65

6.4.4. Sensitivity analysis

A sensitivity analysis was conducted to determine if change in mental health was influenced by possible withdrawal symptoms. This analysis examined if change in mental health scores from baseline to after repeated point-prevalence cessation at both 10 weeks and four months, was associated with relapse at 12 month follow-up. In this sensitivity analysis there were five relapsers, whose mean change (SD) in mental health scores was 0.00 (23.83) and 45 repeated quitters whose mean change in mental health scores was 2.67 (16.05). There was no association between change in mental health from baseline to four month follow, and relapse at 12 month follow-up, OR=0.99 (95% CI: 0.94 to 1.05), P=0.73. Adjustment for covariates did not change the association 0.99 (0.93 to 1.07), P=0.85 (see Appendix 22 for full adjusted and unadjusted models).

6.5. Discussion

Change in mental health during the transition from smoker to quitter was not associated with future relapse, and this association was not altered by adjustment for covariates or during sensitivity analyses.

6.5.1. Limitations, strengths and potential sources of bias

The cohort's size was small and is therefore an issue. However, the purpose of the analysis presented in this chapter was to examine the possibility that worsened mental health may lead to relapse and mental health was measured using the SF-36 which was purposefully designed to detect changes in mental health and is psychometrically sound (Hays et al., 1998). Using this validated tool there was no evidence of worsened mental health for quitters or relapsers.

Pre-cessation scores were measured at baseline while everyone was a smoker and had no immediate plans to quit, only to reduce. Post-cessation mental health scores were obtained at four month follow-up, after biologically-validated, point-prevalence cessation, thus it is possible that some quitters were recently abstinent and were therefore experiencing psychological withdrawal symptoms (Hughes, 2007b). However, use of repeated point-prevalence criteria to ascertain abstinence is likely to produce results similar to continuous abstinence (Hughes et al., 2003; 2010), therefore a sensitivity analysis was conducted and included only those who reported repeated point-prevalence abstinence at both 10 week and four month follow-up. Results from the sensitivity analysis were similar to the main analysis. As the sensitivity analysis replicated the non-significant association, it is likely that those who

were identified as quit using seven day, point-prevalence criteria at four month follow-up were quit for much longer than one week.

Biologically-validated, point-prevalence smoking status at both four and 12 months was used to ascertain outcome (relapse or quit). It is possible that those who were biologically-validated as quit at both time-points may have relapsed in between the four and 12 months follow-ups. However, it would be uncommon to find a smoker who was quit at both time points but smoked in between (Hughes et al., 2003; 2010). Therefore in this study outcome misclassification was a potential issue, but it is unlikely.

6.5.2. Interpretation

Hughes (2007c) suggests that some smokers experience a permanent worsening in mental health after cessation, resulting from either chronic exposure to tobacco or from abstinence of tobacco's therapeutic properties, and as a result are at risk of relapse (previously discussed in sections 1.6, 1.9.2 and 1.10.2). This hypothesis is supported by Yong et al.'s (2010) study which found relapsers' perception of reduced ability to cope with low mood and stress after cessation was associated with increased odds of relapse, and is further supported by smokers' reports that smoking's mental health benefits deter cessation (previously discussed in 1.4). However, data from observational studies that psychometrically measured mental health have failed to replicate these findings (Gruder et al., 2013; Manning et al., 2005). Direction of causation was questionable in these studies because the follow-up measures of mental health and cessation/relapse were measured simultaneously (e.g. did relapse cause worse mental health?), however reverse causation was less questionable in this study, and likewise, it found

no significant association with relapse. Thus, to summarise, studies which rely on participants' perceptions of mental health after cessation report a significant association between worsened mental health after cessation and relapse; whereas studies which scientifically measure mental health change show no evidence of such an association.

Understanding the cognitive processing involved in memory recall may be key to interpreting this association, or lack thereof. The disparity between peoples' reports about symptoms based on memory versus symptoms which have been scientifically measured is a commonly observed phenomenon (Coughlin, 1990; Hassan, 2006; Henkel and Mather, 2007). When participants report on past symptoms they depend on their memory, and research has consistently found that beliefs about the condition in question and other socially-derived information present during recall, can alter the way in which memories about symptoms are reconstructed (Koriat et al., 2000; Robinson and Clore, 2002a; 2002b). Moreover, memory becomes less accurate and increasingly biased by personal and social belief systems overtime (Henkel and Mather, 2007). These notions have been confirmed in a study which compared participants' real-time reports of mood and smoking lapses (recorded via a portable diary), with their memory of the event recorded 12 weeks later (Shiffman et al., 1997). Results indicated that at follow-up participants over-estimated the causal role of negative affect as a reason for lapse. Thus, if memory recall theories are correct, it may not be change in mental health which leads the person to relapse; rather it is the belief that smoking will cure unwanted emotion which biases recollection about reason for relapse.

6.5.1. Implications for cessation treatment

There are many multi-component interventions designed to promote smoking cessation in the UK and it is NHS standard to include an element of relapse prevention (McEwen, 2014). Usually, patients are helped to identify smoking cues and discuss strategies to cope during times of temptation. When applicable, patients are also provided with advice on methods to cope during times of stress or unwanted emotion. Interventions should target belief systems and their influences on decision to relapse during times of stress, and participants should be encouraged to identify previous experiences when their memory about emotions may have been influenced by their own beliefs or the beliefs of others.

6.6. Conclusion

This prospective study reported that change in mental health was not associated with odds of relapse compared with remaining abstinent. Sample size was an issue in this, however the findings are consistent with similar studies which have assessed the association using validated measures; and oppose data reported from studies which rely on relapsers' memories of reasons for relapse. These findings do not support the notion that cessation-induced worsened mental health leads to relapse.

6.7. Chapter summary

It is possible that some smokers experience worse mental health after smoking cessation, compared with when they smoked, therefore they may be more likely to relapse back to smoking; this notion is supported by studies examining relapsers' reports of poor mental health after cessation. To investigate this possibility I conducted a prospective analysis using logistic regression modelling to determine if change in mental health scores from pre-cessation to post-cessation was associated with odds of relapsing, versus maintaining cessation at follow-up. Results displayed no association between change in mental health and this finding was not altered by adjustment for confounding or through sensitivity analyses, however the sample was small in this study which may give rise to imprecision. One interpretation of the null association is that beliefs about the benefits of smoking bias belief systems during recall of relapse.

CHAPTER SEVEN

7. IMPLICATIONS, RECOMMENDATIONS FOR FUTURE RESEARCH AND CONCLUSIONS OF THE THESIS

7.1. Introduction to Chapter Seven

In Chapter Seven I discuss the findings of the thesis, and contextualise the findings in relation to current knowledge and according to Bradford Hill's criteria for inferring causal associations. Secondly, clinical and public health implications of the thesis are discussed and suggestions for future research are made. I conclude the chapter summarising the overall contribution of the thesis.

7.2. Interpretation of findings

Due to the impracticalities of randomizing smokers to stop or to continue smoking, all that is known about the physical health hazards of smoking and the benefits of quitting are from observational data, and these data are considered legitimate. I argue the same attitude should be applied to the use of epidemiological data when considering the mental health harms and benefits of smoking and quitting. This thesis provides evidence that smoking cessation is associated with mental health benefits. The research was observational and is weakened by

the possibility of confounding and other biases. However, methods were adopted to reduce these risks and in turn strengthened the findings.

The thesis aimed to clarify areas of uncertainty arising from the current literature and the chapters in this thesis are novel contributions to the field. No previous systematic review has been able to provide a summary estimate for the impact of cessation on mental health (section 1.10.2), thus Chapter Two presents the first study to combine effect estimates from longitudinal studies comparing change in mental health over time between quitters and smokers. The study showed that cessation was associated with improvements in mental health of a comparable size to anti-depressant treatment, and this study was published in a peer-reviewed journal (Taylor et al., 2014). Another major issue in the current literature is the possibility of bias and unknown confounding, therefore in Chapter Four propensity score matching (PSM) and regression modelling was used to reduce group membership bias and confounding. This technique provided further evidence that smoking cessation was associated with improved mental health; and PSM methodology strengthened a causal interpretation. The analysis of means presented in Chapters Two and Four may have concealed incidences of psychiatric disorder, and previous research examining onset of psychiatric disorder in quitters may have also been biased by group membership (section 5.2). Therefore in Chapter Five use of PSM and risk difference estimates examined the risk of psychiatric disorder after stopping smoking compared with continuing smoking. The study found that six months after quitting ex-smokers did not display evidence of psychiatric disorder whereas some continuing smokers did, this finding was replicated after matching participants on their propensity to quit; however all estimates were inconclusive. Finally, the findings in Chapters Two, Four and Five could be explained by the possibility that some people who quit experience worse

mental health and therefore relapse back to smoking, while quitters who experience mental health benefits continue to be abstinent. Interpretations of previous studies which have examined this hypothesis have been restricted by possible reverse causation or reliance on patients' memory about reasons for relapse (section 6.2). Therefore, in another novel study, Chapter Six tested this hypothesis and presented no evidence that worsened mental health after cessation was associated with future relapse.

The thesis contributes evidence on the validity of three opposing hypotheses which could explain the association between smoking cessation and mental health. None of the findings in this thesis supported the self-medication hypothesis; other studies however have produced evidence for this (Section 1.9.2). Many longitudinal cohorts report that smoking during adolescence and early adulthood is associated with uptake of smoking later on in life, and researchers have argued this occurs because smoking offers mental health benefits. In support of this notion, there are some studies which have shown nicotine offers moderate benefits for depression symptoms and for cognitive performance, although the duration of these effects is unknown. However nicotine is not an isolated constitute of tobacco, there are other chemicals which act independently from and interactively with nicotine, and these interactions are not entirely understood (Borgerding and Klus, 2005; Rose, 2006; 2010; Thielen et al., 2008; United States Environmental Protection Agency, 1992). The few studies showing any benefit from nicotine are contradicted by other studies showing smoking tobacco has no effect on emotional outcomes in non-smokers. Furthermore, the suggestion that tobacco's chemical properties are therapeutic does not stand strong compared with evidence derived from studies showing tobacco leads to unfavourable neuroadaptations in mood regions of the brain (section 1.6). If smoking was therapeutic, surely daily use would alleviate mental disorder, or

symptoms of stress, however the evidence shows tobacco use and poor mental health commonly occur, and studies of people with mood disorders who take up smoking show no evidence of improved mental health later on in life (Boden et al., 2010; Fergusson et al., 2003; Jamal et al., 2012; McGee et al., 2000).

Many studies have found an association between a third factor such as genes, environment or personality traits and the co-occurrence of smoking and mental health problems (section 1.9.3). It is possible that a common factor could cause both improved mental health and smoking cessation. However, there is no evidence that positive life events or changing environment, for example, are associated with sustained cessation. The possibility of a single event leading to both cessation and improved mental health seems less plausible, particularly considering the evidence presented in Chapter Two, where improved mental health was seen nine years after cessation.

The thesis mostly supports the misattribution hypothesis (whereby smokers' perceptions of smoking having positive mental health effects is misattributed to the effects of smoking on relieving withdrawal) which suggests that smoking cessation leads to improved mental health. The hypothesis is bolstered by the vast majority of other longitudinal studies which have examined the association between smoking cessation and mental health (reported in Chapter Two, and section 1.10.1), and is further supported by a plausible biological pathway (discussed in section 1.6). The systematic review in this thesis found that all included studies consistently favoured the quit group who displayed improved mental health. Importantly, one must note that in some of the studies the difference in change was not significantly different between groups, however once the estimates were pooled the association became significant.

Other longitudinal studies reporting the risk of mental health disorder after cessation predominately follow a similar pattern and report that cessation is associated with a reduced risk of disorder, or no association (previously discussed in section 1.10), therefore it is possible that if these studies were meta-analysed the reduced risk may reach significance, in favour of the quit group (these studies were not meta-analysed in Chapter 2 because they reported dichotomous outcomes rather than mean differences).

There are only two studies which have calculated an increased risk of mental disorder after cessation (Glassman, et al., 2001; Tsoh et al., 2000) and it is these studies which have lead to mixed conclusions in two out of the four existing systematic reviews in the field (Hughes 2007c; Ragg et al., 2013). In the first study reported by Glassman et al. (2000) there was a seven-fold increase in depression amongst quitters, however the study had significant differential loss to follow-up, in which outcome data were not available for 39% of smokers, compared with 5% of quitters. This was a likely source of bias (Touloumi et al., 2001) thus limiting the study's findings, and moreover, this study had received previous criticism from experts in the field for producing misleading findings (Prochaska et al., 2008). The second of these studies conducted by Tsoh and colleagues (2000) reported that 14.7% of quitters had major depression after cessation treatment, and that this was significantly increased compared with continuing smokers (13.7%). However, after adjustment for depression history and other covariates, abstinence status was no longer a significant predictor of depression. Thus, the studies by Glassman et al. (2001) and Tsoh et al. (2000) provide weak evidence but have contributed to significant ambiguity in the field. In Hughes' (2007c) review rates of depression were reported to be between 1% and 31% for quitters, and 0% to 14% for continuing smokers. If the Glassman et al. (2001) and Tsoh et al. (2000) studies were

removed, the rates for depression for quitters would have been between 1% and 15%, which was very similar to the smoking group; furthermore in Hughes' review the other included studies were of case reports and descriptive data, and only one study statistically tested their findings. Ragg et al. (2013) also reported mixed evidence for depression, and this was also due to inclusion of the Glassman study, the other studies reported improved mental health or reduced risk for depressed quitters. Thus, these two studies (Glassman et al. (2001) and Tsoh et al. (2000)) have produced unusual results, compared with the plethora of positive data showing cessation is associated with improved mental health or decreased risk of mood disorder (Khaled et al. 2012; Ragg et al. 2013; Sanchez-Villegas et al. 2008; Taylor et al. 2014).

Bradford Hill (1965) proposed a set of guidelines to use for concluding causation from epidemiological evidence and these have been recently updated by Howick et al. (2009). I have summarised evidence investigating smoking cessation and mental health outcomes according to these guidelines. Summary of this evidence shows there is strong argument that cessation leads to improved mental health (Table 7.1).

Table 7.1 The association between smoking cessation and mental health according to Bradford Hill's guidelines (as revised by Howick et al. (2009))[5]

Type of evidence	Guidelines	Evidence	Summary
Direct	Size of effect not attributable to confounding	1) In Chapter 2, section 2.3.9.1 adjusted and unadjusted estimates were not significantly different; 2) Chapter 4 shows the size of the effect was not greatly altered by adjustment for confounding or through PSM techniques; 3) Reduced risk of mental health symptoms after cessation not attributable to confounding in strongest studies (Bolam et al., 2011; Khaled et al., 2012; Sanchez-Villegas et al., 2008; Shahab et al., 2014). Two studies found risk of depression after cessation, however one was confounded by depression history (Tsoh et al., 2000), and the other was of weak evidence (Glassman et al., 2001).	Guideline mostly satisfied
	Appropriate temporal proximity (cause precedes effect and effect occurs after a plausible interval)	Improved mental health occurs after breaking the tobacco withdrawal cycle, data from FMRI studies, self-report and a systematic review (Chapter 2) indicates this occurs at around six weeks of sustained cessation (Hughes, 2007b; Mamede et al., 2007).	Guideline satisfied
	Dose-responsiveness and reversibility	1) Dose-response evidence that higher tobacco consumption is associated with worse mental health (Boden et al., 2010; Jamal et al., 2012).	Guideline mostly satisfied

[5] Copied with permission granted from Jeremy Howick on August 5th, 2014

		2) Cessation associated with improved mental health (Chapter 2); 3) Unsure if reduced tobacco consumption is associated with improved mental health.	
Mechanistic	Evidence for a mechanism of action (biological, chemical)	Chronic smoking is associated with neuroadaptations in mood regions, some of these neuroadaptations have been found to reverse after cessation (previously discussed in section 1.6). However, unsure if tobacco use leads to damage in some pathways. Some evidence that nicotine may offer some benefits, however the evidence is weak and the duration of effect is unknown (section 1.9.2.1).	Guideline mostly satisfied
	Coherence (does the hypothesis cohere to what is currently known?)	No adequate study has found cessation to be associated with worsened mental health. No evidence that a common cause leads to cessation and improved mental health.	Guideline satisfied
Parallel	Replicability (results are similar across the same study designs, using the same outcome)	Chapters Two and Four, Khaled et al. (2012); Ragg et al. (2013); Sanchez-Villegas et al. (2008).	Guideline satisfied
	Similarity (evidence is consistent across similar study designs, using similar outcomes)	Chapters Two and Four; Khaled et al. (2012); Ragg et al. (2013); and Sanchez-Villegas et al. (2008).	Guideline satisfied

7.3. Implications

7.3.1. Cessation is associated with clinically important improvements in mental health

The belief that smoking is therapeutic and that cessation may cause psychological harm is widespread and upheld by both smokers and health professionals. Many health professionals are deterred from treating patients' smoking during times of stress and in patients with mental health problems, and moreover smokers with and without mental health problems state that smoking to cope with stress and low mood is a reason to continue. It is possible that these beliefs have also contributed to health inequalities, such that the smoking population is over-represented by people with mental health disorders (previously discussed in section 1.8).

The thesis shows no evidence that tobacco use offers mental health benefits, but instead supports the hypothesis that smoking worsens mental health as evidenced by my findings that smoking cessation was associated with mental health benefits. The data are primarily from the general population, although included a few studies from psychiatric populations. It can be used in combination with other evidence (Banham and Gilbody 2010; Ragg, Gordon, Ahmed, and Allan 2013) when treating patients with and without mental health disorders.In primary care, general practitioners, nurses and smoking cessation specialists can apply these data when treating patients. Specifically, smokers may report they are too stressed, depressed or anxious to quit, however these data suggest that on average sustained cessation likely leads to improved mental health. In secondary care, recent NICE guidelines have recommended

implementation of smoke-free policies in mental health hospitals. This thesis, in combination with other major works, provides evidence that cessation is not associated with psychological harm in psychiatric populations. Therefore clinicians in these settings can be reassured that cessation is very unlikely to cause psychological harm. Public health campaigns and interventions in these health care settings should be updated to include data about the mental health benefits of cessation.

7.3.2. Cessation interventions should target the misconception that smoking has mental health benefits.

The misattribution hypothesis states that smokers attribute the ability of smoking to relieve withdrawal symptoms as an ability of smoking to relieve stress and other negative emotion. Consequently, many smokers suggest that they return to smoking because they could not cope without cigarettes. However as the findings in Chapter Six and from similar studies suggest (Gruder et al., 2013; Manning et al., 2005), worsened mental health does not predict relapse. It is possible that the belief that smoking can alleviate distress may mediate smokers reports (Yong et al., 2010).

PRIME theory of addiction suggests that smoking behaviour is driven by motivation, defined as "decisions to do or not do things based on an analysis of their costs and benefits" (Baron, 2000; West and Brown, 2013). The theory recognises that relapsing often occurs during exposure to cues that stimulate behavioural or psychological pathways which would have previously led to smoking (West and Brown, 2013). A person's ability to refrain from smoking is mediated by their impulse control, their wants/needs at the time, and the person's

evaluation (belief) about the benefits or costs of smoking in that situation at that time. Thus, during a time of stress or negative emotion, the need/want to alleviate emotional distress is high. If the smoker is someone who strongly believes that smoking can alleviate emotional distress, the benefit of smoking outweighs the costs of relapsing at that time, this will then heighten the person's impulse to smoke, therefore increasing risk of relapse.

There are many multi-component interventions designed to promote smoking cessation in the UK and NHS smoking cessation services usually provide an element of relapse prevention in their care plans (McEwen, 2014). Common behaviour change techniques based upon PRIME theory are used in interventions to enhance motivation during cessation attempts. Usually, patients are educated about the physical health benefits of cessation, helped to identify smoking cues and to discuss coping strategies to use during times of temptation. When applicable, patients are also provided with advice on methods to cope without cigarettes during times of stress or negative emotion. According to PRIME theory targeting these aspects of motivation will strengthen the belief system to support cessation, albeit directly or indirectly.

Many patients are currently informed of alternative emotional coping strategies. However, by suggesting that these are 'alternative' or 'substitute' methods infers that smoking was an adaptive or effective coping strategy, especially if this information is conveyed by a health professional. Health professionals should be cautious of using such language. Alternatively, patients should be informed that there are consistent data showing that smoking relieves withdrawal and that smoking cannot remove stressful circumstances or unwanted emotion. Patients should also be informed that there is very limited evidence to suggest that smoking is

therapeutic; rather there is evidence to show that adaptive coping techniques (relaxation, breathing, exercise, social support) are effective at relieving stress and negative affect. The contrast of evidence between maladaptive (smoking) versus adaptive coping strategies will challenge the patient's belief that smoking was an effective coping strategy.

7.3.3. Public health campaigns

Public health campaigns designed to educate smokers about the physical benefits of cessation are based upon findings observational data. These campaigns should now be updated with observational data from this thesis and other studies, showing that cessation is associated with mental health benefits.

7.4. Future research

7.4.1. Methodological recommendations

Future studies investigating the association between stopping smoking and mental health should use statistical techniques which can strengthen causal inferences from observational research. As propensity score matching is a useful tool for comparing quitters with continuing smokers (previously discussed in section 4.2), future research should use this technique and also examine interactions between variables when calculating propensity scores. In addition, Mendelian randomisation can be used as an instrumental variable approach by using genes or other factors which have a common association with change in mental health and smoking

status. Use of such techniques can strengthen causal inference by minimising bias from confounding and removing possibility of reverse causation.

7.4.2. A new model of smoking and mental health

Previous studies have suggested that other factors such as shared vulnerabilities and self medication effects contribute towards the association between smoking, cessation and mental health. Although the findings in the thesis largely supported the misattribution model, these findings cannot completely discount the validity of other explanatory hypotheses. Other fields have developed models which encompass numerous contributing factors to the development of disease. It is possible that misconceptions about smoking's mental health benefits are restraining the development of comprehensive models in this field. Future research should aim to develop a multi-component model which includes genetic, environmental, psychological, social and neurobiological factors to explain the association between smoking, cessation and mental health.

7.4.3. Repeat methods from Chapter Five using a larger sample

The results from Chapter Five, although inconclusive, found that approximately 2% more smokers reported mood disorders than quitters. It is possible that smoking is a risk factor in the development of psychiatric disorder, and that by removing this factor (by quitting) one reduces their risk of disorder. This notion is supported by other epidemiological studies (Khaled et al., 2012, Sanchez-Villegas et al., 2008) and neurobiological evidence (section 1.6).

Tobacco is commonly referred to as a psychoactive substance, (Benowitz, 2010) however, tobacco is not under the same regulations as other psychoactive drugs. Most drugs with psychoactive effects are under the regulation of the Medicines and Healthcare Products Regulatory Agency (MHRA), which considers a drug to have a common side effect if between one in 10 and one in one-hundred people experience the same symptom. PSM can be used to infer causal estimates (Rosenbaum and Rubin, 1983a) and therefore results from PSM could be used to determine if psychiatric disorder is a side-effect of continuing tobacco use. In Chapter Five about two in every 100 (1.72%) continuing smokers reported evidence of a mood disorder and although this was not significant, this result meets MHRA's definition of a common side-effect. Medicines with similar estimates of psychiatric risk have at a minimum a warning label of this information or are removed from the market. Tobacco packaging in western countries include warnings about the physical health risks associated with smoking, which are founded upon observational data, not randomised data. If a larger study, using PSM methodology displayed that risk of mood disorder was an 'effect' of continued tobacco use, its findings would be supported by other observational data and would have significant implications for policy makers concerning the packaging of tobacco. This is a strong reason for future research to repeat this study using a larger sample.

7.5. Overall conclusion

Smoking damages every aspect of physical health. This thesis is part of a growing body of evidence suggesting that tobacco is not a useful therapeutic substance. I believe the findings of this thesis, in light of the other evidence reviewed should be used to inform smokers that on average, smoking cessation is associated with mental health benefits.

APPENDIX

1. PUBLISHED VERSION OF SYSTEMATIC REVIEW AND META-ANALYSIS (CHAPTER TWO)

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RESEARCH

Change in mental health after smoking cessation: systematic review and meta-analysis

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Abstract

Objective To investigate change in mental health after smoking cessation compared with continuing to smoke.

Design Systematic review and meta-analysis of observational studies.

Data sources Web of Science, Cochrane Central Register of Controlled Trials, Medline, Embase, and PsycINFO for relevant studies from inception to April 2012. Reference lists of included studies were hand searched, and authors were contacted when insufficient data were reported.

Eligibility criteria for selecting studies Longitudinal studies of adults that assessed mental health before smoking cessation and at least six weeks after cessation or baseline in healthy and clinical populations.

Results 26 studies that assessed mental health with questionnaires designed to measure anxiety, depression, mixed anxiety and depression, psychological quality of life, positive affect, and stress were included. Follow-up mental health scores were measured between seven weeks and nine years after baseline. Anxiety, depression, mixed anxiety and depression, and stress significantly decreased between baseline and follow-up in quitters compared with continuing smokers: the standardised mean differences (95% confidence intervals) were anxiety −0.37 (95% confidence interval −0.70 to −0.03); depression −0.25 (−0.37 to −0.12); mixed anxiety and depression −0.31 (−0.47 to −0.14); stress −0.27 (−0.40 to −0.13). Both psychological quality of life and positive affect significantly increased between baseline and follow-up in quitters compared with continuing smokers 0.22 (0.09 to 0.36) and 0.40 (0.09 to 0.71), respectively). There was no evidence that the effect size differed between the general population and populations with physical or psychiatric disorders.

Conclusions Smoking cessation is associated with reduced depression, anxiety, and stress and improved positive mood and quality of life compared with continuing to smoke. The effect size seems as large for those with psychiatric disorders as those without. The effect sizes are equal or larger than those of antidepressant treatment for mood and anxiety disorders.

Introduction

Tobacco is the leading global cause of preventable death, estimated to cause more than five million deaths a year, and this is predicted to rise.[1] The worldwide cost of healthcare from tobacco use has been estimated within the billion dollar range.[2] Smoking is a major risk factor for the development of cancers and cardiovascular and respiratory diseases[3]; stopping smoking substantially reduces these health risks.[4 5] The association between smoking and mental health, however, is less clear cut. Although most smokers report wanting to quit,[6] many continue as they report that smoking provides them with mental health benefits. Both quantitative and qualitative analyses indicate that regular smokers report smoking cigarettes to alleviate emotional problems and feelings of depression and anxiety, to stabilise mood, and for relaxation as well as relieving stress.[7-13] This pattern of behaviour occurs in smokers with and without diagnosed mental disorders.[9 12 13] Unsurprisingly, views about smoking predict whether or not people attempt to quit[14] and whether or not they are successful.[15]

Although smokers think that smoking offers mental health benefits, there is a strong association between smoking and poor mental health, and smokers with mental health disorders tend

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Appendix 1: Supplementary text and tables A-D
Appendix 2: Included studies and population characteristics
Appendix 3: Characteristics of tobacco use and cessation intervention
Appendix 4: Study characteristics that might present risk of bias

to be heavier smokers and more dependent.[16 17] Three broad explanations have been proposed to explain these associations: smoking and poor mental health might have common causes[18]; people with poor mental health smoke to regulate feelings such as low mood and anxiety[19]; or smoking might cause or exacerbate mental health problems.[20] Although smokers with and without mental disorders think that smoking provides mental health benefits, they might be misattributing the ability of cigarettes to abolish nicotine withdrawal as a beneficial effect on mental health. Smokers experience irritability, anxiety, and depression when they have not smoked for a while,[21 22] and these feelings are reliably relieved by smoking[20] thus creating the perception that smoking has psychological benefits, while in fact it is smoking that caused these psychological disturbances in the first place.

Whatever the cause, the association between smoking and poor mental health warrants attention. Smokers might be less likely to stop if they believe their mental health will suffer, and health professionals might be reluctant to intervene with some smokers because they believe that this might be detrimental to their mental health.[23 24] As a result, people with mental health disorders have a life expectancy eight years less than the general population,[25] and much of this difference could be because of smoking.[17] For these reasons, we conducted a systematic review and meta-analysis of observational data to examine the difference in change in mental health between people who stop smoking and people who continue to smoke. Our hypothesis was that smokers who gave up would experience an improvement in mental health as a result because they would no longer experience multiple episodes of negative affect induced by withdrawal.

Methods

This study followed PRISMA[26] and MOOSE reporting guidelines.[27] There was no previously published protocol.

Eligibility criteria

We used broad eligibility criteria to capture all potentially relevant data and then used sensitivity and subgroup analyses to investigate clinical and methodological heterogeneity. Eligibility was decided on based on the following criteria:

- Population—studies of smokers in the general population or any that had selected smokers from populations defined by the presence of a clinical diagnosis
- Exposure—studies that reported data on those who had continued smoking and those who had quit smoking during the study period
- Outcome—any study that had measured mental health immediately before quitting and at least six weeks after quitting.
- Language—no exclusions were made based on language
- Study design— only longitudinal studies (that is, randomised controlled trials and cohort studies).

When data on change in mental health were available from different follow-ups within a single study we took the longest. Any type of measure of mental health was included (such as self report and clinician scored). We included studies that provided sufficient data to calculate the standardised mean difference (SMD) and its variance in change in mental health score from baseline to follow-up between quitters and continuing smokers. The standardised mean difference is the difference in change in mental health between baseline and follow-up divided by the standard deviation (SD) of the change. It is used to overcome the issue that depression, for example, can be measured by different questionnaires with different scoring systems. The questionnaires all measure depression but the different scoring means that they cannot be combined by using a simple mean. An SMD of 1 represents a difference in change in depression score of 1 SD. About 4 SD encompasses 95% of the population.[28]

Information sources and searches

We used searched Web of Science, Cochrane Central Register of Controlled Trials, Medline, Embase, and PsycINFO for studies published from inception to April 2012. We contacted study authors to obtain relevant missing data. We also searched reference lists of included studies. All non-English language studies were translated.

We used a combination of text words and indexed terms related to "mental health," "smoking cessation," and "smoking reduction" (see appendix 1).

Study selection

Our aim was to maximise sensitivity by including studies in initial screens even if data directly relevant to our question were not presented in the abstract. One researcher screened titles of retrieved studies for eligibility. The abstracts of eligible titles were screened twice for inclusion. The researchers met after independently screening abstracts to discuss inclusion/exclusion of each article. If there were disagreements, two researchers obtained and read the full text article.

Data collection process

Two researchers piloted the data extraction form, and appropriate changes were then made. The same two researchers independently extracted data from each paper and agreed on final data extraction in the case of disagreement. The corresponding authors of studies were contacted for additional data when necessary. Studies were excluded only if we could not obtain data on the change in mental health and its variance.

Data items

Participants—We recorded tobacco dependence and number of cigarettes smoked a day, age, sex, and motivation to quit, all at baseline.

Exposure—We extracted data on classification and bioverification of abstinence.

Comparator—The same data items were extracted for continuing smokers.

Outcomes—We extracted data on the change in mental health between baseline and follow-up. When such data were not available, we extracted data to calculate this (see statistical methods). To categorise the mental health outcomes we examined each measure's key reference and questionnaire to determine what it was designed to measure. We extracted the change in mental health unadjusted for confounding and adjusted for confounding using multivariable techniques.

Other items—We also extracted additional data to investigate clinical and methodological heterogeneity within and across studies (see sensitivity analyses for justification and methods). These items included study design, study quality score (Newcastle-Ottawa scale[29]), evidence of outcome reporting bias, follow-up length, covariates adjusted for, mental health management used in the intervention, and number of participants analysed at baseline and follow-up.

Statistical methods

Data extraction

The summary measure was the standardised mean difference (SMD) in change in mental health from baseline to follow-up between continuing smokers and people who managed to stop. Some studies reported either the difference in change or the standardised difference in change between continuing smokers and quitters, and hence data extraction of the effect estimate was straightforward. In some cases, studies presented the mean change for each group and we calculated the differences. In other cases, studies reported the mean at baseline and at follow-up for each group. We calculated change and its variance using a standard formula,[30] imputing a correlation coefficient taken from one of the largest studies included in the review (see appendix 1). In all cases, we also extracted the variance. If the variance was not presented we calculated it from P values, confidence intervals, or F values following standard formula as recommended by the Cochrane Collaboration.[28]

Meta-analysis method

We used a generic inverse variance random effects model to pool the standardised mean difference (SMD) between change in mental health in quitters and continuing smokers, from baseline to follow-up. We chose a random effects model as it incorporates heterogeneity both within and between studies. Statistical heterogeneity was assessed with τ^2 and I^2 tests. We used RevMan5 to conduct the meta-analyses and sensitivity and subgroup analyses.

