Exploring the effectiveness of statins for primary prevention of cardiovascular disease in people with severe mental illness

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Declaration:

I, Ruth Marion Blackburn confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Abstract

Cardiovascular disease (CVD) is the leading cause of death amongst people with severe mental illness (SMI) and drives substantial portion of the 15-20 year deficit in life expectancy experienced by this group relative to the general population. Statins form a core part of CVD prevention in the general population, but the evidence-base for people with SMI is unclear. Evidence on the effectiveness of statins for primary prevention of CVD was systematically searched but did not identify any studies investigating CVD events or associated mortality in people with SMI; therefore highlighting the need for studies on the long term impacts of statin prescribing. Two analytical studies were undertaken using longitudinal data from The Health Improvement Network (THIN) primary care database to investigate: 1) CVD screening and statin prescribing in people with and without SMI and 2) to explore the effectiveness of statins for CVD prevention in individuals with SMI. Collectively the work has established that CVD screening and statin prescribing is increasingly accessed by individuals with SMI at levels that are comparable to people without similar mental health conditions. The results from this study provide the first evidence that statin prescribing to people with SMI is associated with statistically significant reductions in total cholesterol (of 1.2mmol/L for up to 2 years, $p<0.001$). There were small non-significant reductions in the rate of combined MI and stroke (0.89; 95% CI; 0.68-1.15) and all-cause mortality 0.89 (95% CI; 0.78, 1.02). This study provides evidence that statin prescribing to people with SMI may have a magnitude of effectiveness that is broadly similar to the general population.

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Contents

Tables

Abbreviations

ACU	Acceptable computer usage
AMR	Acceptable mortality rate
ATE	Average treatment effect
ATT	Average treatment effect on the treated
BMI	Body mass index
BNF	British National Formulary

CASP	Critical Appraisal Skills Programme
CENTRAL	Cochrane Central Register of Controlled Trials
CHD	Coronary heart disease
CI	Confidence interval
CKD	Chronic kidney disease
COPD	Chronic obstructive pulmonary disease
CPRD	Clinical Practice Research Datalink
CVD	Cardiovascular disease
DSM-V	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
ECG	Electrocardiogram
GP	General practitioner
HDL-C	High density lipoprotein-cholesterol
HMG-CoA reductase	3-hydroxy-3-methyl-glutaryl-CoA reductase
IRR	Incident rate ratio
ICD-10	International Classification of Diseases, Tenth Version
LDL-C	Low density lipoprotein-cholesterol
MAR	Missing at random
MCAR	Missing completely at random
MI	Myocardial infarction
MNAR	Missing not at random
NHS	National Health Service
NRR	UK National Research Register
OR	Odds ratio
PICO	Population, intervention, comparison and outcome
QOF	Quality and outcomes framework
RCT	Randomised controlled trial
RR	Relative risk
SAPC	Society of Academic Primary Care
SMI	Severe mental illness
SREBP	Sterol regulatory element-binding proteins
SSRI	Selective serotonin reuptake inhibitor
THIN	The Health Improvement Network
TIA	Transient ischaemic attack
UK	United Kingdom
USA	United States of America
UKCRN	UK Clinical Research Network
VAMP	Value Added Information Medical Products
VLDL-C	Very low density lipoprotein-cholesterol

Chapter 1 : Background

1 Chapter Content

Cardiovascular disease (CVD) is the leading cause of death amongst people with severe mental illness (SMI) and contributes to the high burden of mortality and morbidity experienced by this group. Statins form a core part of CVD primary prevention in the general population, but the evidence-base for statin use amongst people with SMI is unclear. The research outlined in this thesis therefore aims to explore the effectiveness of statins for primary prevention of CVD amongst people with SMI. This chapter introduces the concepts that are central to statin prescribing for prevention of CVD amongst individuals with SMI. I define SMI and CVD and describe the causes, epidemiology and management of these conditions in the context of the United Kingdom (UK). I introduce the complex network of factors (graphically represented in Figure 5-1) that drives the higher risk of CVD amongst people with SMI and outline the role of statins for primary prevention of CVD. I introduce the research aim of this thesis and outline the objectives addressed within each chapter.

2 Introduction

SMI has been used in psychiatric literature to describe a collection of non-organic psychoses including schizophrenia, schizoaffective disorder and bipolar disorder that have both a long duration - often requiring life-long treatment - and devastating personal implications (Ruggeri et al., 2000). SMI is usually first diagnosed in young adulthood, and although many individuals recover, relapses can occur at any age thus impacting upon long-term quality of life. The financial and societal costs of SMI are high: figures for the UK suggest annual costs are currently £11.8 billion for schizophrenia (Andrew et al., 2012) and £6.2 billion for bipolar disorder (McCrone et al., 2008).

SMI is associated with substantially higher levels of physical comorbidity and premature mortality than the general population. CVD, including myocardial infarction (MI) and stroke, is the leading cause of death amongst people with SMI and accounts for approximately one third (Brown et al., 2010) of the 13-30 year deficit in life expectancy experienced by this group (Lahti et al., 2012;Tiihonen et al., 2009;Hennekens et al., 2005;Colton and Manderscheid, 2006). The scale and cost

of CVD amongst people with SMI highlights the need to find cost-effective strategies for the primary prevention and management of CVD in this group of people.

3 Epidemiology of SMI

Introductory texts on schizophrenia and bipolar disorder often state that, on average, 1 in 100 people will develop SMI during their lifetime (Lawrie and Johnstone, 2014). Although broadly correct, this statistic does not reflect the diverse and complex epidemiology of the spectrum of conditions defined as SMI. SMI encompasses clusters of non-organic psychoses (those with a psychiatric cause) that usually present with features common to specific subgroups such as schizophrenia or bipolar disorder. The incidence of SMI is associated with a wide range of factors including genetics, age, gender, ethnicity, urbanicity, deprivation and living alone (Kirkbride et al., 2012;Markham, 2012;Velakoulis et al., 2006). The most recent meta-review estimated the incidence of non-organic psychosis to 31.7 per 100,000 person years amongst people aged 16-64 years in England between 1950 and 2009 (Kirkbride et al., 2012). However, the certainty with which these incidence rates can be interpreted is limited by heterogeneity between studies (pooled results from eight studies, I^2 statistic = 0.97) and wide 95% confidence interval (CI) (24.6-40.9 per 100,000 person years) around the point estimate. A subset of these studies was further analysed to estimate the incidence of specific psychoses, which was 15.2 per 100,000 person years (95% CI; 11.9-19.5) for schizophrenia and 5.3 per 100,000 person years for bipolar disorder (95% CI; 3.7-7.6) (Kirkbride et al., 2012).

3.1 Schizophrenia, schizo-affective disorder and associated psychoses

3.1.1 Definition

Schizophrenia is a cluster of related disorders characterised by positive symptoms of psychosis including delusion, hallucination or thought disorder. In addition, negative symptoms such as social withdrawal, loss of motivation and flattening of mood are usually present in individuals with schizophrenia (Semple and Smyth, 2011). There are two major classification systems for schizophrenia; the Diagnostic and Statistical Manual of Mental Disorders fifth edition (DSM-V) and the International Classification for Diseases version 10 (ICD-10). DSM-V and ICD-10 criteria for schizophrenia are not identical: however, both outline requirements for the presence of positive and negative symptoms for a minimum of one month.

3.1.2 Burden of disease and life-course

The first acute episode of schizophrenia most commonly presents in late adolescence and often results in admission to secondary care, where a formal diagnosis is made. The prognosis for schizophrenia is variable and related to factors such as prompt diagnosis and intervention (Picchioni and Murray, 2007): over 80% of individuals who experience a first episode of psychosis recover, but less than 20% will have no further episodes (Robinson et al., 1999). The age at which schizophrenia first occurs varies, and is associated with gender, socioeconomic status, ethnicity and environmental factors (Kirkbride et al., 2012;Markham, 2012;Velakoulis et al., 2006). Gender appears to be a particularly important predictor of age at onset, with incidence generally declining with increasing age in both sexes. Peak incidence of schizophrenia occurs in males aged 15-24 and females aged 20-29 years, with some evidence of increased incidence in women (but not men) after the age of 45 years (Hardoon et al., 2013;Markham, 2012;Kirkbride et al., 2012;Munk-Jorgensen, 1987;Hafner et al., 1991).

Late and very late onset schizophrenia are characterised by similar symptoms to schizophrenia but have onset in older age. The minimum age for the first psychotic episode of late or very late onset schizophrenia has been inconsistently defined in the literature but generally centres on an age range of 40 to 60 years (Howard et al., 2000). The symptoms associated with late onset schizophrenia are subtly different to schizophrenia in younger patients and it is unclear if the two conditions are similar in terms of their underlying aetiology. Symptoms of late onset schizophrenia and dementia can be the same and it may take several years to obtain a firm diagnosis for either condition (Howard et al., 2000).

3.1.3 Aetiology

The causes of schizophrenia are multifactorial and, at present, family history is the strongest risk factor; suggesting a causal role for genetic and environmental factors in tandem (Kendler et al., 1993;Cardno et al., 1999). A large number of genetic regions (also termed loci) are over-represented amongst people with schizophrenia compared to those without mental illness, but no single region is strongly associated with schizophrenia (Doherty et al., 2012;Craddock and Sklar, 2013;Sullivan et al., 2012).

Environmental factors appear to play an important role, with stressful life events often preceding the first signs of schizophrenia. Developing research has also highlighted a myriad of other potential associations with schizophrenia. These

include winter or spring season of birth, perinatal infection, birth and pregnancy complications and prenatal starvation, which may subtly impair early brain development (Morgan et al., 2011;Picchioni and Murray, 2007). It is also possible that poorer childhood development - such as speech problems and lower educational test scores – may be predictive of the development of schizophrenia in adulthood (Jones et al., 1994).

The interaction between psychosocial, environmental and genetic factors are important with a higher incidence of schizophrenia reported amongst some ethnic groups, second generation migrants and living in an urban environment (McDonald and Murray, 2000). Further factors, including cannabis use, social isolation, greater deprivation and unemployment may reflect both the causes and consequences of schizophrenia (Morgan et al., 2011;Picchioni and Murray, 2007). To date, understanding of the aetiology of schizophrenia remains incomplete and no single factor has been established as a universal cause (Walker et al., 2004;Picchioni and Murray, 2007).

Further discussion of the potential confounders of the association between schizophrenia and CVD is outlined later in section 5.

3.1.4 Management

UK guidelines for the management of schizophrenia have been developed by the National Institute for Health and Clinical Excellence. These guidelines outline the use of oral antipsychotics for treatment of the first psychotic episode and provision of cognitive behavioural therapy or family therapy (National Institute for Health and Clinical Excellence, 2009). Antipsychotic agents are most effective in reducing positive symptoms of schizophrenia such as psychosis, but may also be used for other medical conditions such as brain damage or toxic delirium (Joint Formulary Committee, 2012). Antipsychotics often need to be taken for prolonged periods of time, both for the purposes of maintenance and prevention of relapse in individuals at risk of episodes of psychosis. Classification of antipsychotic agents is into first or second generation groups: first generation antipsychotics (such as haloperidol, flupentixol, zuclopenthixol and chlorpromazine (Joint Formulary Committee, 2012)) were first formulated in the 1950s. The predominant mode of action for first generation antipsychotics is binding dopamine (D_2) receptors in the brain, although interaction with other receptors may also occur, which can induce unintended side effects that present as movement disorders (termed extra pyramidal side-effects).

Second generation antipsychotics (such as amisulpride, clozapine, olanzapine, quetiapine, risperidone and aripiprazole) have a different binding profile to first generation agents (including blocking serotonin neurotransmitters such as 5-HT_{2A}) and are associated with fewer extra pyramidal side-effects. However, second generation antipsychotics are associated with a range of other unintentional changes to lipid and glucose metabolism, and large increases in weight gain have been attributed to these drugs (Citrome et al., 2011). In addition, some second generation antipsychotics are implicated in cardiovascular side-effects including malignant ventricular arrhythmia: national guidelines therefore recommend that an electrocardiogram (ECG) is taken prior to initiating second generation antipsychotics in patients who are considered at high risk of CVD (National Institute for Health and Clinical Excellence, 2014c). The cardiovascular effects of antipsychotics, in particular the impact on lipids, are described in further detail in section 5.3.

For patients who experience treatment failure with two or more different antipsychotic agents, national guidelines recommend that psychological or psychosocial interventions should be provided in combination with the antipsychotic agent clozapine (National Institute for Health and Clinical Excellence, 2009).