Studies' effect estimates (SMD) were pooled by using the following outcome categories: anxiety, depression, mixed anxiety and depression, positive affect, psychological quality of life, and stress. We used SMD because the scales used to measure each outcome varied within category. This is standard practice for meta-analyses as outlined within the Cochrane Collaboration Handbook of Systematic Reviews and Meta-Analyses,[28] and as used in other high quality meta-analyses of continuous mental health outcomes.[31-33]

We also combined studies with different follow-up periods. We combined each study's longest follow-up period, as suggested by the Cochrane Collaboration. Heterogeneity between studies' follow-up length was accounted for by use of a random effects model. This is standard practice as outlined by the Cochrane Collaboration,[28] and as used in other high-quality meta-analyses of continuous mental health, with varying follow-up periods.[31-33]

Quality assessment

We assessed the quality of the evidence in each study on the association of change in smoking status with change in mental health using the Newcastle-Ottawa quality scale,[29] adapted for this study (see appendix 1). This assesses the quality of evidence based on the selection of the comparison groups, the comparability of the groups, and the quality of the measurement of exposure and outcome. The adapted scale rated studies from 0 to 5, and we deemed studies with a rating of 3 or lower as at higher risk of bias.

Assessment of publication and outcome reporting bias

We examined funnel plots for evidence of asymmetry and conducted Egger tests for evidence of small study bias using Stata 13.[34]

In some studies, data on change in mental health were presented incidentally and the aim was to report on other data. In others, the aim of the report was to present data on change in mental health, therefore the decision to publish might have been contingent on the results. We compared effect estimates between studies in which mental health was the primary outcome and those in which it was not to assess if there was evidence of publication bias.

When studies had relevant data on change in mental health but did not report sufficient data for meta-analysis, we attempted to estimate the direction of association and compare this with those included as this could indicate reporting bias.

Sensitivity analyses and assessment of risk of bias within and across studies

We conducted multiple sensitivity analyses to examine if the pooled effect estimate was influenced by including studies in which the risk of bias was greater or was influenced by characteristics of the study design or population. We either performed subgroup analyses or removed studies presenting a risk of bias and compared the pooled estimates with and without the excluded studies.

Adjustment for covariates

It is possible that change in mental health could be confounded by other differences between continuing smokers and quitters. To account for this, some studies adjusted their data for covariates thought to be associated with change in smoking status. We conducted a subgroup analysis to compare the effect estimate between studies that presented adjusted and unadjusted data.

Loss to follow-up

Some studies reported on change in mental health only in participants who were followed up, thus eliminating from the analysis those who were lost-to-follow-up. Other studies reported data on all participants who were present at baseline and the smaller number present at follow up; thus possibly creating spurious changes in mental health through loss to follow-up. The convention in smoking cessation studies is to regard participants who are lost to follow-up as smokers, so loss to follow-up selectively affects the continuing smoker group. We recorded whether or not studies reported data from a different number of participants at baseline and follow-up.

Ascertainment of smoking status

Some studies might misclassify exposure by using point prevalence smoking abstinence. This could include participants who had been abstinent for only a week in the group we classed as having been abstinent for at least six weeks, though most smokers who are point prevalent abstinent for a week have in truth been abstinent for longer.[35 36] Recently abstinent smokers are likely to experience withdrawal symptoms including low mood.[16] Thus, we recorded whether studies used a measure of prolonged or continuous abstinence (when misclassification could not have occurred) or if they used a point prevalence measure of abstinence. Likewise, particularly in smoking cessation trials, there is a danger that participants claim abstinence when this is not the case; therefore it best practice to bioverify smoking status.[35] Accordingly, we recorded whether or not self reported abstinence was biologically verified.

Motivation to quit

Our hypothesis was that cessation improved mental health, but our outcome measure was the difference in change in mental

health between those who stopped smoking and those who continued. It could be that such a difference would be evident if those who continued smoking had a worsening in mental health rather than those who stopped experiencing an improvement. Trying and failing to quit could worsen mental health, and some studies in the review derived data from smoking cessation trials. In these trials, all continuing smokers had tried but failed to achieve abstinence, and this disappointment could lead to worse mental health. In population cohorts, however, many continuing smokers would not have tried to achieve abstinence and therefore not have experienced this failure. We therefore classified studies as selected or not selected by motivation to quit. Populations in which participants were not selected by motivation to quit were less likely to create this spurious difference between quitters and continuing smokers.

Psychotherapeutic component within cessation intervention

Having a psychotherapeutic intervention can improve mental health. Some smoking cessation interventions include mood management. Successful quitters often attend smoking cessation clinics, while relapsers cease attending, meaning that one group might have had more counselling than the other. We searched for the trial protocols and main report of the outcomes of all smoking cessation intervention trials in which counselling had taken place to assess whether mood management was part of this.

Additional analyses

Clinical population comparison

The studies included in the review enrolled the general population, pregnant women, or patients who were postoperative, had a chronic physical condition, a psychiatric condition, or chronic psychiatric or physical conditions. We examined whether there was evidence of a difference in effect size between these populations.

Study design

Our hypothesis was that stopping smoking improved mental health but any association between cessation and improved mood could be caused by reverse causation—that is, that improved mood caused successful cessation. The studies in this review fell into two groups: those recruiting a general population of smokers and those in which all participants were enrolled in smoking cessation trials. In trials, all participants attempted to quit and therefore the decision to quit was not contingent on mood. Secondary analyses from trials therefore exclude reverse causation.

Length of follow-up

We also examined whether there was evidence of a difference in effect estimate between studies in which change in mental health was assessed from six weeks to six months or more than six months after baseline.

Results

Study selection

The database and reference list searches resulted in 13 050 references. After initial screening we assessed 219 full text articles for eligibility, of which 166 were excluded before data extraction. Twenty seven were then excluded during data extraction (see tables B and C in appendix 1 for details), 15 of which provided sufficient descriptions to include in a narrative synthesis of the direction and/or significance of change in mental health. We included 26 studies in the meta-analyses and for six of these studies authors supplied additional data (fig 1⇓) (the full reference list is in appendix 1).

Outcome categories

The included studies examined six different measures of mental health: anxiety, depression, mixed anxiety and depression, positive affect, psychological quality of life, and stress (appendix 2).

Extraction

Several studies presented data on more than one outcome. Sixteen effect estimates were calculated from groups' mean mental health scores, which were reported at both baseline and follow-up. Seven were calculated from studies that presented each groups' mean change in mental health score from baseline to follow-up. Two were calculated from a non-standardised difference in change. Three were extracted from other types of effect estimates.

Study characteristics

Eleven of the studies were cohort studies, 14 were secondary analyses of cessation interventions, and one was a randomised trial. Study enrolment included the general population (14 studies), populations living with a chronic physical condition (three), pregnant women (two), postoperative patients (one), people with either a chronic physical and/or psychiatric condition (two), and people with psychiatric conditions (four). The median age was 44, and on average 48% were men. On average, participants smoked 20 cigarettes a day and scored 5.4 on the Fagerström test for nicotine dependence, indicating moderate dependence. The median length of follow up was six months (appendix 2 and 3).

In 11 studies, abstinence was measured as continuous abstinence from a point soon after baseline assessment, and in 18 studies abstinence was biologically verified. In seven studies participants received a psychological intervention as part of the cessation intervention. In 17 studies participants were motivated to quit (appendix 4).

Study quality

Twenty studies had high quality scores on the Newcastle-Ottawa scale, and five had medium to low scores; for one study there was insufficient information to determine a score (conference abstract).

Results of meta-analyses

Anxiety

Four studies reported change in anxiety from baseline to follow-up, with follow-ups ranging from seven weeks to 12 months (median six months). Compared with continuing to smoke, quitting smoking was associated with a significant decrease in anxiety from baseline to follow-up (standardised mean difference (SMD) −0.37, 95% confidence interval −0.70 to −0.03; P=0.03). There was substantial statistical heterogeneity between studies (I^2=71%; fig 2⇓).[28]

Mixed anxiety and depression

Five studies reported change in mixed anxiety and depression from baseline to follow-up, with follow-up ranging from three months to six years (median six months). Compared with continuing to smoke, quitting smoking was associated with a significant decrease in mixed anxiety and depression from baseline to follow-up (SMD −0.31, 95% confidence interval −0.47 to −0.14; P<0.001; I^2=0%; fig 2⇓).

Depression

Ten studies reported change in depression from baseline to follow-up, with follow-up ranging from 11 weeks to five years (median 12 months). Compared with continuing to smoke, quitting smoking was associated with a significant decrease in depression from baseline to follow-up (SMD −0.25, 95% confidence interval −0.37 to −0.12; P<0.001; I^2=30%; fig 2⇓).

Stress

Three studies reported change in stress from baseline to follow-up, with follow-up ranging from six months to six years (median 12 months). Compared with continuing to smoke, quitting smoking was associated with a significant decrease in stress (SMD −0.27, 95% CI −0.40 to −0.13; P<0.001) from baseline to follow-up (I^2=0%; fig 2⇓).

Psychological quality of life

Eight studies reported change in psychological quality of life from baseline to follow-up, with follow-ups ranging from two months to nine years (median 12 months). Compared with continuing to smoke, quitting smoking was associated with a significant improvement in psychological quality of life from baseline to follow-up (SMD 0.22, 95% confidence interval 0.09 to 0.36; P<0.001). There was moderate statistical heterogeneity between studies (I^2=63%; fig 3⇓).[28]

Positive affect

Three studies reported change in positive affect from baseline to follow-up, with follow-ups ranging from three months to four years (median 12 months). Compared with continuing to smoke, quitting smoking was associated with a significant increase in positive affect from baseline to follow-up (SMD 0.40, 95% confidence interval 0.09 to 0.71; P=0.01; I^2=49%; fig 3⇓).

Sensitivity and subgroup analyses

We conducted numerous sensitivity and subgroup analyses to investigate clinical and methodological heterogeneity and to investigate risk of bias within and across studies.

Study quality

Removal of studies with medium to low scores on the Newcastle-Ottawa scale did not greatly change the summary estimates (table 1⇓).

Publication and outcome reporting bias

There were sufficient studies to create funnel plots for anxiety, depression, mixed anxiety and depression, and psychological quality of life. The plots were symmetrical for depression, anxiety, and mixed anxiety and depression and asymmetrical for psychological quality of life. Egger tests indicated that small studies measuring psychological quality of life provided larger effect estimates than studies with larger samples (P=0.017). Seven out of eight of the pooled studies, however, had sample sizes ranging from 34 to 323. Thus, the result of the Egger test is likely influenced by the only large study (Sarna 2008, see appendix 1), which analysed data from 11 809 participants, and accounted for 25.7% of the pooled effect estimate. There was no evidence of small study bias for studies that measured anxiety (P=0.184), depression (P=0.064), mixed anxiety and depression (P=0.307), positive affect (P=0.179), or stress (P=0.705).

In 20 of the 26 studies, the main aim was to report on change in mental health and the decision to publish could have been contingent on the strength or significance of the finding (appendix 4). The main aim of the six other studies was to report on other outcomes, and they reported only psychological quality of life and positive affect. Subgroup analysis showed no evidence of a difference in effect between studies that did not primarily report on change in mental health and those that did so for psychological quality of life (P=0.19) and positive affect (P=0.14). One of the 26 studies showed evidence of multiple testing and selectively reported the only significant result (appendix 4).

Results of narrative synthesis

We excluded 15 studies because there were insufficient data to extract an effect size or its variance, despite contact with the authors (see table C in appendix 1). Nine of the 15 studies reported on the significance of the difference in change between quitters and continuing smokers (see table D in appendix 1): three reported no significant difference, five favoured quitters, and one study showed a difference favouring continuing smoking. Of the nine studies, seven reported that mental health improved in quitters, one showed no change, and one showed a worsening in mental health for quitters. Five of nine studies reported information on change in mental health for continuing smokers; three studies reported that mental health had worsened at follow-up and two reported that it had improved.

Adjustment for covariates

Two studies supplying estimates for three outcomes (anxiety, depression, and positive affect) provided effect sizes of the difference in change in mental health both unadjusted and adjusted for confounders. The confounders included demographics, information pertaining to tobacco consumption, and/or treatment allocation. Comparison of these estimates indicates that adjustment did not greatly change the results (table 2⇓).

We also compared the summary effect estimates from studies that supplied only unadjusted effect estimates with studies that supplied only adjusted effect estimates. Studies adjusted for several potential confounders. For anxiety one study adjusted for covariates, for depression four studies adjusted for covariates, for psychological quality of life five studies adjusted for covariates, for positive affect two studies adjusted for covariates, and for stress and mixed anxiety and depression no studies adjusted for covariates. The effect sizes were similar for studies that did and did not adjust for covariates for all outcomes except anxiety. Studies that adjusted for covariates showed a significantly bigger difference between quitters and smokers than those that did not adjust (table 3⇓).

Loss to follow-up

Twelve of the 26 studies reported means at baseline on a larger number than contributed to the mean at follow-up. Removal of these 12 did not greatly change the effect estimates (table 4⇓).

Ascertainment of smoking status

Eleven studies did not report continuous abstinence, classification of smoking status was not clear in four studies, and eight did not biochemically confirm abstinence; exclusion of these did not change the results (table 5⇓).

Motivation to quit

In a subgroup analysis we compared the 16 studies in which participants were all attempting to quit with the 10 studies in which participants were not selected by motivation to quit. There was no evidence of subgroup differences (table 6⇓, suggesting that deterioration in mental health as a reaction to failing to quit was an unlikely cause of the difference between quitters and continuing smokers.

Psychotherapeutic component within cessation intervention

Seven studies included a psychotherapeutic element in the cessation intervention to help participants manage symptoms of anxiety or low mood. Removal of these studies did not greatly change the summary estimate (table 7⇓).

Additional analyses

Comparison of clinical population

Fourteen studies enrolled smokers from the general population, four enrolled patients with psychiatric disorders, three enrolled patients with chronic physical conditions, two enrolled patients with either psychiatric or physical conditions, two enrolled pregnant women, and one enrolled patients after surgery. There was no evidence that the effect size differed across these different clinical populations (table 8⇓).

We were especially interested in the population with psychiatric disorders, and data were available on change in depression, mixed anxiety and depression, and positive affect. The effect estimates for this subgroup compared with the general population were −0.39 (95% confidence interval −0.63 to −0.14) versus −0.30 (−0.48 to −0.12) for depression; −0.21 (−1.07 to 0.65) versus −0.32 (−0.53 to −0.11) for mixed anxiety and depression; 0.40 (−0.03 to 0.83) versus 0.15 (−0.01 to 0.30) for psychological quality of life; and 0.68 (0.24 to 1.12) versus 0.16 (−0.14 to 0.46) for positive affect.

Study design

Eleven studies were cohort studies, 14 were secondary analyses of cessation interventions, and one was a randomised trial. There was no evidence of subgroup differences between these study designs (table 9⇓).

Length of follow-up

The effect sizes were similar for studies that assessed mental health between six weeks and six months and those with follow-ups longer than six months (table 10⇓). We also ordered studies according to follow-up length in forest plots (figures 2 and 3[2]⇓), which indicated no clear chronological pattern in effect estimates.

Discussion

There is consistent evidence that stopping smoking is associated with improvements in depression, anxiety, stress, psychological quality of life, and positive affect compared with continuing to smoke. The strength of association is similar for both the general population and clinical populations, including those with mental health disorders. There is no evidence that methodological heterogeneity or short comings explained these associations nor is there substantial evidence of publication bias.

Strength of the study

The strengths of this study lay in the broad search terms that we used to retrieve literature, including hand searching to avoid missing available literature and also checking reference lists of included studies. We also contacted authors and calculated data from papers in which, in most cases, the data were not provided in a directly usable form.

In most included studies, the quality of measurement of exposure status—smoking—was adequate. Nearly half of the studies reported prolonged or continuous abstinence that was biologically verified; this removed the threat of misclassification of exposure. Sensitivity analysis showed no evidence that studies that assessed smoking in other ways could have altered the results. Inclusion of such studies would, in general, underestimate the true strength of the association. Likewise, assessment of outcome was good, with participants completing validated self reported mental health questionnaires before they stopped smoking and at follow-up. Assessors were, in that sense, blind to exposure status, and no study was set up primarily to investigate change in mental health on cessation.

Confounding is usually a major threat to the validity of most associations based on observational data. In this case, there was limited scope for confounding because we compared change within individuals between groups. Confounders associated with mental health at baseline and at follow-up will not affect the validity of association. Confounding will occur only if the strength or direction of association changes between baseline and follow-up and that change differs by exposure group (quitters and continuing smokers). The latter case is not so plausible. In support of this, adjustment for potential confounders, which were mostly factors associated with propensity to achieve cessation, had only small effects in the studies that reported such data. We consider that the data within each study are robust and the association is unlikely to arise through bias or confounding.

The validity of the review rests on whether the search retrieved appropriate literature. We aimed to retrieve a large number of cohort studies that might have contained data, even when this was not readily apparent. Doing so, we uncovered several studies that would have been missed if we had confined the search to studies that seemed to be about smoking cessation and mental health. In all cases, the data were derived from secondary analyses of studies investigating other hypotheses (for example, secondary analyses of cessation interventions, population cohorts). It could be that authors of similar studies analysed the data in the same way but found no association so might have chosen not to publish the data. We found one example when a study reported quantitative data only for the significant (and presumably stronger) association and did not report other non-significant associations. Other studies that reported on the association but not completely enough for us to assess quantitatively, however, seemed to give similar results to those in which the data were more clearly presented. Overall, we found little evidence of publication bias, but this cannot be excluded.

Possible interpretations

We believe that the data are valid and propose three possible explanations for the association. The first is that smoking cessation causes the improvement in mental health, the second

is that improving mental health causes cessation, and the third is that a common factor explains both improved mental health and cessation. Observational data can never prove causality, but almost all we know about the harms of smoking and the benefits of cessation derive from observational studies as randomised trials to examine this have insurmountable ethical and practical difficulties.

Could a common factor explain both cessation and improved mental health? This supposes that a single factor—such as positive life events—can cause people to attempt or achieve cessation and improve mental health. As far as we know, there is no evidence that positive life events lead to sustained cessation. In addition, mental health outcomes were assessed anywhere from seven weeks to nine years after baseline, and it seems implausible that such events are associated with positive mental health changes during this entire period.

An obvious explanation for the association is that improvements in mental health prompt people to attempt cessation and that this explains the association. This is contradicted by the data, however. Over half the studies were secondary analyses of randomised trials. In these studies everyone attempted cessation and therefore the decision to quit was not contingent on change in mental health. Subgroup analyses that split data by whether they were derived from such trials or from population cohorts showed no evidence of a difference and a significant difference in change in smokers who quit compared with those who continued in the trial based analyses. Further data support the notion that cessation improves mood. In some but not all of the studies we could calculate the change in mental health in quitters and continuing smokers, rather than just the difference in the change as we have presented. We calculated the weighted mean change for both groups, though formal statistical analysis was not possible to compare groups (data available on request). These data indicate little change in mental health from baseline to follow-up in continuing smokers, while smokers who quit showed reductions in adverse mental health symptoms and improvements in positive affect and quality of life. One of the studies in the review was a trial in which participants were randomised to continue smoking or quit. Obviously adherence to this instruction was not absolute, but analysis of the data by trial arm showed a modest benefit of cessation compared with continuing to smoke. The trial was not powered to detect this difference and it was not significant, but it does provide further evidence to support the notion that stopping smoking leads to improvements in mental health.

Data from a systematic review of randomised trials support the notion that cessation improves mental health. Banham and Gilbody systematically reviewed eight trials of smoking cessation interventions in people with severe mental illnesses.[37] All trials that assessed psychological function typically used several scales at multiple times. Most showed no difference between active and control groups, but the two studies that reported significant differences favoured the intervention groups. Another study reported after this review randomised people with serious mental illness to cessation support or usual care. It showed that cessation support reduced readmissions for worsening mental illness.[38] These data do not directly estimate the effect of cessation on mental health because most people who were randomised to the intervention did not quit. But these findings, in people with serious mental illness, support the findings in our review that psychological outcomes improve on cessation.

Possible mechanisms

The hypothesis that cessation improves mood is supported by a plausible biological mechanism. Chronic tobacco smoking is associated with neuroadaptations in nicotinic pathways in the brain. Neuroadaptations in these pathways are associated with occurrence of depressed mood, agitation, and anxiety shortly after a cigarette is smoked.[39-42] This is known as the withdrawal cycle and is marked by fluctuations in a smoker's psychological state throughout the day[40 41] and could worsen mental health.[20] A study reported that the neurological functioning of quitters returned to the same level as non-smokers by three weeks after cessation,[43] consistent with reports that withdrawal symptoms abate after a few weeks.[21] The misattribution hypothesis is that smokers attribute these symptoms as arising from stress or poor mental health and conclude from the ability of cigarettes to ameliorate these symptoms that cigarettes improve mental health.

Not all data, however, support this causal interpretation. An epidemiological study exploiting mendelian randomisation examined the causal link between current smoking and current anxiety and depression.[44] Although there was some evidence that smoking causes anxiety, the results as a whole did not support a causal link between smoking status and current mental health problems. These data argue against the misattribution hypothesis, whereby periods of psychological changes related to withdrawal from smoking are eliminated by neurological adaptation to permanent deprivation of nicotine.

If the associations we found in this review are causal then the effect size is clinically important. Fournier and colleagues meta-analysed trials of selective serotonin reuptake inhibitors and estimated the effect size.[45] For mild to severe depression the effect estimates ranged from −0.17 to −0.11; this is lower than the effect size for smoking cessation. A meta-analysis of 34 randomised controlled trials assessed the effect of antidepressants on generalised anxiety disorder.[46] These effect estimates ranged from −0.23 (−0.43 to −0.13) to −0.50 (−0.77 to −0.23); this is similar to smoking cessation at −0.37. This result is particularly important in view of our findings in patients with psychiatric disorders. There was no evidence that the effect size differed between population subgroups based on clinical diagnosis, and the effect on depression, psychological quality of life, and positive affect was significant in people who had mental disorders. These data should reassure doctors treating patients with mental illness that cessation is unlikely to exacerbate their symptoms and might indeed be therapeutic.

We recommend that future studies investigating the association between stopping smoking and change in mental health should use statistical techniques that can strengthen the causal inferences that could be drawn from observational research. Propensity score matching can be used to balance the distribution of baseline covariates that could influence disposition to group membership (smoking status). In addition, mendelian randomisation can be used as an instrumental variable approach by using genes that have a common association with change in mental health and smoking status.

Conclusions

Whether or not smoking cessation directly causes the observed improvement in mental health, there are direct clinical implications. Smokers can be reassured that stopping smoking is associated with mental health benefits. This could also overcome barriers that clinicians have toward intervening with smokers with mental health problems. Furthermore, challenging

the widely held assumption that smoking has mental health benefits could motivate smokers to stop.

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Contributors: GT was involved in study design, systematic search, pilot of data extraction form, title/abstract scanning, obtaining full text, determining eligibility of articles, correspondence with authors of eligible papers, quality checks of included articles, data extraction, data synthesis/analysis, data interpretation, literature search, and writing manuscript and appendix 1. AMcN was involved in study design, pilot of data extraction form, determining eligibility of articles, quality checks of included articles, data extraction, data interpretation, literature search, and writing manuscript and appendix 1. AG was involved in determining eligibility of articles, data extraction, data synthesis/analysis, data interpretation, and writing manuscript and appendix 1. AF was involved in data synthesis/analysis, data interpretation, writing manuscript and appendix 1. NL-H was involved in title/abstract scanning and writing manuscript. PA was involved in study design, systematic search, pilot data of extraction form, title and abstract scanning, determining eligibility of articles, quality checks of included articles, data extraction, data synthesis/analysis, data interpretation, literature search, writing manuscript and appendix 1. GT and PA are guarantors.

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Ethical approval: None required.

Data sharing: Statistical formulas and dataset are available from corresponding authors.

Transparency: GT affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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What is already known on this topic

Many smokers want to stop but continue smoking as they believe smoking has mental health benefits

In addition, health professionals are reluctant to deal with smoking in people with mental disorders in case stopping smoking worsens mental health

What this study adds

Smoking cessation is associated with an improvement in mental health in comparison with continuing to smoke

The effect estimates are equal or larger to those of antidepressant treatment for mood disorders

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Tables

Table 1| **Effect of smoking cessation on mental health. Sensitivity analysis after removal of studies of low quality (medium-low scores on Newcastle-Ottawa scale)**

			Standardised mean difference (95% CI)	
Outcome	**No of studies included**	**No of studies excluded**	**Effect estimate**	**Original effect estimate**
Anxiety	4	0	−0.37 (−0.70 to −0.03)	−0.37 (−0.70 to −0.03)
Depression	9	1	−0.29 (−0.42 to −0.15)	−0.25 (−0.37 to −0.12)
Mixed anxiety and depression	4	1	−0.36 (−0.58 to −0.14)	−0.31 (−0.47 to −0.14)
Psychological quality of life	4	4	0.17 (−0.02 to 0.35)	0.22 (0.09 to 0.36)
Positive affect	1	2	0.68 (0.24 to 1.12)	0.40 (0.09 to 0.71)
Stress	2	1	−0.23 (−0.39 to −0.07)	−0.27 (−0.40 to −0.13)

Table 2| **Effect of smoking cessation on mental health. Comparison of unadjusted and adjusted estimates from studies in which both were presented**

			Standardised mean difference (95% CI)	
Study	**Covariates adjusted for**	**Outcome (measure)**	**Unadjusted estimate**	**Adjusted estimate**
Blalock (2008)*	Baseline CO expiration, baseline nicotine withdrawal score, treatment group allocation	Beck's depression inventory	−0.54 (−1.42 to 0.34)	−0.58 (−1.00 to −0.16)
		Positive and negative affect schedule (positive affect subscale)	0.59 (−0.29 to 1.47)	0.68 (0.24 to 1.12)
McDermott (2012)†	Age, nicotine dependence, and daily cigarette consumption	State trait anxiety inventory-6	−0.62 (−0.88 to −0.36)	−0.74 (−1.00 to −0.48)

*Blalock JA, Robinson JD, Wetter DW, Schreindorfer LS, Cinciripini PM. Nicotine withdrawal in smokers with current depressive disorders undergoing intensive smoking cessation treatment. *Psychol Addict Behav* 2008;22:122-8.

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Table 3| **Effect of smoking cessation on mental health. Subgroup analysis with comparison of effect estimates between studies that did and did not adjust for covariates**

Outcome	Standardised mean difference (95% CI)			Test for subgroup differences
	Original estimate	Adjusted estimate	Unadjusted estimate	
Anxiety*	−0.37 (−0.70 to −0.03) (4 studies)	−0.74 (−1.00 to −0.48) (1 study)	−0.34 (−0.61 to −0.07) (4 studies)	χ^2=4.40, P=0.04
Depression*	−0.25 (−0.37 to −0.12) (10 studies)	−0.41 (−0.65 to −0.17) (4 studies)	−0.15 (−0.27 to−0.03) (7 studies)	χ^2=3.49, P=0.062
Mixed anxiety and depression	−0.31 (−0.47 to −0.14) (5 studies)	No data	−0.31 (−0.47 to −0.14) (5 studies)	Not applicable
Positive affect	0.40 (0.09 to 0.71) (3 studies)	0.28 (−0.02 to 0.57) (2 studies)	0.68 (0.24 to 1.12) (1 study)	χ^2=2.22, P=0.14
Psychological quality of life	0.22 (0.09 to 0.36) (8 studies)	0.24 (0.07 to 0.40) (5 studies)	0.22 (−0.13 to 0.57) (3 studies)	χ^2=0.01, P=0.92
Stress	−0.27 (−0.40 to −0.13) (3 studies)	No data	−0.27 (−0.40 to −0.13) (3 studies)	Not applicable

*Please note that for anxiety and depression some studies provided both adjusted and unadjusted estimates, so these were compared within corresponding subgroup analysis.

Table 4| **Effect of smoking cessation on mental health. Sensitivity analysis with removal of studies in which different numbers of participants were analysed at baseline and follow-up**

			Standardised mean difference (95% CI)	
Outcome	**No of studies included**	**No of studies excluded**	**Effect estimate**	**Original effect estimate**
Anxiety	4	0	−0.37 (−0.70 to −0.03)	−0.37 (−0.70 to −0.03)
Depression	3	7	−0.30 (−0.67 to 0.07)	−0.25 (−0.37 to −0.12)
Mixed anxiety and depression	3	2	−0.26 (−0.44 to −0.07)	−0.31 (−0.47 to −0.14)
Positive affect	3	0	0.40 (0.09 to 0.71)	0.40 (0.09 to 0.71)
Psychological quality of life	5	3	0.18 (0.02 to 0.33)	0.22 (0.09 to 0.36)
Stress	2	1	−0.27 (−0.42 to −0.12)	−0.27 (−0.40 to −0.13)

Table 5| **Effect of smoking cessation on mental health. Sensitivity analyses after ascertainment of smoking status**

			Standardised mean difference (95% CI)	
Removed studies and outcome	**No of studies included**	**No of studies excluded**	**Effect estimate**	**Original effect estimate**
Smoking status not biochemically verified				
Anxiety	4	0	−0.37 (−0.70 to −0.03)	−0.37 (−0.70 to −0.03)
Depression	7	3	−0.32 (−0.50 to −0.13)	−0.25 (−0.37 to −0.12)
Mixed anxiety and depression	3	2	−0.35 (−0.59 to −0.10)	−0.31 (−0.47 to −0.14)
Psychological quality of life	4	4	0.17 (−0.02 to 0.35)	0.22 (0.09 to 0.36)
Positive affect	1	2	0.68 (0.24 to 1.12)	0.40 (0.09 to 0.71)
Stress	2	1	−0.23 (−0.39 to −0.07)	−0.27 (−0.40 to −0.13)
Point prevalence smoking status				
Anxiety	2	1	−0.51 (−1.04 to 0.03)	−0.37 (−0.70 to −0.03)
Depression	6	4	−0.34 (−0.52 to −0.16)	−0.25 (−0.37 to −0.12)
Mixed anxiety and depression	3	2	-0.29 (-0.52 to -0.07)	−0.31 (-0.47 to -0.14)
Psychological quality of life	1	7	0.37 (0.07 to 0.67)	0.22 (0.09 to 0.36)
Positive affect	2	1	0.39 (−0.11 to 0.90)	0.40 (0.09 to 0.71)
Stress	2	1	−0.27 (−0.42 to −0.12)	−0.27 (−0.40 to −0.13)

Table 6| **Effect of smoking cessation on mental health. Subgroup analysis with comparison of studies in which participants were motivated or not motivated to quit**

Population (No of studies)	Standardised mean difference (95% CI)	Test for subgroup differences
Anxiety		
Overall (4)	−0.37 (−0.70 to −0.03)	—
Motivated to quit (3)	−0.41 (−0.81 to −0.00)	χ^2=2.77, P=0.10
Not motivated to quit (1)	−0.19 (−0.68 to 0.30)	
Depression		
Overall (10)	−0.25 (−0.37 to −0.12)	—
Motivated to quit (6)	−0.31 (−0.53 to −0.09)	χ^2=1.16, P=0.28
Not motivated to quit (4)	−0.17 (−0.30 to −0.05)	
Mixed anxiety and depression		
Overall (5)	−0.31 (−0.47 to −0.14)	
Motivated to quit (3)	−0.35 (−0.59 to −0.10)	χ^2=0.19, P=0.66
Not motivated to quit (2)	−0.27 (−0.50 to −0.04)	
Psychological quality of life		
Overall (8)	0.22 (0.09 to 0.36)	—
Motivated to quit (4)	0.20 (0.03 to 0.38)	χ^2=0.17, P=0.68
Not motivated to quit (4)	0.26 (0.04 to 0.49)	
Positive affect		
Overall (3)	0.40 (0.09 to 0.71)	—
Motivated to quit (2)	0.39 (−0.11 to 0.90)	χ^2=3.95, P=0.11
Not motivated to quit (1)	0.47 (0.04 to 0.90)	
Stress		
Overall (3)	−0.27 (−0.40 to −0.13)	—
Motivated to quit (2)	−0.23 (−0.39 to −0.07)	χ^2=0.74, P=0.39
Not motivated to quit (1)	−0.36 (−0.61 to −0.11)	

Table 7| **Effect of smoking cessation on mental health. Sensitivity analysis after removal of studies with psychological component within cessation intervention**

			Standardised mean difference (95% CI)	
Outcome	**No of studies included**	**No of studies excluded**	**Effect estimate**	**Original effect estimate**
Anxiety	4	0	−0.37 (−0.70 to −0.03)	−0.37 (−0.70 to −0.03)
Depression	6	4	−0.15 (−0.26 to −0.03)	−0.25 (−0.37 to −0.12)
Mixed anxiety and depression	3	2	−0.28 (−0.46 to −0.10)	−0.31 (−0.47 to −0.14)
Psychological quality of life	5	3	0.15 (−0.01 to 0.31)	0.22 (0.09 to 0.36)
Positive affect	1	2	0.47 (0.04 to 0.90)	0.40 (0.09 to 0.71)
Stress	3	0	−0.27 (−0.40 to −0.13)	−0.27 (−0.40 to −0.13)

Table 8| **Effect of smoking cessation on mental health. Subgroup analysis with comparison of effect estimates between different clinical populations**

Outcome and population (No of studies)	Effect estimate standardised mean difference (95% CI)	Test for subgroup differences
Anxiety		
Overall	−0.37 (−0.70 to −0.03)	—
General (3)	−0.48 (−0.81 to −0.15)	χ^2=2.77, P=0.10
Pregnant (1)	−0.06 (−0.42 to 0.30)	
Depression		
Overall	−0.25 (−0.37 to −0.12)	—
General (5)	−0.30 (−0.48 to −0.12)	χ^2=5.86, P=0.053
Psychiatric condition (3)	−0.39 (−0.63 to −0.14)	
Pregnant (2)	−0.07 (−0.23 to 0.09)	
Mixed anxiety and depression		
Overall	−0.31 (−0.47 to −0.14)	—
General (3)	−0.32 (−0.53 to −0.11)	χ^2=0.08, P=0.96
Psychiatric condition (1)	−0.21 (−1.07 to 0.65)	
Chronic physical and/or psychiatric condition (1)	−0.29 (−0.57 to −0.01)	
Psychological quality of life		
Overall	0.22 (0.09 to 0.36)	—
General (3)	0.15 (−0.01 to 0.30)	χ^2=5.25, P=0.25
Psychiatric condition (1)	0.40 (−0.03 to 0.83)	
Chronic physical and/or psychiatric condition (1)	0.60 (0.17 to 1.03)	
Chronic physical condition (1)	0.16 (−0.11 to 0.43)	
Postoperative (1)	0.62 (−0.27 to 1.51)	
Positive affect		
Overall	0.40 (0.09 to 0.71)	—
Chronic physical and/or psychiatric condition (1)	0.47 (0.04 to 0.90)	χ^2=3.95, P=0.11
General (1)	0.16 (−0.14 to 0.46)	
Psychiatric condition (1)	0.68 (0.24 to 1.12)	
Stress		
Overall	−0.27 (−0.40 to −0.13)	—
General (2)	−0.32 (−0.52 to −0.12)	χ^2=0.51, P=0·48
Chronic physical condition (1)	−0.22 (−0.40 to −0.04)	

Table 9| **Effect of smoking cessation on mental health. Subgroup with comparison of effect estimates between different study designs**

Study design *No of studies)	Effect estimate standardised mean difference (95% CI)	Test for subgroup differences
Anxiety		
Overall	−0.37 (−0.70 to −0.03)	—
Cohort (1)	−0.06 (−0.42 to 0.30)	χ^2=4.07, P=0.13
Randomised controlled trial (1)	−0.19 (−0.68 to 0.30)	
Secondary analyses of cessation intervention (2)	−0.57 (−0.93 to −0.21)	
Depression		
Overall	−0.25 (−0.37 to −0.12)	—
Cohort (3)	−0.12 (−0.25 to 0.01)	χ^2=5.15, P=0.08
Randomised controlled trial (1)	−0.39 (−0.88 to 0.10)	
Secondary analyses of cessation intervention (6)	−0.36 (−0.53 to −0.18)	
Mixed anxiety and depression		
Overall	−0.31 (−0.47 to −0.14)	—
Cohort (3)	−0.28 (−0.46 to −0.10)	χ^2=0.76, P=0.38
Secondary analyses of cessation intervention (2)	−0.51 (−0.99 to −0.03)	
Psychological quality of life		
Overall	0.22 (0.09 to 0.36)	—
Cohort (5)	0.28 (0.08 to 0.48)	χ^2=0.95, P=0.33
Secondary analyses of cessation intervention (3)	0.15 (−0.04 to 0.33)	
Positive affect		
Overall	0.40 (0.09 to 0.71)	—
Cohort (2)	0.28 (−0.02 to 0.57)	χ^2=2.22, P=0.14
Secondary analyses of cessation intervention (1)	0.68 (0.24 to 1.12)	
Stress		
Overall	−0.27 (−0.40 to −0.13)	—
Cohort (1)	−0.36 (−0.61 to −0.11)	χ^2=0.74, P=0.39
Secondary analyses of cessation intervention (2)	−0.23 (−0.39 to −0.07)	

Table 10| **Effect of smoking cessation on mental health. Subgroup analysis after comparison of effect estimates between studies with follow-up periods from baseline to follow-up between six weeks to six months and studies with follow-ups from baseline to more than six months**

	Standardised mean difference (95% CI)			
Outcome	**Original estimate**	**6 weeks to <6 months**	**>6 months**	**Test for subgroup differences**
Anxiety	−0.37 (−0.70 to −0.03)	−0.35 (−0.83 to 0.12) (3 studies)	−0.37 (−0.72 to −0.02) (1 study)	χ^2=0.00, P=0.95
Depression*	−0.25 (−0.37 to −0.12)	−0.18 (−0.31 to −0.05) (8 studies)	−0.23 (−0.41 to −0.06) (5 studies)	χ^2=0.25, P=0.62
Mixed anxiety and depression*	−0.31 (−0.47 to −0.14)	−0.37 (−0.58 to −0.15) (4 studies)	−0.27 (−0.50 to −0.04) (2 studies)	χ^2=0.34, P=0.56
Positive affect	0.40 (0.09 to 0.71)	0.68 (0.24 to 1.12) (1 study)	0.28 (−0.02 to 0.57) (2 studies)	χ^2=2.22, P=0.14
Psychological quality of life*	0.22 (0.09 to 0.36)	0.30 (0.15 to 0.44) (7 studies)	0.23 (0.09 to 0.37) (8 studies)	χ^2=0.36, P=0.92
Stress	−0.27 (−0.40 to -0.13)	−0.25 (−0.58 to 0.08) (1 study)	−0.27 (−0.42 to −0.12) (2 studies)	χ^2=0.01, P=0.92

*Please note some studies measured outcome at multiple follow-ups, so these were compared within corresponding subgroup analysis

Figures

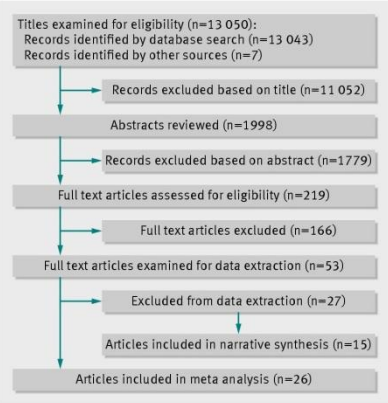


Fig 1 Flow and identification of studies to include in review of change in mental health after smoking cessation

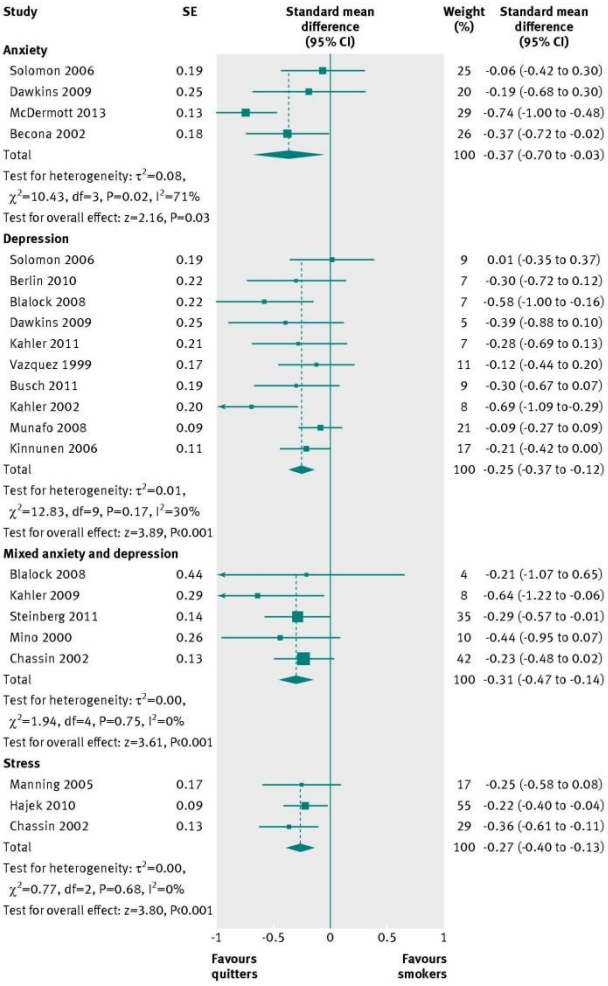


Fig 2 Difference between change in mental health outcomes (anxiety, mixed anxiety and depression, depression, stress) from baseline to longest follow-up in people who stopped smoking or continued to smoke. Study by McDermott was in submission during search

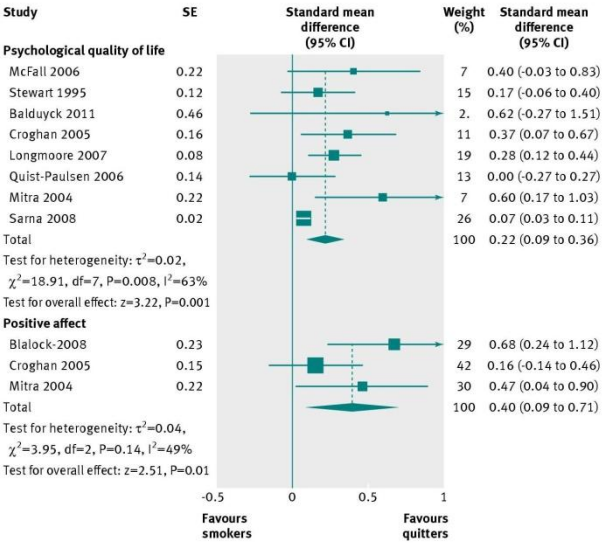


Fig 3 Difference between change in mental health outcomes (positive affect, psychological quality of life) from baseline to longest follow-up in people who stopped smoking or continued to smoke

2. EXAMPLE SEARCH STRATEGY (CHAPTER TWO)

Appendix 2 has been previously published:

Taylor, G., McNeill, A. and Girling, A. et al. (2014). Change in mental health after smoking cessation: systematic review and meta-analysis. **BMJ,** 348 (g1151).

Example search strategy from Medline, inception (1955) to April 13th, 2012 (via OVID)
1. SR.mp.
2. reduc$ smoking.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests and measures]
3. exp "tobacco use cessation"/ or exp smoking cessation/
4. modified tobacco consumption.mp.
5. modification of cig$.mp.
6. modification of smoking.mp.
7. cigarette reduction.mp.
8. reduced cig$.mp.
9. reduction in cig$.mp.
10. Harm Reduction/
11. harm reduction.mp.
12. reduced tobacco consumption.mp.
13. tobacco consumption.mp.
14. cold turkey.mp.
15. abrupt.mp.
16. smoking cessation.mp.
17. quit$ smoking.mp.
18. stop$ smoking.mp.
19. give$ smoking.mp.

20. cease smoking.mp.

21. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20

22. mental health.mp. or *Mental Health/

23. *Stress, Psychological/ or psychological health.mp.

24. psycholog$.mp.

25. psychological well?being.mp.

26. *Anxiety/ or Anxiety Disorders/ or anxiety.mp.

27. anxious.mp.

28. *Depression/ or depression.mp.

29. depressive.mp.

30. exp Emotions/ or psychological process$.mp.

31. mental hygiene.mp.

32. quality of life.mp.

33. mental well?being.mp.

34. well?being.mp.

35. *"Quality of Life"/

36. affect.mp. or *Affect/

37. emotion.mp. or *Emotions/

38. psychological resilience.mp. or *Resilience, Psychological/

39. emotional problem?.mp.

40. Affective Symptoms/ or psychological disturbance?.mp.

41. 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40

42. 21 and 41

43. limit 42 to yr="1955 -Current"

3. FORMULAE USED IN META-ANALYSIS (CHAPTER TWO)

Appendix 3 has been previously published:

> Taylor, G., McNeill, A. and Girling, A. et al. (2014). Change in mental health after smoking cessation: systematic review and meta-analysis. **BMJ,** 348 (g1151).

The formulae and guidance provided within Chapter Seven of the Cochrane handbook for systematic reviews of interventions was followed (Higgins and Green, 2011) with additional advice from statisticians.

Calculating change and its variance using a standard formula: The standard error of the mean change over time was not reported for some studies, though it is needed for inverse-variance weighting. Where necessary it was estimated by adjusting the expression for the standard error of the difference between two independent samples to take account of within-subject correlation (Follmann, Elliott, Suh, and Cutler 1992). Thus the SE of the mean change:

$$= \sqrt{1-r} \times \sqrt{\frac{s_1^2}{n_1} + \frac{s_2^2}{n_2}}$$

Where s1, s2 are the standard deviations at the two time points and n1, n2 are the corresponding sample sizes – notionally equal but which may differ because of data incompleteness or patient drop-out. A generic value of r = 0.312 was assumed from a secondary analysis of individual-level patient data from a randomised controlled trial of multi-component treatment for smoking cessation (Marteau et al., 2012). These data were used to conduct a Pearson correlation using SPSS17. The variables input into the Pearson correlation were: Smokers' and non-smokers' anxiety scores (State-Trait Anxiety Inventory

(STAI) (Marteau and Bekker, 1992) at baseline, and at six month follow-up (N=491). The baseline and follow-up scores showed a significant positive correlation (r =0.312, P<0.001). This correlation co-efficient was then entered into the above formulae.

4. ADAPTED VERSION OF THE NOS (CHAPTER TWO)

Appendix 4 has been previously published:

> Taylor, G., McNeill, A. and Girling, A. et al. (2014). Change in mental health after smoking cessation: systematic review and meta-analysis. **BMJ,** 348 (g1151).

Justification for adaptations to the Newcastle-Ottawa scale

The association between smoking cessation (exposure) and mental health (outcome) in this review affects the validity of NOS quality scores. Therefore, the current review uses an adapted version of the NOS. The adapted version's maximum rating is five stars. The following adaptations have been made (see Table A for adapted version).

Adaptation one — ascertainment of exposure: The NOS aims to assess the validity of exposure ascertainment. It cites use of secure records, structured interview and written self-report as methods to establish the cohorts' exposure status. The current review's exposure is smoking status. Smoking status is principally established via self-report or biological verification; rather than by secure records or structured interviews. Thus, this section was adapted to include only these methods of ascertainment of exposure status. In smoking-cessation research some participants claim to be non-smokers when they are still smoking, this can overestimate the number of people quit in a study (Gorber et al., 2009). The most accurate way to ascertain smoking status is via biological verification (West et al., 2005). Valid methods of biological verification were considered as: expired air carbon monoxide (CO) or level of continine concentration (saliva, urine or plasma). If a study reported

biologically-validated smoking status it was awarded one star and no stars if only self-report was used or if there was no description of how the exposure was ascertained.

Adaptation two — demonstration that outcome of interest was not present at start of study: The NOS awards a star if the outcome of interest was not present at the start of the study. However, this is based upon the diagnosis of the presence or absence of a disease. The current review is not assessing a dichotomous outcome. Our outcome was the change in mental health as measured by continuous scales. Thus, it is not possible for a study to demonstrate that change in mental health was present at the start of the study. Accordingly, this item was not included in the adapted version of the NOS.

Adaptation three — comparability of cohorts on the basis of the design or analysis: The NOS awards a star if the study controls for the "most important factor" which is likely to influence the main outcome, and one star if the study controls for an additional factor which is likely to influence the main outcome. However, not all studies included in the current analysis investigated change in mental health as their primary outcome, thus not all studies controlled for covariates which influence mental health. Accordingly, this item was not included in the adapted version of the NOS.

Adaptation four — assessment of outcome: The NOS awards a star if the study's outcome has been assessed via an independent blind assessment or record linkage, and awards no star if the outcome has been assessed via self-report or no description. The outcome for the current review could only be assessed via a self-report questionnaire or a structured-interview. Firstly, for assessment of mental health to be clinically useful, psychometric assessments need to be

standardised (Hunsley et al., 2003). Secondly, psychological questionnaires cannot be blindly assessed, as the participant completes the answers. Thus independent-blind assessment in the self-report category was not considered. Structured interviews can be assessed by someone who is blinded to study hypotheses, thus this has been considered for outcomes assessed via interview. Accordingly, one star was awarded for use of a standardised self-report questionnaire, or standardised interview schedule with blind assessor, and zero stars were awarded for use non-standardised self-report questionnaires, non-standardised interview schedules and standardised interview schedules with an un-blinded assessor. In the case that a study used a standardised self-report questionnaire and a standardised interview schedule, only one star was awarded; as use of both types of outcome assessment does not improve the study's quality for the purpose of this review.

Adaptation five— length of follow-up: The NOS awards a star if the study's follow-up was long-enough for the outcome to occur. However, I included studies that assessed mental health is assessed after the end of the withdrawal period (six weeks). Thus our inclusion criterion ensures that the follow-up is long enough for outcomes to occur. Accordingly, this item was not included in the adapted version of the NOS.

Adaptation six — determining an attrition threshold: The NOS awards a star if a study reports that all subjects were accounted for at follow-up. The NOS also awards a star if "a small number" of subjects are lost to follow-up, or if the study provides a description of those who were lost. The scale allows the researcher to select their own adequate rate (%) of attrition. There are no empirical studies which determine an agreed attrition threshold for observational studies of smoking populations. Other quality assessment tools for observational studies

recommend the use 80% to 100% follow-up to determine the lowest attrition-bias, and 60% to 79% to determine moderate attrition-bias (Thomas et al., 2004). Lundth and Gotzsche (2008) conducted a review of trials in aim to provide a list of recommendations for assessing the methodological quality of studies. They reported that the use of arbitrarily defined cut-off points is not empirically justified. Fewtrell et al. (2008) conducted a review of nutritional interventions and concluded that there are no universally agreed criteria for acceptable follow-up rates in nutrition cohort studies.

Thus, there is no empirical evidence to adopt a specific cut-off percentage for determining attrition bias. However, there is empirical evidence that drop-out from a study may affect the study's results (Touloumi et al., 2001), in turn affecting the study's validity. Although there is no agreed cut off, a method of determining attrition bias is necessary. Thus GT, PA and AM discussed different cut-off points and factors which may influence attrition. A consensus was made that if loss to follow-up was >30% overall or >20% difference between the arms then there is a possibility of bias. Accordingly if there was a complete follow-up or if loss to follow-up was less than 30% overall and there was a difference of less than 20% between the arms the study was awarded one star. If the study did not meet these criteria or if there was no statement on follow-up rates the study did not receive a star.

Newcastle-Ottawa quality assessment scale cohort studies (NOS) adapted version			
		Star awarded system	**Star (*) awarded**
Study's selection criteria			
1) Representativeness of the exposed cohort (maximum 1 star)	a) truly representative of the average _____ (describe) in the community	*	
	b) somewhat representative of the average _____ in the community	*	
	c) selected group of users e.g. nurses, volunteers	(no star)	
	d) no description of the derivation of the cohort	(no star)	
2) Selection of the non-exposed cohort (maximum 1 star)	a) drawn from the same community as the exposed cohort	*	
	b) drawn from a different source	(no star)	
	c) no description of the derivation of the non-exposed cohort	(no star)	
3) Ascertainment of exposure (maximum 1 star)	a) bio-validated smoking status	*	
	b) smoking status validated only by self-report	(no star)	
	c) no description	(no star)	
Study's outcome criteria			
1) Assessment of outcome (maximum 1 star)1	a) standardised self-report questionnaire	*	
	b) standardised interview schedule with blind assessor	*	
	c) non-standardised self-report questionnaire or non-standardised interview schedule	(no star)	
	d) no description	(no star)	
2) Adequacy of follow-up of cohorts (maximum 1 star) 2	a) complete follow-up - all subjects accounted for □	*	
	b) subjects lost to follow-up unlikely to introduce bias - small number lost - > __ % (select an adequate %) follow-up, or description provided of those lost) □	*	
	c) follow-up rate < __% (select an adequate %) and no description of those lost	(no star)	
	d) no statement	(no star)	
Final Score			
1 In the case that a study has used a standardised self-report questionnaire and a standardised interview schedule, only one star will be awarded. This is as use of both outcome assessments will not improve the study's quality for the purpose of this review. 2 Describe based on attrition from enrolment to final follow-up			

5. ARTICLES EXCLUDED AFTER EXAMINATION OF FULL TEXT (CHAPTER TWO)

Appendix 5 has been previously published:

> Taylor, G., McNeill, A. and Girling, A. et al. (2014). Change in mental health after smoking cessation: systematic review and meta-analysis. **BMJ,** 348 (g1151).

References of articles excluded based on examination of full text and reasons for exclusion	
Reference (N=166)	**Reason for exclusion**
Abrams, D.B., Monti, P.M. and Pinto, R.P. et al. (1987). Psychosocial stress and coping in smokers who relapse or quit. Health Psychology, 6 (4): 289-303.	No baseline measures of mental health taken prior to attaining/not attaining abstinence.
Abrantes, A.M., Palm, K.M. and Strong, D.R. et al. (2006). Cigarette smokers who have difficulties quitting: The role of negative mood. Medicine and Health, 89 (5): 169-71.	Review of cessation interventions.
Acri, J.B. and Grunberg N.E. (1992). A psychophysical task to quantify smoking cessation-induced irritability: The reactive irritability scale (RIS). Addictive Behaviour, 17 (6): 587-601.	Mental health outcome was measured during the withdrawal period.
Ahlberg, J., Savolainen A. and Rantala M. et al. (2004). Reported bruxism and bio-psychosocial symptoms: A longitudinal study. Community Dentistry and Oral Epidemiology, 32 (4): 307-11.	No mental health outcome.
Allen, A.M., Prince, C.B. and Dietz, P.M. (2009). Postpartum depressive symptoms and smoking relapse. American Journal of Preventative Medicine, 36 (1): 9-12.	Relapse as the outcome.
Almeida, O.P., Garrido, G.J. and Alfonso, H. et al. (2011). 24-month effect of smoking cessation on cognitive function and brain structure in later life. Neuroimage, 55 (4): 1480-9.	Mental health outcome was measured during the withdrawal period.

Baker, A., Richmond, R. and Lewin, T.J. et al. (2010). Cigarette smoking and psychosis: Naturalistic follow-up 4 years after an intervention trial. Australian and New Zealand Journal of Psychiatry, 44 (4): 342-50.	Does not compare smokers with quitters. Randomised controlled trial follow-up.
Berg, C.J., Thomas, J.L. and Guo, H. et al. (2010). Predictors of smoking reduction among Blacks. Nicotine and Tobacco Research, 12 (4): 423-31.	Smoking status was the outcome. No mental health outcome.
Bercaw, E.L. (2008). A behavioural activation approach to smoking cessation for depressed smokers at veterans affairs medical centres. Dissertation Abstracts International: Section B: The Sciences and Engineering, 68 (8-B): 5557.	Smoking status as outcome.
Billert, H., Gaca, M. and Adamski, D. et al. (2006). Significance of smoking and cigarette abstinence regarding anxiety in gynecologic patients in a perioperative period. Przeglad Lekarski, 63 (10): 870-7.	Mental health outcome was measured during the withdrawal period.
Borrelli, B., Niaura, R. and Keuthen, N.J. et al. (1996). Development of major depressive disorder during smoking-cessation treatment. Journal of Clinical Psychiatry, 57 (11): 534-8.	Does not report mental health data by smoking status.
Boudrez, H. (2009). Psychological factors and long-term abstinence after smoking cessation treatment. Journal of Smoking Cessation, 4 (1), 10-17.	Smoking status as outcome. Mental health as predictor.
Breslau, N., Novak, S.P. and Kessler, R.C. (2004). Psychiatric disorders and stages of smoking. Biological Psychiatry, 55 (1): 69-76.	No quit group. Age range below 18.
Catley, D., Ahluwalia, J.S. and Resnicow, K. et al. (2003). Depressive symptoms and smoking cessation among inner-city African Americans using the nicotine patch. Nicotine and Tobacco Research, 5 (1): 61-8.	Smoking status as outcome.
Cohen, S.B. (1999). Tranquilizing effects of smoking cessation. American Journal of Psychiatry, 156 (4): 666-7.	Review article.
Cooley, M.E., Sarna, L. and Kotlerman, J. et al. (2009). Smoking cessation is challenging even for patients recovering from lung cancer surgery with curative intent. Lung Cancer, 66 (2): 218-25.	Smoking status as outcome.

Covey, L.S., Glassman, A.H. and Stetner, F. (1997). Major depression following smoking cessation. American Journal of Psychiatry, 154 (2): 263-5.	No continuing smoker group.
Covey, L.S., Bomback, A. and Yan, G.W. (2006). History of depression and smoking cessation: A rejoinder. Nicotine and Tobacco Research, 8 (2): 315-9.	Meta-analysis of smoking status as the outcome.
Dalack, G.W., Becks, L. and Hill, E. et al. (1999). Nicotine withdrawal and psychiatric symptoms in cigarette smokers with schizophrenia. Neuropsychopharmacology, 21 (2): 195-202.	Mental health outcome was measured during the withdrawal period.
Dempsey, J.P. and Cohen, L.M. Commentary on Hajek et al. (2010). Investigating the stress reduction in smoking cessation. Addiction, 105 (8): 1472-3.	Commentary article.
Etter, J.F. and Hughes, J.R. (2006). A comparison of the psychometric properties of three cigarette withdrawal scales. Addiction, 101 (3): 362-72.	Mental health outcome was measured during the withdrawal period.
ez-Ganan, L., Guallar-Castillon, P. and Banegas, J.R. et al. (2002). Subjective health of male ex-smokers: Relationship with time since smoking cessation, intensity and duration of tobacco consumption. Preventative Medicine, 35 (4): 320-5.	No mental health outcome.
Frederick, S.L., Hall, S.M. and Humfleet, G.L. et al. (1996). Sex differences in the relation of mood to weight gain after quitting smoking. Experimental and Clinical Psychopharmacology, 4 (2): 178-85.	Does not report baseline or follow-up mental health scores of quitters and continuer smokers.
Frederick, S., Reus V. and Ginsberg, D. et al. (1998). Cortisol and response to dexamethasone as predictors of withdrawal distress and abstinence success. Biological Psychiatry, 43 (7): 525-530.	Mental health outcome was during the withdrawal period.
Garces, Y.I., Yang, P. and Parkinson J. et al. (2004). The relationship between cigarette smoking and quality of life after lung cancer diagnosis.	Does not measure mental health.

Chest, 126 (6): 1733-41.	
Gelenberg, A.J., de Leon, J. and Evins, A.E. et al. (2007). Smoking cessation in patients with psychiatric disorders. Journal of Clinical Psychiatry, 68 (9): 1404-10.	Commentary article.
Gilbert, D.G., McClernon, F.J. and Rabinovich, N.E. et al. (1998). Effects of smoking abstinence on mood and craving in men: Influences of negative-affect-related personality traits, habitual nicotine intake and repeated measurements. Personality and Individual Differences, 25 (3): 399-423.	Mental health outcome was measured during the withdrawal period.
Gilbert, D.G., McClernon, F.J. and Rabinovich, N.E. et al. (1999). EEG, physiology, and task-related mood fail to resolve across 31 days of smoking abstinence: Relations to depressive traits, nicotine exposure, and dependence. Experimental and Clinical Psychopharmacology, 7 (4): 427-43.	Mental health outcome was measured during the withdrawal period.
Gilbert, D.G., McClernon, F.J. and Rabinovich, N.E. et al. (2002). Mood disturbance fails to resolve across 31 days of cigarette abstinence in women. Journal of Consulting and Clinical Psychology, 70 (1): 142-52.	Mental health outcome was measured during the withdrawal period.
Gilbert, H.M. and Warburton, D.M. (2003). Individual variation in psychological and psychomotor symptoms following smoking cessation: The implications for treatment. Psychology and Health, 18 (5): 613-24.	Mental health outcome was measured during the withdrawal period.
Ginsberg, D., Hall, S.M. and Reus VI. et al. (1995). Mood and depression diagnosis in smoking cessation. Experimental and Clinical Psychopharmacology, 3 (4): 389-95.	Smoking status as outcome.
Giskes, K., van Lenthe, F.J. and Turrell G. et al. (2006). Smokers living in deprived areas are less likely to quit: A longitudinal follow-up. Tobacco Control: An International Journal, 15 (6), 485-8.	Cessation status as outcome.
Glassman, A.H., Covey, L.S. and Dalack, G.W. et al. (1992). Cigarette smoking, major depression, and schizophrenia. Clinical Neuropharmacology, 15: 561A.	Commentary article.
Glassman, A.H. and Hercher, L.S. (1999). Which aspects of nicotine	Commentary article.