3.2 Bipolar disorder and associated conditions

3.2.1 Definition

Bipolar disorder is a spectrum of conditions that is characterised by transition between extreme elation (mania/hypomania) and depressed mood: these mood episodes may also be accompanied by symptoms of psychosis such as hallucination or delusion. Bipolar disorder is a severe and long-term mental illness that can lead to substantial decline in social functioning and quality of life. As with schizophrenia, DSM-V and the ICD-10 are the major classification systems for bipolar disorder. ICD-10 criteria distinguish between episodes with mild/moderate or severe depression in individuals with bipolar disorder, and the presence or absence of mania and/or psychosis. Similarly, criteria for DSM-V outline at least two categories of bipolar disorder (termed bipolar disorder I and II), as well as cyclothymia, which is characterised by lower grade mood cycling than bipolar disorder I and II. Bipolar disorder I and II differ in terms of the frequency and magnitude of manic (predominant in bipolar I) versus major depressive (predominant in bipolar II) episodes.

3.2.2 **Burden of disease and life-course**

The lifetime risk of bipolar disorder is approximately 2%, although there is substantial variation in estimated rates (Merikangas et al., 2007;Merikangas et al., 2011). The age at which the symptoms of bipolar disorder most commonly begin is between 15 and 24 years and typically before the age of 30 years (Hardoon et al., 2013); although obtaining a firm diagnosis may take several years. According to a national survey undertaken in the United States of America (USA) it takes an average of 5 years to obtain a correct diagnosis of bipolar disorder from the first onset of symptoms (Hirschfeld et al., 2003). There are conflicting views regarding the relative prevalence of bipolar disorder by gender: either that bipolar disorder is predominantly experienced by women or that there is no gender difference (Diflorio and Jones, 2010). The prognosis for individuals with a diagnosis of bipolar disorder is varied; intervals between episodes of illness may become shorter over time and – amongst individuals who have been hospitalised for bipolar disorder – episodes may account for an average of 20% of their lifetime thereafter (Angst and Sellaro, 2000).

3.2.3 Aetiology

The underlying biological mechanisms of bipolar disorder are poorly understood, and a complex array of genetic and environmental factors appears to play a role in the development and progression of bipolar disorder. There is now sufficient evidence from genetic studies to conclude that some groups of related genes are over-represented in people with bipolar disorder, but that bipolar disorder is not caused by a single gene or gene cluster (Craddock and Sklar, 2013).

Negative life events and chronic stress appear to be triggers for the initial and subsequent depressive episodes in bipolar disorder (Hillegers et al., 2004;Kim et al., 2007). One possible mechanism through which these factors may act is via disruption of sleep and circadian rhythm (Miklowitz and Johnson, 2009). Additionally, individuals with bipolar disorder may be more sensitive to goal attainment than people without bipolar disorder, and this response could potentially contribute to the development of mania. In laboratory-based behavioural studies goal pursuit was more strongly associated with excitement, and failed pursuit more highly predictive of irritability and rage, amongst individuals with bipolar disorder than controls (Miklowitz and Johnson, 2009).

Epidemiological studies provide mixed evidence on the association – or lack thereof – between bipolar disorder and gender, urbanicity and/or season of birth (Kroon et al., 2013;Lloyd et al., 2005). However, there is substantial evidence of an increased

burden of bipolar disorder amongst individuals with non-white ethnicity, greater deprivation, poor diet, greater numbers of sexual partners and individuals who are physically inactive, smoke and use drugs or alcohol (Kroon et al., 2013;Lloyd et al., 2005;Scott and Happell, 2011). These associations are likely to reflect both risk factors for the development of bipolar disorder, and consequences of the condition.

Further discussion of the potential confounders of the association between bipolar disorder and CVD is outlined later in Section 5.

3.2.4 Management

Recommendations for the management of bipolar disorder focus on the stabilisation of acute mood episodes using separate treatment for mania and depression. Treatment often also draws upon a selection of additional therapies including family interventions and cognitive behavioural therapy to supplement pharmacological treatment of bipolar disorder (National Institute for Health and Clinical Excellence, 2014a). In the UK, mania in patients with bipolar disorder may be managed (treatment and/or prophylaxis) using; benzodiazapines (e.g. lorazepam), antipsychotics (e.g. olanzapine, quetiapine and risperidone; as described in section 3.1.4 above), which can be given in combination with mood stabilisers (lithium, valproic acid, carbamazepine or lamotrigine) if response to treatment is poor (Joint Formulary Committee, 2012).

Management of depressive episodes may require the use of antidepressants such as selective serotonin re-uptake inhibitors (SSRIs) (including fluoxetine) or tricyclic and related antidepressants such as trazodone hydrochloride (Joint Formulary Committee, 2012). However, the evidence-base underpinning the use of antidepressants for treatment of bipolar-related depression is relatively weak (Geddes and Miklowitz, 2013) and is further complicated by the potential for inducing antidepressant-induced switches to mania (Sidor and MacQueen, 2012). Even in patients who are given appropriate pharmacological interventions for bipolar disorder, the effectiveness of current medication regimens is limited with one third of patients responding to treatment in naturalistic studies (Judd et al., 2002;Judd et al., 2005;Perlis et al., 2006;Geddes and Miklowitz, 2013).

At present, the biological mechanism underpinning bipolar disorder and the action of pharmacological agents used in its treatment are poorly understood. Hypothyroidism (associated with symptoms of tiredness and weight gain) is a possible side-effect of lithium therapy and is particularly common in women with bipolar disorder, although rates are raised in both sexes relative to the general population (Baldassano et al.,

2005;Kupka et al., 2003;Johnston and Eagles, 1999). Lithium is also associated with reduced kidney function (McKnight et al., 2012): for this reason renal monitoring is an important aspect of safe clinical use and lithium therapy is avoided in individuals with chronic kidney disease (CKD) (Kripalani et al., 2009). The association between drugs used for treatment of bipolar disorder and cardiovascular risk is discussed further in Section 5.3.

4 Epidemiology of CVD

4.1 Definition and background

CVD is the most common cause of adult death and morbidity across the globe and is associated with a huge burden of preventable disease and vast financial costs (WHO, 2007;Lozano et al., 2012). In the USA alone, CVD costs amounted to $172 billion in 2010 and are forecast to increase to $276 billion (a 61% increase) by 2030 (Heidenreich et al., 2011).

Atherosclerosis is a major cause of CVD including myocardial infarction (MI) and stroke. Atherosclerosis occurs through the deposition of cellular and lipid-based substances on arterial walls, which accumulate to form plaques that gradually become hardened over time, but may not cause any noticeable symptoms for decades. Chronic inflammation and restriction or blockage of arteries are common consequences of atherosclerosis and can result in CVD events (Hansson and Hermansson, 2011). The stability of the plaque strongly influences the likelihood of a CVD event occurring: greater stability is characterised by increased calcification, increased smooth muscle cell density, less inflammation and a small lipid core. Rupture of a plaque releases the lipid core into the bloodstream and initiates a clotting cascade that may block or restrict blood flow. Blockage of arteries serving the heart presents as unstable angina when blood flow is partially restricted or MI if blockage is complete (Toth and Maki, 2008). Restriction of blood flow to the brain can occur due to blockage of blood vessels in the heart or of arteries supplying the brain (ischaemic stroke) or due to rupture of blood vessels within the brain (haemorrhagic stroke). Symptoms of stroke include muscle weakness or paralysis, slurred speech and confusion: symptoms that subside within 24 hours are classed as transient ischaemic attack (TIA) (McArthur et al., 2011).

Low and very low density lipoprotein cholesterol particles (LDL-C and VLDL-C, respectively) facilitate the development of atherosclerosis. Lipoproteins are made up of a cholesterol core that is solubilised in blood by apolipoprotein B and a

phospholipid membrane. Retention of LDL-C and VLDL-C particles in arterial walls results in their oxidation, which triggers a complex immune response that promotes plaque generation. High density lipoprotein-cholesterol particles (HDL-C) (for which apolipoprotein AI is the major protein constituent) reduce the generation of plaque by relocating cholesterol from cells in the arterial wall to the liver for excretion. The quantity of HDL-C and LDL-C is correlated with apolipoprotein AI and B levels (respectively): cholesterol fraction is therefore used as an indicator of apolipoprotein concentration and the risk of atherosclerosis (Toth and Maki, 2008).

4.2 Epidemiology

The mechanisms driving CVD in the general population have been well studied, with smoking (Mons et al., 2015), physical inactivity (Bassuk and Manson, 2005), poor diet (de Souza et al., 2015;Strazzullo et al., 2009;Malik et al., 2010), obesity (Klein et al., 2004) and high alcohol consumption (Ronksley et al., 2011) (Reynolds et al., 2003) identified as the major modifiable risk factors that can be targeted to prevent CVD events. Meta-analysis of data from large prospective studies of CVD and mortality have established that dyslipidaemia is a key modifiable risk factor, with 1mmol/L reductions in total cholesterol associated with a halving of mortality in people aged 40-49 years and reductions of 17-33% amongst 50-89 year olds (Lewington et al., 2007).

The INTERHEART case-control study provides a further indication of the magnitude of association between modifiable risk factors and MI in thirty-thousand participants recruited across 52 countries between 1999 and 2003. The results from this study identified lipids as having the greatest population-attributable risk for MI, with elevated ratios of LDL-C to HDL-C accounting for half (49%) of global population-attributable risk for MI. Similarly, smoking, psychosocial factors, abdominal obesity and hypertension were found to be major causes of MI, accounting for 18-38% of global population-attributable risk (Yusuf et al., 2004).

The presence of the metabolic syndrome is also strongly correlated with the likelihood of having a CVD event. The metabolic syndrome may be defined as having three or more of i) central obesity (a waist circumference including or exceeding 88cm in women and 102cm in men), ii) triglyceride levels of 1.69mmol/L or higher, iii) HDL-C of less than 1.03 or 1.29mmol/L (for men and women, respectively), iv) blood pressure exceeding 130/85mmhg, v) fasting glucose levels of ≥5.56mmol/L or higher, or treatment for vi) dyslipidaemia, vii) hyperglycaemia or viii) hypertension (Grundy et al., 2004). Some definitions may use body mass index

(BMI) as a proxy for waist circumference (Mottillo et al., 2010). The risk of CVD is over twice as high in people with the metabolic syndrome, compared to those without: pooled results from 16 studies combining subtly different definitions for the metabolic syndrome yielded a relative risk (RR) of 2.35 (95% CI: 2.02-2.73) (Mottillo et al., 2010).

Risk factors for CVD are widely acknowledged to cluster and to act multiplicatively on CVD risk (Jackson et al., 2005;Dawber et al., 1951). This knowledge has promoted the use of multivariable risk prediction algorithms to estimate an individual's absolute risk of future CVD events within a given timeframe. Such algorithms are primarily derived from large scale cohort studies that collect data over many decades to assess the contribution made by different types of factors to the risk of having a CVD event (Conroy et al., 2003;de la Iglesia et al., 2011;Hippisley-Cox et al., 2010;D'Agostino et al., 2008). One classic example is the Framingham study, which was initiated in 1948 and continues to operate having enrolled in excess of 10,000 participants across several cohorts. Data on a subset of 8,491 participants from the original Framingham cohort were used to develop algorithms for estimating 10 year CVD risk using information on each participant's age and sex, blood pressure, smoking and diabetes status and either BMI or and cholesterol concentration (D'Agostino et al., 2008): detailed information on the estimation of CVD risk scores is outlined in Chapter 3, section 3.2.6. UK national guidance on CVD prevention recommends that General Practitioners (GPs) use risk scores similar to Framingham (including QRisk2, which is outlined in further detail in section 4.4) to identify individuals at high risk of CVD and to implement appropriate measures to prevent the development of CVD (National Institute for Health and Clinical Excellence, 2014b).

4.3 **Burden of disease and life-course:**

In the UK in 2006, the prevalence of CVD exceeded 2.2 million people including over 1.2 million cases of MI, at least 978,000 cases of stroke and 1.7 million people were living with angina (Townsend et al., 2012). The incidence of MI amongst British men declined by 62% over a 25 year period (Hardoon et al., 2008) and mortality from CVD has decreased by 50% (Townsend et al., 2012). Despite the substantial decline in incidence, CVD is still a leading cause of death and accounted for 28% of all deaths in England and Wales in 2013 (Office for National Statistics, 2014). CVD is causally associated with a range of risk factors, for which age is the most important: CVD events are rare in people under the age of 30 years (Anderson et al., 1991;O'Flaherty et al., 2008).

4.4 Prevention and management

Guidance for the UK recommends annual physical health checks for all people aged 40-74 years, which may include calculating a 10 year CVD risk score for the individual and using this estimate to guide action to reduce CVD risk (Department of Health, 2008). Initial action to manage CVD risk should aim to improve health through measures such as increased physical activity, dietary control of sugar, salt intake, lipid levels and smoking cessation. However, a pharmacological intervention may be prescribed for individuals who are at greater risk of CVD, or for those who have been unsuccessful in modifying their CVD risk through lifestyle changes alone (National Institute for Health and Clinical Excellence, 2011;National Institute for Health and Clinical Excellence, 2014b).