addiction should concern mental health professionals? Harvard Mental Health Letter, 16 (2): 8.	
Goldberg, J.O. and Van E.J. (2008). Longitudinal rates of smoking in a schizophrenia sample. Tobacco Control, 17 (4): 271-5.	No mental health outcome.
Goto, R. and Takahashi, Y. and Nishimura, S. et al. (2009). A cohort study to examine whether time and risk preference is related to smoking cessation success. Addiction, 104 (6): 1018-24.	Smoking cessation status as outcome.
Grassi, M.C, Enea, D. and Ferketich, A.K. et al. (2011). Effectiveness of varenicline for smoking cessation: A 1-year follow-up study. Journal of Substance Abuse Treatment, 41 (1): 64-70.	Randomised controlled trial. Analysis by treatment group.
Gritz, E.R., Carr, C.R. and Marcus, A.C. (1991). The tobacco withdrawal syndrome in unaided quitters. British Journal of Addiction, 86 (1): 57-69.	No continuing smoker group.
Gross, J. and Stitzer, M.L. (1989). Nicotine replacement: ten-week effects on tobacco withdrawal symptoms. Psychopharmacology, 98 (3): 334-41.	No continuing smoker group.
Grunberg, N.E. (2003). The tobacco use crisis and mental health. Psychiatry, 66 (3): 200-1.	Commentary article.
Guiterrez-Bedmar, M., Segui-Gomez, M. and Gomez-Gracia E. et al. (2009). Smoking status, changes in smoking status and health-related quality of life: findings from the SUN ("Seguimiento Universidad de Navarra") cohort. International Journal of Environmental Research and Public Health, 6 (1): 310-20.	No psychological outcome data presented at baseline.
Hajek, P. and Belcher, M. (1991). Dream of absent-minded transgression: An empirical study of a cognitive withdrawal symptom. Journal of Abnormal Psychology, 100 (4), 487-91.	No mental health outcome. No continuing smoker group.
Hall, S.M, Bachman, J. and Henderson, J.B. (1983). Smoking cessation in patients with cardiopulmonary disease: An initial study. Addictive Behaviour, 8 (1): 33-42.	Smoking reduction status as outcome
Hall, S.M., Munoz, R. and Reus, V. (1990). Smoking cessation, depression	Mental health outcome was

and dysphoria. NIDA Research Monograph, 105: 312-3.	measured during the withdrawal period.
Harris, G.T., Parle, D. and Gagne, J. (2007). Effects of a tobacco ban on long-term psychiatric patients. Journal of Behavioural Health Services and Research, 34 (1): 43-55.	No mental health outcome. No quit group.
Hartlapp, J. (1992). Smoking cessation: What happens in the body. Medizinische Monatsschrift fur Pharmazeuten, 15 (1): 17-9.	Commentary article.
Hawkins, J., Hollingworth, W. and Campbell, R. (2010). Long-term smoking relapse: A study using the British Household Panel Survey. Nicotine and Tobacco Research, 12 (12): 1228-35.	No mental health outcome.
Hayes, R.B, Dunsiger, S. and Borrelli, B. (2010). The influence of quality of life and depressed mood on smoking cessation among medically ill smokers. Journal of Behavioural Medicine, 33 (3): 209-18.	Smoking cessation status as outcome.
Hayford, K.E, Patten, C.A. and Rummans, T.A. et al. (1999). Efficacy of bupropion for smoking cessation in smokers with a former history of major depression or alcoholism. British Journal of Psychiatry, 174: 173-8.	Randomised controlled trial. Analysis by treatment group.
Heffner, J.L., DelBello, M.P. and Anthenelli, R.M. et al. (2012). Cigarette smoking and its relationship to mood disorder symptoms and co-occurring alcohol and cannabis use disorders following first hospitalization for bipolar disorder. Bipolar Disorders, 14 (1): 99-108.	Mental health was measured during the withdrawal period.
Heffner, J.L, DelBello, M.P. and Anthenelli R.M. et al. (2012). Relationship between cigarette smoking and symptoms of bipolar disorder following first hospitalization for a manic or mixed episode. Bipolar Disorders, 14 (1): 99-108.	Data published in Heffner (2012)
Heinold, J.W., Garvey, A.J. and Goldie, C. et al. (1982). Retrospective analysis in smoking cessation research. Addictive Behaviours, 7 (4): 347-353.	No mental health outcome.
Herd, N., Borland, R. and Hyland, A. (2009). Predictors of smoking relapse	Cessation status as

by duration of abstinence: Findings from the International Tobacco Control (ITC) Four Country Survey. Addiction, 104 (12): 2088-99.	outcome.
Hirdes, J.P., Maxwell, C.J. (1994). Smoking cessation and quality of life outcomes among older adults in the Campbell's survey on well-being. Canadian Journal of Public Health, 85 (2): 99-102.	No mental health outcome.
Hoogenveen, R.T., Van Baal, P.H., Boshuizen, H.C. et al. (2008). Dynamic effects of smoking cessation on disease incidence, mortality and quality of life: The role of time since cessation. Cost Effectiveness and Resource Allocation, 6 (1): 1.	Methodology paper for determining effect of cessation on disease.
Hoogwegt, M.T., Hoeks, S.E. and Pedersen S.S. et al. (2010). Smoking cessation has no influence on Quality of Life in patients with peripheral arterial disease 5 years post-vascular surgery. European Journal of Vascular and Endovascular Surgery, 40 (3): 355-62.	Modelling paper.
Horn, K., Dino, G. and Kalsekar, I. et al. (2004). Exploring the relationship between mental health and smoking cessation: A study of rural teens. Prevention Science, 5 (2):113-26.	Participants were teenagers.
Hughes, J.R. and Carpenter, M.J. (2006). Stopping smoking: carpe diem? Tobacco Control, 15 (5): 415-16.	Commentary article.
Hughes, J.R. (1992). Tobacco withdrawal in self-quitters. Journal of Consulting and Clinical Psychology, 60 (5): 689-697.	Mental health was measured during the withdrawal period.
Hurt, R.D., Offord, K.P. and Hepper, N.G. et al. (1998). Long-term follow-up of persons attending a community-based smoking-cessation program. Mayo Clinic Proceedings, 63 (7): 681-90.	No mental health outcome.
Hurt, R.D., Sachs, D.P. and Glover, E.D. et al. (1997). A comparison of sustained-release bupropion and placebo for smoking cessation. New England Journal of Medicine, 337 (17): 1195-202.	Randomised controlled trial. Analysis by treatment group.
Iglesias, C., Lopez, G. and Alonso, M. J. (2008). Effects of smoking ban in a	Study about patients'

general hospital psychiatric unit. Actas Espanolas de Psiquiatria, 36 (1): 60-62.	thoughts on the smoking ban.
Jacobsen, L.K., Krystal, J.H. and Mencl, W.E. et al. (2005). Effects of smoking and smoking abstinence on cognition in adolescent tobacco smokers. Biological Psychiatry, 57 (1): 56-66.	Participants were teenagers.
Jang, A.S, Park, S.W. and Kim, D.J. et al. (2010). Effects of smoking cessation on airflow obstruction and quality of life in asthmatic smokers. Allergy, Asthma and Immunology Research, 2 (4): 254-9.	No mental health outcome.
Japuntich, S.J., Smith, S.S. and Jorenby, D.E. et al. (2007). Depression predicts smoking early but not late in a quit attempt. Nicotine and Tobacco Research, 9 (6): 677-86.	Smoking cessation attempt status was the outcome.
Jenner, D.A., Puddey, I.B. and Beilin, L.J. et al. (1998). Lifestyle and occupation-related changes in blood pressure over a six-year period in a cohort of working men. Journal of Hypertension, 6 (4): S605-S607.	No quit group.
Jimenez-Ruiz, C.A., Ulibarri, M.M. and Besada, N.A. et al. (2009). Progressive reduction using nicotine gum as a prelude to quitting. Nicotine and Tobacco Research, 11 (7): 847-50.	No mental health outcome.
Johnson, E.O. and Breslau, N. (2006). Is the association of smoking and depression a recent phenomenon? Nicotine and Tobacco Research, 8 (2): 257-62.	Cessation as outcome.
Johnson, E.O. and Novak, S.P. (2009). Onset and persistence of daily smoking: The interplay of socioeconomic status, gender, and psychiatric disorders. Drug and Alcohol Dependence, 104: S50-7.	Onset of smoking as outcome.
Jorenby, D.E., Hatsukami, D.K. and Smith, S.S. et al. (1996). Characterization of tobacco withdrawal symptoms: transdermal nicotine reduces hunger and weight gain. Psychopharmacology, 128 (2): 130-8.	No continuing smoker group.
Judit, B.J., Simon, E. and Lukacs, M. et al. (2011). Psychosocial factors influencing smoking cessation in patients with coronary artery disease.	Cessation as outcome

European Journal of Cardiovascular Prevention and Rehabilitation, 18 (1): S41.	
Kahler, C.W., Strong, D.R. and Niaura, R. et al. (2004). Hostility in smokers with past major depressive disorder: relation to smoking patterns, reasons for quitting, and cessation outcomes. Nicotine and Tobacco Research, 6 (5): 809-18.	Mental health was measured during the withdrawal period.
Kahler, C.W., Spillane, N.S. and Metrik, J. (2010). Alcohol use and initial smoking lapses among heavy drinkers in smoking cessation treatment. Nicotine and Tobacco Research, 12 (7): 781-5.	No quit group. No continuing smoker group.
Kahn, R.S., Certain, L. and Whitaker, R.C. (2002). A re-examination of smoking before, during, and after pregnancy. American Journal of Public Health, 92 (11): 1801-8.	Cessation status as outcome.
Kenney, B.A., Holahan, C.J. and Holahan, C.K. et al. (2009). Depressive symptoms, drinking problems, and smoking cessation in older smokers. Addictive Behaviour, 34 (6-7): 548-53.	Cessation status as outcome.
Khaled, S.M., Bulloch, A. and Exner, D.V. et al. (2009). Cigarette smoking, stages of change, and major depression in the Canadian population. Canadian Journal of Psychiatry, 54 (3): 204-8.	Does not present data of change in mental health.
Killen, J.D., Robinson, T.N., Ammerman, S. et al. (2004). Major depression among adolescent smokers undergoing treatment for nicotine dependence. Addictive Behaviour, 29 (8): 1517-26.	All participants were teenagers.
Kouvonen, A., Oksanen, T. and Vahtera, J. et al. (2008). Work-place social capital and smoking cessation: the Finnish Public Sector Study. Addiction, 103 (11): 1857-65.	Smoking cessation as outcome.
Lagrue, G., Dupont, P. and Fakhfakh, R. (2002). Anxiety and depressive disorders in tobacco dependence. Encephale-Revue de Psychiatrie Clinique Biologique et Therapeutique, 28 (4): 374-377.	Cross-sectional data.
Lam, C.Y., Robinson, J.D. and Versace, F. et al. (2012). Affective reactivity	Mental health was

during smoking cessation of never-quitters as compared with that of abstainers, relapsers, and continuing smokers. Experimental and Clinical Psychopharmacology, 20 (2): 139-50.	measured during the withdrawal period.
Lam, T.H., Stewart, S.M. and Ho, S.Y. et al. (2005). Depressive symptoms and smoking among Hong Kong Chinese adolescents. Addiction, 100 (7): 1003-11.	All participants were teenagers
Lerman, C., Niaura, R. and Collins, B.N. et al. (2004). Effect of bupropion on depression symptoms in a smoking cessation clinical trial. Psychology of Addictive Behaviours, 18 (4): 362-6.	Randomised controlled trial. Analyses data by treatment group.
Lerman, C. and Audrain-McGovern, J. (2010). Reinforcing effects of smoking: more than a feeling. Biological Psychiatry, 67 (8): 699-701.	Review article.
Levin, E.D, Westman, E.C. and Stein, R.M. et al. (1994). Nicotine skin patch treatment increases abstinence, decreases withdrawal symptoms, and attenuates rewarding effects of smoking. Journal of Clinical Psychopharmacology, 14 (1): 41-9.	Randomised trial presenting data by treatment group.
Levine, M.D., Marcus, M.D., Kalarchian, M.A. et al. (2010). Weight concerns, mood, and postpartum smoking relapse. American Journal of Preventative Medicine, 39 (4): 345-51.	Cessation as outcome.
Lima, J.E, Reid, M.S. and Smith, J.L. et al. (2009). Medical and mental health status among drug dependent patients participating in a smoking cessation treatment study. Journal of Drug Issues, 39 (2): 293-311.	Not a study of the association between cessation and mental health change.
Ludman, E.J., McBride, C.M. and Nelson, J.C. et al. (2000). Stress, depressive symptoms, and smoking cessation among pregnant women. Health Psychology, 19 (1): 21-7.	Cessation as outcome.
Lumley, M.A, Downey, K. and Stettner, L. et al. (1994). Alexithymia and negative affect: relationship to cigarette smoking, nicotine dependence, and smoking cessation. Psychotherapy and Psychosomatics, 61 (3-4): 156-62.	Three studies but none of which are studies of the association between

	cessation and change in mental health.
Margery, J., Margery, D. and Goutier, K. et al. (2007). Smoking cessation in adolescence: Questionnaire study of 248 students. Revue des Maladies Respiratoires, 24 (5): 663-4.	Participants were teenagers
McClure, J.B, Swan, G.E. and Jack, L. et al. (2009). Mood, side-effects and smoking outcomes among persons with and without probable lifetime depression taking varenicline. Erratum. Journal of General Internal Medicine, 24 (10): 1173.	Randomised controlled trial. Analysed data by treatment group.
McDermott, L., Dobson, A. and Owen, N. (2008). Smoking reduction and cessation among young adult women: a 7-year prospective analysis. Nicotine and Tobacco Research, 10 (9): 1457-66.	Cessation status as outcome.
McGee, H.M., Doyle, F. and Conroy, R.M. et al. (2006). Impact of briefly-assessed depression on secondary prevention outcomes after acute coronary syndrome: A one-year longitudinal survey. BMC Health Services Research, 6:9.	No data presented by smoking status.
Moreno-Coutino, A., Calderon-Ezquerro, C., Drucker-Colin, R. (2007). Long-term changes in sleep and depressive symptoms of smokers in abstinence. Nicotine and Tobacco Research, 9 (3): 389-96.	Continuing smoker group includes recent relapsers.
Morris, C.D, Waxmonsky, J.A. and May, M.G. et al. (2001). Smoking reduction for persons with mental illnesses: 6-month results from community-based interventions. Community Mental Health Journal, 47 (6): 694-702.	Randomised controlled trial. Analyses data by treatment group.
Morton, K. and Pradhan, S.C. (2001). Smoking cessation and major depression. Lancet, 358 (9286): 1011.	Commentary article.
Mulder, I., Tijhuis, M., Smit, H.A. et al. (2001). Smoking cessation and quality of life: The effect of amount of smoking and time since quitting. Preventative Medicine, 33 (6): 653-60.	Cross-sectional data.

Mykletun, A., Overland, S. and Aaro, L.E. et al. (2008). Smoking in relation to anxiety and depression: evidence from a large population survey: the HUNT study. European Psychiatry, 23 (2): 77-84.	Cross-sectional data.
Niaura, R., Britt, D.M. and Borrelli, B. et al. (1991). History and symptoms of depression among smokers during a self-initiated quit attempt. Nicotine and Tobacco Research, 1 (3): 251-7.	No continuing smoker group.
Niaura, R. and Abrams, D.B. (2001). Stopping smoking: A hazard for people with a history of major depression? Lancet, 357 (9272): 1900-1.	Commentary article.
Nielsen, P.E. Smoking cessation. Ugeskr Laeger, 154 (5): 245.	Commentary article.
Norcross, J.C. and Vangarelli, D.J. (1988). The resolution solution: longitudinal examination of New Year's change attempts. The Journal of Substance Abuse Treatment, 1 (2): 127-34.	No mental health outcome.
Norman, R.M. and Malla, A.K. (1991). Subjective Stress in Schizophrenic-Patients. Social Psychiatry and Psychiatric Epidemiology, 26 (5): 212-6.	No continuing smoker group. No quit group.
Norman, S.M. (1996). Psychological factors need attention in persons quitting smoking. American Family Physician, 54 (2): 690.	Commentary article.
O'Hara, P., Portser, S.A. and Anderson, B.P. (1989). The influence of menstrual cycle changes on the tobacco withdrawal syndrome in women. Addictive Behaviours, 14 (6): 595-600.	No continuing smoker group. Measurement of mental health during the withdrawal period.
Papadopoulos, G., Vardavas, C.I. and Limperi, M. et al. (2011). Smoking cessation can improve quality of life among COPD patients: validation of the clinical COPD questionnaire into Greek. BMC Pulmonary Medicine, 11: 13.	No continuing smoker group.
Park, E.R., Chang, Y. And Quinn, V. et al. (2009). The association of depressive, anxiety, and stress symptoms and postpartum relapse to smoking: a longitudinal study. Nicotine and Tobacco Research, 11 (6): 707-14.	Smoking status as outcome.

Patten, C.A., Rummans, T.A. and Croghan, I.T. et al. (1999). Development of depression during placebo-controlled trials of bupropion for smoking cessation: Case reports. Journal of Clinical Psychiatry, 60 (7): 436-41.	Case study.
Pederson, L.L., Wanklin, J.M., Lefcoe, N.M. (1988). Self-reported long-term smoking cessation in patients with respiratory disease: prediction of success and perception of health effects. International Journal of Epidemiology, 17 (4): 804-9.	Smoking status as outcome.
Pepper, T. (2007). An analysis of smoking demographics in HMS DRAKE and an update on smoking cessation support. Journal of the Royal Naval Medicine Service, 93 (2): 67-74.	Cross-sectional data.
Pergadia, M.L., Agrawal, A. and Heath, A.C. et al. (2010). Nicotine withdrawal symptoms in adolescent and adult twins. Twin Research and Human Genetics, 13 (4): 359-69.	Retrospective study of withdrawal in twins.
Perkins, K.A., Marcus, M.D., Levine M.D. et al. (2001). Cognitive-behavioural therapy to reduce weight concerns improves smoking cessation outcome in weight-concerned women. Journal of Consulting and Clinical Psychology, 69 (4): 604-13.	Randomised controlled trial. Analyses data by treatment group.
Piasecki, T.M., Fiore, M.C. and Baker, T.B. (2001). Profiles in discouragement: two studies of variability in the time course of smoking withdrawal symptoms. Journal of Abnormal Psychology, 107 (2): 238-51.	No continuing smoker group.
Piasecki T.M., Kenford, S.L. and Smith, S.S. et al. (1997). Listening to nicotine: Negative affect and the smoking withdrawal conundrum. Psychological Science, 8 (3): 184-9.	No continuing smoker group.
Piper, M.E., Kenford, S. and Fiore, M.C. et al. (2012). Smoking Cessation and Quality of Life: Changes in Life Satisfaction Over 3 Years Following a Quit Attempt. Annals of Behavioural Medicine, 43 (2): 262-70.	No mental health outcome.
Polgar, S., McGartland, M. and Borlongan, C.V. et al. (1996). Smoking cessation programmes are neglecting the needs of persons with	Commentary article.

neuropsychiatric disorders. Australian and New Zealand Journal of Medicine, 26 (4): 572-3.	
Polosa, R. (2006). Smoking cessation: A critical investigative tool in COPD. European Respiratory Journal, 27 (4): 860-1.	Commentary article.
Prochaska, J.O. and DiClemente, C.C. (1984). Self change processes, self efficacy and decisional balance across five stages of smoking cessation. Progress in Clinical and Biological Research, 156: 131-40.	No mental health outcome
Prochaska, J.O. (1993). Working in harmony with how people quit smoking naturally. Rhode Island Medicine, 76 (10): 493-5.	Review article.
Puddey, I.B., Vandongen, R. and Beilin, L.J. et al. (1985). The effect of stopping smoking on blood pressure: A controlled trial. Journal of Chronic Disease, 38 (6): 483-93.	Randomised controlled trial. Analyses data by treatment group.
Raherison, C., Marjary, A. and Valpromy, B. et al. (2005). Evaluation of smoking cessation success in adults. Respiratory Medicine, 99 (10): 1303-10.	Smoking status as outcome.
Raymond, C.B. and Naylor, H.K. (2010). Smoking cessation in patients with chronic kidney disease. CANNT Journal, 20 (4): 24-9.	Review article.
Reus, V. I., Hall, S. and Ginsberg, D. et al. (1993). Cortisol, Depression, and Smoking Cessation. Biological Psychiatry, 33 (6A): A61.	Requested paper. The author stated the results were reported in Frederick (1998). In this article the mental health outcomes were assessed during the withdrawal period.
Rogge, N. (2003). Smoking cessation and the course of major depression: A follow-up study: Comment. Schweizerische Rundschau fur Medizin – Praxis, 92 (43): 1833.	Commentary article.
Royce, J.M., Gorin, S.S. and Edelman, B. et al. (1990). Student nurses and	Intervention trial. Analysis

smoking cessation. Progress Clinical and Biological Research, 339: 49-71.	by smoking cessation treatment group.
Russek, H.I. (1964). Tobacco consumption and emotional stress in etiology of coronary heart disease. Geriatrics, 19 (6): 425-33.	No quit group.
Rutter, S. (1990). Cigarette-smoking reduction in university students. Psychological Reports, 66: 186.	No mental health outcome.
Ryan, B., Coffin, K. and Smillie, C. et al. (1990). Smoking cessation in Nova Scotia: Results of the time to quit program. Canadian Journal of Public Health, 81(2):166-7.	No mental health outcome.
Ryan, P.J, Forster, N.J. and Holder, D. (1990). Evaluation of a worksite smoking-cessation program. Journal of Occupational and Environmental Medicine, 44 (8): 703-4.	Evaluation of intervention.
Ryan, S. (2000). Chronic obstructive pulmonary disease: Boosting quality of life. Community Nurse, 6 (3): 31-2.	Review article.
Sachs-Ericsson, N., Schmidt, N.B. and Zvolensky, M.J. et al. (2009). Smoking cessation behaviour in older adults by race and gender: the role of health problems and psychological distress. Nicotine and Tobacco Research, 11 (4): 433-43.	Smoking status as outcome.
Sagall, R.J. (1992). Smoking cessation. The Journal Of Family Practice, 35 (5): 495-6.	Commentary article.
Schlede, C.M. (1996). Smoking cessation. The Journal of the Florida Medical Association, 83 (2): 108-12.	Commentary article.
Schwartz, J.L. and Dubitzky, M. (1968). Changes in anxiety, mood, and self-esteem resulting from an attempt to stop smoking. The American Journal of Psychiatry, 124 (11): 1580-4.	No figures presented in paper.
Scott, W.D., Beevers, C.G. and Mermelstein, R.J. (2008). Depression vulnerable and nonvulnerable smokers after a failure experience: examining cognitive self-regulation and motivation. Behaviour Modification, 32 (4):	No data on change in mental health by smoking status.

519-39.	
Seidman, D.F, Westmaas, J.L. and Goldband, S. et al. (2010). Randomized controlled trial of an interactive internet smoking cessation program with long-term follow-up. Annals of Behavioural Medicine, 39 (1): 48-60.	Randomised controlled trial. Analyses data by treatment group.
Shadel, W. and Mermelstein, R. (1993). Cigarette smoking under stress: The role of coping expectancies among smokers in a clinic-based smoking cessation program. Health Psychology, 12 (6): 443-50.	Smoking status and urges as outcome.
Shaw, J,W, Coons, S.J. and Foster, S.A. et al. (2001). Responsiveness of the Smoking Cessation Quality of Life (SCQoL) questionnaire. Clinical Therapeutics, 23 (6): 957-69.	Mental health outcome measured during the withdrawal period
Shi, Y., Hooten, W.M. and Warner, D.O. (2011). Effects of smoking cessation on pain in older adults. Nicotine and Tobacco Research, 13 (10): 919-25.	Pain as outcome.
Shiffman, S. (1982). Relapse following smoking cessation: a situational analysis. Journal of Consulting and Clinical Psychology, 50 (1): 71-86.	Smoking status as outcome.
Shiffman, S. (2005). Dynamic influences on smoking relapse process, Journal of Personality, 73 (6):1715-1748.	Smoking status as outcome.
Shiffman, S. and Waters, A. J. (2004). Negative Affect and Smoking Lapses: A Prospective Analysis. Journal of Consulting and Clinical Psychology, 72 (2): 192-201.	Smoking status as outcome.
Shipley, R.H. (1987). Smoking-reduction programs help businesses snuff out health problems. Occupational Health and Safety, 56 (1): 73-8.	Review article.
Siahpush M. and Carlin, J.B. (2006). Financial stress, smoking cessation and relapse: Results from a prospective study of an Australian national sample. Addiction, 101 (1): 121-7.	Smoking status as outcome.
Sirota, A.D., Rohsenow, D.J. and MacKinnon, S.V. et al. (2010). Intolerance for smoking abstinence questionnaire: Psychometric properties and relationship to tobacco dependence and abstinence. Addictive	Factor analysis for development of a new psychometric questionnaire.

Behaviours, 35 (7): 686-693.	
Sloan R.P., Dimberg L. and Welkowitz, L.A. et al. (1990). Cessation and relapse in a year-long workplace quit-smoking contest. Preventative Medicine, 19 (4): 414-23.	Smoking status as outcome.
Stein M.D., Weinstock, M.C. and Anderson, B.J. et al. (2007). Relationship of depression to smoking outcomes in a methadone-maintained population. Journal of Addictive Diseases, 26 (1): 35-40.	Smoking status as outcome.
Stott, P. (2006). Smoking cessation: Trying hard; but could do better. International Journal of Clinical Practice, 60 (9): 1025-6.	Commentary article.
Strasser, A.A., Kaufmann V. and Jepsonm C. et al. (2001). Effects of different nicotine replacement therapies on post-cessation psychological responses. Addictive Behaviours, 30 (1): 9-17.	Randomised controlled trial. Analyses data by treatment group.
Strong, D.R., Kahler, C.W. and Leventhal, A.M. et al. (2009). Impact of bupropion and cognitive-behavioural treatment for depression on positive affect, negative affect, and urges to smoke during cessation treatment. Nicotine and Tobacco Research, 11(10):1142-53.	Randomised controlled trial. Analyses data by treatment group.
Szklo, A.S., Coutinho, E.S. and Spitz, R. et al. (2009). Gains of stopping smoking: portraits of the dialogue between public health promotion, art and design. International Journal of Epidemiology, 38 (6): 1459-63.	Commentary article.
Tariman, J.D. (2006). Smoking cessation in men. Advance for Nurse Practitioners, 14 (6): 21.	Review paper.
Taylor, G.H. and Graham, M.J. (1992). Smoking cessation. The New Zealand Medical Journal, 105 (930): 100-1.	Commentary article.
Thomas CB. (1978). Personality differences between smokers and non-smokers. Maryland State Medical Journal, 27 (5): 63-6.	Cross-sectional
Thorndike, A.N., Regan S. and McKool K. et al. (2008). Depressive symptoms and smoking cessation after hospitalization for cardiovascular disease. Archives of International Medicine, 168 (2): 186-91.	Smoking status as outcome.

Thorsteinsson, H.S., Gillin, J.C. and Patten, C.A. et al. (2001). The effects of transdermal nicotine therapy for smoking cessation on depressive symptoms in patients with major depression. Neuropsychopharmacology, 24 (4): 350-8.	Mental health was measured during the withdrawal period.
Tonnesen, P., Pisinger, C. and Hvidberg, S. et al. (2005). Effects of smoking cessation and reduction in asthmatics. Nicotine and Tobacco Research, 7 (1): 139-48.	The quitter group includes people who had only recently quit.
Tsoi, D.T. and Webster, A.C. (2010). Interventions for smoking cessation and reduction in individuals with schizophrenia. Cochrane Database of Systematic Reviews, 16 (6): CD007253.	Meta-analysis of interventions.
Vidrine, D.J., Arduino, R.C. and Gritz, E.R. (2007). The effects of smoking abstinence on symptom burden and quality of life among persons living with HIV/AIDS. Aids Patient Care STD, 21 (9): 659-66.	Change in mental health measured during the withdrawal period.
Wang, Y.Z., Chen, H.H. and Yeh, M.L. et al. (2010). Auricular acupressure combined with multimedia instruction or alone for quitting smoking in young adults: A quasi-experimental study. International Journal of Nursing Studies, 47 (9): 1089-95.	No continuing smoker group. No quitter group.
West, R., Gilsenan, A. and Coste, F. et al. (2006). The ATTEMPT cohort: A multi-national longitudinal study of predictors, patterns and consequences of smoking cessation; introduction and evaluation of internet recruitment and data collection methods. Addiction, 101 (9): 1352-61.	Smoking status as outcome.
West, R. and Hajek, P. (1997). What happens to anxiety levels on giving up smoking? American Journal of Psychiatry, 154 (11): 1589-92.	No continuing smoker group.
West, R. and Hajek, P. (2004). Evaluation of the mood and physical symptoms scale (MPSS) to assess cigarette withdrawal. Psychopharmacology, 177 (1-2): 195-9.	No continuing smoker group. Mental health was assessed during the withdrawal period.
Wewers, M.E and Ahijevych, K.L. (1991). Work stress after smoking	No continuing smoker

cessation. American Association of Occupational Health Nurses, 39 (12): 547-51.	group. Analysis of a relapse group.
Yoder, Y.B. (1991). Smoking cessation and stress. Journal of the American Board of Family Practice, 4 (3): 198.	Commentary article.
Zelman, D.C., Brandon, T.H. and Jorenby, D.E. et al. (1992). Measures of affect and nicotine dependence predict differential response to smoking cessation treatments. Journal of Consulting and Clinical Psychology, 60 (6): 943-52.	Randomised controlled trial. Analysis by treatment group.
Ziegelstein, R.C. Smoking cessation and the risk for type 2 diabetes mellitus. Annuals of International Medicine; 152 (1): 10-7.	Commentary article.

6. ARTICLES EXCLUDED FROM META-ANALYSIS (CHAPTER TWO)

Appendix 6 has been previously published:

> Taylor, G., McNeill, A. and Girling, A. et al. (2014). Change in mental health after smoking cessation: systematic review and meta-analysis. **BMJ,** 348 (g1151).

References of articles excluded from meta-analysis and reasons for exclusion	
Reference (N=27)	**Reason for exclusion**
Bolam B, West R, Gunnell D. Does smoking cessation cause depression and anxiety? Findings from the ATTEMPT cohort. Nicotine and Tobacco Research 2011; 13: 209-14.	Binary outcome.
Bolliger CT, Zellweger JP, Danielsson T, et al. Influence of long-term smoking reduction on health risk markers and quality of life. Nicotine and Tobacco Research 2002; 4: 433-9.	Does not report any data on individuals who quit. No response to additional data.
Breslau N, Peterson EL, Schultz LR. et al. Major depression and stages of smoking: A longitudinal investigation. Archives of General Psychiatry 1998; 55:161-6.	Binary outcome.
Carey MP, Kalra DL, Carey KB. et al. Stress and unaided smoking cessation: a prospective investigation. Journal of Consulting and Clinical Psychology 1993; 61:831-8.	Provides only a verbal description of change in mental health. The author no longer has access to the requested data.
Cohen S, Lichtenstein E. Perceived stress, quitting smoking, and smoking relapse. Health Psychology 1990; 9:466-78.	Does not provide enough data to calculate mean change for each group. The author no longer has access to the requested data.
George TP, Vessicchio JC, Termine A. et al. Effects of smoking abstinence on visuospatial working memory function in schizophrenia. Neuropsychopharmacology 2002; 26:75-85.	Does not present enough data at the final follow-up. The author sent additional data, however

	the data were not presented by smoking status.
Glassman AH, Covey LS, Stetner F. et al.Smoking cessation and the course of major depression: A follow-up study. Lancet 2001; 16:1929-32.	Percentage outcome.
Hughes JR, Gust SW, Skoog K. et al. Symptoms of tobacco withdrawal: A replication and extension. Archives of General Psychiatry 1991; 48:52-9.	Extracted data. However, as the M scores were calculated by ruler. All the SEs were assumed as less than 1. The research team decided that the calculations were based on too many assumptions to be accurate.
John U, Meyer C, Rumpf HJ. et al.Smoking, nicotine dependence and psychiatric comorbidity-a population-based study including smoking cessation after three years. Drug and Alcohol Dependence 2004 ; 76(3):287-95.	Binary outcome.
Kaetsu A, Fukushima T, Moriyama M. et al.Change of the smoking behaviour and related lifestyle variables among physicians in Fukuoka, Japan: a longitudinal study. Journal of Epidemiology 2002 May; 12:208-16.	Binary outcome.
Khaled SM, Bulloch AG, Williams . et al. Persistent heavy smoking as risk factor for major depression (MD) incidence: Evidence from a longitudinal Canadian cohort of the National Population Health Survey. Journal of Psychiatric Research 2012; 46:436-43.	Binary outcome.
Marqueta A, Jimenez-Muro A, Beamonte A. et al. Evolution of anxiety during the smoking cessation process at a Smoking Cessation Clinic. Adicciones 2010; 22:317-24.	Does not report follow-up data by smoking status. No response to request for additional data.
McMahon SD, Jason LA. Stress and coping in smoking cessation: A	Does not state how many people

longitudinal examination. Anxiety Stress and Coping 1998; 11:327-43.	were in quit group and continuing smoking group at baseline or follow-up. No response to request for additional data.
McMahon SD, Jason LA, Salina D. Stress, Coping, and Appraisal in a Smoking Cessation Intervention. Anxiety Stress and Coping 1994; 7:161-71.	Data reported in McMahon (1998)
Pertschuk MJ, Pomerleau OF, Adkins D. et al. Smoking cessation: The psychological costs. Addictive Behaviours 1979; 4:345-8.	Frequency of event outcome.
Prochaska JJ, Hall SM, Tsoh JY. et al. Treating tobacco dependence in clinically depressed smokers: Effect of smoking cessation on mental health functioning. American Journal of Public Health 2008; 98:446-8.	Provides only a verbal description of change in mental health. No response to request for additional data.
Sales MP, Oliveira MI, Mattos IM. et al. The impact of smoking cessation on patient quality of life. Jornal Brasileiro de Pneumologia 2009; 35:436-41.	Not enough data to calculate SDs. No response to request for additional data.
Sanchez-Villegas A, Serrano-Martinez M, Alonso A. et al. Role of the tobacco use on the depression incidence in the SUN cohort study. Medicina Clinica 2008; 130:405-9.	Binary outcome.
Schwartz JL, Dubitzky M. One-year follow-up results of a smoking cessation program. Canadian Journal of Public Health 1968; Revue:161-5.	Narrative description and a P-value only. Could not locate either authors' contact details to request additional data.
Segan CJ, Borland R, Wilhelm KA. et al. Helping smokers with depression to quit smoking: collaborative care with Quit-line. Medical Journal of Australia 2011; 195:7-11.	Percentage outcome.
Siahpush M, Spittal M, Singh GK. Association of smoking cessation	Binary outcome.

with financial stress and material well-being: Results from a prospective study of a population-based national survey. American Journal of Public Health 2007; 97:2281-7.	
Tranel D, McNutt A, Bechara A. Smoking Cessation After Brain Damage Does Not Lead to Increased Depression: Implications for Understanding the Psychiatric Complications of Varenicline. Cognitive and Behavioural Neurology 2012; 25:16-24.	Not enough data to calculate mean and SD at baseline. No response to request for additional data.
Tsoh JY, Humfleet GL, Munoz RF. et al. Development of major depression after treatment for smoking cessation. Am J Psychiatry 2000; 157:368-74.	Binary outcome.
Ward KD, Relyea G, Weg et al. Changes in quality of life after smoking cessation among older adults. Nicotine and Tobacco Research 2005; 7(4):700.	Conference abstract. Emailed author for mean mental health scores and standard deviations. Author response: no longer has access to the data.
Wiggers LC, Oort FJ, Peters RJ. et al. Smoking cessation may not improve quality of life in atherosclerotic patients. Nicotine and Tobacco Research 2006; 8:581-9.	Does not provide baseline data for quit group or mean changes. No response to request for additional data.
Weinberger AH, Hitsman B, Papandonatos GD. et al. Predictors of abstinence and changes in psychiatric symptoms in a pooled sample of smokers with schizophrenia receiving combination pharmacotherapy and behavioural therapy for smoking cessation. Journal of Clinical Psychopharmacology 2009; 29:601-3.	Not enough data to calculate M and SD for continuing smoker group. No response to request for additional data.
Zillich AJ, Ryan M, Adams A. et al. Effectiveness of a pharmacist-based smoking-cessation program and its impact on quality of life. Pharmacotherapy 2002; 22:759-65.	Not enough data to calculate SDs for quitter and continuing smoker groups. Requested additional data from author; however the author sent data of

	combined groups.