In the UK there are three major groups of pharmacological interventions for reducing CVD risk. Statins, antihypertensives and nicotine replacement therapy are used for lipid modification, lowering blood pressure and quitting smoking (respectively): statins are the most commonly prescribed intervention for the prevention of CVD. Statins lower blood cholesterol concentration by inhibiting the cholesterol synthesising enzyme 3-hydroxy-3-methyl-glutaryl-coenzyme-A reductase (HMG-CoA reductase) and promoting expression of LDL-C receptors, which bind and thereby remove these lipoproteins from blood. In the general population, statins are most frequently taken as a single daily dose and treatment is usually required for the duration of a patient's lifetime.

Statins have a generally good safety profile and there is a low frequency of adverse events associated with their use. However, the side-effects most commonly attributed to statins include gastro-intestinal symptoms, rash, headache and generally feeling unwell (e.g. aches and fatigue): these effects are usually relatively mild and transient but may be unpleasant enough to deter continued medication. Further quantification of non-adherence to statin medication is outlined in Chapter 3 section 5.2.2. Less common but important side-effects of statins include increases in liver transaminases (occurring in up to 1% of individuals) and myopathy (muscle weakness; occurring in 0.2% of statin trial participants) (Bellosta et al., 2004). In addition, statin use has been associated with increased risk of developing type II diabetes, although the magnitude of risk is likely to be modest (Rajpathak et al., 2009;Parker et al., 2015).

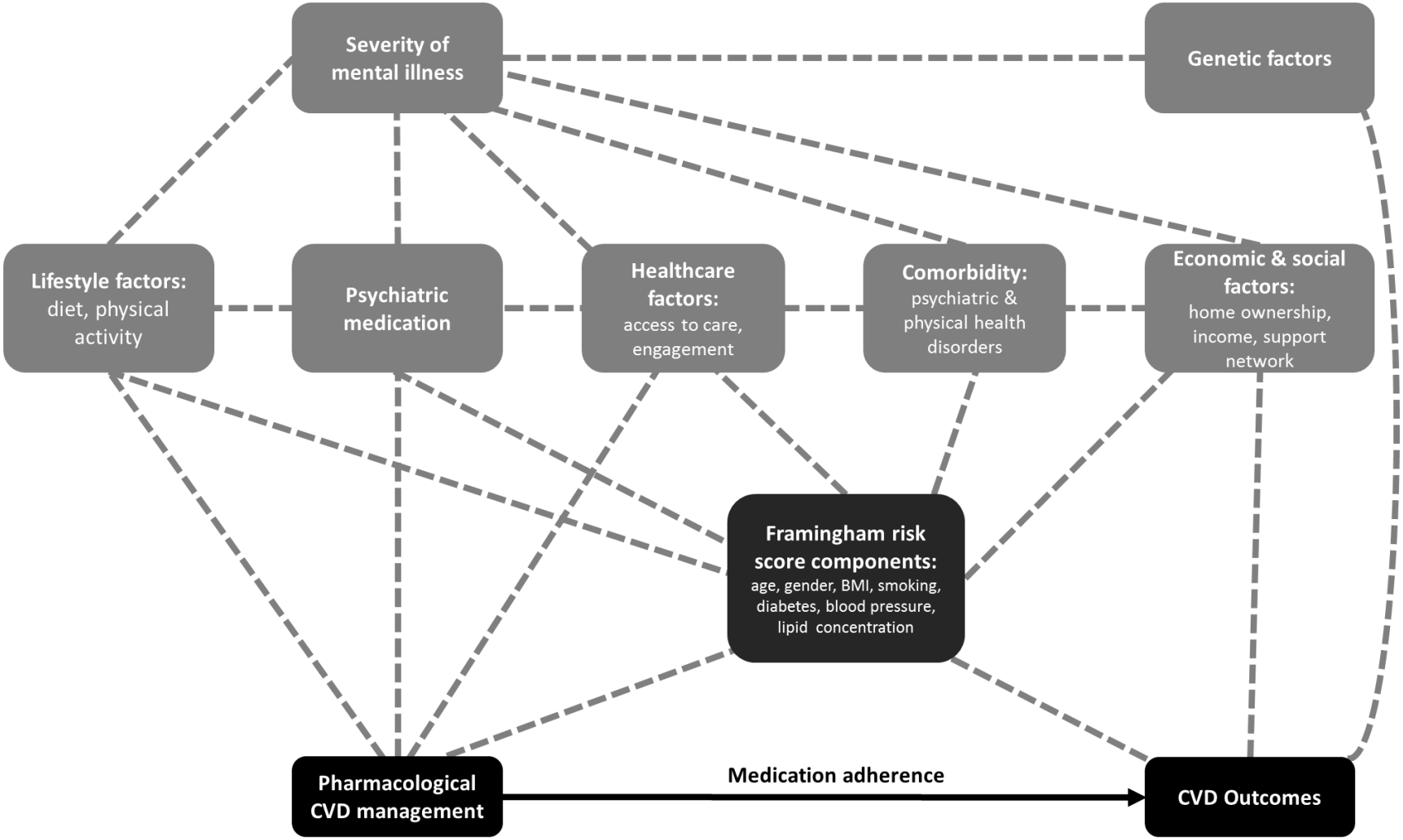
Randomised controlled trials (RCTs) have shown long term statin use to be a clinically efficacious and cost-effective means of preventing CVD events in high risk

people (Taylor et al., 2013). Until July 2014, the recommended threshold for pharmacological intervention with statins - first line treatment with simvastatin - for the general population (excluding individuals with familial hypercholesterolaemia) was set at a risk score of 20% or higher. However, current guidelines have lowered the risk threshold to 10% (National Institute for Health and Clinical Excellence, 2008b;National Institute for Health and Clinical Excellence, 2014b). In addition, guidance now specifies that risk scores should be calculated using the QRisk2 algorithm (Hippisley-Cox et al., 2010;Hippisley-Cox et al., 2008) and suggests that atorvastatin should be initiated in preference to other types of statins (National Institute for Health and Clinical Excellence, 2014b). Additional detail on health policy of relevance to statin prescribing for primary prevention in the UK is outlined at the start of Chapter 5. Separate guidance is issued for adults with familial hypercholesterolaemia, for which statin therapy may be initiated on the basis of lipid or genetic testing (National Institute for Health and Clinical Excellence, 2008a).

5 CVD risk in people with SMI

In the UK the risk of developing CVD is at least twofold higher in people with SMI than the general population (Osborn et al., 2007a). CVD risk is both greater amongst people with SMI and occurs at an earlier age than for the general population, with the largest RR of CVD seen in adults aged less than 30 years of age (Osborn et al., 2007a). Furthermore, people with SMI experience poorer CVD outcomes, with associated mortality being approximately three times higher than the general population (Lahti et al., 2012). The risk of CVD in people with SMI is driven by a complex network of factors (Figure 5-1) that ultimately reflect the causes and consequences that SMI has on social disadvantage, including social gradient, stress, social exclusion and unemployment (World Health Organization, 2003). These social and economic factors are adversely associated with maintaining a healthy lifestyle and accessing healthcare, and influence markers of CVD risk that are incorporated into the Framingham Risk score including lipid profile, BMI, blood pressure and diabetes (De Hert et al., 2011b;De Hert et al., 2011a). Further detail on the hypothesised directionality of effect for the main analysis undertaken in this thesis is outlined in Chapter 3 (Figure 3-2).

Figure 5-1: Graphical representation of the factors associated with CVD and its management in people with SMI



5.1 Lipid profile

Of particular importance to this thesis is lipid profile as a marker of atherosclerosis and CVD risk, and because LDL-C is the primary target for statin therapy.

Dyslipidaemia, defined as an abnormal level of lipids in the bloodstream, may be driven by a range of factors such as genetics, diet, lack of exercise and obesity. In addition, some second generation antipsychotics have been implicated in dyslipidaemia, potentially resulting from interaction with the sterol regulatory binding elements that control lipid synthesis (Ferno et al., 2005;Raeder et al., 2006;Nasrallah, 2008). These determinants of dyslipidaemia and CVD risk are discussed in further detail for the remainder of this chapter.

The clinical thresholds for dyslipidaemia (reflecting raised lipid levels) are often defined as ≥5mmol/L for total cholesterol and ≥3mmol/L for LDL-C (2005), although these criteria are not universal. Dyslipidaemia is estimated to occur in approximately 63% of the general population in the UK (Townsend et al., 2012), and is at comparable levels amongst people with SMI: standardised mean difference of -0.10 (95% CI: -0.55, 0.36)(Osborn et al., 2008). However, individuals with SMI may have relatively lower concentrations of HDL-C but higher concentrations of LDL-C fractions and this is associated with an elevated risk of CVD (Meyer et al., 2008).

5.2 Other components of the Framingham score for CVD risk

5.2.1 BMI

Poorer diet, lower levels of physical activity in combination with the side-effects of some types of psychotropic medication are associated with an increased risk of obesity and weight gain in people with SMI. Antipsychotics are implicated in weight gain through a range of mechanisms that can alter appetite (Baptista, 1999;Casey, 2005). Second generation antipsychotics are most strongly associated with weight gain, with differential increases by antipsychotic type: clozapine and olanzapine are generally considered to lead to the greatest increases in weight, which may amount to a 6kg gain over a 10 week period (Citrome et al., 2011).

Individuals with schizophrenia have been reported as having a 2.8 to 3.5 fold increased risk of obesity (BMI ≥30mg/m^3) relative to people without SMI (Scott et al., 2008) and appear to have an increased propensity for abdominal obesity that is irrespective of treatment with antipsychotic agents (Ryan et al., 2004). By contrast, individuals with

mood disorders have a 1.2-1.5 increased likelihood of obesity (Scott et al., 2008;Simon et al., 2006;Petry et al., 2008). Weight gain is an important risk factor for CVD as it may contribute to the development of abdominal obesity, which is a defining feature of the metabolic syndrome and increases the likelihood of developing insulin resistance and type II diabetes.

5.2.2 Diabetes mellitus

The prevalence of type II diabetes and insulin resistance is 1.7 (pooled RR 95% CI: 1.2-2.4) times higher amongst people with SMI than the general population (Osborn et al., 2008), with a magnitude of risk that is associated with type of mental illness, antipsychotic use and antipsychotic type (Lean and Pajonk, 2003;Wirshing et al., 2002;Koro et al., 2002). Second generation antipsychotics are associated with a 20-30% increased risk of diabetes relative to first generation drugs, and diabetes outcomes are worst for people prescribed olanzapine or clozapine (Holt and Peveler, 2006;Smith et al., 2008;Treuer et al., 2009;Koller and Doraiswamy, 2002). However, there is insufficient evidence to determine whether or not this relationship is truly causal as antipsychotic use is associated with established risk factors for diabetes (Holt and Peveler, 2006).

5.2.3 Smoking

Smoking is a well-established driver of premature mortality and physical morbidity including MI and stroke. Meta-analysis of international studies identified that the odds ratio (OR) for smoking were over 3 times higher in women (OR 3.3 95% CI: 3.0-3.6) and 7 times higher in men (OR 7.2 95% CI: 6.1-8.3) with schizophrenia, compared to people without SMI (de Leon and Diaz, 2005). A large study estimated that mortality was twice as high amongst people with schizophrenia who were smokers, compared to those who did not smoke (Brown et al., 2010). In the same study, 70% of the excess mortality from natural causes was attributed to smoking-related diseases amongst people with schizophrenia: however, this may reflect a disproportionately high prevalence of smoking (73%) within the cohort. Other studies examining the prevalence of smoking have consistently reported rates that are higher amongst people with SMI (ranging from 53% to 73%) than the general population, which is approximately 24% across all ages (Townsend et al., 2012;Tran et al., 2009;Brown et al., 2010). The proportion of individuals with SMI who smoke heavily (20-30 cigarettes per day) is also greater than for the general population (Williams and Foulds, 2007;Williams and Ziedonis, 2004;Dixon et al., 2007). There is therefore a greater

burden of smoking amongst individuals with SMI both in terms of the relative abundance of smokers and the quantity consumed within a given timeframe.

There is evidence to suggest that smoking cessation with nicotine replacement therapy, bupropion and group or individual therapy is effective in people with SMI (Banham and Gilbody, 2010). However, smoking cessation rates amongst people with SMI are approximately half that of the general population and it is unclear if this is due to a lack of effective smoking cessation strategies, access to services or other barriers (Williams and Foulds, 2007). At present, the cost-effectiveness of such strategies is unknown and evaluation is ongoing (Peckham et al., 2015).