7. EXAMINATION OF 15 PAPERS WHERE AUTHORS COULD NOT SUPPLY ADDITIONAL DATA (CHAPTER TWO)

Appendix 7 has been previously published:

Taylor, G., McNeill, A. and Girling, A. et al. (2014). Change in mental health after smoking cessation: systematic review and meta-analysis. **BMJ,** 348 (g1151).

Direction, strength and statistical significance of change in mental health between continuing smokers and quitters in 15 papers where the authors could not supply additional data			
First author and year of publication	**Reason for exclusion from meta-analysis**	**In-text quote or verbal summary of results**	**Summary of results**
Bolliger 2002	Does not provide any data on the quit group. No response to request for additional data.	Does not report any data on individuals who quit.	Unclear
Carey 1993	Provides only a verbal description of change in mental health. The author no longer has access to the	"Quitters perceived less stress during their quit efforts than did non-quitters"	Quitters improve compared with

	requested data.		continuing smokers. Direction of change: quitters improve. No indication of change for continuing smokers
Cohen 1990	Does not provide enough data to calculate mean change for each group. The author no longer has access to the requested data.	"Relapsers had higher stress levels than those remaining abstinent at all lags. Quitters had lower stress levels that those who continued to smoke at all lags" "Changes from smoking to abstinence were associated with decreased feelings of stress, whereas changes from abstinence to smoking were associated with increased feelings of stress. Stress levels did not change for subjects whose smoking status did not change.	Quitters improve in comparison to continuing smokers. Direction of change: Quitters improve, continuing smokers show no change.
George 2002	Does not present enough data for the final follow-up. The author sent additional data, however the data were not presented by smoking status.	Does not report follow-up BDI scores.	Unclear

Hughes 1991	Extracted data. However, the mean scores were extracted from a diagram and all the SEs were assumed to be less than 1. The research team decided that the calculations were based on too many assumptions to be accurate. Author no longer had access to the data.	Does not directly discuss the change in anxiety from baseline to 6 month follow-up for either group. Graphs which present the time sequence of change are presented. From the graphs it is clear that continuing smokers and quitters decreased in anxiety, however the decrease appears greater in quitters. This was not statistically assessed.	Unclear
Marqueta 2012	Not enough data to calculate M and SDs. No response to request for additional data.	Does not report 3-month STAI results for quitters and continuing smokers.	Unclear
McMahon 1998	Does not state how many people were in quit group and continuing smoking group at baseline or follow-up. No response to request for additional data.	Presents table of raw M and SD data but does not state how many people were in each group at any time point.	Both groups improve. Unsure if the difference is significant. Direction of change: Both groups show improvement in mental health but it was greater in quitters
Prochaska	Provides only a verbal description of change in mental	"Time effects for BDI-II scores indicated significant reductions	No difference between

2008	health. No response to request for additional data.	from baseline levels and no difference by smoking status." "both groups exhibited a significant decline in depressive symptoms and days with emotional problems over time"	groups. Direction of change: Both groups show improvement in mental health.
Sales 2009	Not enough data to calculate M SDs for the continuing smoker group. No response to request for additional data.	"quitters presented a statistically significant improvement in vitality (positive affect) and the mental component summary (P<0.05)" "the quitters presented higher post-intervention scores than did the non-quitters for the vitality and mental health domains, as well as for the mental component summary"	Quitters improve compared with continuing smokers. Direction of change: quitters improve, no indication of direction for continuing smokers
Schwartz 1968	Narrative description and a P-value only. Could not locate either author's contact details to request additional data.	"both before and during treatment, successful subjects scored less anxious on the mood scale than persons who did not change (P<0.5)"	Quitters improve compared with continuing smokers.

			Direction of change: quitters improve, no indication of direction for continuing smokers.
Tranel 2012	Not enough data to calculate mean and SD at baseline. No response to request for additional data.	1.) At follow-up "For the BDI-II the mean scores did not differ statistically: 10.1 between quitters and 12.3 for non-quitters." 2.) "At follow-up for the BAI, the mean was somewhat higher in the non-quitters (13.0) than quitters (8.5), but the difference was not statistically significant." 3.) "we checked each group for patients who had substantially elevated scores on the depression outcomes... we found no significant between group differences: 10 quitters and 16 non quitters"	No difference between groups Direction of change: no indication of direction for either group.
Ward 2005	Conference abstract. Presents verbal description of change in for quitters and smokers. Emailed author for additional data. Author response: no longer has access to the data.	"A significant time by smoking status interaction was observed for energy/fatigue indicating that non-quitters worsened substantially over time while quitters experienced no change. " "QOL was greater in quitters compared with non-quitters for	Significant difference between groups. Direction of change: quitters show no change,

		emotional well-being"	continuing smokers worsen.
Wiggers 2006	Does not provide baseline data for quit group or mean changes. No response to request for additional data.	"We found no effects of smoking status on patients' mental QOL"	No difference between groups. No indication of direction of change.
Weinberger 2009	Not enough data to calculate M and Ds for continuing smoker group. No response to request for additional data.	Abstinence was associated with a 2.97-U increase in BDI scores as compared with no change in BDI scores for non-abstinence participants.	Quitters increase in depression compared with continuing smokers. Direction of change: quitters worsen, no change for continuing smokers.
Zillich 2002	Not enough data to calculate SDs for quitter and continuing smoker groups. Requested additional data from author; however the author sent data of	"In those who remained abstinent... (change in scores from) baseline to 3 months revealed statistically significant improvements for vitality and mental health"	Quitters improve. No comparison with continuing smokers.

	combined groups.		Direction of change: quitters improve, no data for continuing smokers.

8. REFERENCES OF STUDIES INCLUDED IN THE META-ANALYSIS (CHAPTER TWO)

Appendix 8 has been previously published:

> Taylor, G., McNeill, A. and Girling, A. et al. (2014). Change in mental health after smoking cessation: systematic review and meta-analysis. **BMJ,** 348 (g1151).

References of final studies included in the meta-analysis

Becona E, Vazquez FL, Miguez MD. Smoking cessation and anxiety in a clinical sample. Personality and Individual Differences 2002; 32(3):489-94.

Balduyck B, Sardari NP, Cogen A. et al. The effect of smoking cessation on quality of life after lung cancer surgery. European Journal of Cardio-Thoracic Surgery 2011; 40(6):1432-7.

Berlin I, Chen H, Covey LS. Depressive mood, suicide ideation and anxiety in smokers who do and smokers who do not manage to stop smoking after a target quit day. Addiction 2010; 105(12):2209-16.

Blalock JA, Robinson JD, Wetter DW. et al. Nicotine withdrawal in smokers with current depressive disorders undergoing intensive smoking cessation treatment. Psychology of Addictive Behaviours 2008; 22(1): 122-128.

Busch AM, Wagener TL, Gregor KL. et al. Utilizing reliable and clinically significant change criteria to assess for the development of depression during smoking cessation treatment: The importance of tracking idiographic change. Addictive Behaviours 2011; 36(12):1228-32.

Chassin L, Presson CC, Sherman SJ. et al. Long-term psychological sequelae of smoking cessation and relapse. Health Psychology 2002; 21(5):438-43.

Croghan IT, Schroeder DR, Hays JT. et al. Nicotine dependence treatment: Perceived health status improvement with 1-year continuous smoking abstinence. European Journal of Public Health 2005; 15(3): 251-255.

Dawkins L, Powell JH, Pickering A. et al. Patterns of change in withdrawal symptoms, desire to smoke, reward motivation and response inhibition across 3 months of smoking abstinence. Addiction 2009; 104(5):850-8.

Hajek P, Taylor T, McRobbie H. The effect of stopping smoking on perceived stress levels. Addiction 2010; 105(8):1466-71.

Kahler CW, Brown RA, Ramsey SE. et al. Negative mood, depressive symptoms, and major depression after smoking cessation treatment in smokers with a history of major depressive disorder. Journal of Abnormal Psychology 2002; 111(4):670-5.

Kahler CW, Spillane NS, Leventhal AM. et al. Hostility and smoking cessation treatment outcome in heavy social drinkers. Psychology of Addictive Behaviours 2009; 23(1):67-76.

Kahler CW, Spillane NS, Busch AM. et al. Time-varying smoking abstinence predicts lower depressive symptoms following smoking cessation treatment. Nicotine and Tobacco Research 2011; 13(2):146-50.

Kinnunen T, Haukkala A, Korhonen T. et al. Depression and smoking across 25 years of the normative aging study. International Journal of Psychiatry in Medicine 2006; 36(4):413-26.

Longmore LS, Buchanan DM, Xiao L. et al. Smoking cessation is associated with better mental health outcomes after myocardial infarction. Circulation 2007; 115(21):E551-E552.

McFall M, Atkins DC, Yoshimoto D. et al. Integrating tobacco cessation treatment into mental health care

for patients with posttraumatic stress disorder. American Journal on Addictions 2006; 15(5):336-44.

Manning BK, Catley D, Harris KJ. et al. Stress and quitting among African American smokers. Journal of Behavioural Medicine 2005; 28(4):325-33.

McDermott M, Marteau T, Hollands G. et al. Change in anxiety following successful and unsuccessful attempts at smoking cessation: cohort study. The British Journal of Psychiatry 2013; 202: 62-67. (In press in 2012)

Mino Y, Shigemi J, Otsu T. et al. Does smoking cessation improve mental health? Psychiatry and Clinical Neurosciences 2000; 54(2):169-172.

Mitra M, Chung MC, Wilber N. et al. Smoking status and quality of life: a longitudinal study among adults with disabilities. American Journal of Preventive Medicine 2004; 27(3):258-60.

Munafo MR, Heron J, Araya R. Smoking patterns during pregnancy and postnatal period and depressive symptoms. Nicotine and Tobacco Research 2008; 10(11):1609-20.

Quist-Paulsen P, Bakke PS, Gallefoss F. Does smoking cessation improve quality of life in patients with coronary heart disease? Scandinavian Cardiovascular Journal 2006; 40(1):11-6.

Sarna L, Bialous SA, Cooley ME. et al. Impact of smoking and smoking cessation on health-related quality of life in women in the Nurses' Health Study. Quality of Life Research 2008; 17(10):1217-27.

Solomon LJ, Higgins ST, Heil SH. et al. Psychological symptoms following smoking cessation in pregnant smokers. Journal of Behavioural Medicine 2006; 29(2):151-60.

Steinberg MB, Bover MT, Richardson DL. et al. Abstinence and psychological distress in co-morbid smokers using various pharmacotherapies. Drug and Alcohol Dependence 2011; 114[1]: 77-81.

Stewart A, King A, Killen J. et al. Does smoking cessation improve health-related quality-of-life? Annals of Behavioural Medicine 1995; 17(4):331-8.

Vazquez FL, Becona E. Depression and smoking in a smoking cessation programme. Journal of Affective Disorders 1999; 55(2-3): 125-32.

9. FUNNEL PLOTS FOR EVIDENCE OF PUBLICATION BIAS (CHAPTER TWO)

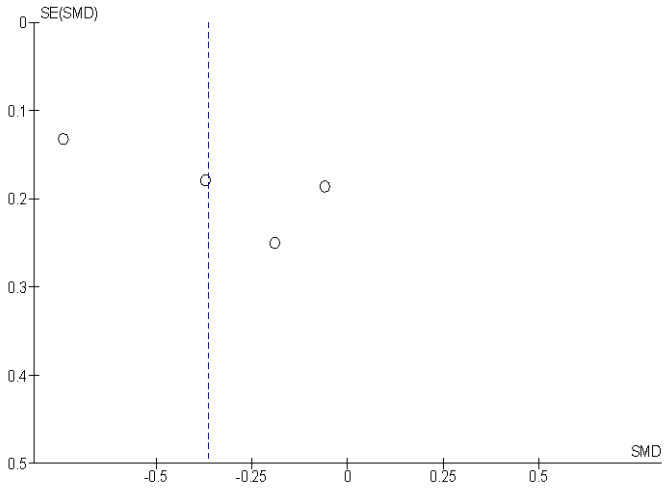


Figure 9.1 Funnel plot of SMD (SE) and SMD, for studies measuring anxiety

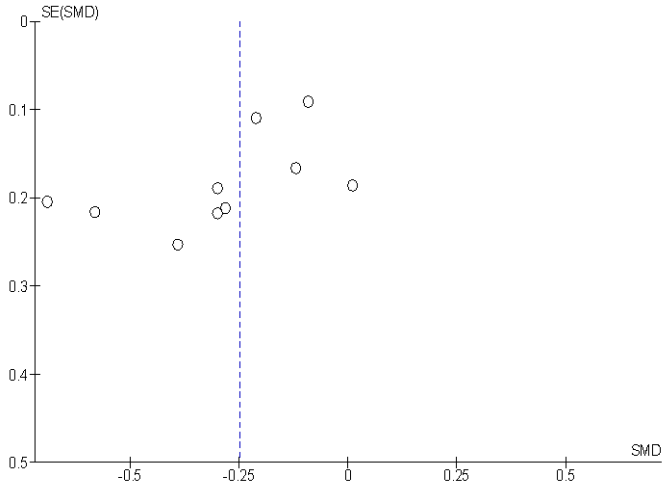


Figure 9.2 Funnel plot of SMD (SE) and SMD, for studies measuring depression

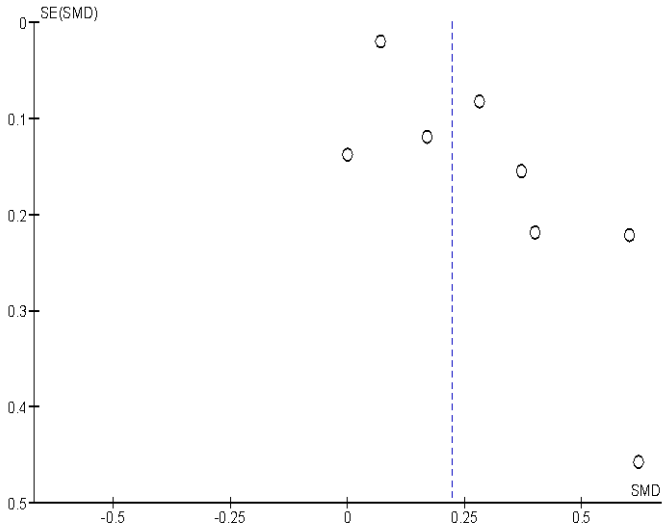


Figure 9.3 Funnel plot of SMD (SE) and SMD, for studies measuring psychological QOL

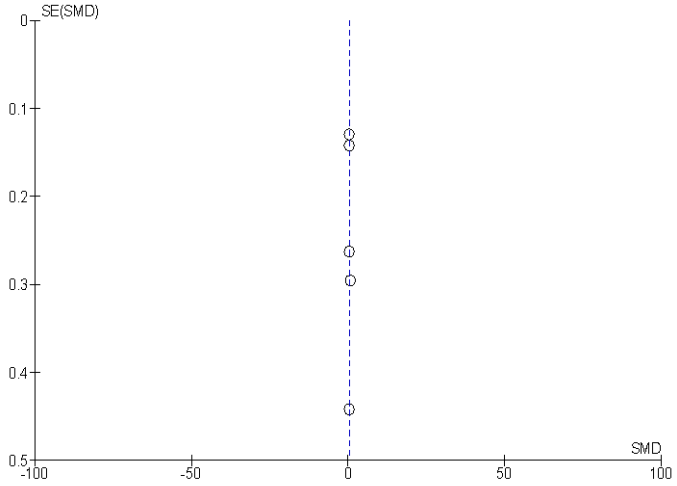


Figure 9.4 Funnel plot of SMD (SE) and SMD, for studies measuring mixed anxiety and depression

10. SENSITIVITY AND SUBGROUP ANALYSES (CHAPTER TWO)

Appendix 9 has been previously published:

> Taylor, G., McNeill, A. and Girling, A. et al. (2014). Change in mental health after smoking cessation: systematic review and meta-analysis. **BMJ,** 348 (g1151).

Sensitivity analysis with removal of studies in which different numbers of participants were analysed at baseline and follow-up				
			Standardised mean difference (95% CI)	
Outcome	**No of studies included**	**No of studies excluded**	**Effect estimate**	**Original effect estimate**
Anxiety	4	0	–0.37 (–0.70 to –0.03)	–0.37 (–0.70 to –0.03)
Depression	3	7	–0.30 (–0.67 to 0.07)	–0.25 (–0.37 to –0.12)
Mixed anxiety and depression	3	2	–0.26 (–0.44 to –0.07)	–0.31 (–0.47 to –0.14)
Positive affect	3	0	0.40 (0.09 to 0.71)	0.40 (0.09 to 0.71)
Psychological quality of life	5	3	0.18 (0.02 to 0.33)	0.22 (0.09 to 0.36)
Stress	2	1	–0.27 (–0.42 to –0.12)	–0.27 (–0.40 to –0.13)

Sensitivity analyses after ascertainment of smoking status				
			Standardised mean difference (95% CI)	
Removed studies and outcome	**No of studies included**	**No of studies excluded**	**Effect estimate**	**Original effect estimate**
Smoking status not biochemically validated				
Anxiety	4	0	–0.37 (–0.70 to –0.03)	–0.37 (–0.70 to –0.03)

Depression	7	3	−0.32 (−0.50 to −0.13)	−0.25 (−0.37 to −0.12)
Mixed anxiety and depression	3	2	−0.35 (−0.59 to −0.10)	−0.31 (−0.47 to −0.14)
Psychological quality of life	4	4	0.17 (−0.02 to 0.35)	0.22 (0.09 to 0.36)
Positive affect	1	2	0.68 (0.24 to 1.12)	0.40 (0.09 to 0.71)
Stress	2	1	−0.23 (−0.39 to −0.07)	−0.27 (−0.40 to −0.13)
Point-prevalence smoking status				
Anxiety	2	1	−0.51 (−1.04 to 0.03)	−0.37 (−0.70 to −0.03)
Depression	6	4	−0.34 (−0.52 to −0.16)	−0.25 (−0.37 to −0.12)
Mixed anxiety and depression	3	2	−0.29 (−0.52 to −0.07)	−0.31 (−0.47 to −0.14)
Psychological quality of life	1	7	0.37 (0.07 to 0.67)	0.22 (0.09 to 0.36)
Positive affect	2	1	0.39 (−0.11 to 0.90)	0.40 (0.09 to 0.71)
Stress	2	1	−0.27 (−0.42 to −0.12)	−0.27 (−0.40 to −0.13)

Subgroup analysis with comparison of studies in which participants were motivated or not motivated to quit		
Population (No of studies)	**Standardised mean difference (95% CI)**	**Test for subgroup differences**
Anxiety		
Overall (4)	–0.37 (–0.70 to –0.03)	
Motivated to quit (3)	–0.41 (–0.81 to –0.00)	χ^2=2.77, P=0.10
Not motivated to quit (1)	–0.19 (–0.68 to 0.30)	
Depression		
Overall (10)	–0.25 (–0.37 to –0.12)	
Motivated to quit (6)	–0.31 (–0.53 to –0.09)	χ^2=1.16, P=0.28
Not motivated to quit (4)	–0.17 (–0.30 to –0.05)	
Mixed anxiety and depression		
Overall (5)	–0.31 (–0.47 to –0.14)	
Motivated to quit (3)	–0.35 (–0.59 to –0.10)	χ^2=0.19, P=0.66
Not motivated to quit (2)	–0.27 (–0.50 to –0.04)	
Psychological quality of life		
Overall (8)	0.22 (0.09 to 0.36)	
Motivated to quit (4)	0.20 (0.03 to 0.38)	χ^2=0.17, P=0.68
Not motivated to quit (4)	0.26 (0.04 to 0.49)	
Positive affect		
Overall (3)	0.40 (0.09 to 0.71)	
Motivated to quit (2)	0.39 (–0.11 to 0.90)	χ^2=3.95, P=0.11
Not motivated to quit (1)	0.47 (0.04 to 0.90)	
Stress		
Overall (3)	–0.27 (–0.40 to –0.13)	
Motivated to quit (2)	–0.23 (–0.39 to –0.07)	χ^2=0.74, P=0.39

Not motivated to quit (1)	–0.36 (–0.61 to –0.11)	

Sensitivity analysis after removal of studies with psychological component within cessation intervention				
Outcome	**No of studies included**	**No of studies excluded**	**Standardised mean difference (95% CI)**	
			Effect estimate	**Original effect estimate**
Anxiety	4	0	–0.37 (–0.70 to –0.03)	–0.37 (–0.70 to –0.03)
Depression	6	4	–0.15 (–0.26 to –0.03)	–0.25 (–0.37 to –0.12)
Mixed anxiety and depression	3	2	–0.28 (–0.46 to –0.10)	–0.31 (–0.47 to –0.14)
Psychological quality of life	5	3	0.15 (–0.01 to 0.31)	0.22 (0.09 to 0.36)
Positive affect	1	2	0.47 (0.04 to 0.90)	0.40 (0.09 to 0.71)
Stress	3	0	–0.27 (–0.40 to –0.13)	–0.27 (–0.40 to –0.13)

Subgroup with comparison of effect estimates between different study designs		
Study design	**Effect estimate standardised mean difference (95% CI)**	**Test for subgroup differences**
Anxiety		
Overall	–0.37 (–0.70 to –0.03)	—
Cohort (1 study)	–0.06 (–0.42 to 0.30)	χ^2=4.07, P=0.13
Randomised controlled trial (1 study)	–0.19 (–0.68 to 0.30)	
Secondary analyses of cessation intervention (2 studies)	–0.57 (–0.93 to –0.21)	
Depression		
Overall	–0.25 (–0.37 to –0.12)	—
Cohort (3 studies)	–0.12 (–0.25 to 0.01)	χ^2=5.15, P=0.08
Randomised controlled trial (1 study)	–0.39 (–0.88 to 0.10)	
Secondary analyses of cessation intervention (6 studies)	–0.36 (–0.53 to –0.18)	
Mixed anxiety and depression		
Overall	–0.31 (–0.47 to –0.14)	—
Cohort (3 studies)	–0.28 (–0.46 to –0.10)	χ^2=0.76, P=0.38
Secondary analyses of cessation intervention (2 studies)	–0.51 (–0.99 to –0.03)	
Psychological quality of life		
Overall	0.22 (0.09 to 0.36)	—
Cohort (5 studies)	0.28 (0.08 to 0.48)	χ^2=0.95, P=0.33
Secondary analyses of cessation intervention (3 studies)	0.15 (–0.04 to 0.33)	
Positive affect		

Overall	0.40 (0.09 to 0.71)	—
Cohort (2 studies)	0.28 (–0.02 to 0.57)	χ^2=2.22, P=0.14
Secondary analyses of cessation intervention (1 study)	0.68 (0.24 to 1.12)	
Stress		
Overall	–0.27 (–0.40 to –0.13)	—
Cohort (1 study)	–0.36 (–0.61 to –0.11)	χ^2=0.74, P=0.39
Secondary analyses of cessation intervention (2 studies)	–0.23 (–0.39 to –0.07)	

Subgroup analysis after comparison of effect estimates between studies with follow-up periods from baseline to follow-up between six weeks to six months and studies with follow-ups from baseline to >6 months				
Outcome	**Standardised mean difference (95% CI)**			**Test for subgroup differences**
	Original estimate	**6 weeks to <6 months**	**>6 months**	
Anxiety	–0.37 (–0.70 to –0.03)	–0.35 (–0.83 to 0.12) (3 studies)	–0.37 (–0.72 to –0.02) (1 study)	χ^2=0.00 P=0.95
Depression*	–0.25 (–0.37 to –0.12)	–0.18 (–0.31 to –0.05) (8 studies)	–0.23 (–0.41 to –0.06) (5 studies)	χ^2=0.25 P=0.62
Mixed anxiety and depression*	–0.31 (–0.47 to –0.14)	–0.37 (–0.58 to –0.15) (4 studies)	–0.27 (–0.50 to –0.04) (2 studies)	χ^2=0.34 P=0.56
Positive affect	0.40 (0.09 to 0.71)	0.68 (0.24 to 1.12) (1 study)	0.28 (–0.02 to 0.57) (2 studies)	χ^2=2.22 P=0.14
Psychological quality of life*	0.22 (0.09 to 0.36)	0.30 (0.15 to 0.44) (7 studies)	0.23 (0.09 to 0.37) (8 studies)	χ^2=0.36 P=0.92
Stress	–0.27 (–0.40 to –0.13)	–0.25 (–0.58 to 0.08) (1 study)	–0.27 (–0.42 to –0.12) (2 studies)	χ^2=0.01 P=0.92
*Please note some studies measured outcome at multiple follow-ups, these were compared within the corresponding subgroup analysis				

11. PROTOCOL FOR MCNEIL STUDIES (CHAPTER THREE)

PROTOCOL: A PROSPECTIVE COHORT STUDY TO EXAMINE THE EFFECTS OF SMOKING CESSATION ON MENTAL HEALTH

Authors: Taylor, G., Aveyard, P. and McNeil, A.

The University Of Birmingham

BACKGROUND

Smokers believe that smoking reduces stress and provides psychological benefits. McEwen et al. (2008b) examined smokers' motives to continue smoking. Stress relief, boredom relief and enjoyment were the highest rated motives to continue smoking. This suggests that smokers believe smoking cigarettes can alleviate negative emotions, and that by stopping smoking they may be losing a mechanism which facilitates positive emotions.

However, smokers' beliefs about smoking do not coincide with research which investigates the relationships between smoking status and psychological well-being. The 2004 Surgeon General's report collated evidence from ecological, cross-sectional, cohort, case-control studies and intervention trials, reference lists from important publications, consultations with experts and a extensive literature searches. The report concluded that the reviewed evidence provides a clear indication that smokers report more negative mental health symptoms

compared with non-smokers. The report showed strong evidence of poor psychological well-being within the smoking population. However, the causal relationship is unclear. It is possible that smoking causes poor mental health, poor mental health causes smoking, or that both have a common cause.

There is some evidence that smoking may cause poor mental health. Parrott (2003) reviewed longitudinal studies investigating the relationship between smoking initiation and subsequently occurring psychological well-being. The studies reviewed by Parrott (2003) indicated that nicotine dependency is associated with heightened psychological distress in tobacco smokers.

The misattribution hypothesis seeks to explain why smokers can feel that smoking is stress relieving in the face of evidence that smoking may cause psychological distress (Parrott, 1999). The hypothesis is based upon research which indicates that smokers experience the distressing psychological symptoms of nicotine withdrawal shortly after finishing smoking a cigarette. Psychological withdrawal symptoms include anxiety, irritability, stress, depression, restlessness and difficulty concentrating. In nicotine dependent smokers these negative changes in mood are relieved by smoking a cigarette. However, the relief only takes the smoker back to a normal mood state (Parrott, 1998). As a result, nicotine dependent smokers suffer many periods of poor mood every day, with nicotine dependency being a cause of negative mood (Parrott, 1994). The re-occurrence of negative mood causes the dependent smoker to experience a worse daily mood; in turn lowering overall psychological well-being.

Withdrawal effects, offset effects and psychological well-being

The abstinent smoker will experience various negative psychological symptoms during the withdrawal period. The length of the withdrawal period varies. Two cohort studies reported that depression and negative mood states last longer than four weeks post-cessation (Gilbert et al., 2002; Gilbert et al., 1998). However, in Gilbert et al.'s (1998, 2002) studies individuals were considered as abstinent even if they smoked up to 10 cigarettes during the abstinence period. Including smokers smoking occasionally may have prolonged withdrawal in these studies. Hughes (2007d) systematically reviewed cohort studies examining the occurrence of tobacco withdrawal symptoms after abstinence and found that anxiety, depression, and negative mood states (e.g. anger, impatience) peak within the first week of abstinence and last two to four weeks. Thus to assess the association between maintained smoking cessation and change in psychological well-being measurement of psychological well-being should take place from four weeks onwards post-cessation.

There is uncertainty pertaining to whether some psychological symptoms display a unidirectional change after cessation (known as an offset effect) (Hughes, 2007a; Hughes, 2007e). If an offset effect occurs, the level of symptom is abnormal. For example if depression displays an offset effect, this would mean that the person will permanently display a lower level of psychological well-being. Hughes (2007b, 2007c) argues that there are two interpretations of the offset effect. Firstly, the person's level of psychological well-being may have been low before they began to use tobacco. This is supported by the self-medication hypothesis, which suggests that the chemical properties of nicotine are used by the smoker to alleviate psychological distress (Khantzian, 1997). Another explanation is that the post-

abstinence level of psychological well-being is a new level caused by long-term use of tobacco.

Research suggests that cessation may be associated with an offset of depressive symptoms. For example Glassman et al. (2001) conducted a longitudinal analysis and found that smokers with a history of depression who abstain from smoking display an increased risk of developing a new episode of depression (OR=7.17, 95% CI 1.5-34.5) at six-months. Tsoh et al. (2000) compared the risk of developing depression between quitters and continuing smokers and found that both groups displayed a similar rate of incidence of depression (N=25 of 170, 14.7% versus N=18 of 134, 13.4%. However, the reported incidence of post cessation depression was higher amongst those with a history of depression (23.7%, N=23 of 97 versus 9.7%, N=20 of 207). These results suggest that not everyone reports depression upon cessation; but a subgroup of individuals are susceptible to this offset effect

Smoking cessation and change in psychological well-being

If the misattribution hypothesis is correct then smokers who maintain cessation should experience a decrease in negative psychological symptoms. There is evidence to support this. Cohen et al. (1990) compared change in levels of perceived stress from baseline to six-months, between individuals who remained continuously abstinent with individuals who continued smoking. Those who remained continuously abstinent displayed a greater reduction in perceived stress than those who did not quit. Carey et al. (1993) reported that those who remained continuously abstinence displayed decreased stress in comparison to non-quitters at a twelve-month follow-up. Parrot et al. (1995) examined stress levels at six months

after cessation accounting for daily stressors. Successful quitters displayed reduced stress levels even though there was no reduction in environmental stressors Hughes et al. (1992) prospectively investigated anxiety and depression levels after cessation. Anxiety and depression decreased but the authors did not compare quitters to continuing smokers. Thus, long-term studies are consistent with the misattribution hypothesis.

There are some data that do not fit well with the misattribution hypothesis. Chassin et al. (2002) examined change in perceived stress and negative affect from baseline to six years in people who stopped smoking and those who continued. Although perceived stress was reduced in quitters, there were no significant reductions in other symptoms of negative affect. This suggests that reduced stress may not improve psychological well-being. However, Chassin et al.'s (2002) study used measures of negative affect that are of uncertain validity.