5.2.4 Systolic blood pressure

Hypertension is a risk factor for stroke and coronary heart disease (CHD) as well as other conditions such as kidney failure. It has been estimated that every 10mmHg decrease in systolic blood pressure is associated with a 25% decrease in CHD events and a 30% reduction in stroke (Law et al., 2009). At present, estimates of the proportion of people with schizophrenia who are hypertensive are imprecise, with some studies suggesting high levels of untreated hypertension (34-50%) (Smith et al., 2007;Daumit et al., 2008), but with little evidence of raised risk of hypertension relative to the general population (pooled RR; 1.11, 95% CI: 0.91-1.35) (Osborn et al., 2008).

5.3 Psychiatric medication

Some types of antipsychotic drugs – particularly second generation agents – have been implicated in weight gain, dyslipidaemia, the development of type II diabetes and are thereby associated with conventional risk factors for CVD (De Hert M. et al., 2012). However, the causal link between antipsychotic agents and CVD events is less clear cut. Some studies have identified evidence of increases in the risk of MI (Brauer et al., 2011;Brauer et al., 2015), amongst individuals prescribed antipsychotic medication; particularly in the month after first initiation. Similarly, the risk of stroke appears to be higher amongst individuals taking antipsychotic medication; especially in those with a dementia diagnosis (Douglas and Smeeth, 2008). However, it is unclear whether this increased CVD risk may be explained by changes in behaviour (such as smoking, illicit drug use, sleep deprivation or unhealthy eating) that are attributed to acute episodes of mental illness requiring pharmacological treatment, rather than a direct consequence of the antipsychotic drug itself (Swain et al., 2015).

At present, there is no evidence to suggest a causal mechanism for CVD events and antipsychotic agents that is independent of other known CVD risk factors (including

dyslipidaemia, obesity and type II diabetes). However, some types of antipsychotic agents – particularly sertindole; which was withdrawn from the market in 1999 - have been implicated in cardiotoxic effects that may result in higher incidence of cardiomyopathy or myocarditis than the general population (Bagnall et al., 2003). There is also some evidence that some types of antipsychotic drugs are associated with higher rates of orthostatic (postural) hypotension especially in older individuals and those on blood pressure medication (Muench and Hamer, 2010). Mood-stabilisers and antidepressants are also known to be correlated with conventional CVD risk factors such as weight gain, although there is no consistent evidence of a direct association with CVD events (Correll et al., 2015;Douglas et al., 2011;McKnight et al., 2012).

5.4 Lifestyle factors

Amongst people with SMI, diet has been shown to be generally poorer than the general population, although there is conflicting evidence to support whether this is driven by income constraints or other factors such as a lack of knowledge about diet (Osborn et al., 2007b;Roick et al., 2007;Samele et al., 2007;Fagiolini and Goracci, 2009). People with SMI are more likely to have diets with significantly less fruit and fibre (Stokes and Peet, 2004;Brown et al., 1999) but more saturated fat (Dipasquale et al., 2013) than people without SMI and these dietary habits are associated with being overweight or obese. Levels of physical activity are also lower amongst individuals with schizophrenia than people without SMI (Roick et al., 2007;Daumit et al., 2005), with over one third of individuals in one study reporting no physical activity in the past month (Daumit et al., 2005).

5.5 Economic and social factors

Social and economic factors associated with both CVD and mental illness include social support, income, employment and ethnicity (encompassing social factors such as cultural identity, lifestyle and behavioural factors; as well as genetic factors (National Research Council (US) Panel on Race Ethnicity and Health in Later Life, 2004)). The primary mechanism through which these factors are likely to be associated with CVD is through impacting upon health behaviours, such as smoking, diet, physical activity or healthcare utilization (Hemingway and Marmot, 1999a;Hemingway and Marmot, 1999b). Given the breadth of social and economic factors and their wide-reaching implications for CVD health it is perhaps not surprising that the relative contribution of these factors has not been quantified for people with SMI. However, studies have shown that some - but not all - of the disparity in CVD risk between people with and

without SMI can be explained by specific socio-economic factors such as unemployment (Osborn et al., 2006).

5.6 Comorbidity

People with SMI are also more likely to have other psychiatric comorbidities: with half of individuals with schizophrenia receiving a lifetime diagnosis of substance abuse, depression or anxiety disorders (Buckley et al., 2009). Similarly, depressive episodes often form part of the diagnosis of bipolar disorder and may be indicative of a greater risk of future relapses of acute illness (Perlis et al., 2006). Anxiety and substance abuse are also associated with bipolar disorder (Krabbendam et al., 2004) and individuals with either comorbidity experience poorer outcomes (Coryell et al., 2012;Coryell et al., 2009). Schizophrenia and bipolar disorder are associated with comorbid alcohol use: up to half of men and one third of women with a SMI may develop an alcohol disorder (Frye et al., 2003;Hendrick et al., 2000;Drake and Mueser, 2002).

Individuals with SMI are at increased risk of a range of comorbid physical health conditions including diabetes, arthritis, digestive disease and liver disease (Perron et al., 2009;Dixon et al., 1999). One study used the Charlson Comorbidity Score (Charlson et al., 1987) to summarise the level of physical morbidity amongst individuals with schizophrenia or bipolar disorder - relative to individuals without psychiatric healthcare contact - and found that comorbidity scores were approximately doubled amongst people with SMI (Laursen et al., 2011). Much of the increased burden of physical comorbidity is likely to stem from lifestyle, health behaviours and treatment factors amongst individuals with SMI. For example, elevated levels of liver disease may be attributable to viral hepatitis B or C infection, or alcohol induced liver damage, which reflect higher levels of injecting drug and alcohol use amongst people with psychosis (Frye et al., 2003;Hendrick et al., 2000;Grant et al., 2009).

5.7 Genetic factors

Genetic factors influencing comorbid physical health conditions and SMI are not well characterised, however, there is a growing body of evidence that people with SMI may be more susceptible to molecular changes associated with somatic comorbidity and premature mortality. Examples include reduced telomere length, which is associated with physical conditions such as diabetes and hypertension that may ultimately contribute to premature death (Fernandez-Egea et al., 2009). Furthermore, at least ten genetic regions are implicated in both CVD and schizophrenia; indicating that these

genes may play a causal role in both conditions (Andreassen et al., 2013;Hansen et al., 2011).

5.8 Healthcare Factors

Provision of health services for people with SMI may also contribute to poorer management of CVD (De Hert et al., 2011a). Care pathways for people with SMI are complex and necessitate access to both physical and mental healthcare services, which are often geographically and organisationally separated (Reilly et al., 2012;Prince et al., 2007). Furthermore, physical health needs of patients at risk of CVD may be overlooked or delayed for a range of reasons including prioritisation of mental health treatment, lack of awareness about physical health in people with SMI and a paucity of services providing physical healthcare (Smith et al., 2013;Buhagiar et al., 2011;Shuel et al., 2010). This phenomenon – termed diagnostic overshadowing – describes the process through which people with mental illness receive sub-optimal care because their physical symptoms are misattributed to their mental illness, or the physician focuses their time with them on management of their mental illness and misses opportunities for preventative physical health care (Jones et al., 2008). Although little is known about the provision of healthcare for primary prevention of CVD, there is evidence that medications for physical illness are at less frequently prescribed to people with SMI (pooled OR 0.74 (95% CI; 0.63-0.86)): this disparity is largely accounted for by CVD drugs, including statins (OR of 0.61 (95% CI; 0.39-0.94)) (Mitchell et al., 2012).

6 Management of CVD in people with SMI

The National Institute for Health and Clinical Excellence has recognised the need for improved management of CVD in people with SMI and recommends that CVD and metabolic indicators should be routinely monitored (National Institute for Health and Clinical Excellence, 2014c;National Institute for Health and Clinical Excellence, 2014a). These indicators should be used in conjunction with guidance for the general population on managing CVD risk and lipid modification, although it is acknowledged that CVD risk is underestimated by standard risk scores for people with SMI (National Institute for Health and Clinical Excellence, 2014b). Statin therapy for primary prevention of CVD is recommended for people with SMI on the same basis as the general population: however, the evidence-base for this patient group is weak (an evaluation of the evidence-base is outlined in Chapter 2).

7 Context

The work described in this thesis forms part of PRIMROSE (Prediction and Management of CVD Risk for People with SMI), a five year National Institute for Health Research funded programme to improve CVD risk management in people with SMI in primary care. PRIMROSE is establishing the evidence-base needed to design, implement and assess the clinical- and cost-effectiveness of a new package of care to prevent CVD in people with SMI. This package of care aims to promote behaviour change to support both pharmacological and lifestyle modification to manage CVD risk and therefore comprises a raft of interventions related to medication adherence, physical activity, smoking cessation and diet.

8 Summary and scope of this thesis

In the general population, CVD risk is associated with economic and social factors that reflect high levels of inactivity, poor diet, smoking, excessive drinking and diabetes. These risk factors are particularly prevalent amongst people with SMI and appear to explain much of the additional burden of CVD in this population. Furthermore, prolonged exposure to antipsychotic drugs is implicated in weight gain and changes in lipid and glucose metabolism, which may contribute to the development of type II diabetes. There is some evidence that people with SMI may have reduced access to CVD prevention services. Mortality and morbidity rates following CVD are also much higher amongst people with SMI, thus highlighting the importance of understanding the extent to which provision of measures to prevent primary CVD meets the needs of this patient group.

Statins are the most common pharmacological intervention for managing CVD risk and are cost-effective for preventing CVD in high risk people in the general population. However, the evidence-base for statin use in people with SMI is unclear.

9 Research aims and objectives

This thesis aims to explore the effectiveness of statins for primary prevention of CVD in people with SMI by addressing the following objectives:

1. Evaluate the evidence-base for statin prescribing for prevention of CVD in people with SMI (Chapter 2)

2. Describe the strengths and limitations of using UK primary care data to investigate the impact of statin prescribing on CVD in people with SMI (Chapter 3)

3. Explore methods to reduce confounding and handle missing data to support estimates of effectiveness derived from primary care data (Chapter 4)

4. Investigate the uptake of CVD screening and statin prescribing in UK primary care amongst people with and without SMI (Chapter 5)

5. Estimate the effectiveness of statin prescribing in UK primary care for prevention of CVD in people with SMI (Chapter 6)

6. Discuss the collective interpretation of the findings from these objectives and their significance in terms of policy, practice and research (Chapter 7)

Chapter 2 : Systematic review of the effectiveness of statins for the primary prevention of CVD in individuals with SMI

1 Chapter Content

Evidence from randomised controlled trials (RCTs) has shown prevention of cardiovascular disease (CVD) with statins to be cost-effective for high risk individuals in the general population. However, the risk of CVD is two-to-threefold higher amongst individuals with SMI and patterns of statin medication adherence and exposure to antipsychotic drugs may differ amongst people with SMI relative to trial participants: the effectiveness of statin therapy is therefore unclear for this group. This chapter initially describes the rationale for investigating the effectiveness of statin therapy in people with SMI with respect to effectiveness for primary prevention of CVD in the general population. The chapter then identifies evidence on the effectiveness of statins at primary prevention of CVD in people with SMI by systematically searching literature and trials databases for studies evaluating the impact of statins on CVD events, estimated CVD risk or changes in lipid levels. I describe the methods used for undertaking the search, evaluate the quality of the studies identified and summarise the results. The strengths and limitations of the search strategy are considered and the implications of the results for the objectives of the subsequent planned work, regarding statins in people with SMI are outlined.

This work was peer-reviewed and subsequently accepted for a short oral presentation at the UK Society of Academic Primary Care (SAPC) annual conference (July 2014 - Edinburgh). The associated abstract is outlined in the appendix; section 18.

2 Rationale for investigating the effectiveness of statins for primary prevention of CVD in people with SMI

A recent systematic review evaluating the effectiveness of interventions for primary prevention of CVD risk in people with SMI highlighted the lack of evidence for lipid modification for this group (Gierisch et al., 2014). Statin therapy potentially offers an effective means of managing CVD risk in people with SMI and is particularly important given the absence of evidence on viable alternatives to manage dyslipidaemia.

2.1 Evidence-base for statin prescribing for primary prevention of CVD in the general population

RCTs have shown statins to be effective for primary prevention of CVD (Taylor et al., 2013). Meta-analysis of data on 56,934 participants identified from 18 RCTs produced a rate ratio of 0.75 and 95% confidence interval (CI) of 0.70-0.81, suggesting a 25% reduction in the frequency of combined fatal and non-fatal CVD events in individuals who were randomised to receive a statin. From the same study, the rate ratios for combined fatal and non-fatal coronary heart disease (CHD) were 0.73 (0.67-0.80) and 0.86 (0.79-0.94) for all-cause mortality, all suggesting a protective effect of statin therapy (Taylor et al., 2013).

Observational studies (outlined in greater detail in Chapter 4) have also investigated the impact of statin prescribing for primary prevention of CVD and have identified effect estimates that are compatible with RCTs of statins (Heart Protection Study Collaborative Group, 2002). Fully adjusted hazard ratios (HRs) for first myocardial infarction (MI) were 0.87 (0.77-0.98), first stroke; 0.86 (0.77-0.96) and all-cause mortality; 0.79 (0.75-0.83) amongst a cohort of individuals with a diagnosis of atherosclerosis (Smeeth et al., 2009) and thus confirm the effectiveness of statins in clinical practice.

2.2 To what extent does the evidence-base for statin use in randomised trials reflect the effectiveness in people with SMI?

Although there is strong evidence from randomised studies that statins are effective for primary prevention of CVD events within trial populations, statins may have a different level of effectiveness when prescribed to people with SMI because this population is likely to differ in terms of CVD risk profile, medication adherence and antipsychotic exposure.

Studies that contributed half of the total study population (50%; n=28,390) for the most recent meta-analysis of statins for primary prevention of CVD (Taylor et al., 2013) explicitly excluded participants with psychological conditions (Ridker, 2003;Heart Protection Study Collaborative Group, 2002;Shepherd et al., 1995). In addition, a further 20% (n=10,797) of the total meta-analysis study population was obtained from studies that excluded individuals who were perceived as less likely to be compliant with treatment (Beishuizen et al., 2005;Nakamura et al., 2006;Knopp et al., 2006;Baldassarre et al., 2000). Together these studies account for the majority (69%) of observations included in the meta-analysis, meaning that the effect estimates

derived from the meta-analysis may not accurately reflect the effectiveness of statins administered to people with SMI.

Direct comparison of the characteristics of individuals with SMI and people enrolled into statins trials has not been undertaken: however, the relative risk (RR) of CVD events is two-to-threefold higher amongst people with SMI than those without SMI (Osborn et al., 2007a). Furthermore, medication adherence may be different for individuals with SMI: estimates specific to statin medication or people with psychosis are not known, however, mental illness is more generally associated with poorer medication adherence (Osterberg and Blaschke, 2005;Maningat et al., 2013;Ruokoniemi et al., 2014).

In addition, *in vitro* studies indicate that some antipsychotic agents interact with transcription factors for sterol regulatory element-binding proteins (SREBP) (Ferno et al., 2005). SREBP proteins are responsible for activating several genes that encode enzymes for cholesterol and fatty acid synthesis (including HMG-CoA reductase, which is the primary binding site for statins) (Horton et al., 2002). Antipsychotic and SREBP interaction appears to result in increased cholesterol concentration and could therefore counteract the cholesterol-lowering action of statins. The degree of interaction between the antipsychotic and SREBP transcription factors varies by the type of drug and appears to be more strongly correlated with agents such as clozapine, which are associated with weight gain (Raeder et al., 2006;Nasrallah, 2008).

3 Aims

This review aims to identify evidence on the effectiveness of statins at preventing CVD in people with SMI. I seek to evaluate the impact on CVD risk reduction that is attributable to the administration of statins in a statin-naïve population (i.e. individuals for whom statin therapy is being newly administered) with SMI by measuring CVD events, estimated CVD risk or changes in lipid levels. The Cochrane Handbook (The Cochrane Collaboration, 2011) was used for methodological guidance, and the research question is considered within the standard framework of target population, intervention, comparison and outcome measures (PICO). The protocol for this review is registered on PROSPERO (ID: CRD42014009589).

4 Methods

4.1 Population, Intervention, Comparison and Outcome (PICO) criteria

- **Population:** people with SMI (primarily schizophrenia or bipolar disorder), who do not have a diagnosis of CVD and who are statin-naïve
- **Intervention:** being prescribed statin medication
- **Comparison:** statin-naïve individuals with SMI who are not prescribed a statin and do not have a CVD diagnosis
- **Outcome:** incidence of CVD events, CVD risk (derived using standard calculations) / or lipid levels (i.e. total cholesterol, high density lipoprotein-cholesterol (HDL-C), low density lipoprotein-cholesterol (LDL-C) or triglycerides)

In addition, I applied the following eligibility criteria to assist with screening citations identified through the search.

Inclusion criteria

I. People with a SMI diagnosis (in any care setting): defined as schizophrenia, bipolar disorder and non-organic psychosis
II. Studies evaluating statin treatment (i.e. any drug classed as a statin, taken orally at any dose and treatment duration)
III. Any of the following outcomes; mortality, CVD events (fatal or non-fatal), lipid concentration or estimated CVD risk

Exclusion criteria

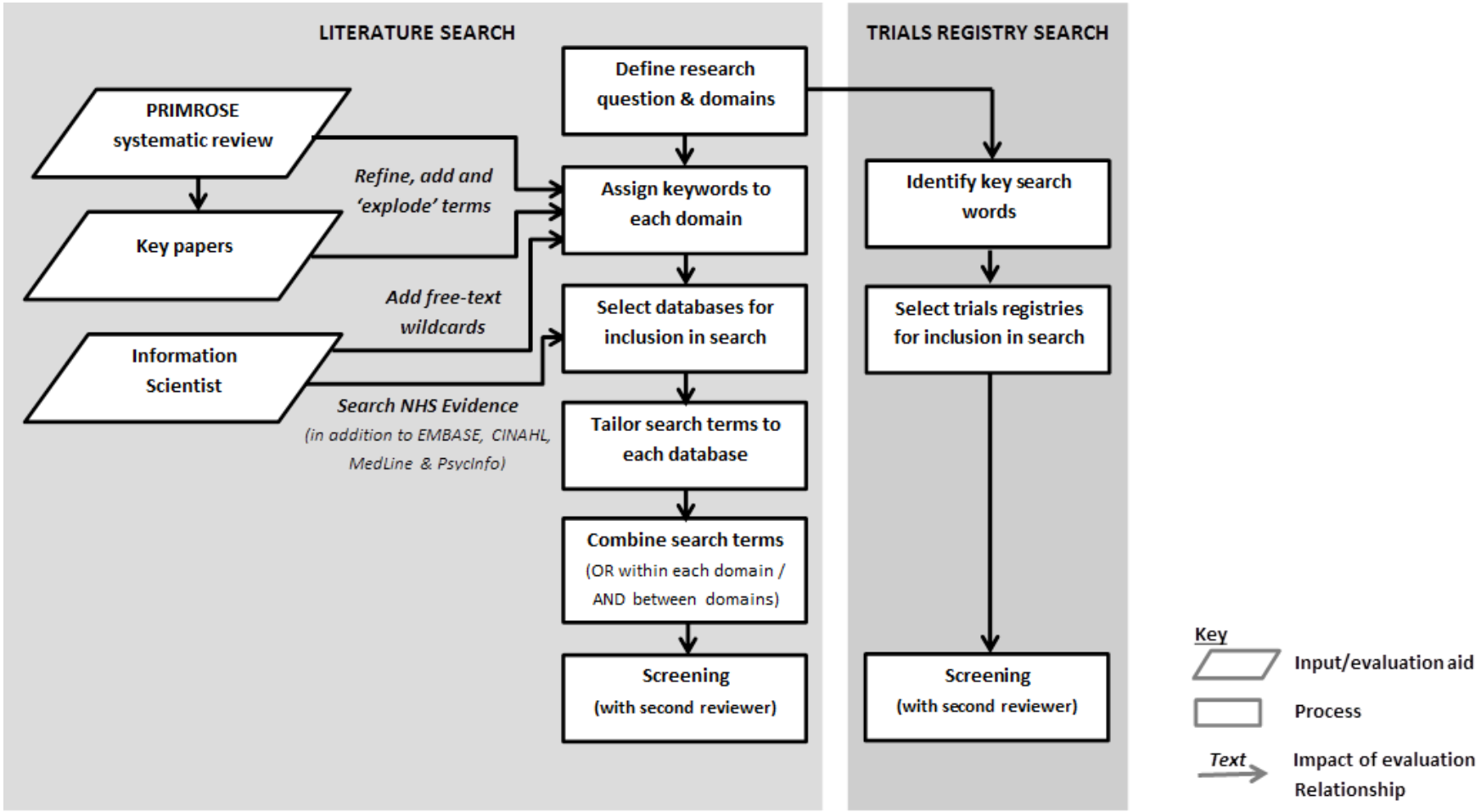
IV. People with a diagnosis of non-psychotic mental illness (only), such as severe depression
V. People with a prior diagnosis of CVD, or who have current or very recent exposure to statins

4.2 Overarching search strategy and methodology

I carried out an independent systematic search of the literature and trials registries and used work developed as part of the PRIMROSE programme to inform the selection of search terms and evaluate my search strategy. The process of developing the literature and trials search strategy is outlined in Figure 4-1. My search strategy adapted the PRIMROSE search for CVD risk interventions in people with SMI to focus on statins

(Atkins et al., 2013). This strategy was further developed through discussion with an Information Scientist at the Royal Free Hospital Medical Library, and I additionally searched NHS Evidence as well as MedLine, PsycInfo, EMBASE and CINAHL, to ensure coverage of a broad selection of scientific and health disciplines. I also searched for registered trials across a range of registry databases.

Figure 4-1: Development process for searching for literature and trials on the effectiveness of statins for primary prevention of CVD in people with SMI



4.3 Searching for literature

Three key search domains were derived from the research question: 1) CVD risk; 2) statins; and 3) SMI. Synonyms and related words were established for each domain, and these were mapped to appropriate medical subject headings for searching via the Ovid (MedLine, PsycInfo and EMBASE) or CINAHL interfaces. The search tailored terms for each of the databases are outlined in the appendix; section 17.

Table 4-1: Research question domains and terms used for searching the literature

Domain	Synonyms/related terms	Subject heading term (exploded)	Free-text
Effectiveness (on risk of CVD)	CVD	"cardiovascular diseases"	cardio*
	Cholesterol	Cholesterol	cholesterol*
	Lipids	Lipids	lipid*
	Dyslipidaemia	Dyslipidemias	metabolic*
	Hyperlipidaemia	Hyperlipidemias	
	Metabolic syndrome	"Metabolic Syndrome X"	
Statins	Statin / *statin	"Hydroxymethylglutaryl-CoA Reductase Inhibitors"	statin* OR Hydroxymethylglutaryl-CoA Reductase Inhibitor*
	Hydroxymethylglutaryl-cardio*CoA Reductase Inhibitors		
SMI	Bipolar disorder	"Bipolar Disorder"	Bipolar OR mani* OR manic* Or hypomani* OR psychotic OR postpsychotic OR "post psychotic" OR "rapid cycling" OR schizoaffective OR psychosis OR psychoses
	Schizophrenia	Schizophrenia	
	Psychotic disorders	"Psychotic Disorders"	
	Antipsychotic agents	"Antipsychotic Agents"	

The Ovid or CINAHL interfaces allow users to identify subject headings and build up complex searches that can also include free-text. By contrast, NHS Evidence is searched using only free-text (similar to search engines such as Google) and the number of hits therefore tends to be larger.

4.3.1 Developing the initial search strategy

The search strategy mapped each of the three search domains to key search headings. The resulting subject headings were then combined into a single domain using the Boolean operator 'OR'. Searches were undertaken i) separately for each domain, ii) in combination with each other domain (using 'AND'), and lastly iii) in

combination with all other domains (using 'AND'). The original systematic review search undertaken for PRIMROSE did not identify any RCTs of statins that recruited people with SMI: however, the search did find four non-randomised studies (Ojala et al., 2008;Landry et al., 2008;Hanssens et al., 2007;De Hert M. et al., 2006) that were relevant in terms of subject area. These four studies helped validate how well my search strategy was performing and to further develop the search.

4.3.1.1 "Exploding" search terms

Comparison of the subject heading terms for the four non-randomised studies and my initial search strategy confirmed that my selection of subject headings was comprehensive in terms of subject matter, but also highlighted a need to capture articles that were indexed to lower level subheadings without being linked to the root subject heading. This problem was overcome by 'exploding' each subject heading term: for example one paper (Landry et al., 2008) was indexed to the term 'pravastatin', but not 'Hydroxymethylglutaryl-CoA Reductase Inhibitors'. Exploding the overarching subject heading term 'Hydroxymethylglutaryl-CoA Reductase Inhibitors' therefore enabled the search to capture articles indexed only to named statins.

4.3.1.2 Adding free text and wildcard terms

Although subject headings should ultimately be assigned to all papers in MedLine, PsycInfo, EMBASE and CINAHL, there is often a delay between the paper entering the database and being indexed. I therefore modified the strategy to include free-text search terms with the aim of capturing newer articles that had not yet been indexed. Wildcards - single or multiple letter variations or truncations (for example, "mani*" will retrieve all terms that start with "mani"; including mania and manic) - were included as free-text terms to further reduce the likelihood of missing relevant publications.