Other data are incompatible with the misattribution hypothesis I found two reviews which found evidence to suggested that smoking cessation is associated with worsening mental health (Hughes 2007c; Parrott 2003). Parrott (2003) noted the association between adverse effects of smoking cessation on psychological well-being (Gilbert et al. 1998c; Glassman et al. 1990). However, Gilbert et al. (1998b) assessed mental health outcomes at thirty days; as discussed above, this is within the withdrawal period. Accordingly, this study does not provide sufficient evidence to show that smoking cessation worsens psychological well-being. Hughes (2007b) identified seven studies which examined the incidence of major depressive disorder (MDD) among individuals who had maintained cessation for seven to sixty four weeks. Hughes' (2007a) analysis found that the incidence of MDD over two to twelve months post-cessation varied in the studies between 1% and 31% amongst smokers who remained

abstinent. Hughes (2007b) review did not compare the occurrence of MDD of successful quitters with unsuccessful quitters, thus this study provides no evidence of an association between abstinence and MDD.

Smoking reduction and change in psychological well-being

Smoking reduction is an intervention which aims to assist smokers who have no immediate plans to quit to reducing their daily cigarette consumption. According to the misattribution hypothesis, reduction may change psychological well-being in three ways. Firstly, the smoker may not become less dependent; and as the smoker increases the length of time between cigarettes smoked, they will experience longer periods of withdrawal and in-turn experience an increase in negative psychological symptoms. Secondly, if an individual successfully reduces the number of cigarettes consumed daily they may become less dependent on tobacco and experience a decrease in withdrawal symptoms between cigarettes, in-turn experiencing less negative psychological symptoms. Thirdly, there may be no change in mood symptoms because of compensation. Compensation means inhaling the reduced number of cigarettes more intensively, thus extracting as much nicotine as when smoking normally (National Cancer Institute, 2001). Hughes and Carpenter (2005) reviewed fifteen studies and found that when smokers reduce their daily consumption of cigarettes, compensatory inhalation occurs. If compensation occurs, smokers may not experience changes in psychological well-being. It is therefore unclear how reduction may affect psychological well-being under the misattribution hypothesis.

There is little research examining the effect of smoking reduction on psychological well-being. There are two systematic reviews in this area: Pisinger et al. (2007) and Banham and Gilbody (2010). Pisinger et al. (2007) conducted a systematic review of the association between smoking reduction and subsequent health. This review identified one study which examined the effect of smoking reduction on psychological well-being (Bolliger et al., 2002). Bollinger et al. (2002) reported an increase in emotional well-being from baseline to twenty-four months in individuals who had successfully reduced their smoking by at least 50%. However, this increase in emotional wellbeing was not significant compared with the change in emotional well-being of non-reducers. However, the sample sizes used in the analysis are too small to exclude an effect at (N=25) and non-reducers (N=285). Furthermore, the non-reducer group included people who had reduced their smoking by less than 50%. Thus the two groups may not have been very different in their reduction status, which perhaps explains the null effect.

Understanding the association between smoking reduction and change in psychological well-being is important as smoking reduction is currently being proposed as a means to quit for individuals with mental health problems. Thus it is especially important to understand the possible impact on mental health for these people. Banham and Gilbody (2010) systematically reviewed trials of smoking cessation interventions in psychiatric populations. The review included eight RCTs which used validated mental health symptom scales as outcome measures. The review showed that people randomized to assistance with cessation were more likely to stop than those getting usual care or placebos. In people randomized to cessation assistance there was no evidence of a marked deterioration and perhaps some evidence of an improvement in mental health. However, the trials obviously did not compare

individuals who stopped smoking to those who continued nor did they compare people who reduced their smoking to people who continued at the same rate thus the review does not show if smoking reduction is associated with a change in mental health.

Smoking cessation, smoking reduction and change in positive affect

The focus on positive affect is an emerging branch of psychology which focuses on promoting positive affect (e.g. happiness, positive emotions), rather than a sole focus on the absence of psychological disorder or low mood (Seligman et al., 2005). The Action on Mental Health report published by the European Commission (2004) suggested that mental health (or psychological well-being) has two dimensions: positive mental health (feeling well) and negative mental health (experiencing symptoms of psychological disorder). The report called for research into positive mental health.

There is little research on the association between smoking cessation (or reduction) and positive affect. One study reported that current smokers were 2.68 (95% CI=2.00-3.59) times more likely to report low levels of happiness with their lives compared to non-smokers (Koivumaa-Honkanen et al., 2003). In contrast, smokers most commonly endorsed reason for smoking is enjoyment (McEwan et al., 2008). This indicates that smokers' feel they may be less happy without cigarettes. It may encourage smokers to quit if they were confronted with evidence that this belief is wrong.

There are no studies which investigate the association between smoking reduction and change in positive affect. There are two studies which investigate the association between smoking

cessation and happiness. A cross-sectional survey of 879 ex-smokers' reported changes in happiness following cessation (Shahab and West, 2009); 69.3% (95% CI=66.2 to 72.3) percent of ex-smokers reported feeling happier compared to when they were smokers, 26.6% reported feeling the same (95% CI: 23.7 to 29.5) and 3.3% reported that they were less happy. In a second study, (Shahab and West, 2012) analysed the association between length of abstinence in ex-smokers and happiness. Smokers who had been abstinent for more than a year reported being happier than smokers and were as happy as never smokers. These studies do not show that stopping smoking improves happiness Firstly, reports of change in post-cessation happiness are retrospective, thus may be susceptible to recall bias. Recall bias occurs when the respondents' answer is susceptible to inaccuracies in memory (Coughlin, 1990). Secondly, one cannot be sure if the smoker became happy and then quit, or if the smoker quit and then became happy. Finally, both studies are reporting analyses of the same data from the UK Smoking Tool Kit Study (West 2006).

Post cessation change in psychological well-being and the association with relapse

Smoker's cite stress relief as a motive for smoking (McEwen et al., 2008); thus if a smoker's psychological well-being worsens as a results of a post-cessation offset effect they may be more likely to relapse to smoking to relieve unwanted emotion.

Research indicates that adverse mood prior to quitting is associated with relapse to smoking. Zvolensky et al. (2009) reported that depression and anxiety symptoms at baseline were associated with an increased likelihood to relapse two weeks after quit day (OR=1.3, P=.01) (Zvolensky et al., 2009). Perez et al. (2008) reported that depressive symptoms prior to

quitting was associated with an increased likelihood to relapse at six months among patients hospitalized for acute coronary syndrome (OR=2.54, 95% CI: 1.51 to 4.27). Allen et al. (2009) reported that women who had given up smoking in pregnancy and then experienced postpartum depressive symptoms were 1.86 (95% CI: 1.31 to 2.65) times more likely to relapse compared to those who did not experience postpartum depressive symptoms. Zhou et al. (2009) systematically reviewed cohort studies to identify predictors of relapse. They reported that individuals who reported being bothered by symptoms of anxiety and depression in the past three months were more likely to relapse back to smoking (OR=1.42, 95% CI: 1.02 to 1.99). These studies show that there is an association between psychological distress and subsequent relapse. However, this does not indicate that post-cessation change in psychological well-being (or an offset effect) is associated with relapse.

I conducted a literature review of Embase, PsychInfo and Medline using terms related to "relapse" AND "smoking" AND "mental health" to find cohort studies which reported the association between post-cessation change in psychological well-being and relapse to smoking. After reviewing titles and abstracts of the search results: two studies were located.

Burgess et al. (2002) conducted a cluster analysis to identify patterns of change in depression symptoms two weeks after cessation. They identified five patterns of change in depression symptoms: depression symptoms rapidly increased or decreased, slowly increased or decreased, or rapidly increased then decreased. Burgess et al. (2002) then analysed the association between patterns of change in depression symptoms and rates of abstinence using generalised estimating equations. They reported that individuals who displayed a rapid increase or slow increase in depression symptoms were less likely to be abstinent at twelve

months (respectively, OR=5.95, P <0.01; OR=0.66, P<0.02). However, the findings of this study are limited. The change in depression symptoms was assessed during the withdrawal period; thus, these results may be explained if those with worse withdrawal were more likely to relapse rather than the occurrence of long-term mood changes after cessation represent withdrawal severity, rather than an established change in post-cessation psychological well-being.

Yong et al. (2010) conducted a prospective cohort study of over 2000 adult smokers. They reported that participants' who reported that their psychological well-being had worsened were more likely to relapse (OR=1.33, 95% CI, 1.00-1.76). However, these results are limited, as a participants' change in psychological well-being is a retrospective opinion; thus is susceptible to recall bias and does not indicate an empirically measured change in psychological well-being. The most accurate method to determine post-cessation change in psychological well-being would be to calculate the difference between mental health scores pre-cessation and before the time at which the individual relapsed.

In sum, the studies reviewed show that change in mood is associated with an increased likelihood to relapse. However, these studies do not provide robust evidence that changes in mood after cessation prompt people to relapse. It is important to investigate this for two reasons. Firstly, it is important to understand an offset effect is associated with increased relapse. Secondly, it could be that some smokers do use smoking to self-medicate and prevent negative psychological symptoms or improve psychological well-being. If they relapse because cessation uncovers this, then knowing that this is the case is the first stage of being able to prevent this in future.

CONCLUSION

Firstly, research investigating the effect of smoking cessation on change in psychological well-being is limited. Some studies are not applicable to long-term changes in psychological well-being as they assess well-being during the withdrawal period (Gilbert et al., 1998a). Secondly, the most robust longitudinal data (Cohen and Lichtenstein, 1990; Parrott, 1995) (Carey et al., 1993) only show a reduction in negative psychological symptoms follows smoking cessation; which does not necessarily imply that positive affect increases. Furthermore, to improve rigor studies require use of a biochemically validated measure of cessation, and instruments known to provide valid assessments of psychological well-being.

Secondly, there is very little research examining the effect of smoking reduction on changes in psychological well-being. There is only one study with a longitudinal design (Bolliger et al., 2002); but the study may have lacked power to detect a plausible influence of reduction on psychological distress.

Thirdly, there are two cross-sectional studies showing that ex-smokers report feeling happier since quitting smoking (Shahab and West, 2009; Shahab and West, 2012). However, there are no longitudinal cohort studies investigating the change in positive affect post cessation or reduction.

Research indicates that psychological distress prior to cessation are associated with an increased likelihood of relapse (Allen et al., 2009; Perez et al., 2008; Zvolensky et al., 2009; Zhou et al. 2009). However, there have been no studies to date which show if worsening

psychological well-being occurring after cessation but outside of the normal withdrawal period is associated with relapse. There are three studies which provide insight into the association between post-cessation change in psychological well-being and smoking cessation. However in one study the timing of outcome assessment does not warrant a robust conclusion (Park, 2009), another study is likely to be assessing withdrawal severity (Burgess et al., 2002) and the final study is susceptible to recall bias (Yong et al., 2009).

Primary study objectives

An analysis of the McNeil trials will permit us to analyse the associations in a prospective longitudinal study with a sufficiently large sample, using biochemically validated cessation and valid measures of psychological distress and positive affect. Analysis of these data will allow us to examine the association between smoking cessation, smoking reduction and changes in psychological distress and positive affect. Also, these data will permit us to examine whether worsening mood occurring perhaps as an offset effect after cessation is associated with relapse.

Primary questions

Is successful abstinence from cigarette consumption associated with changes in psychological distress and positive affect?

Is successful reduction in daily cigarette consumption associated with an changes in psychological distress and positive affect?

Is successful abstinence or successful reduction in smoking associated with a higher or lower risk of an adverse mental health event?

Are post-cessation and post-reduction changes in psychological well-being associated with an increase risk of relapse?

Secondary study objectives

If time and resources permit, these data will also be used to provide a descriptive account of changes in people's smoking behaviour. Smoking reduction is a novel public health strategy. It is currently being considered by the English National Health Service (NICE, 2011) (National Centre of Smoking Cessation and Training, 2011). However, there is uncertainty about the whether or not encouraging reduction promotes cessation or deters cessation; and, in particular, whether people can maintain a reduced consumption level.

I will be able to assess how many people have successfully maintained reduction, successfully reduced-to-quit, relapsed after attempting to reduce.

METHOD

Required variables

Data from seven randomised controlled trials of nicotine replacement therapy for use in smoking reduction interventions will be provided by McNeill pharmaceutical company. I will require access to the following baseline data for each participant

–Date of birth or age

–Sex

–Participant randomization ID

–Intention/interest to quit

–Contemplation ladder

–Stages of change

I will require the following individual participant data, recorded at every available time-point (including baseline):

–Which follow-up point the data were recorded (e.g. baseline, week one, etc) and date of the participant's visit

–Any adverse event information recorded at follow-up visits

–CO ppm measurement after 15 smoke free minutes and time for CO measurement

–Self-reported cigarettes consumed per day (CPD)

–Single question responses from the RAND-36

–Global score for the RAND-36

–Single question responses from the Withdrawal Symptoms Questionnaire

–Fagerström Test of Nicotine Dependence Score

–Smoking history

–Smoking status

Analysis

Firstly, participants will be categorised according to their smoking behaviours. All participants who were enrolled and followed up during the McNeill trials will have stopped, reduced and continued smoking at different time points. Accordingly, each participant will need to be categorised based upon their individual smoking patterns. Participants will be categorised according to the groups described below.

Assessing baseline

Baseline will be assessed for each person. Each participant's baseline characteristics will be recorded at the closest time-point, to the first change in smoking status which was used to categorise them (i.e. pre-cessation or pre-reduction)

Participants

Reducers: Some participants may permanently reduce the number of cigarettes consumed per day (CPD). The definition of reducers will be based upon a key review on the feasibility of smoking reduction conducted by Hughes and Carpenter (Hughes and Carpenter, 2005). Hughes (2005) defined smoking reduction as an achievement of ≥ 50% reduction in CCPD. However, ≥ 50% reduction in CPD from baseline will also include people who have completely stopped smoking. As smoking zero cigarettes per day is total abstinence, the current study will consider any amount of daily, first-hand cigarette inhalation from 'one puff' daily up to a reduction in CPD ≥ 50% from daily baseline consumption.

Successful reduction will be defined as reporting <50% of baseline consumption for a minimum of two consecutive months will be considered a successful reducer. Self-reported smoking reduction must also be validated by an expired CO concentration lower than baseline on every occasion.

Successful abstainers: Successful abstainers will be considered individuals who maintain two continuous abstinence starting at any time before the end of treatment. This is a robust measurement of smoking abstinence (West et al., 2005). Self-reported abstinence at each follow-up must be biochemically validated by an expired CO level of <10 ppm. Biologically-validated cessation must be reported at each time their mental health scores are considered for analysis (except pre-cessation scores).

Reduction relapsers: Relapse is defined as smoking more than 50% of baseline consumption or having a CO>baseline.

Cessation relapsers: This is defined as smoking more than 5 cigarettes since last observed or having a CO >=10ppm.

Continuing smokers (matched comparison group for study questions 1 and 2): Not all participants quit. Continuing smokers will be considered as individuals who have reported to have continued smoking from the initial assessment, and at every subsequent time point and who do not meet the criteria for reduction.

The continuing smokers group will be used in the main analysis to compare the change in mental health between those who are successful reducers or abstainers. However, the review of the literature suggests that continuing smokers are likely to suffer from higher negative affect at baseline compared to abstainers or reducers. Likewise, the groups may differ in other ways that may influence the change in psychological symptoms or well-being. I will therefore account for these baseline differences in the study. Accordingly, it is important to remove the influence of potential confounding variables in the analysis. One method of doing so is to use propensity matching.

Propensity score matching (PSM)

Propensity score matching will be used to match groups on baseline sociodemographic and psychological covariates rather than adjusting for covariates. There are several advantages to using propensity score matching in comparison to adjusting for covariates.

Random assignment of participants to groups is gold standard methodology to obtain interferences about causality. Random assignment ensures that the groups are similar in terms of background characteristics; this enables a sound comparison of the groups' outcomes. However, when analyzing observational data, one cannot randomize participants to groups. For example, in the current study will compare quitters with continuing smokers, however one cannot randomize people to maintain abstinence, nor to continuing smoking. Thus, one cannot assert that the groups are similarly matched on background characteristics.

One method of accounting for this problem is to fit a linear regression which includes background characteristics as covariates, however, the groups in the analysis may still differ. Propensity score matching differs from regression models as it balances the distribution of background characteristics between the groups. Regression models have been criticized for producing misleading results when including too many covariates (Concato et al., 1993); this can be overcome by matching groups, rather than adjusting for numerous covariates. Additionally, interpretation of a regression model is limited when the number of cases for each covariate characteristic is low. This has been found to bias the parameter estimates, in turn affecting validity of the regression coefficients (Cepeda et al., 2003; Peduzzi et al., 1996).

Propensity score matching procedure for groups

To ensure the continuing smoker group will be an adequate comparison group I will use propensity score matching. A propensity score is a conditional probability that represents how likely a participant is to be a case (reducer or abstainer) compared to a control (continuing smoker), based on their baseline characteristics. Matching Propensity score matching will balance the distribution of socio-demographic and psychological covariates between the continuing smokers group and other groups (Thoemmes and Kim, 2011). Propensity score matching will involve three stages.

Stage 1: Estimation of propensity score

Participants' propensity scores will be estimated using logistic regression (conducted on SPSS) in which smoking status category will be used as the outcome variable and the covariates as predictors.

Covariates available in the McNeil dataset will be chosen based upon their association with one's motivation to quit (Haukkala, 2000), their association with likelihood of attempting to quit (Zhou et al., 2009), changing smoking status (Berlin and Covey, 2006) or relapsing (Zhou et al., 2009). The following covariates will be used to determine each participant's propensity score: age, sex, treatment group, baseline CPD, baseline RAND-36 MCS, baseline Fagerström Test of Nicotine Dependence score, number of years smoking, number of previous quit attempts and baseline intention/interest to quit score. These covariates will then be entered into a regression model using a backward stepwise technique. This will determine which covariates have the highest association with the participants' smoking status. Only covariates which reach statistical significance ($P<0.05$) will be entered into the final propensity score model.

Stage 2: Matching participants' propensity scores

Participants will be matched using a 1:1 nearest neighbour technique, which will be based upon an optimal matching algorithm. This will match participants who have approximately the same propensity scores; scores will be matched in a manner which will minimise the average absolute distance between the propensity scores of all units in the whole matched sample (Thoemmes and Kim, 2011).

Stage 3: Checking model adequacy and underlying assumptions

A propensity score model will be checked to ensure that a balance of means and variances has been achieved for covariates (known as the balance property) and to determine the overlap between the propensity score distribution (the common support region) (Thoemmes and Kim, 2011). To check the balance property between the groups, I will examine the standardised differences of each groups' covariates before and after matching.

To ensure the propensity score distribution has sufficient overlap I will examine the range of the propensity score distributions in both groups. If the overlap between the two propensity score distributions is broad, this allows for causal effects estimates over the full range of propensity scores in the sample. Whereas small common support regions restrict the estimation of a causal effect. Units (a matched pair) which fall outside of the common support region will be removed from the analysis; this is advised to improve the balance between the matched groups (Ho et al., 2007)

Outcome measures

The current study will use the following data as primary outcome measures during statistical analyses.

Mental health: The RAND-36 (SF-36) (Hays et al., 1993) is a short form self-report questionnaire designed to detect changes in health status. The scale includes two composite scores which are of interest in the current study; the mental health composite score (MHC) and the Energy and Vitality Index (EVI). The MCS will be used to measure changes in

negative mood (Gill et al., 2007; Hays and Morales, 2001). Low scores on the MHC indicate that the participant is likely to be experiencing psychological symptoms which may impede life functioning (Hays et al., 1998). The EVI will be used to measure changes in positive psychological-wellbeing (Ware et al., 1993). High scores on the EVI indicate higher levels of positive psychological well-being.

Withdrawal symptoms questionnaire (WSQ): The current study will only analyse anxiety and depression single scale items from the WSQ (American Psychiatric Association, 1994). These will be used to represent change in anxiety and depression. These items are ranked using a five-point likert scale to assess the degree of nicotine withdrawal (0=not at all, 1=somewhat, 2=moderately so, 3=very much so, 4=extremely so). This is ordinal data however is it also a continuous scale, thus will be considered a continuous variable in the analysis.

Adverse mental health events: All McNeil studies recorded adverse events at all follow-up time-points. The following events will be considered a sign of an adverse mental health event: new diagnosis of anxiety or depression mental health disorder, admission to a mental health unit for anxiety or depression, referral to psychology or counselling for anxiety or depression and referral to psychiatry for anxiety or depression.

The following variables will be used for analyses:

Groups: rapid reducers, gradual reducers, long-term reducers,

successful abstainers, rapid reduction relapsers, gradual reduction relapsers, long-term reduction relapsers, cessation relapsers, relapse improvers and decliners (see section 3.7.4), continuing smokers (matched comparison group)

Mental health measures: MCS, EVI, anxiety WSQ, depression WSQ, adverse events.

Statistical procedures for study objectives

Firstly, mental health composite and subscale scores will be calculated for each participant. All participants' responses on the RAND-36 will be scored to determine mental health composite scores (MCS) and the energy and vitality scores (EVI) and global scores. The procedure outlined by Hayes et al. (1993) and Ware et al. (1993) for scoring composite scores will be followed. This scoring method will be applied to the data acquired at each time point that the participant completed the RAND-36. This will provide a negative mental health score (MCS) and positive mental health score (EVI) and a quality of life score (RAND-36 total score) for each individual participant at every follow-up visit they attended. If there are any missing responses on the RAND-36 the individual's data for that time point will be excluded from analysis.

Is successful abstinence from cigarette consumption associated with an improvement or worsening of psychological well-being?

SPSS for Windows will be used to create a linear regression model to determine if smoking status is associated with a change in mental health. Successful abstainers and continuing smokers will be coded as categorical predictor variables (1 and 0). A separate model using

abstainers and continuing smokers as the predictive variable will be fit for each mental health outcome: MSC, EVI, anxiety WSQ, depression WSQ. A separate model will be run for each month.

Is successful reduction in daily cigarette consumption associated with an improvement or worsening of psychological well-being?

To determine the effect of smoking reduction on psychological well-being SPSS for windows will be used to conduct a simple linear regression. This analysis will determine if smoking status associated with a change in mental health. Successful reducers and intervention continuing smokers will be coded as categorical predictor variables (1 and 0). A separate model for each reduction group successful reducers and continuing smokers as the predictive variable will be fit for each mental health outcome: MSC, EVI, RAND-36 anxiety WSQ, depression WSQ. A regression will be run on a month by month basis, in which there are a sufficient number of participants.

Statistical procedure: is successful abstinence or successful reduction in smoking associated with an increased risk of an adverse mental health event?

A Cox regression (Cox proportional hazards model) will be conducted using SPSS 17 to determine there is an increased risk of experiencing an adverse mental health event following cessation or reduction in comparison to continuing smokers. The use of a Cox regression model will allow us to determine the adjusted hazard ratio (HR). This method is not common in smoking cessation research. However, the adjusted HR will allow us to account for the

occurrence of censored data. Censored data in the current study will occur as one is only able to assert that the patient remained free of an adverse mental health event during the timeframes outlined by the dataset.

I will match groups using propensity score matching. Groups will be matched on covariates which can influence likelihood of experiencing anxiety and depression. The following factors have been found associated with an increased likelihood of experiencing anxiety or depression; sex (Piccinelli and Wilkinson, 2000), age (Christensen et al., 1999) and previous report of negative psychological well-being (MHC) (Horwath et al., 1992).

Statistical procedure for question four: Is post-cessation and post reduction improvement or worsening or psychological well-being associated with an increase risk of relapse?

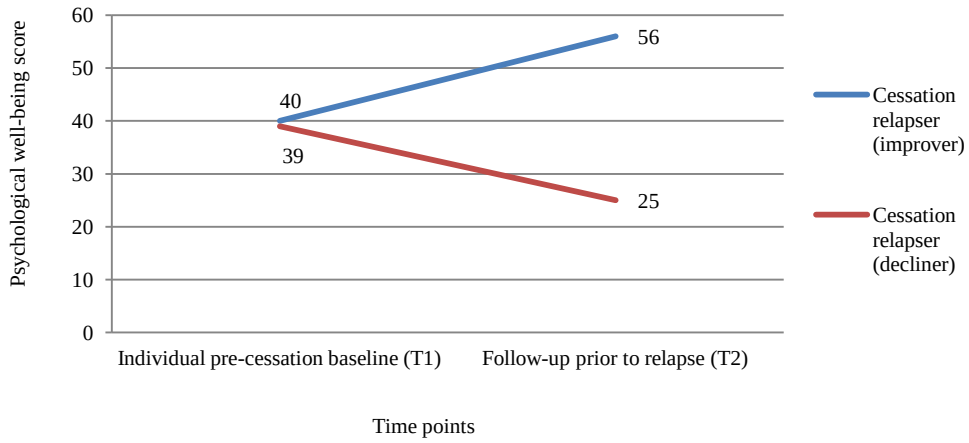
Step one: stratification of relapser groups

Firstly, participants in relapse groups will be stratified classified into those where psychological well being improved and those where it decreased after cessation (Figure 1). To determine the direction of change the individual's MHC and EVI scores at baseline (T1) will be used (see section 2.4 for assessment of individual baseline), and the individual's MHC and EVI scores at the closest follow-up prior to the relapse event (T2) in which the individual reports a minimum of six weeks (Biologically-validated) abstinence. The individuals MHC score at T1 will be subtracted from the individual's MHC score at T2; this will give us the difference between the MHC scores. The difference will be used to determine the direction of change in psychological well being.

$$T2 - T1 = difference$$

This will be repeated to calculate the change EVI scores. The difference in T2 and T1 scores will result in a positive (+) or a negative number (-); it is the +/-. Will represent a positive (+) or negative (-) change in psychological well being. It is the +/- value of the number which will be used to stratify the relapsers.

Figure 1. Visualisation of stratification of cessation relapsers



There will be two groups for each smoking status category categorized depending on the direction of change in psychological well-being (Table 1). These will be developed according to interpretation of the MHC and EVI scores. Low scores (≤38) on the MHC are likely to indicate the presence of psychological symptoms which may impede life functioning, high scores (≥53) on the MHC are not likely to perceive psychological symptoms which may impede life functioning (Hays et al., 1998). Therefore, a positive difference will indicate an improvement in mental health, and a negative difference will indicate a worsening of mental

health. Low scores on the EVI indicate a lower level of happiness; high scores on the EVI indicate a higher level of happiness. Therefore, therefore a positive difference will indicate an increase in happiness, and a negative difference will indicate a decrease in happiness.

Table 1: groups to be developed from stratification technique	
Long-term reduction relapsers	Improvers1
	Decliners2
Abstainers	Improvers1
	Decliners2
1= determined by a positive (+) change in psychological well-being, 2=determined by a negative (-) change in psychological well-being	

Thus, if an individual displays negative changes in MHC and EVI scores this will indicate that their psychological well-being worsened prior to relapse (Decliner). And, if an individual displays positive changes in MHC and EVI scores this will indicate that their psychological well-being improved prior to relapse (Improver). Each type of smoking category relapse group will be stratified based on this technique (Table 1). Please see Table 2 for an example of the stratification technique.

Table 2: stratification of relapsers based on direction of change in MHC and EVI scores

Relapse group	MHC score at baseline1	MHC at closest time-point prior to relapse2	Direction of difference in MSC scores	EVI score at baseline1	EVI score at closest time-point prior to relapse2	Direction of difference in EVI scores	Stratification based on change in psychological well-being
Reduction relapser	30	38	+8	50	55	+5	Improver (rapid reduction)
Reduction relapser	52	40	-12	48	44	-4	Decliner (long-term reduction)
Cessation relapser	40	35	-5	45	39	-6	Decliner (gradual reduction)
Cessation relapser	38	42	+4	43	48	+5	Improver (cessation)

Baseline MHC and EVI scores will be obtained at the closest time point prior to the change in smoking behaviour in which dictates the participants smoking category (e.g. rapid reducer or abstainer).

Pre-relapse MHC and EVI scores will be obtained at the closest time-point to relapse. The individual must report at least six weeks Biologically-validated abstinence at this time point.

Survival curve analysis of time to relapse

To determine the pattern of relapse related to pre-relapse change in mental health a survival curve will be plot. The survival curve will show the time to relapse between decliners and improvers (Figure 2.). This will provide a visualisation of the number of decliners and number of improvers who maintained abstinent or reduced on a monthly basis.

Calculating the hazard ratio (HR) to determine the likelihood of relapse

A Cox regression (Cox proportional hazards model) will be conducted using SPSS 17 to determine if there are any significant differences between the time to relapse of improvers and decliners. The use of a Cox regression model will allow us to determine the adjusted HR. The adjusted HR will allow us to control for variables which may also affect relapse rate. I will control for age, baseline FTND score and previous number of failed quit attempts (as recorded via smoking history section); these factors have all been found associated with an increased likelihood to relapse (Zhou et al., 2009).

Secondary study objectives: Descriptive statistics of smoking reduction behaviour

I will be able to report descriptive data showing how many people have successfully maintained reduction, successfully reduced then quit, and relapsed after reducing (Table 3).

Table 3: Descriptive statistics of smoking reduction behavior	
Number of people who successfully maintained reduction	N(%)
Number of successful successfully reduced then quit	N(%)
Number of people who relapsed after reducing	N(%)

CONCLUSIONS

These data will show that smoking cessation and smoking reduction are associated with either an improvement or worsening of psychological well-being. These data will also elucidate if there is an offset effect from smoking cessation, and if this offset effect is associated with an increased likelihood to relapse back to smoking. Thirdly, I will be able to show if smoking reduction is maintainable and how many people quit after reducing their smoking.

12. METHODS FOR COMBINING MCNEIL TRIAL DATA (CHAPTER THREE)

McNeil pharmaceutical company uploaded each trial's data to a secured server held by Johnson and Johnson. Each trial's data were uploaded to a separate folder by McNeil, and downloaded separately by GT. Each trial's folder contained 10 or more text (.txt) files. Each text file contained numerous variables in a tab-delimitated format (Table 11.1 below).

Most trials text files were labelled the same and within each file was similar variable content. However, the number of variables within each text file differed between the trials. For example, the "adverse event" text file contained seventeen variables which measured adverse events for Trial 1, but for Trial 2 the "adverse events" file contained twenty variables which also measured adverse events. These differences between trials existed as some trials included additional variables to measure the same construct.

Table 11.1 Trials' original data contents				
Original text file label	Text file content	Description of variables	Trials which supplied text file	Number of variables within text file
AE	Adverse events	Dates pertaining to start, end of event, comments of event, severity of event, coding information for event.	Trial 1 Switzerland	17
			Trial 2 Denmark	20
			Trial 3 Australia	21
			Trial 4 US	18
			Trial 5 Germany	24
			Trial 6 Switzerland	21
CRAVEQ	Relief of craving questionnaire	Self-reported effects of smoking on withdrawal symptoms	Trial 1 Switzerland	13
			Trial 2 Denmark	12
			Trial 3 Australia	Located in different file
			Trial 4 US	12
			Trial 5 Germany	12
			Trial 6 Switzerland	Not available
DEM	Demography	Age, sex	Trial 1 Switzerland	4
			Trial 2 Denmark	4
			Trial 3 Australia	4
			Trial 4 US	4
			Trial 5 Germany	4
			Trial 6 Switzerland	4

DOS	Dispensed nicotine replacement therapy	Amount of dispensed NRT medication	Trial 1 Switzerland	26
			Trial 2 Denmark	10
			Trial 3 Australia	23
			Trial 4 US	23
			Trial 5 Germany	23
			Trial 6 Switzerland	9
FTN	Fagerström Test for Nicotine Dependence	Self-reported answers to items on the FTND questionnaire and global score	Trial 1 Switzerland	18
			Trial 2 Denmark	18
			Trial 3 Australia	18
			Trial 4 US	18
			Trial 5 Germany	18
			Trial 6 Switzerland	18
INTQUIT	Intention to quit	Self-reported answers pertaining to intention to quit or reduce smoking	Trial 1 Switzerland	12
			Trial 2 Denmark	11
			Trial 3 Australia	18
			Trial 4 US	18
			Trial 5 Germany	18
			Trial 6 Switzerland	10
LAB	Laboratory results	Blood test results 2	Trial 2 Denmark	22
			Trial 3 Australia	22
NU	Nicotine use	Results for expired carbon monoxide	Trial 1 Switzerland	10
			Trial 2 Denmark	10

			Trial 3 Australia	10
			Trial 4 US	10
			Trial 5 Germany	10
			Trial 6 Switzerland	11
QOL DATA	SF-36 subscales	SF-36 subscale scores	Trial 1 Switzerland	9
			Trial 2 Denmark	9
			Trial 3 Australia	9
			Trial 4 US	9
			Trial 5 Germany	9
			Trial 6 Switzerland	Not recorded
SMINCHK	Smoking status check	CPD, self-reported current smoking behaviour	Trial 1 Switzerland	18
			Trial 2 Denmark	18
			Trial 3 Australia	22
			Trial 4 US	19
			Trial 5 Germany	18
			Trial 6 Switzerland	15
SMKHIST	Smoking history	Past smoking behaviour	Trial 1 Switzerland	41
			Trial 2 Denmark	37
			Trial 3 Australia	39
			Trial 4 US	44
			Trial 5 Germany	39
			Trial 6 Switzerland	16

TRT	Allocation of treatment groups	Randomisation sequence	Trial 1 Switzerland	5
			Trial 2 Denmark	5
			Trial 3 Australia	7
			Trial 4 US	5
			Trial 5 Germany	7
			Trial 6 Switzerland	7
VISIT	Visit dates	Each participants visit dates	Trial 1 Switzerland	7
			Trial 2 Denmark	10
			Trial 3 Australia	10
			Trial 4 US	11
			Trial 5 Germany	11
			Trial 6 Switzerland	10
WSQ	Withdrawal symptoms questionnaire	Cognitive and psychological nicotine withdrawal symptoms	Trial 1 Switzerland	21
			Trial 2 Denmark	21
			Trial 3 Australia	28
			Trial 4 US	21
			Trial 5 Germany	21
			Trial 6 Switzerland	Not recorded

Transforming downloaded data into useable files

Original file format: Within each text file the variables were stored in a ‘long’ format. This means that the file was horizontally sorted by variable, vertically sorted by participant identifier and then vertically sorted by follow-up point (Figure 11.1, below). For the secondary analyses the data needed to be in a ‘wide’ format. ‘Wide’ means that the file is horizontally sorted by variable, then by follow-up point, and vertically sorted by participant identifier (Figure 11.2).