4.4 Searching for registered clinical trials

I searched the following trials registries for relevant articles:

- Cochrane Central Register of Controlled Trials (CENTRAL)
- International Standard RCT Number Register
- ClinicalTrials.gov (US National Institutes of Health service)
- UK National Institute for Health Research Register (NRR archive)
- UK Clinical Research Network study portfolio database (UKCRN)

These registries were searched using the terms: 1) schizophrenia AND statin; 2) bipolar AND statin; 3) “SMI” AND statin.

4.5 Updating the review

I updated the results sections of this review in September 2014 to capture information that had not been published at the time of the original literature search (in April 2013). Publications identified as a result of this update are outlined in section 6.

5 Screening literature and registered trials identified from the systematic review search

5.1 Literature search

The number of articles yielded by each stage of the searches in MedLine, PsychInfo, EMBASE, CINAHL and NHS Evidence is outlined in Table 5-1. The final searches conducted in MedLine, PsycInfo, CINAHL and EMBASE retrieved 41, 15 and 72 and 1779 hits, respectively.

The number of articles retrieved by NHS Evidence was large (820) and included a substantial volume of material that was not primary research (including clinical guidelines and reviews): I therefore decided (after seeking further guidance from the Information Scientist) to filter on information type to include only ‘primary research’. This decision is justified by the research question, which aims to identify evidence from RCTs or other study designs. After excluding articles that were not primary research, the search conducted in NHS Evidence yielded 56 articles.

Table 5-1: Numbers of articles retrieved by searching MedLine, PsychInfo, EMBASE, CINAHL and NHS Evidence

Domain/s	No. of articles retrieved (to 10th April 2013)				
	MedLine	**PsycInfo**	**Embase**	**CINAHL**	**NHS Evidence**
1)	3,160,683	77,844	4,221,556	414,566	53,663
2)	33,736	3,638	96,215	10,076	9,166
3)	252,098	151,892	399,620	34,258	11,373
1+2)	26,696	569	78,629	9,419	6,065
1+3)	24,099	4,933	2,918	2,923	5,043
2+3)	97	116	62,830	79	1,105
1+2+3)	41	15	1,799	72	820
FINAL					56*
No. unique references	1,965				

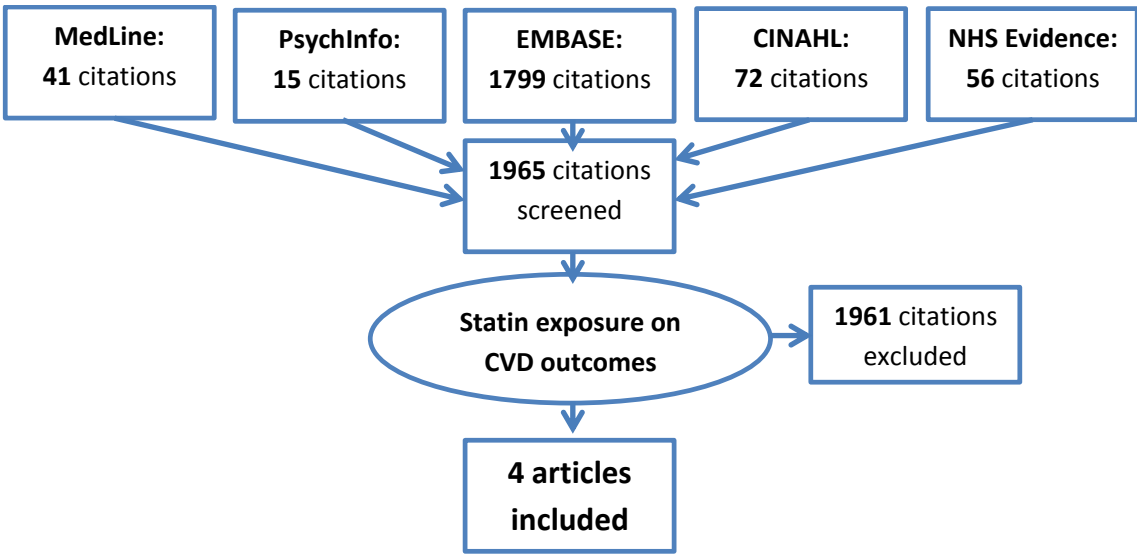
* 1 + 2 + 3 + information type ='primary research'

All references were imported into Reference Manager (version 12) and I identified duplicates (articles with the same title, authors and journal citation) by manual review of the database as the in-built duplicate search function was overly sensitive to minor differences in spelling and punctuation. A total of 1965 unique references were identified by searching MedLine, PsychInfo, EMBASE, CINAHL and NHS Evidence.

Two separate copies of the Reference Manager databases were used to independently screen and identify articles meeting the PICO criteria. The screening process was undertaken independently by myself and another researcher (George Salaminios Research Assistant, UCL Division of Psychiatry), and our selection of 'relevant' articles was compared to identify studies for inclusion in the review. We planned in advance to resolve any discrepancy in our selection of relevant trials through further review and discussion: in the event of non-resolution, a third reviewer would cast the deciding vote.

There were no RCTs evaluating the effectiveness of statins in people with SMI and only the four key papers (De Hert M. et al., 2006;Hanssens et al., 2007;Ojala et al., 2008;Landry et al., 2008) were identified as relevant. The screening process for the literature searches is shown in Figure 5-1: comparison of the independently assessed literature showed that there was total concordance between the reviewers.

Figure 5-1: PRISMA diagram of the results for the literature search citations



5.1.1.1 Cross-referencing the search results against the four key papers

As an additional check that the adapted search strategy was correctly specified, I crossed-referenced the results of each of the searches undertaken in the five databases with the four studies that had previously been identified (Table 5-2): all four studies were retrieved from MedLine and EMBASE when the three components of the research question were included as search terms. The search undertaken in PsycInfo yielded three of the four key references: the fourth reference (Landry *et al*.) was not captured because the keywords for this paper did not include 'statin' (or a synonym). Instead, this paper was indexed to the search term 'drug therapy', which presumably reflects the range of lipid-lowering medications investigated by the study. None of the key references were held in either CINAHL or NHS Evidence, and therefore could not be captured by these searches.

Table 5-2: The number of key references that were retrieved using each of the databases

Database	Number of key references retrieved
MedLine	4
PsycInfo	3*
Embase	4
CINAHL	N/A (key references were not available via CINAHL)
NHS Evidence	N/A (key references were not available via NHS evidence)

*Landry *et al*. was not retrieved because the keywords for this paper did not include statin (or a synonym)

5.2 Registered trials

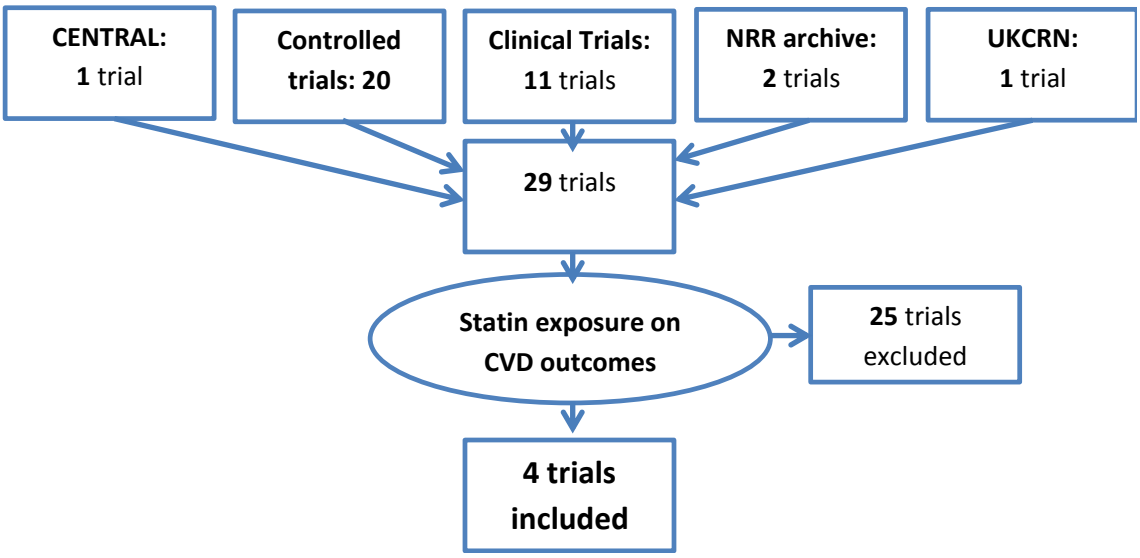
A total of 29 unique trials were identified: the number of trials captured by each of the trial registries is outlined in Table 5-3. The searches conducted were simplistic and, as the number of results retrieved was small, it was not necessary to apply additional filters or search terms.

Table 5-3: Numbers of trials retrieved by searching CENTRAL, Controlled trials, Clinical trials and NRR archive Trial Registries

Search terms	CENTRAL	Controlled trials	Clinical trials	NRR archive	UKCRN
schizophrenia AND statin	1	12	11	0	1
bipolar AND statin	0	9	2	0	1
“SMI” AND statin	0	5	0	5	1
Number of unique trials	1	20	11	2	1
Total unique trials	29				

Details of registered clinical trials were compiled into a spreadsheet and vetted against the PICO criteria for eligibility. The Principal Investigator (or other named primary contact) was contacted for all trials where the description appeared to be relevant or where the relevance was unclear. Investigators were asked for details of any publications or results, and also if they were aware of any other statins trials in people with SMI. The screening process for the trials registry searches is shown in Figure 5-2.

Figure 5-2: PRISMA diagram of the results for the trials registry citations



6 Results

6.1 Literature

The literature search identified four key references. Two of these papers (Hanssens et al., 2007;De Hert M. et al., 2006) were developed by the same team and some patients were included in the study population for both papers. A summary of the studies, results and an appraisal of their quality is outlined in Table 6-1 and Table 6-2, respectively, and discussed in greater depth in the following text. Key results from these studies are outlined in Table 6-3.

Table 6-1: Summary of published literature investigating the effectiveness of statins in people with SMI

Author	Study design and time period	Methods	Participants	Intervention/Exposure	Comparison	Outcomes	Follow up	Risk of bias
Landry (2008)	Single-arm retrospective cohort (time period not outlined)	Review of routinely collected clinical data including lipid levels. Changes in the lipid parameters recorded in individuals who had dyslipidaemia recorded after clozapine treatment: differences were assessed using a paired t-test.	9 adult outpatients and inpatients with hospital pharmacy records indicating concomitant use of clozapine (for schizophrenia) and lipid-lowering drugs. Lipid lowering drugs were initiated after clozapine use.	Lipid lowering medication (pravastatin, atorvastatin, fenofibrate, gemfibrozil or lovastatin)	None	Total cholesterol, LDL-C, HDL-C, triglyceride concentration	Variable: mean = 4.4 (±3.6) years	No comparison arm. Small sample size. Individuals with pre-existing CVD or a prior statin prescription were not excluded.
Landry (2008)	Single-arm retrospective cohort (time period not outlined)	Review of routinely collected clinical data including lipid levels. Changes in the lipid parameters recorded in individuals who had dyslipidaemia recorded before clozapine treatment: differences were assessed using a paired t-test.	9 adult outpatients and inpatients with hospital pharmacy records indicating concomitant use of clozapine (for schizophrenia) and lipid-lowering drugs. Lipid lowering drugs were initiated before clozapine use.	Lipid lowering medication (pravastatin, atorvastatin, fenofibrate, gemfibrozil or lovastatin)	None	Total cholesterol, LDL-C, HDL-C, triglyceride concentration	Variable: mean = 4.4 (±3.6) years	No comparison arm. Small sample size. Individuals with pre-existing CVD or a prior statin prescription were not excluded.

Author	Study design and time period	Methods	Participants	Intervention/Exposure	Comparison	Outcomes	Follow up	Risk of bias
Ojala (2008)	Single-arm retrospective cohort (1st January 2002 – 31st May 2004)	Review of hospital inpatient case notes including laboratory data from routine annual health screens. Differences in the lipid parameters recorded before and after statin treatment were assessed using a paired t-test.	28 adult inpatients at a Finnish state mental hospital who had continuous second generation antipsychotic use, used statins as sole lipid modifiers, and had available data on lipid profiles at baseline and follow up. Most patients (26 of 28) had a diagnosis of schizophrenia. 100% of participants were male.	Statin treatment (primarily atorvastatin)	None	Total cholesterol, LDL-C, HDL-C, triglyceride concentration	Variable: mean = 31 days (±10), range = 14-56 days	No comparison arm. Small sample size. Individuals with pre-existing CVD or a prior statin prescription were not explicitly excluded.

Author	Study design and time period	Methods	Participants	Intervention/Exposure	Comparison	Outcomes	Follow up	Risk of bias
Hanssens (2007)	Prospective cohort study (with no comparison group) (from November 2003)	All participants had a full fasting laboratory screen, clinical assessment, electrocardiogram and oral glucose tolerance test at three months before baseline, baseline (when statin therapy was initiated) and at three months. The study was naturalistic and did not randomise individuals. ANOVA was used to investigate changes in lipid concentration.	46 adult outpatients and inpatients at a Belgian hospital who had a schizophrenia or schizoaffective disorder diagnosis and were either stable on medication for >9 months or newly started on an antipsychotic. To be eligible, patients had to have a diagnosis of severe dyslipidaemia (according to SCORE criteria for low risk countries). 80% of participants were male.	Statin treatment (10mg rosuvastatin, atorvastatin and pravastatin) plus dietary advice at baseline	None	Total cholesterol, LDL-C, HDL-C, triglyceride concentration	3 months	No comparison arm. Small sample size. Individuals with pre-existing CVD or a prior statin prescription were not explicitly excluded.

Author	Study design and time period	Methods	Participants	Intervention/Exposure	Comparison	Outcomes	Follow up	Risk of bias
De Hert (2006)	Prospective cohort study (November 2003 – December 2005)	All participants had a full fasting laboratory screen, clinical assessment, electrocardiogram and oral glucose tolerance test at baseline and at three months. The study was naturalistic and did not randomise individuals. ANOVA was used to investigate changes in lipid concentration.	100 adult outpatients and inpatients at a Belgian hospital with a diagnosis of schizophrenia or schizoaffective disorder and were prescribed antipsychotics. To be eligible, patients had to have a diagnosis of severe dyslipidaemia (according to SCORE[1] criteria for low risk countries) and had to continue the same antipsychotic treatment. 78% of participants were male.	Rosuvastatin treatment plus dietary advice at baseline	No statin therapy plus dietary advice at baseline	Total cholesterol, LDL-C, HDL-C, triglyceride concentration	3 months	The mechanism for statin assignment prescribing is not reported. Relatively small sample size. Individuals with pre-existing CVD or a prior statin prescription were not explicitly excluded.

[1](Perk et al., 2012)

Table 6-2: Quality Assessment of literature retrieved through the search, using the CASP (Critical Appraisal Skills Programme) checklist for cohort studies

CASP question:	Landry	Ojala	Hanssens	De Hert
Did the study address a clearly focused issue?	Yes	Yes	Yes	Yes
Was the cohort recruited in an acceptable way?	?	Yes	Yes	Yes
Was the exposure accurately measured to minimise bias?	?	Yes	?	Yes
Was the outcome accurately measured to minimise bias?	Yes	Yes	Yes	Yes
Have the authors a) identified and b) accounted for all important confounding factors?	No (e.g. weight)	No (e.g. no adjustment for statin dose)	No (e.g. no multivariable adjustment)	No (e.g. no multivariable adjustment)
Was the follow-up of subjects complete and long enough?	?	No	No	No
What are the results of this study?	Reductions in average triglyceride and total cholesterol concentrations in both study groups	49% Reduction in LDL-C and 39% reduction in total cholesterol in individuals taking statins	46% Reduction in LDL-C and 37% reduction in total cholesterol in individuals taking statins	46% Reduction in LDL-C and 38% reduction in total cholesterol in individuals taking statins
How precise are the results?	95% CIs outlined in Table 6-3	95% CIs outlined in Table 6-3	95% CIs outlined in Table 6-3	95% CIs outlined in Table 6-3
Do you believe the results?	Direction of results is plausible, but confounders and small sample size may introduce bias	Confidence in the results is reduced by the lack of statin-free comparison	Confidence in the results is reduced by the lack of statin-free comparison	Direction of results is plausible, but confounders and small sample size may introduce bias
Can the results be applied to the local population?	No - hospital patients only	No – male prison population	No - rosuvastatin use only	No - rosuvastatin use only
Do the results fit with other available evidence?	Yes	Yes	Yes	Yes
What are the implications of this study for practice?	Lipid-lowering medication may be effective in individuals with prior antipsychotic use	Statins may be effective in individuals with SMI	Lipid-lowering medication may be effective in individuals with prior antipsychotic use	Lipid-lowering medication may be effective in individuals with SMI

Table 6-3: Summary of publications investigating the effectiveness of statins in people with SMI

First Author	Exposure	Parameter	Exposed (mmol/L ± 95% CI) N	Baseline	End	P	Diff (%)	Unexposed (mmol/L ± 95% CI) N	Baseline	End	p	Diff (%)	Total diff mmol/L	%	P value
Landry	Lipid lowering medication exposure after clozapine treatment	TG	9	4.30 ± 1.17	2.00 ± 1.04	0.001	-53	--					--		
		TC	9	6.60 ± 0.55	4.48 ± 0.65	0.001	-32								
		LDL-C	9	3.76 ± 0.84	3.05 ± 1.04	0.2	-19								
		HDL-C	9	0.78 ± 0.26	0.85 ± 0.21	0.5	9								
Landry	Lipid lowering medication exposure before clozapine treatment	TG	9	3.33 ± 1.20	2.18 ± 1.20	0.03	-35	--					--		
		TC	9	6.43 ± 1.13	4.77 ± 1.66	0.018	-25								
		LDL-C	9	4.21 ± 0.31	2.01 ± 0.24	0.002	-52								
		HDL-C	9	1.08 ± 0.46	1.25 ± 0.73	0.34	16								
Ojala	Statin (exposed) plus continuous second generation antipsychotic use	TG	28	3.4	2.6	<0.001	-23	--					--		
		TC	28	6.2	4	<0.001	-35								
		LDL-C	19	4.3	2.2	<0.001	-49								
		HDL-C	28	0.8	0.8	0.575	0								
De Hert	10 mg daily rosuvastatin (exposed) or no statin (unexposed)	TG	52	3.09 ± 1.60[a]	1.85 ± 0.79[a]	0.011	-40	48	2.56 ± 0.55[a]	3.15 ± 0.69[a]	<0.001	23	-1.83[a]	-56	<0.001
		TC	52	6.82 ± 0.84[a]	4.22 ± 0.54[a]	<0.001	-38	48	6.19 ± 0.47[a]	6.52 ± 0.51[a]	0.001	9	-2.93[a]	-35	<0.001
		LDL-C	52	4.25 ± 0.51[a]	2.30 ± 0.35[a]	<0.001	-46	48	3.82 ± 0.56[a]	3.90 ± 0.52[a]	--	3	-2.03[a]	-49	<0.001
		HDL-C	52	1.13 ± 0.18[a]	1.18 ± 0.20[a]	"NS"	4	48	1.25 ± 0.02[a]	1.17 ± 0.18[a]	--	-6	0.13[a]	10	0.02
Hanssens	10 mg daily Rosuvastatin	TG	46	3.18 ± 3.07[a]	1.87 ± 1.55[a]	0.005	-41	--					--		
		TC	46	6.81 ± 1.62[a]	4.27 ± 1.03[a]	<0.001	-37								
		LDL-C	46	4.19 ± 0.99[a]	2.25 ± 0.65[a]	<0.001	-46								
		HDL-C	46	1.15 ± 0.35[a]	1.20 ± 0.40[a]	0.182	4								
Vincenzi*	40 mg daily pravastatin (exposed) versus placebo (unexposed)	TG	30	1.97 ± 0.64[a]	1.52 ± 0.37[a]	--	-23	30	1.64 ± 0.42[a]	1.53 ± 0.33[a]	--	-7	-0.34[a]	-16	0.3
		TC	30	4.65 ± 0.31[a]	4.17 ± 0.32[a]	--	-10	30	4.62 ± 0.27[a]	4.63 ± 0.26[a]	--	0.2	-0.49[a]	-11	0.001
		LDL-C	30	2.75 ± 0.26[a]	2.21 ± 0.24[a]	--	-20	30	2.70 ± 0.21[a]	2.70 ± 0.18[a]	--	0.2	-0.55[a]	-20	<0.001
		HDL-C	30	1.25 ± 0.12[a]	1.24 ± 0.11[a]	--	-0.4	30	1.18 ± 0.09[a]	1.23 ± 0.10[a]	--	4	-0.06[a]	-5	0.91

[a]Units converted from mg/dL to mmol/L (assuming conversion factors of 38.6 and 88.5 for cholesterol and triglycerides, respectively)
TG; triglyerides, TC; total cholesterol, LDL-C; low density lipoprotein-cholesterol, HDL-C; high density lipoprotein cholesterol
Diff; percentage difference between baseline and study end. Total diff; percentage difference between exposed and unexposed participants.
* Publication identified through an update to this review in September 2014.

6.1.1 Landry et al. (2008)

This study was a retrospective cohort that aimed to document the clinical efficacy of lipid-lowering medications on hyperlipidaemia in Canadian hospital inpatients and outpatients concomitantly treated with clozapine. The study examined the impact of lipid-lowering medication in people who developed dyslipidaemia either before or after clozapine use, making prior clozapine use the exposure of interest. The study outcomes were cholesterol (total, LDL-C and HDL-C fractions) and triglyceride concentrations, which were measured over time. The authors sourced the study population retrospectively from pharmacy records for patients with clozapine and lipid-lowering medication use. These records included data on a range of relevant factors such as age, gender, type and duration of psychiatric and medical diagnoses, and laboratory results over the course of several years. It is unclear from the publication (a letter rather than a full research paper) whether the population included all eligible patients or whether any other exclusion criteria were applied. In addition, some important information on factors such as weight, was not readily available and was not included the analysis.

The study examined 18 patients with concomitant use of clozapine and a lipid-lowering medication; changes in lipid levels were evaluated in two equally sized patient groups: those with prior exposure to clozapine and those initiating clozapine prior to lipid-lowering medication. In the first of these groups, a patient's lipid levels were compared at two time points: before the introduction of clozapine and at the last available time-point where both lipid-lowering medication and clozapine were prescribed (average duration of follow-up of 4.4 years (±3.6 years)). By contrast, the second group, who were existing users of clozapine, compared lipid measurements taken before the introduction of the lipid-lowering medication with the last available time-point where both lipid-lowering medication and clozapine were prescribed (average follow-up time was not outlined in the publication). The prescribed lipid-lowering medications were: pravastatin (5 patients), atorvastatin (4 patients), fenofibrate (3 patients), gemfibrozil (3 patients) and lovastatin (3 patients). A total of two patients stopped taking lipid-lowering medication during the study period.

The key results were statistically significant reductions in average triglyceride and total cholesterol concentrations of 4.3 ±1.17 to 2.0 ±1.04mmol/L (p=0.001) and 6.60 ±0.55 to 4.48 ±0.65mmol/L (p=0.001), respectively for the group initiating lipid-lowering medication after clozapine. A similar trend was also observed in the patient group initiating lipid-lowering medication prior to clozapine treatment; triglycerides and total

cholesterol were reduced from 3.33 ±1.2 to 2.18 ±1.2mmol/L (p=0.03) and 6.43 ±1.13 to 4.77 ±1.66mmol/L (p=0.018), respectively. The level of variation between patients was large and ranged from reductions of 4-81% for triglycerides and 1-48% for total cholesterol. The two study groups differed slightly in terms of the reduction in LDL-C, which was statistically significant for patients without prior exposure to clozapine (4.21±0.31 to 2.01±0.24mmol/L, p=0.002), but not for group with prior exposure (3.76±0.84 to 3.05±1.04mmol/L, p=0.2). HDL-C levels were slightly increased in both groups, but not to significantly different levels (p>0.3 in both cases).

This study aimed to answer a different research question to mine, with the author's choice of research question implying that statin treatment is assumed to be effective in people with SMI. Consequently, the study does not include a comparison group that is unexposed to statins, thus making it difficult to comment on the effectiveness of statins. However, the average triglyceride and total cholesterol concentrations of patients in both clozapine groups (naïve or prior exposure) were lowered during the course of the study, which is compatible with the hypothesis that statins are effective in reducing CVD risk in people with SMI. It would be incorrect to draw any stronger conclusions from this study because of the lack of a control group, the small number of subjects and because the follow-up period was relatively long providing the opportunity for other factors (such as dietary interventions) to affect lipid levels.

6.1.2 Ojala et al. (2008)

This retrospective cohort study aimed to evaluate the effect of statins on dyslipidaemia amongst psychiatric inpatients taking second generation antipsychotics in a Finnish state mental hospital between January 2002 and May 2004. The authors sampled all consecutive patients receiving continuous second generation antipsychotic treatment who also had a statin as their sole lipid-lowering medication and who had obtainable lipid profiles at baseline and follow-up. Cholesterol (total, LDL-C and HDL-C fractions) and triglyceride concentrations were the outcomes of interest, which were measured during statin treatment (at 14-59 days after the study start).