Trial 1

Subject ID	Follow-up	Variable 1	Variable 2
1	Baseline	123	10
1	Week 3	120	12
1	Month 6	115	8
2	Baseline	100	9
2	Week 3	102	10
2	Month 6	100	11
3	Baseline	115	9
3	Week 3	121	7
3	Month 6	112	13

Figure 11.1 Trial in 'long format'

Converting data to ‘wide’ format

To convert each text file from a ‘long’ format I first had to develop a continuous time variable for when the follow-up data were recorded. Each text file contained a follow-up point variable as a string which was converted to a continuous variable of weeks in the year. For example: ‘baseline’, ‘week 3’, ‘month 6’ became, ‘0’, ‘3’, ‘26’ weeks. Then the ‘reshape’ command was used to convert each text file into a ‘wide’ format in STATA12. Random

checks of the files against the original text files were performed to ensure that there were no errors.

Trial 1						
Subject ID	Variable1-0	Variable1-3	Variable 1-26	Variable 2-0	Variable 2-3	Variable 2-26
1	123	120	115	10	12	8
2	100	102	100	9	10	11
3	115	121	112	9	7	13

Figure 11.2 Trial in 'wide format'

Differences between trials' measurement of variables

I examined each trial's text files to determine consistency of variable content across trial's text files. All text files which did not have relevant data for this study were excluded. Next all text files were against each trials' questionnaire/outcome-set to ensure that the variables within the text files were consistently named, stored, and measured across the trials. Variables used to determine exposure and outcome variables (smoking status and mental health outcomes) were consistently labelled, stored and measured across the trials. Adverse events, demographic information, prescribed NRT, Fagerström Test of Nicotine Dependence (FTND), expired CO, smoke history, smoking status, VISIT, relief from craving and withdrawal symptoms were the also the same across trials, except for in Trial 6.

Trial 6 was missing SF-36 data, which was used as an outcome variable in Chapter Four, an important covariate in Chapter Five, and the exposure variable in Chapter Six. In addition, Trial 6 was missing the 'Relief from craving questionnaire' which was an important covariate

required for the propensity scoring matching techniques used in Chapters 4 and 5. For these reasons, Trial 6 was excluded from the McNeil trial analyses.

Variables within 'Relief of craving', 'Intention to quit' and 'treatment allocation' varied between trials. For 'Relief of craving', all trials measured the same three questions; however the remaining four questions were measured differently across all trials. Variables measured for 'Intention to quit' were also different. Each trial used different questions and a different number of questions to measure 'Intention to quit', and also participant's answers were not consistently coded as categorical or continuous across the trials. Ideally each variable would have measured its content in the same manner, however, as this was not the case, this was accounted for by within trial analyses described in Chapters 4 to 6.

'Treatment allocation' was slightly different for each trial. This is as some trials had two active treatment groups (e.g. 2mg gum and 4mg gum), whereas some trials had one active treatment group. Secondly, the treatments were different between the trials. To account for these differences participants were coded as allocated to receive either active or placebo NRT. This is justified for three reasons 1.) This study concerns receipt of treatment, rather than the type of treatment 2.) The treatments were quite similar and 3.) There is no difference in effectiveness between different forms of NRT (Stead et al., 2012). Finally, potential differences between trials' treatments were accounted for by adjustment for Trial ID when necessary, as described within Chapters 4 to 6.

There was a slight variation between the trials' variables recorded within the SF-36 text files. The US trial included an additional section on the SF-36 which included questions about

"smoking-related quality of life", these assessed smoking related symptoms such as coughing and phlegm. However, these additional questions were not used to calculate the subscale of interest to this thesis (emotional well-being subscale). Therefore this difference between the trials' versions of the SF-36 did not influence the analyses reported in this thesis.

Importantly, all variables used to determine each secondary analyses 'exposure' and 'outcome' variables were measured in the same manner across trials. All differences between covariates were accounted for by a series of sensitivity analyses and statistical adjustment as described within each chapter.

Combining text files within trials

The next step was to combine all text files within each trial, by participant ID. This produced one dataset per trial, within which one can browse each participant's variables at each time-point, by participant ID. For example, in Figure 11.3 text files 1 and 2 from trial 1 have been merged for each participant. To combine trials text files the 'merge 1:1' command was used in STATA12. Random checks were performed against the original trial files to ensure no errors were made.

Trial 1, file 1

Subject ID	Variable 1	Variable 2	Variable 3
1	123	10	55
2	100	12	62
3	115	8	45

+

Trial 1, file 2

Subject ID	Variable 4	Variable 5	Variable 6
1	3	80	0
2	5	75	1
3	2	72	1

=

Trial 1 (Files 1 + 2)

Subject ID	Variable 1	Variable 2	Variable 3	Variable 4	Variable 5	Variable 6
1	123	10	55	3	80	0
2	100	12	62	5	75	1
3	115	8	45	2	72	1

Figure 11.3 Combining variable text files for the same trial

Appending the trials

The ‘append’ command (STATA13) in was used to append each trial’s merged data to form one dataset (Figure 11.4). Variables which were measured differently, or which measured similar constructs were not appended. Only variables which measured to the exact same question/variable, and which were measured in exactly the same manner were combined across trials (Table 3.1, Chapter 3). However, as excluding variables which were measured differently may have omitted important information about the associations in question, a series of within-trial sensitivity analyses were conducted to explore this (described in Chapters Four to Six).

Trial 1

Subject ID	Trial ID	Variable 1	Variable 2	Variable 3	Variable 4	Variable 5
1	1	123	10	55	3	80
2	1	100	12	62	5	75
3	1	115	8	45	2	72

+

Trial 2

Subject ID	Trial ID	Variable 1	Variable 2	Variable 3	Variable 4	Variable 5
1001	2	101	9	42	1	81
1002	2	120	10	60	5	85
1003	2	112	11	51	4	79

=

Combined trials

Subject ID	Trial ID	Variable 1	Variable 2	Variable 3	Variable 4	Variable 5
1	1	123	10	55	3	80
2	1	100	12	62	5	75
3	1	115	8	45	2	72
1001	2	101	9	42	1	81
1002	2	120	10	60	5	85
1003	2	112	11	51	4	79

Figure 11.4 Appending different trials into one dataset

13. MANUSCRIPT SUBMITTED FOR PUBLICATION IN THE BRITISH JOURNAL OF PSYCHIATRY (CHAPTER FOUR)

TITLE

Does smoking cessation result in improved mental health? A comparison of regression modelling and propensity score matching.

WORD COUNT

3030

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ABSTRACT

Background: Smokers report that smoking is therapeutic; a recent meta-analysis suggests the contrary. However, the association in that review may be explained by group-membership bias and confounding.

Aim: Propensity score matching (PSM) produces causal estimates from observational data. We examined the association between cessation and change in mental health before and after PSM.

Method: A secondary analysis of prospective data from five placebo-controlled randomised trials for smoking reduction. Smoking status was assessed over six months and change in mental health (SF-36, scored 0-100) was compared between quitters and continuing smokers with and without adjustment and after PSM.

Results: Before matching, quitters' mental health scores improved compared to smokers; mean difference: 5.5; 95% confidence intervals (1.6 to 9.4). After adjustment, the difference was 18% lower: 4.5 (0.6 to 8.5). After PSM the difference was 38% lower: 3.4 (-2.2 to 8.9).

Conclusions: Most of the association between cessation and improved mental health appears not to be explained by confounding or group membership bias, strengthening the evidence that the association is causal.

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BACKGROUND

Most smokers want to quit (1;2) but report continuing to smoke because they feel that smoking helps them to cope with stress and offers other mental health benefits (3-9). Our recent systematic review found strong and consistent evidence that the opposite was true (10). Smokers who quit showed marked decreases in negative affect and increases in positive affect over-time, while smokers who continued smoking changed little during the same period. We concluded that the strongest explanation for this finding was that cessation caused the improvement in mental health. However, critics countered that selection bias or unmeasured confounders were possible explanations of the findings (11). Very few studies in this review made any attempt to control confounding and none addressed selection bias.

As it is not possible to assign participants randomly to smoking/not smoking or stopping smoking/not stopping smoking, observational studies are the only of source of data to assess the association between smoking and quitting on mental health. Regression modelling is commonly used to account for confounding by adjusting the association of interest for the effect of other variables associated both with the outcome and the exposure variable. However, adjustment cannot account for selection bias arising from any unmeasured factors which differ by smoking status and are associated with the outcome. An alternative method that may account for selection bias as well as confounding is propensity score matching (PSM). PSM involves matching individuals within a sample based upon on their propensity to belong to an exposure group, or here, matching on the propensity to quit or continue smoking without considering the association of those variables with the outcome (12). Thus by balancing covariate distribution between groups, confounding by those variables is eliminated. In addition, unmeasured factors associated both with propensity to quit smoking may also be equalised by this process, reducing selection bias, providing an unbiased estimate of the association between cessation and improved wellbeing (12).

One disadvantage of PSM is that it reduces the size of the sample available to estimate the strength of the association between cessation and mental wellbeing because it requires participants to be matched. If the association between stopping smoking and mental health is influenced by group-membership bias or other unmeasured confounding, effect estimates derived from a sample of participants matched on their propensity to quit will show a weaker association. The aim of this study was to estimate the strength of the association between

cessation and change in wellbeing using a regression model adjusting for covariates, and compare this with the estimate derived from PSM.

METHOD

This study followed STROBE reporting guidelines for observational studies (13). PSM procedures were conducted and reported following criteria outlined by a review of PSM methodology (14).

Study design & setting

This was a secondary analysis of prospective individual level patient data from five merged placebo-controlled randomised trials (RCTs) of nicotine replacement therapy (NRT) for smoking reduction; these data were provided by McNeil pharmaceutical company (see reports of trials for further details (15-19)).

Study size

There were 2066 participants enrolled in the trials, which took place between 1997 and 2003. In total, 937 participants provided data at both 6 and 12 month follow-ups. Of these 68 were confirmed as abstinent at six and 12 months and 589 as continuous smokers at both follow ups. Attrition rates are similar to other trials of NRT (20).

Participants

All participants were adult smokers selected because they wanted to reduce but not stop smoking and had smoked for at least three years. Participants were excluded if they were pregnant/breastfeeding, under psychiatric care, deemed to be unfit by a general practitioner, or part of a cessation programme.

At baseline, investigators gathered data on participants' demographic details and age started smoking, cigarettes per day (CPD), nicotine dependence (Fagerström Test of Nicotine Dependency (FTND))(21), intention to quit, intention to reduce, smoking history (e.g. number of previous quit attempts, longest period without smoking), self-rated effects from smoking ("Relief from smoking questionnaire")(19), mental health (SF-36) (see Appendix Table 5 for further details). To preserve anonymity, some demographic data were unavailable to us for this secondary analysis.

Participants were followed up to eight to ten times over two years and on each occasion they were encouraged to reduce smoking by using NRT or placebo and given behavioural

strategies to assist. In addition, investigators collected data on CPD, 7-day point prevalence abstinence, recorded an expired air carbon monoxide reading (CO), and at baseline and at some other follow-ups measured quality of life using the RAND-36. This scale is also known as the SF-36; however the RAND-36 uses slightly different scoring algorithms Mental health was measured by the emotional wellbeing subscale (22). On this subscale, scores range from 0 to 100, scores of ≤38 indicate a probable mental health problem (23); in the general population the subscale mean and standard deviation (SD) are 70.4(22.0). A minimally important difference on the emotional wellbeing subscale has been defined as a standardised effect size ranging between 0.09 and 0.28 (24).

Exposure

We classified a person has having achieved prolonged cessation if they were abstinent at both six and 12 months and were verified to be so on both occasions by having a CO reading of <10ppm. We classified a person as smoking continuously if they reported smoking at both times and had a CO reading of ≥10ppm. We excluded from analysis anyone not meeting either definition.

Outcome

The primary outcome was change in mental health from baseline (when all participants were smoking) to 12 month follow-up (after at least six months of continuous abstinence or continued smoking).

Analysis

If participants were missing any relevant data they were excluded from the analysis. In the first model, we used linear regression to examine the association between cessation and change in mental health, including baseline mental health as a covariate and adding a dummy variable representing cessation. We then adjusted for FTND score and treatment allocation (active/placebo), age, sex and Trial ID. For the second model we repeated this regression model using the propensity score matched groups (described below). To determine if the association was clinically important we calculated Cohen's d before and after matching (24).

PSM involved three steps towards building a logistic regression model to derive predictors of quitting. 1.) Propensity scores were developed using covariates which predicted smoking

status: nicotine dependency (FTND)(25) and treatment allocation (26) were forced into the model; and a forward stepwise procedure was used to determine whether baseline mental health, intention to quit, intention to reduce, sex, age, smoking history, SF-36, CPD, rated relief from smoking questionnaire, were also associated with quitting at the $p<0.10$ level. 2) This logistic regression model was combined with the PSMATCH2 command in STATA 13 to calculate propensity scores for the estimated probability of quitting contingent upon each participant's characteristics(27). Quitters were matched to the continuing smoker with the closest propensity score on a ratio of 1:1 using a nearest neighbour greedy algorithm with no replacement, matching was restricted to the common support region. 3) We performed various checks to ensure the adequacy of the model. We checked the balance of means and variances of covariates after matching (Thoemmes & Kim, 2011) by examining the standardized mean differences between smokers and quitters, before and after matching. After matching bias should be ≤5% (28) to determine an adequate model. We calculated the achieved percentage of reduction in bias (28) and examined scatter plots comparing each covariate's standardised % bias before and after matching were examined. We also examined the kernel density estimate of the probability distribution of the propensity scores before and after matching.

Sensitivity analyses

We developed three sensitivity analyses using different PSM models. Our adjusted regression model was rerun for each PSM sensitivity analysis, and we compared the regression coefficients between the sensitivity models. The trials measured key baseline variables consistently; each trial also measured some variables in a different manner compared to the other trials. Therefore we 1) matched participants across trials including variables measured consistently; 2) matched participants within trials using all relevant variables. We repeated matching across or within trials, with and without common support restrictions (Table 1).

<INSERT TABLE 1 HERE>

RESULTS

Unmatched participants

Sixty-eight participants were biologically-validated as continuous quitters and 589 as continuous smokers. Three smokers and one quitter were excluded for missing baseline mental health scores. Twenty-six smokers were missing outcome data. Smokers excluded for missing data were psychologically healthy at baseline (23); mental health scores were M(SD)= 74.0(15.7) similar to included smokers (Table 3). After exclusion for missing data, 67 participants were biologically-validated as quit and 560 as smokers. Table 2 displays baseline characteristics of unmatched smokers and quitters. There were differences between groups' FTND scores ($p<0.001$) and the proportion who received active treatment ($p=0.001$).

<INSERT TABLE 2 HERE>

The association between smoking cessation and change in mental health in the unmatched sample

Mental health scores improved in both groups. The mean change in the quit group was 4.9 (95% CI: 1.1 to 8.7) compared with 1.0 (95% CI: -0.4 to 2.4) in continuing smokers (**Error! Reference source not found.**). The difference between groups adjusted only for baseline mental health was 5.5; 95% CI: 1.6 to 9.4; P<0.001). After further adjustment for FTND, treatment status, age, sex and Trial ID the difference between groups remained significant (B=4.5, 95% CI: 0.6 to 8.5, P= 0.025).

<INSERT FIGURE 1 HERE>

PSM main model

Table 3 presents odds ratios (OR) and 95% CIs for baseline covariates which predicted smoking status at P<0.10, after forced entry of FTND and treatment allocation. Covariates which predicted smoking status were different within trials and included: FTND scores, active treatment, age started smoking, report of calming effects from smoking, report of unpleasant symptoms from smoking, length of time to last cessation attempt, experience from last cigarette, longest period without smoking, SF-36 mental health (1 trial).

<INSERT TABLE 3 HERE>

Main model adequacy checks

In all cases, variables which were significantly imbalanced between groups before matching were no longer significantly imbalanced after matching. There were no cases where variables became significantly imbalanced after matching.

Difference in bias between groups after matching was examined to determine which variables were adequately matched. For trial 1, 3/6 variables were adequately matched; trial 4, 0/2 and trial 5, 3/6 variables were adequately matched. In trials 2 & 3 all variables were adequately matched. In sum, matching led to a ≥90% reduction in bias for 13/20 variables. (Appendix Table 7).

As shown in **Figure 2**, there was a common support area to perform PSM and participants were predominately matched within a common region.

<INSERT FIGURE 2 HERE>

Participants after PSM

The main PSM model included 67 biologically-validated continuous quitters who were matched to 67 smokers with similar propensity scores. Sixteen participants, eight per matched sample, were lost as they did not fall within the common support, those excluded did not differ from the included sample at baseline (Excluded participants baseline mental health scores were (M(SD)) 77.0(14.6) for smokers and 73.5(16.4) for quitters. FTND scores of excluded smokers were 4(2.4) and 3.4(1.9) for quitters. Six excluded smokers and 7 excluded quitters received active NRT treatment.). Before PSM there were significant differences between the groups' nicotine dependency scores (FTND) and the number of people receiving active treatment (Table 2). After matching, the sample became balanced on all baseline characteristics Table 4.

<INSERT TABLE 4 HERE>

The association between smoking cessation and mental health between matched and unmatched samples

After matching, quitters showed an improvement in mental health 4.5 (95% CI: 0.4 to 8.7) and smokers displayed a slight worsening in mental health -0.2 (95% CI: -4.8 to 4.3) (Figure

3). The difference between groups after adjustment for baseline values and covariates was 3.4; -2.2 to 8.9; p=0.229).

<INSERT FIGURE 3 HERE>

Minimal clinically important difference

Cohen's d for the standardised effect size was *d*=0.41 (95%CI: 0.2 to 0.7) for the unmatched sample; which suggests a clinically important association. After matching the effect became imprecise 0.16 (95%CI: -0.2 to 0.5), although the direction of the association remained to favour the quit group.

PSM sensitivity models

When matching was repeated across trials (Appendix Table 6) variables that contributed to the propensity score were similar to when matching was conducted within trials. When the models were run without restricting to the area of common support smokers and quitters still presented balanced baseline mental health scores (Appendix Table 8). At follow-up smokers' mean scores indicated either a slight improvement or slight worsening, and in all analyses quitters showed a moderate improvement in mental health. The coefficients for the difference between quitters and continuing smokers ranged from regression coefficient B=4.0 (95% CI: -1.0 to 8.9) to 3.6 (-1.3 to 8.4) (Appendix Table 8), suggestive of an association between smoking cessation and improvement in mental health regardless of matching criteria.

Risk of bias

Risk of bias was assessed using an adapted version of the Newcastle-Ottawa Scale. This study scored 4/5 indicating a low risk of bias (Appendix **Table 9**).

DISCUSSION

Regression modelling showed evidence that cessation was associated with improved mental health compared with continuing to smoke and this finding was not altered by adjustment for confounding. Propensity score matching offers potential to control selection bias as well as confounding. Using this technique we achieved a good match between smokers that continued smoking and those that stopped. Doing so, the regression coefficient for the difference between smokers and quitters differed only slightly from that achieved by regression methods but it was no longer significant.

There were some important strengths of the study. Data were collected in a rigorous way with clear biologically verified criteria to differentiate continuing smokers from quitters. We included all the key covariates that a systematic review reported were associated with likelihood of achieving abstinence (25). Mental health was assessed using a psychometrically sound tool (23;24) and participants in the trials were not aware of our hypothesis so there were no demand characteristics that might have biased the results. The Newcastle-Ottawa score suggested that the results were unlikely to be subject to bias. After propensity score matching we achieved good balance of covariates and extensive sensitivity analysis showed no evidence that the results were sensitive to the methodological decisions we made.

There were some limitations. The regression analysis was based on a large sample and gave sufficient precision to give a statistically significant result. The analysis using propensity score matching necessarily limited the sample size and the estimate was no longer as precise and was not significant. Importantly, though, the regression coefficient did not change in size after matching. Although PSM theoretically balances unobserved covariates between groups (12;29) one cannot be certain. The overlap of propensity scores in unmatched groups shows there was a small to medium region to conduct matching and a small common support region may restrict the estimation of a causal effect by changing the observed population (30). However, sensitivity analyses showed the association was similar regardless of matching within or outside the common region. Furthermore, those excluded during support restrictions had similar baseline characteristics to the entire cohort suggesting that restriction to the common area did not introduce bias. Multiple sensitivity analyses showed no evidence that change in the analysis method altered the effect estimate. To protect patient confidentiality this analysis did not include certain demographic characteristics, such as ethnicity, social class

and education as covariates. These demographics are possible predictors of change in smoking status; however a recent systematic review did not find consistent evidence to support this (25). It is also possible that these demographics may predict the likelihood of experiencing change in mental health. However, for example if ethnicity predicts change in mental health, this is likely to be true in both quitters and smokers. Therefore, although these characteristics may appear important, confounding occurs only if the strength or direction of association changes between baseline and follow-up and that change differs by group. For these reasons, it is unlikely that excluding these characteristics from the analysis influenced the association. However, interactions may still be possible.

These effect size reported here is similar to a recently reported systematic review (10) which examined studies similar to this in that mental health was measured before and after cessation in quitters and at corresponding time points in continuing smokers. None of the studies in the review had used propensity score matching and few of them had used regression to adjust for potential confounders. This study therefore goes further than previously in allaying concerns that the apparent benefits of cessation on mental health are spurious and arise instead from unmeasured differences between those who stop and those who do not stop smoking. It therefore strengthens the case that the cessation of smoking caused the improvement.

In the systematic review (10), we proposed that the improvement in mental health was because after cessation regular smokers no longer experience periods of withdrawal-induced negative affect between cigarettes. This would imply that smoking may cause symptoms of depression and anxiety. However, a Mendelian randomisation study found only scant evidence to suggest any association between the genetic instrument and anxiety and depression symptoms (31). This might suggest that the improvement in mental health that appears to arise after cessation is not due to relief of the smoking induced withdrawal symptoms.

The effect size reported here is similar in size to that reported in systematic reviews of the effects of antidepressants for anxiety and depression (32;33) and is larger than that deemed clinically important on the mental health subscale of the RAND-36. This study adds to the growing band of evidence from observational research that cessation interventions in the general population (10) and in those with mental health problems at least does no harm and may indeed be therapeutic. This evidence is supported by trials of cessation interventions in

people with mental health problems, which show no evidence of harm and small suggestions of benefit to mental health from cessation interventions(34;35).

In summary, this study used propensity score matching to try to control selection bias and confounding and found a similar effect size to that observed using regression modelling alone. This suggests that selection bias or confounding is not the cause of the apparent benefit of cessation on mental health and strengthens the case that cessation itself is the cause.

FIGURES

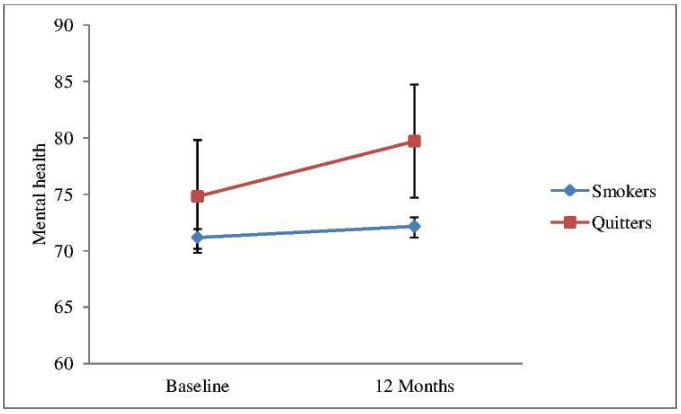

Figure 1 Unmatched groups' mental health scores M(SE) at baseline and follow-up

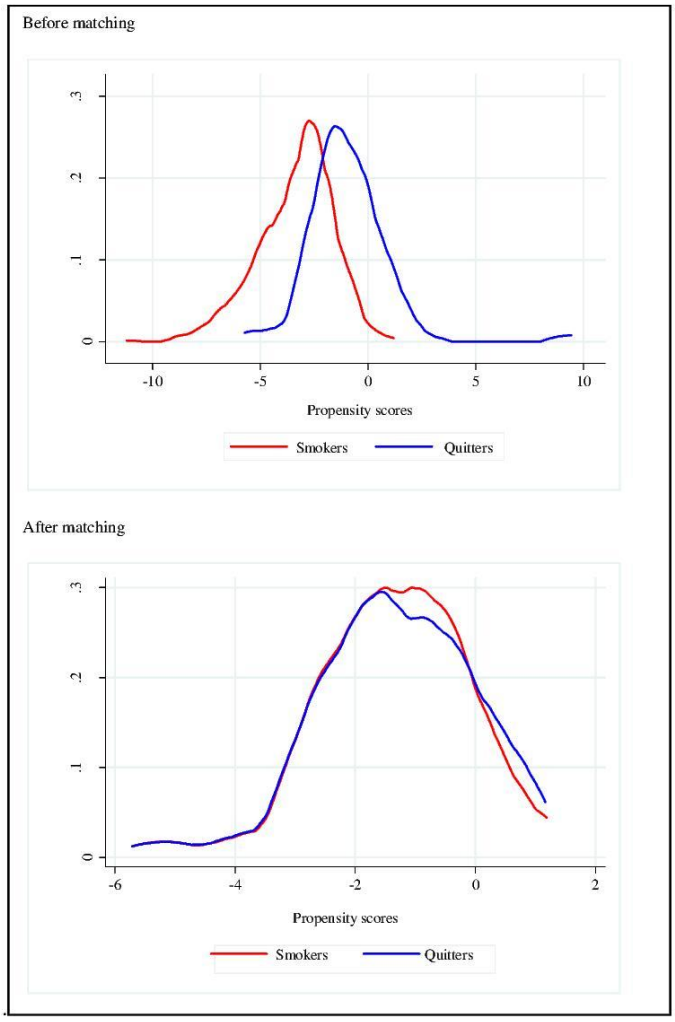

Figure 2 Overlay of Kernel density distributions of quitters' and smokers' propensity scores before and after PSM

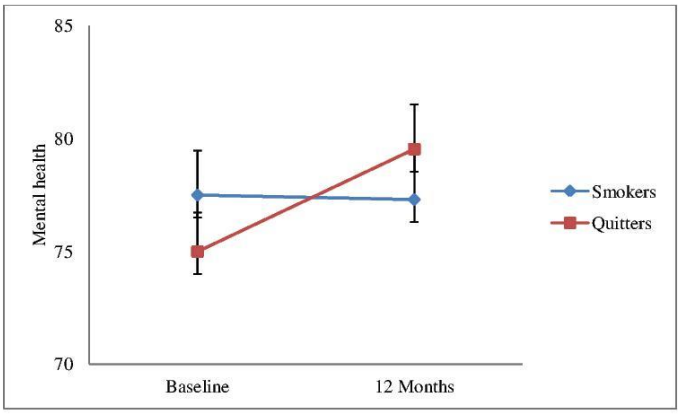

Figure 3 Matched groups' mental health scores M(SE) at baseline and follow-up

TABLES

Table 1 Analysis breakdown: PSM analyses and linear regressions conducted after matching

Matching within/across trials	**Within/without common support restriction**	**Predictor**	**Outcome**	**Adjusted for**
Within trials	Within (primary model)*	Smoking status	Mental health (SF-36)[1] at 12M follow-up	Baseline mental health, age, sex
	Without	Smoking status	Mental health (SF-36) [1] at 12M follow-up 36)	Baseline mental health, age, sex
Across trials	Without	Smoking status	Mental health (SF-36) [1] at 12M follow-up	Baseline mental health, age, sex, Trial ID
	Within	Smoking status	Mental health (SF-36) [1] at 12M follow-up	Baseline mental health, age, sex, Trial ID

*main model

[1] Emotional wellbeing subscale

Table 2 Baseline characteristics in unmatched sample				
	Smokers (n=560)	**Quitters (n=67)**	**Test of significance**	**P-value**
Age, M(SD)	45.6(10.6)	46.2(10.2)	T = -0.52	0.607
Sex, % male (N)	48% (258)	52% (35)	Chi^2= 0.42	0.515
FTND, M(SD)	6.2(1.9)	5.3(2.5)	T= 3.42	<0.001
SF-36 Mental health, M(SD)	71.2 (17.5)	74.8 (13.6)	T = -1.64	0.101
Treatment status, % received active (N)	50% (280)	72% (48)	Chi^2=11.42	0.001

Table 3 Main PSM model: Odds ratios and 95% CI for baseline predictors of smoking status at follow up

Trial ID	Covariate	OR (quit=1)	95%CI	P-value
1	FTND (high score = more dependent)	0.52	0.36 to 0.74	<0.001***
	Active treatment (active=1)	0.41	0.09 to 1.86	0.25
	Age started smoking	1.38	1.18 to 1.62	<0.001***
	Calming effect from smoking (high score = maximum effect)	2.15	1.15 to 4.00	0.016*
	Number of unpleasant symptoms from smoking	2.17	1.12 to 4.2	0.021*
	Time to last cessation attempt	3.74	0.85 to 16.38	0.080*
2	FTND (high score = more dependent)	0.87	0.59 to 1.27	0.460
	Active treatment (active=1)	11.65	1.38 to 98.17	0.024*
	Pleasant experience from last cigarette (high rating = maximum enjoyment)	2.36	1.0 to 5.41	0.043*
3	FTND (high score = more dependent)	0.98	0.74 to 1.30	0.907
	Active treatment (active=1)	3.06	0.77 to 12.14	0.112
	Longest period without smoking	1.87	1.07 to 3.26	0.028*
4	FTND (high score = more dependent)	0.80	0.55 to 1.16	0.241
	Active treatment (active=1)	2.91	0.50 to 16.79	0.232
5	FTND (high score = more dependent)	0.85	0.62 to 1.16	0.316
	Active treatment (active=1)	6.07	1.75 to 21.05	0.004**
	Pleasant experience from last cigarette (high rating = maximum enjoyment)	0.43	0.24 to 0.77	0.005**
	SF-36 mental health (high score=better mental health)	1.05	1.01 to 1.09	0.021*
	Age started smoking	0.77	0.59 to 1.00	0.046*
	Age	1.07	1.00 to 1.15	0.043*

*P<0.1, **P<0.01, ***P<0.001

Table 4 Baseline characteristics after PSM				
	Smokers (n=59) M(SD)	**Quitters (n=59) M(SD)**	**Test of significance**	**P-value**
Age	48.34(10.39)	45.76(8.97)	t=1.44	0.152
Sex (% male)	46%	53%	Chi^2= 0.54	0.461
FTND	5.58(2.13)	5.56(2.43)	t=0.04	0.968
SF-36 Mental health	77.49(15.07)	74.98(13.28)	t=0.95	0.340
Treatment status (% received active)	29%	31%	Chi^2=0.04	0.840

ONLINE SUPPLEMENT LIST OF APPENDICES

Table 5 Characteristics of baseline variables entered into logistic regression models to determine smoking status at follow up

Variable group	Across trials	Within trials				
		Trial 96NNIN016	98NNCG014	96NNIN027	98NNCG017	980CHC90210013
Nicotine dependency	FTND (continuous variable; range 0 to 10; 0=low dependency)	FTND	FTND	FTND	FTND	FTND
Treatment status	Treatment status (binary variable; 0=placebo 1=active)	Treatment status	Treatment status	Treatment status	Treatment status	Treatment status
Demographic	Age (continuous variable)	Age	Age	Age	Age	Age
	Sex (Categorical variable, 1=Male 2=female)	Sex	Sex	Sex	Sex	Sex
Intention to quit		How much does a part of you want to go on smoking? (continuous variable; range 0 to 3; 0=not at all, 3=a lot)	Motivation to quit smoking? (continuous; range 0 to 10; 10=maximum)	Likelihood of not smoking in one year (continuous; range 0 to 10; 10=maximum)	Likelihood of not smoking in one year	Likelihood of not smoking in one year
				Likelihood of quitting smoking during the next 6 months (continuous; range 0 to 10; 10=maximum)		Likelihood of quitting smoking during the next 6 months
Intention to reduce		What is your personal goal in terms of cigarettes per day? (continuous variable)	Motivation to reduce smoking from current level? (continuous; range 0 to 10; 10=maximum)	Likelihood within one year from now will be smoking at least 50% less than current level (continuous; range 0 to 10; 10=maximum)	Likelihood within one year from now will be smoking at least 50% less than current level	Likelihood within one year from now will be smoking at least 50% less than current level
				Likelihood of making a serious attempt to reduce smoking during the next month (continuous; range 0 to 10; 10=maximum)	Likelihood of making a serious attempt to reduce smoking during the next month	Likelihood of making a serious attempt to reduce smoking during the next month
				Likelihood of reducing smoking by 50% (continuous; range 0 to 10; 10=maximum)	Likelihood of reducing smoking by 50%	Likelihood of reducing smoking by 50%
Smoking history	Age started regular smoking (continuous variable)	Age started regular smoking	Age started regular smoking	Age started regular smoking	Age started regular smoking	Age started regular smoking
	Time since last tried to quit (continuous variable	Time since last tried to quit)	Time since last tried to quit	Time since last tried to quit	Time since last tried to quit	Time since last tried to quit
	How long time was the last time you tried to stop? (categorical variable; range 1 to 3; 1= 0-6 months, 3= >12 months)*	How long time was the last time you tried to stop?	How long time was the last time you tried to stop?	How long time was the last time you tried to stop?	How long time was the last time you tried to stop?	How long time was the last time you tried to stop?
	Longest period without smoking (categorical variable; range 1 to 4; 1= <1 week, 4= >3 months)*	Longest period without smoking	Longest period without smoking	Longest period without smoking	Longest period without smoking	Longest period without smoking
	Times Tried to Quit Smoking? (categorical variable; range 0 to 4; 0=never, 4=more than 10 times)*	Times Tried to Quit Smoking	Times tried to quit smoking	Times tried to quit smoking	Times tried to quit smoking	Times tried to quit smoking
SF-36	SF-36 mental health score (continuous variable; range 0 to 100; 0=worse mental health)	SF-36 mental health score	SF-36 mental health score	SF-36 mental health score	SF-36 mental health score	SF-36 mental health score
CPD	Number of cigarettes smoked per day (continuous variable)	Number of cigarettes smoked per day	Number of cigarettes smoked per day	Number of cigarettes smoked per day	Number of cigarettes smoked per day	Number of cigarettes smoked per day
Relief from smoking questionnaire	Experience from last cigarette (continuous variable; range 1 to 5; 1=very unpleasant, 5=very pleasant)	Experience from last cigarette	Experience from last cigarette	Experience from last cigarette	Experience from last cigarette	Experience from last cigarette
	Calming effect of smoking (continuous variable; range 0	Calming effect of smoking	Calming effects of	Calming effect of smoking	Calming effect of	Calming effect of smoking

	to 10; 10=maximum)		smoking		smoking	
		Unpleasant symptoms from your last cigarette (continuous variable; range 0 to 4; 0=not at all, 4=very strong)				
	Pepping up feeling from smoking (continuous variable; range 0 to 10; 10=maximum)	Pepping up feeling from smoking	Pepping up feeling from smoking	Pepping up feeling from smoking	Pepping up feeling from smoking	Pepping up feeling from smoking
			Strength of urges to smoke (continuous; range 0 to 10; 10=maximum)	Strength of urges to smoke	Strength of urges to smoke	Strength of urges to smoke
			Satisfaction from smoking (continuous; range 0 to 10; 10=maximum)	Satisfaction from smoking	Satisfaction from smoking	Satisfaction from smoking
			Frequency of urges to smoke (continuous; range 0 to 10; 10=maximum)	Frequency of urges to smoke	Frequency of urges to smoke	Frequency of urges to smoke

Highlight in grey indicates variable was measures consistently across trials

* indicates categorical variable treated as continuous

Table 6 PSM sensitivity analysis: Odds ratios and 95% CI for baseline predictors of smoking status at follow up across trials

Trial ID	Important predictors across trials	OR (quit=1)	95% CI
	FTND (high score = more dependent)	0.81	0.71 to 0.92
	Active treatment (active=1)	2.85	1.61 to 5.04
	Longest period without smoking (higher number = longer period)	1.45	1.14 to 1.83
	Calming effect from smoking (high score=maximum effect)	1.11	1.02 to 1.19
	Pleasant experience from last cigarette (high score=maximum enjoyment)	0.73	0.56 to 0.95

Table 7 Main PSM model: Within trial balance of matching variables before and after PSM: means, % bias difference and % reduction in bias								
			Mean		% bias		T-test	
	Variable	Unmatched /matched	Quitters	Smokers	% bias difference	% reduction bias	t	p
Trial 1	FTND	Unmatched	4.07	6.10	-88.00	95.90	-3.89	0.00
		Matched	4.08	4.00	3.60		0.08	0.94
	Treatment received	Unmatched	0.60	0.51	16.90	100.00	0.64	0.525
		Matched	0.50	0.50	0.00		0.00	1.000
	Age started smoking	Unmatched	23.2	17.15	87.30	98.60	6.14	0.000
		Matched	19.41	19.5	-1.20		-0.04	0.971
	Rate the calming effect from smoking	Unmatched	1.67	0.93	66.80	66.20	2.51	0.013
		Matched	1.67	1.42	22.60		0.50	0.625
	Rate unpleasant symptoms from smoking	Unmatched	0.87	0.34	45.60	53.00	2.39	0.018
		Matched	0.75	0.50	21.40		0.53	0.601
	How long time was the last time tried to stop	Unmatched	1.8-0	1.78	3.40	-803.50	0.13	0.898
		Matched	1.92	2.08	-30.40		-0.79	0.436
Trial 2	FTND	Unmatched	6.10	6.35	-16.4	100	-0.46	0.649
		Matched	6.10	6.10	0.00		0.00	1.000
	Treatment received	Unmatched	0.90	0.47	101.90	100	2.63	0.010
		Matched	0.90	0.90	0.00		0.00	1.000
	Experience from last cigarette	Unmatched	4.10	3.47	73.40	100	2.00	0.048
		Matched	4.10	4.10	0.00		0.00	1.000
Trial 3	FTND	Unmatched	6.15	6.35	-8.00	56.40	-0.32	0.752
		Matched	6.58	6.50	3.50		0.09	0.932
	Treatment received	Unmatched	0.77	0.52	52.40	100.00	1.70	0.091
		Matched	0.75	0.75	0		0.00	1.000
	Longest period without smoking	Unmatched	3.31	2.50	75.40	100.00	2.26	0.026
		Matched	3.25	3.25	0.00		0.00	1.000
Trial 4	FTND	Unmatched	5.86	6.54	-26.40	-21.9	-0.85	0.395
		Matched	6.50	7.33	-32.20		-0.60	0.565
	Treatment received	Unmatched	0.71	0.51	40.50	17.00	1.01	0.315
		Matched	0.67	0.83	-33.60		-0.62	0.549
Trial 5	FTND	Unmatched	5.09	5.47	-19.4	72.5	-0.84	0.402
		Matched	5.26	5.16	5.3		0.16	0.871
	Treatment received	Unmatched	.68	.43	50.7	100	2.07	0.041
		Matched	.68	.68	0		0.00	1.000
	Experience from last cigarette	Unmatched	2.91	3.55	-66	91.8	-2.80	0.006
		Matched	3.05	3.11	-5.4		-0.16	0.877
	SF-36 Mental health	Unmatched	77.27	67.00	62.8	98	2.43	0.017
		Matched	76.21	76.00	1.3		0.05	0.962
	Age started smoking	Unmatched	16.59	18.29	-51.5	93.8	-1.83	0.071
		Matched	17.05	17.16	-3.2		-0.16	0.873
	Age	Unmatched	44.96	42.29	30.3	80.3	1.22	0.224
		Matched	45.37	44.84	6		0.17	0.863

Table 8 PSM sensitivity models: Comparison of effect estimates between main model and sensitivity models					
Matching occurred within/ across trials	**Within/without common support restrictions**	**Group (n)**	**Baseline SF-36 mental health m(SE)**	**Follow-up SF-36 mental health M(SE)**	**B (95% CI)**
Within trials (adjusted for baseline mental health, age and sex)	Within	Smokers(n=67)	77.43(1.82)	76.72(1.97)	3.37 (-2.15 to 8.90)
		Quitters(n=67)	74.81(1.66)	79.70(1.79)	
	Without	Smokers(n=67)	77.43(1.82)	76.72(1.97)	3.97 (-1.00 to 8.93)
		Quitters(n=67)	74.81(1.66)	79.70(1.79)	
Across Trials (adjusted for baseline mental health, Trial ID, age and sex)	Without	Smokers(n=67)	74.09(1.94)	75.82(1.91)	3.74 (-1.19 to 8.66)
		Quitters(n=67)	74.81(1.66)	79.70(1.79)	
	Within	Smokers(n=66)	74.06(1.97)	75.76(1.94)	3.55 (-1.29 to 8.40)
		Quitters(n=66)	74.85(1.68)	79.88(1.80)	
*Highlighted in blue indicates main analysis					

Table 9 Quality assessment of study				
Newcastle-Ottawa quality assessment scale cohort studies (NOS) adapted version				
		Star awarded system	**Star (*) awarded**	**Reasons**
Study's selection criteria				
1) Representativeness of the exposed cohort (maximum 1 star)	a) truly representative of the average _____ (describe) in the community	*		
	b) somewhat representative of the average _____ in the community	*	*	Somewhat representative of the average smoker. Not motivated to quit, they were motivated to reduce.
	c) selected group of users e.g. nurses, volunteers	(no star)		
	d) no description of the derivation of the cohort	(no star)		
2) Selection of the non-exposed cohort (maximum 1 star)	a) drawn from the same community as the exposed cohort	*	*	Both groups were derived from the same sample.
	b) drawn from a different source	(no star)		
	c) no description of the derivation of the non-exposed cohort	(no star)		
3) Ascertainment of exposure (maximum 1 star)	a) bio-validated smoking status	*	*	
	b) smoking status validated only by self-report	(no star)		
	c) no description	(no star)		
Study's outcome criteria				
1) Assessment of outcome (maximum 1	a) standardised self-report questionnaire	*	*	
	b) standardised interview schedule with blind assessor	*		

star)[1]	c) non-standardised self-report questionnaire or non-standardised interview schedule	(no star)		
	d) no description	(no star)		
2) Adequacy of follow up of cohorts (maximum 1 star) [2]	a) complete follow up - all subjects accounted for ⊿	*		
	b) subjects lost to follow up unlikely to introduce bias - small number lost - > ____ % (select an adequate %) follow up, or description provided of those lost) ⊿	*		
	c) follow up rate < ____% (select an adequate %) and no description of those lost	(no star)		* Overall 47% loss to follow-up.
	d) no statement	(no star)		
Final Score		4*		

[1] In the case that a study has used a standardized self-report questionnaire and a standardized interview schedule, only one star will be awarded. This is as use of both outcome assessments will not improve the study's quality for the purpose of this review.

[2] Describe based on attrition from enrolment to final follow-up

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14. CHARACTERISTICS OF BASELINE COVARIATES (CHAPTER FOUR)

Characteristics of baseline variables entered into logistic regression models to determine smoking status at follow-up						
Variable group	**Across trials**	**Within trials**				
		Trial 96NNIN016	**98NNCG014**	**96NNIN027**	**98NNCG017**	**980CHC90210013**
Nicotine dependency	FTND (continuous variable; range 0 to 10; 0=low dependency)	FTND	FTND	FTND	FTND	FTND
Treatment status	Treatment status (binary variable; 0=placebo 1=active)	Treatment status	Treatment status	Treatment status	Treatment status	Treatment status
Demographic	Age (continuous variable)	Age	Age	Age	Age	Age
	Sex (categorical variable, 1=Male 2=female)	Sex	Sex	Sex	Sex	Sex
Intention to quit		How much does a part of you want to go on smoking? (continuous variable; range 0 to 3; 0=not at all, 3=a lot)	Motivation to quit smoking? (continuous; range 0 to 10; 10=maximum)	Likelihood of not smoking in one year (continuous; range 0 to 10; 10=maximum)	Likelihood of not smoking in one year	Likelihood of not smoking in one year
				Likelihood of quitting smoking		Likelihood of quitting

				during the next 6 months (continuous; range 0 to 10; 10=maximum)		smoking during the next 6 months
Intention to reduce		What is your personal goal in terms of cigarettes per day? (continuous variable)	Motivation to reduce smoking from current level? (continuous; range 0 to 10; 10=maximum)	Likelihood within one year from now will be smoking at least 50% less than current level (continuous; range 0 to 10; 10=maximum)	Likelihood within one year from now will be smoking at least 50% less than current level	Likelihood within one year from now will be smoking at least 50% less than current level
				Likelihood of making a serious attempt to reduce smoking during the next month (continuous; range 0 to 10; 10=maximum)	Likelihood of making a serious attempt to reduce smoking during the next month	Likelihood of making a serious attempt to reduce smoking during the next month
				Likelihood of reducing smoking by 50% (continuous; range 0 to 10; 10=maximum)	Likelihood of reducing smoking by 50%	Likelihood of reducing smoking by 50%
Smoking history	Age started regular smoking (continuous variable)	Age started regular smoking	Age started regular smoking	Age started regular smoking	Age started regular smoking	Age started regular smoking
	Time since last tried to quit (continuous variable	Time since last tried to quit)	Time since last tried to quit	Time since last tried to quit	Time since last tried to quit	Time since last tried to quit
	How long time was the last time you tried to stop?	How long time was the last time you tried to stop?	How long time was the last time you tried to stop?	How long time was the last time you tried to stop?	How long time was the last time you tried to	How long time was the last time you tried to

	(categorical variable; range 1 to 3; 1= 0 to 6 months, 3= >12 months)*				stop?	stop?
	Longest period without smoking (categorical variable; range 1 to 4; 1= <1 week, 4= >3 months)*	Longest period without smoking	Longest period without smoking	Longest period without smoking	Longest period without smoking	Longest period without smoking
	Times Tried to Quit Smoking? (categorical variable; range 0 to 4; 0=never, 4=more than 10 times)*	Times Tried to Quit Smoking	Times tried to quit smoking	Times tried to quit smoking	Times tried to quit smoking	Times tried to quit smoking
SF-36	SF-36 mental health score (continuous variable; range 0 to 100; 0=worse mental health)	SF-36 mental health score	SF-36 mental health score	SF-36 mental health score	SF-36 mental health score	SF-36 mental health score
Cigarettes per day (CPD)	CPD (continuous variable)	CPD	CPD	CPD	CPD	CPD
Relief from smoking questionnaire	Experience from last cigarette (continuous variable; range 1 to 5; 1=very unpleasant, 5=very pleasant)	Experience from last cigarette	Experience from last cigarette	Experience from last cigarette	Experience from last cigarette	Experience from last cigarette

	Calming effect of smoking (continuous variable; range 0 to 10; 10=maximum)	Calming effect of smoking	Calming effects of smoking	Calming effect of smoking	Calming effect of smoking	Calming effect of smoking
		Unpleasant symptoms from your last cigarette (continuous variable; range 0 to 4; 0=not at all, 4=very strong)				
	Pepping up feeling from smoking (continuous variable; range 0 to 10; 10=maximum)	Pepping up feeling from smoking	Pepping up feeling from smoking	Pepping up feeling from smoking	Pepping up feeling from smoking	Pepping up feeling from smoking
			Strength of urges to smoke (continuous; range 0 to 10; 10=maximum)	Strength of urges to smoke	Strength of urges to smoke	Strength of urges to smoke
			Satisfaction from smoking (continuous; range 0 to 10; 10=maximum)	Satisfaction from smoking	Satisfaction from smoking	Satisfaction from smoking
			Frequency of urges to smoke (continuous; range 0 to 10; 10=maximum)	Frequency of urges to smoke	Frequency of urges to smoke	Frequency of urges to smoke
Highlight in grey indicates variable was measures consistently across trials * indicates categorical variable treated as continuous						

15. PSM SENSITIVITY MODELS (CHAPTER FOUR)

PSM sensitivity models: Odds ratios and 95% CI for baseline predictors of smoking status at follow-up				
Within/across trials	**Trial ID**	**Important predictors**	**OR (quit=1)**	**95% CI**
Within trials	1	FTND (high score = more dependent)	0.52	0.36 to 0.74
		Active treatment (active=1)	0.41	0.09 to 1.86
		Age started smoking	1.38	1.18 to 1.62
		Calming effect from smoking (high score=maximum effect)	2.15	1.15 to 4.00
		Number of unpleasant symptoms from smoking	2.17	1.12 to 4.2
	2	FTND	0.87	0.59 to 1.27
		Active treatment	11.65	1.38 to 98.17
		Time to last cessation attempt	3.74	0.85 to 16.38
	3	FTND (high score = more dependent)	0.98	0.74 to 1.30
		Active treatment (active=1)	3.06	0.77 to 12.14
		Longest period without smoking	1.87	1.07 to 3.26
	4	FTND (high score = more dependent)	0.80	0.55 to 1.16
		Active treatment (active=1)	2.91	0.50 to 16.79
	5	FTND (high score = more dependent)	0.85	0.62 to 1.16

		Active treatment (active=1)	6.07	1.75 to 21.05
		Pleasant experience from last cigarette (high score=maximum enjoyment)	0.43	0.24 to 0.77
		SF-36 mental health (high score=better mental health)	1.05	1.01 to 1.09
		Age started smoking	0.77	0.59 to 1.00
		Age	1.07	1.00 to 1.15
Across Trials	–	FTND (high score = more dependent)	0.81	0.71 to 0.92
		Active treatment (active=1)	2.85	1.61 to 5.04
		Longest period without smoking	1.45	1.14 to 1.83
		Calming effect from smoking (high score=maximum effect)	1.11	1.02 to 1.19
		Pleasant experience from last cigarette (high score=maximum enjoyment)	0.73	0.56 to 0.95
*Highlighted in blue indicates main analysis				

16. MAIN PSM MODEL: BIAS DIFFERENCE AND REDUCTION IN BIAS (CHAPTER FOUR)

Main PSM model: Within trial balance of matching variables before and after PSM: means, % bias difference and % reduction in bias*								
			Baseline value		**% bias**		**T-test**	
	Variable	**Unmatched /matched**	**Quitters**	**Smokers**	**% bias difference**	**% reduction bias**	**T**	**P**
Trial 1	FTND	Unmatched	4.07	6.10	–88.00	95.90	–3.89	0.00
		Matched	4.08	4.00	3.60		0.08	0.94
	Treatment received	Unmatched	0.60	0.51	16.90	100.00	0.64	0.525
		Matched	0.50	0.50	0.00		0.00	1.000
	Age started smoking	Unmatched	23.2	17.15	87.30	98.60	6.14	0.000
		Matched	19.41	19.5	–1.20		–0.04	0.971
	Rate the calming effect from smoking	Unmatched	1.67	0.93	66.80	66.20	2.51	0.013
		Matched	1.67	1.42	22.60		0.50	0.625
	Rate unpleasant symptoms from smoking	Unmatched	0.87	0.34	45.60	53.00	2.39	0.018
		Matched	0.75	0.50	21.40		0.53	0.601
	How long time was the last time tried to stop?	Unmatched	1.8 0	1.78	3.40	–803.50	0.13	0.898
		Matched	1.92	2.08	–30.40		–0.79	0.436

Trial 2	FTND	Unmatched	6.10	6.35	–16.4	100	–0.46	0.649
		Matched	6.10	6.10	0.00		0.00	1.000
	Treatment received	Unmatched	0.90	0.47	101.90	100	2.63	0.010
		Matched	0.90	0.90	0.00		0.00	1.000
	Experience from last cigarette	Unmatched	4.10	3.47	73.40	100	2.00	0.048
		Matched	4.10	4.10	0.00		0.00	1.000
Trial 3	FTND	Unmatched	6.15	6.35	–8.00	56.40	–0.32	0.752
		Matched	6.58	6.50	3.50		0.09	0.932
	Treatment received	Unmatched	0.77	0.52	52.40	100.00	1.70	0.091
		Matched	0.75	0.75	0		0.00	1.000
	Longest period without smoking	Unmatched	3.31	2.50	75.40	100.00	2.26	0.026
		Matched	3.25	3.25	0.00		0.00	1.000
Trial 4	FTND	Unmatched	5.86	6.54	–26.40	-21.9	–0.85	0.395
		Matched	6.50	7.33	–32.20		–0.60	0.565
	Treatment received	Unmatched	0.71	0.51	40.50	17.00	1.01	0.315
		Matched	0.67	0.83	–33.60		–0.62	0.549
Trial 5	FTND	Unmatched	5.09	5.47	–19.4	72.5	–0.84	0.402
		Matched	5.26	5.16	5.3		0.16	0.871
	Treatment received	Unmatched	0.68	.43	50.7	100	2.07	0.041
		Matched	0.68	.68	0		0.00	1.000
	Experience from last cigarette	Unmatched	2.91	3.55	–66	91.8	–2.80	0.006

		Matched	3.05	3.11	–5.4		–0.16	0.877
	SF-36 Mental health	Unmatched	77.27	67.00	62.8	98	2.43	0.017
		Matched	76.21	76.00	1.3		0.05	0.962
	Age started smoking	Unmatched	16.59	18.29	–51.5	93.8	–1.83	0.071
		Matched	17.05	17.16	–3.2		–0.16	0.873
	Age	Unmatched	44.96	42.29	30.3	80.3	1.22	0.224
		Matched	45.37	44.84	6		0.17	0.863
*The standardised percent bias is the percent difference of the sample means in the quitters and continuing smokers (whole or matched sample), as a percentage of the square root of the average of the sample variances in each group								

17. PSM SENSITIVITY MODELS: COMPARISON OF EFFECT ESTIMATES (CHAPTER FOUR)

PSM sensitivity models: Comparison of effect estimates between main model and sensitivity models					
Matching occurred within/ across trials	**Within/without common support restrictions**	**Group (N)**	**Baseline SF-36 mental health M(SE)**	**Follow-up SF-36 mental health M(SE)**	**B (95% CI)**
Within trials (adjusted for baseline mental health, age and sex)	Within	Smokers(N=67)	77.43(1.82)	76.72(1.97)	3.37 (–2.15 to 8.90)
		Quitters(N=67)	74.81(1.66)	79.70(1.79)	
	Without	Smokers(N=67)	77.43(1.82)	76.72(1.97)	3.97 (–1.00 to 8.93)
		Quitters(N=67)	74.81(1.66)	79.70(1.79)	
Across Trials (adjusted for baseline mental health, Trial ID, age and sex)	Without	Smokers(N=67)	74.09(1.94)	75.82(1.91)	3.74 (–1.19 to 8.66)
		Quitters(N=67)	74.81(1.66)	79.70(1.79)	
	Within	Smokers(N=66)	74.06(1.97)	75.76(1.94)	3.55 (–1.29 to 8.40)
		Quitters(N=66)	74.85(1.68)	79.88(1.80)	
*Highlighted in blue indicates main analysis					

18. QUALITY ASSESSMENT OF STUDY (CHAPTER FOUR)

Quality assessment of study presented in Chapter Four				
Newcastle-Ottawa quality assessment scale cohort studies (NOS) adapted version				
		Star awarded system	**Star (*) awarded**	**GT reasons**
Study's selection criteria				
1) Representativeness of the exposed cohort (maximum 1 star)	a) truly representative of the average ___ (describe) in the community	*		
	b) somewhat representative of the average ___ in the community	*	*	Somewhat representative of the average smoker. Not motivated to quit, they were motivated to reduce.
	c) selected group of users e.g.. nurses, volunteers	(no star)		
	d) no description of the derivation of the cohort	(no star)		
2) Selection of the non-exposed cohort (maximum 1 star)	a) drawn from the same community as the exposed cohort	*	*	Both groups were derived from the same sample.
	b) drawn from a different source	(no star)		
	c) no description of the derivation of the non-exposed cohort	(no star)		
3) Ascertainment of exposure (maximum 1 star)	a) Biologically-validated smoking status	*	*	
	b) smoking status validated only by self-report	(no star)		
	c) no description	(no star)		
Study's outcome criteria				
1) Assessment of	a) standardised self-report questionnaire	*	*	

outcome (maximum 1 star)1	b) standardised interview schedule with blind assessor	*		
	c) non-standardised self-report questionnaire or non-standardised interview schedule	(no star)		
	d) no description	(no star)		
2) Adequacy of follow-up of cohorts (maximum 1 star) 2	a) complete follow-up - all subjects accounted for □	*		
	b) subjects lost to follow-up unlikely to introduce bias - small number lost > ___ % (select an adequate %) follow-up, or description provided of those lost) □	*		
	c) follow-up rate < ___% (select an adequate %) and no description of those lost	(no star)		Overall 47% loss to follow-up.
	d) no statement	(no star)		
Final Score		4*		

1 In the case that a study has used a standardised self-report questionnaire and a standardised interview schedule, only one star will be awarded. This is as use of both outcome assessments will not improve the study's quality for the purpose of this review.
2 Describe based on attrition from enrolment to final follow-up

19. PSM SENSITIVITY ANALYSES (CHAPTER FIVE)

Risk difference estimates after PSM sensitivity analyses					
Within/across trials	**Within/without common support**	**Group (N)**	**% reported psychiatric disorders (N)**	**Risk difference (95% CI)**	**McNemar's Chi^2**
Within trials	Within common support	Smokers (N=60)	1.67% (N=1)	–0.02 (–0.07 to 0.03)	1.00
		Quitters (N=60)	0% (N=0)		
	Without common support	Smokers (N=67)	2.99% (N=2)	–0.03 (–0.09 to 0.03)	2.00
		Quitters (N=67)	0% (N=0)		
Across Trials	Without common support	Smokers (N=68)	0% (N=0)	N/a	N/a
		Quitters (N=68)	0% (N=0)		
	Within common support	Smokers (N=68)	0% (N=0)	N/a	N/a
		Quitters (N=68)	0% (N=0)		
*Highlighted in blue indicates main analysis *P>0.05, **P>0.01, ***P>0.001					

20. QUALITY ASSESSMENT OF STUDY (CHAPTER FIVE)

Quality assessment of study in Chapter Five				
Newcastle-Ottawa quality assessment scale cohort studies (NOS) adapted version				
		Star awarded system	**Star (*) awarded**	**GT reasons**
Study's selection criteria				
1) Representativeness of the exposed cohort (maximum 1 star)	a) truly representative of the average ____ (describe) in the community	*		
	b) somewhat representative of the average _____ in the community	*	*	Not motivated to quit, they were motivated to reduce.
	c) selected group of users e.g.. nurses, volunteers	(no star)		
	d) no description of the derivation of the cohort	(no star)		
2) Selection of the non-exposed cohort (maximum 1 star)	a) drawn from the same community as the exposed cohort	*	*	Both groups were derived from the same sample.
	b) drawn from a different source	(no star)		
	c) no description of the derivation of the non-exposed cohort	(no star)		
3) Ascertainment of exposure (maximum 1 star)	a) Biologically-validated smoking status	*	*	Bio-validated
	b) smoking status validated only by self-report	(no star)		
	c) no description	(no star)		
Study's outcome criteria				
1) Assessment of outcome (maximum 1 star)1	a) standardised self-report questionnaire	*		
	b) standardised interview schedule with blind assessor	*	*	Key terms were coded according to MedDRA. Original data recorded by blinded researches as

				they were unaware of this study's aim.
	c) non-standardised self-report questionnaire or non-standardised interview schedule	(no star)		
	d) no description	(no star)		
2) Adequacy of follow-up of cohorts (maximum 1 star) 2	a) complete follow-up - all subjects accounted for □	*		
	b) subjects lost to follow-up unlikely to introduce bias - small number lost > ____ % (select an adequate %) follow-up, or description provided of those lost) □	*		
	c) follow-up rate < ___% (select an adequate %) and no description of those lost	(no star)		Overall 47% loss to follow-up.
	d) no statement	(no star)		
Final Score		4*		
1 In the case that a study has used a standardised self-report questionnaire and a standardised interview schedule, only one star will be awarded. This is as use of both outcome assessments will not improve the study's quality for the purpose of this review. 2 Describe based on attrition from enrolment to final follow-up				

21. QUALITY ASSESSMENT OF STUDY (CHAPTER SIX)

Quality assessment of study				
Newcastle-Ottawa quality assessment scale cohort studies (NOS) adapted version				
		Star awarded system	**Star (*) awarded**	**GT reasons**
Study's selection criteria				
1) Representativeness of the exposed cohort (maximum 1 star)	a) truly representative of the average _____ (describe) in the community	*		
	b) somewhat representative of the average _____ in the community	*	*	Not motivated to quit, they were motivated to reduce.
	c) selected group of users e.g.. nurses, volunteers	(no star)		
	d) no description of the derivation of the cohort	(no star)		
2) Selection of the non-exposed cohort (maximum 1 star)	a) drawn from the same community as the exposed cohort	*	*	Both groups were derived from the same sample.
	b) drawn from a different source	(no star)		
	c) no description of the derivation of the non-exposed cohort	(no star)		
1) Assessment of exposure (maximum 1 star)1	a) standardised self-report questionnaire	*	*	Sf-36
	b) standardised interview schedule with blind assessor	*		
	c) non-standardised self-report questionnaire or non-standardised interview schedule	(no star)		
	d) no description	(no star)		
Study's outcome criteria				
Assessment of outcome (maximum 1 star)	a) Biologically-validated smoking status	*	*	Biologically-validated relapse status from 4 to 12

				months
	b) smoking status validated only by self-report	(no star)		
	c) no description	(no star)		
2) Adequacy of follow-up of cohorts (maximum 1 star) 2	a) complete follow-up - all subjects accounted for □	*		
	b) subjects lost to follow-up unlikely to introduce bias - small number lost <___ % (select an adequate %) follow-up, or description provided of those lost) □	*		
	c) follow-up rate < __% (select an adequate %) and no description of those lost	(no star)		Overall 47% loss to follow-up.
	d) no statement	(no star)		
Final Score		4*		

1 In the case that a study has used a standardised self-report questionnaire and a standardised interview schedule, only one star will be awarded. This is as use of both outcome assessments will not improve the study's quality for the purpose of this review.
2 Describe based on attrition from enrolment to final follow-up

22. SENSITIVITY ANALYSIS (CHAPTER SIX)

Sensitivity analysis for continuous quitters: regression model			
	Variable	**OR (1=relapsed)**	**P-value**
Unadjusted	Pre to post cessation change in mental health	0.99 (0.94 to 1.05)	0.73
Adjusted	Pre to post cessation change in mental health	0.99 (0.93 to 1.07)	0.85
	Baseline SF-36 mental health	0.83 (0.92 to 1.10)	0.83
	Treatment status (1=active)	1.01 (0.08 to 12.12)	0.99
	Nicotine dependency FTND	1.11 (0.70 to 1.75)	0.65
	Sex (Female)	0.88 (0.12 to 6.45)	0.91
	Age	0.96 (0.86 to 1.08)	0.51

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