The population selected for this study was specialised: all patients were hospitalised with a court ruling of insanity following criminal activity; all study subjects were male. The authors report reductions of 49% (2.1 ±0.6mmol/L, 95%CI 1.8-2.4) for LDL-C cholesterol and 36% (2.2 ±0.8mmol/L; 95%CI 1.9-2.5) for total cholesterol, which they state is in-line with results obtained through clinical trials in the general population. However, no attempts were made to statistically adjust for the possible impact of a

range of important confounders or factors such as the statin type and dosage, although this information was measured and made available in the text of the publication.

The major limitation of this study, with respect to my research question, was the lack of a comparison arm without statin treatment; it is therefore difficult to conclude that the reduction in lipid levels results from statin medication alone. However, all 28 patients included in the study had reductions in total and LDL-C, which could be compatible with statins being effective in people with SMI. In addition, the nature of the high security setting of the study is likely to impact upon the demographics (e.g. women were not represented in this group), lifestyle factors and medication adherence of the study population and the results may therefore not be generalizable to other settings.

6.1.3 Hanssens et al. (2007)

This study was a prospective cohort (without a non-statin comparison group) that aimed to evaluate the effects of treatment of severe hyperlipidaemia with statins in inpatients and outpatients with schizophrenia at a Belgian hospital. All consecutive patients with schizophrenia or schizoaffective disorder were enrolled prospectively into the study from November 2003 to develop two cohorts, which differed in terms of previous antipsychotic exposure. The first cohort included patients who had been stable on antipsychotic medication for 9 months or more, and the second cohort included patients who were recently started antipsychotic medication. Patients within these two cohorts were eligible for inclusion in the study if they had severe dyslipidaemia that met European guidelines (SCORE) for low risk countries (Conroy et al., 2003). All patients with dyslipidaemia were given dietary advice at the start of follow-up. All patients were initiated with lipid-lowering medication at baseline with 41 (89%) prescribed 10mg rosuvastatin, four patients atorvastatin or pravastatin, and one patient fenofibrate.

The study recorded full metabolic screening including oral glucose tolerance testing at three months before baseline, baseline (when statins were initiated) and three months after baseline. Analysis of variance with repeated measures was used to assess the association between statin therapy and lipid levels.

Of the 200 patients stable on antipsychotic treatment, more than one quarter (27%) had severe dyslipidaemia, compared to 15% of the 65 patients that had recently started antipsychotic medication. It was not possible to undertake metabolic re-evaluation at 3 months for 17 patients, leaving a total of 46 study participants. These individuals were predominantly male (80%) and virtually all (98%) were white Belgians. The average

age of participants was 39.5 years (standard deviation 9.8 years) with duration of illness being 13.4 years (standard deviation 7.8 years). A total of 78% of patients had a diagnosis of schizophrenia, with the remaining 22% schizoaffective disorder. Over one fifth of patients (21.7%) were treated with an antipsychotic for less than 3 months, with the majority (86.9%) being second generation drugs (olanzapine and clozapine accounted for over half of all antipsychotic usage). Polypharmacy was common with almost 60% of patients taking antidepressants and 46% taking somatic medication such as antihypertensives. There were significant decreases in total cholesterol (37% decrease), triglyceride (41% decrease) and LDL-C (46% decrease) levels after 3 months of statin therapy. Non-significant increases in HDL-C were also observed during the study period (p=0.18). Statin treatment was stopped in one patient who developed abnormally high levels of creatine kinase after five months of statin therapy. No other negative impacts of statins were reported, and there was no evidence of changes in weight, waist circumference or fasting glucose measurements.

Although this study has several strengths, the results are of limited value in terms of estimating the effectiveness of statins in people with SMI because there was no comparison arm. However, it is reassuring that this larger study mirrors results published by Ojala and Landry, which outline significant reductions in triglycerides, total and LDL-C. Whilst this study does not provide robust evidence to demonstrate the effectiveness of statins in people with SMI, the results are compatible with the hypothesis that statins are effective in lowering total cholesterol, LDL-C cholesterol and triglycerides.

6.1.4 De Hert et al. (2006)

This study was a prospective cohort that aimed to evaluate the effectiveness of rosuvastatin in lowering lipid concentrations in individuals with schizophrenia and schizoaffective disorder. The study population outlined in this paper overlaps with the previous paper led by Hanssens: however, the extent of overlap is not reported. All consecutive hospital inpatients and outpatients with a diagnosis of schizophrenia or schizoaffective disorder were prospectively invited to participate in extensive screening and follow-up of their metabolic parameters; the study started in November 2003 and available data extending to the period December 2005 were included in the paper. The study sample comprised 100 patients receiving antipsychotic treatment who had severe dyslipidaemia (meeting SCORE criteria (Conroy et al., 2003)). Treatment with rosuvastatin was initiated in 52 patients, who were compared with 48 patients who did not receive a statin. Although the method of treatment allocation is not detailed in the paper, further communication with the authors has confirmed that patients were

enrolled into the comparison group if they had laboratory parameters that could have warranted use of a statin, but did not receive one during the study period (De Hert, M. Personal Communication 2/8/2013). Both patient groups received dietary advice at the start of the study. A full metabolic screen was undertaken three months before baseline (and the start of statin treatment in the intervention arm), and then three months after baseline. The authors used analysis of variance with repeated measures to assess the association between statin therapy and lipid levels.

A total of 100 patients participated in the study; 78% were male and 98% were white Belgians. The average age was 38.5 (standard deviation 10.1) years and the mean duration of illness was 13.1 (standard deviation 9.6) years. A total of 80% of patients had a diagnosis of schizophrenia with the remaining being diagnosed with schizoaffective disorder. The two study arms were balanced at baseline in terms of demographic variables, treatment regimen or the proportion of patients with abnormal lipid parameters. All participants received antipsychotic treatment during the study but the duration of continuous treatment with the same agent was less than three months for over one quarter (28%) of patients. The majority of patients (92%) used second generation antipsychotics with 16% of patients taking more than one type of antipsychotic at baseline. Olanzapine (30%), risperidone (26%) and clozapine (24%) were the most frequently prescribed antipsychotics, and concomitant use of antidepressant and somatic medications was common (41% and 48% of patients, respectively).

During the three month period between the study start date and baseline, the authors reported a worsening of the lipid profiles of participants in both arms of the study. These changes were statistically significant for total cholesterol, LDL-C and triglyceride levels ($p \leq 0.04$ in all instances). At the end of the study period the proportion of patients with abnormal lipid profiles had decreased in the statin group and increased in the control group, and there differences between the two groups was found to be strongly statistically significant ($p \leq 0.0001$ in all instances) for all parameters except HDL-C. In the statin arm of the study, the changes from baseline were greatest for LDL-C (45.9% reductions), triglycerides (41.1% reductions) and total cholesterol (38.1%). There were no statistically significant effects of statin therapy on other parameters measured by the study team, although a non-significant (the authors do not report a p-value) increase in weight and waist circumference was observed in both groups. Statin treatment was stopped in one patient who developed abnormally high levels of creatine kinase.

This paper suggests that clinically relevant reductions in lipid levels are feasible with rosuvastatin over a 12 week duration for people with a diagnosis of SMI. However,

rosuvastatin would be expected to achieve greater reductions in lipids than statins such as simvastatin or atorvastatin (Law et al., 2003), which are more widely used for first line treatment in the UK (National Institute for Health and Clinical Excellence, 2014b). A major limitation of this study is that measured and unmeasured confounding factors may not be equally distributed across both arms of the study because patients were not randomised to each arm. The other limitations of this study are that the number of patients enrolled is moderately small (n=100) and conducted at only one site. Furthermore, the analysis was not adjusted for potential confounders, although the authors did not find any evidence of a difference between the groups in terms of the distribution of measured demographic and clinical characteristics at baseline.

6.2 Registered trials

A total of four relevant studies were identified through trials registries and a summary of these studies is outlined in Table 6-4. The studies identified were:

1. Add-on simvastatin in schizophrenia trial, Gross (2008)
2. Cardio risk of acute schizophrenia olanzapine Duke (CRASOD), McEvoy (2008)
3. Effects of Pravastatin on cholesterol, inflammation and cognition in schizophrenia, Henderson (2010)
4. Improving symptoms of schizophrenia and schizoaffective disorder by supplementing medications with pravastatin, Brar (2005)

Two trials (Gross (2008) and McEvoy (2008)) were terminated early due to recruitment problems (with no available results). A third trial (Brar (2005)) was completed but the Principal Investigator has reported a decision not to publish because the results were negative (Brar, J., personal communication, 23/4/2012) and was not able to provide me with data for the study.

The remaining trial (Henderson (2010)) has been completed and the results are incorporated into this review Table 6-3 (previously) and Table 6-5 (Vincenzi et al., 2014). However, the publication was not identified in the initial literature search because it was undertaken before the manuscript was published. A quality appraisal of the trial is outlined in Table 6-6. The study examined the impact of randomly assigning a 12 week course of 40mg pravastatin daily or placebo to 60 adult outpatients with a diagnosis of schizophrenia or schizoaffective disorder from a single centre in the United States of America. The authors reported statistically significant decreases in LDL-C and total cholesterol (but not HDL-C or triglycerides) at 6 and 12 weeks after baseline.

At 6 weeks after baseline total cholesterol and LDL-C were each lowered by an additional 0.8mmol/L in statin users (reductions of 18% and 28%, respectively) (Vincenzi et al., 2014). Between baseline and 12 weeks total cholesterol was reduced by 0.5mmol/L and LDL-C lowered by 0.6mmol/L in the statin user arm relative to the placebo group. Although these absolute differences are modest, the relative decreases of 11% and 20% are substantial and reflect relatively low baseline lipid concentrations. The mechanism for randomisation and details of any measures to ensure blinding were not reported, however, the randomised design and placebo-control group means that the internal validity of this study is likely to be high. Conversely, the modest sample size and recruitment from a single site may limit the generalizability of the results.

Table 6-4: Summary of registered trials investigating the effectiveness of statins in people with SMI

Title of trial	Objective	Population	Intervention	Comparison	Relevant Outcome	Target Sample size	Status	Sponsors
Add-on Simvastatin in Schizophrenia Trial	To determine whether simvastatin is effective in the treatment of symptoms of schizophrenia	Individuals with schizophrenia aged 18-70 years	Simvastatin	Treatment as usual	Cholesterol concentration at 12 weeks	Not known	Terminated due to slow recruitment (no results available)	New York State Psychiatric Institute, Stanley Medical Research Institute, Sheba Medical Centre, Merck Sharp & Dohme Corp.
Cardio Risk of Acute Schizophrenia Olanzapine Duke (CRASOD)	Four arm trial to determine whether metformin and simvastatin (either separately or in combination) are effective in reducing CVD risk during olanzapine treatment	Individuals with schizophrenia aged 18-60 years	Metformin and/or simvastatin	Treatment as usual	Non-HDL-C at 28 days	120 patients	Study withdrawn due to lack of funding	Duke University, North Carolina

Title of trial	Objective	Population	Intervention	Comparison	Relevant Outcome	Target Sample size	Status	Sponsors
Effects of Pravastatin on Cholesterol, Inflammation and Cognition in Schizophrenia	To determine whether pravastatin can lower cholesterol, decrease inflammation and improve cognition in patients with schizophrenia	Individuals with schizophrenia or schizoaffective disorder aged 18-68 years	Pravastatin	Placebo	LDL-C at 6 and 12 weeks	60 patients	Published (Vincenzi, 2014)	Massachusetts General Hospital, Stanley Medical Research Institute, North Suffolk Mental Health Association
Improving Symptoms of Schizophrenia and Schizoaffective Disorder by Supplementing Medications With Pravastatin	To determine whether the addition of pravastatin to usual care improves symptoms of schizophrenia	Individuals with schizophrenia or schizoaffective disorder aged 18-65 years	Pravastatin	Treatment as usual	Lipid enzyme levels	Not known	Study lead reported that the results were negative and that they will not be published	University of Pittsburgh, Stanley Medical Research Institute

Table 6-5: Summary of trials (with results) investigating the effectiveness of statins in people with SMI

Author	Study design and time period	Methods	Participants	Intervention/Exposure	Comparison	Outcomes	Follow up	Risk of bias
Vincenzi (2014)	Randomised placebo-controlled pilot study (time period not outlined)	Individuals were randomised to receive either a 12-week supply of pravastatin (40mg/day) or placebo. Physical and mental health indicators (weight, waist measurement, lipids, glucose, C-reactive protein, psychopathology and cognition) were measured at baseline, 6 and 12 weeks.	60 adult outpatients with a diagnosis of schizophrenia or schizoaffective disorder recruited from the Freedom Trail Clinic at the Erich Lindemann Mental Health Centre (Massachusetts, USA). Subjects were not eligible to participate if they did not comply with their psychiatric drug regimen, could not provide informed consent or had health conditions including severe CVD, current alcohol or substance abuse, diabetes requiring insulin treatment or were using anti-inflammatory drugs.	40mg pravastatin treatment daily for 12 weeks	Placebo	LDL-C, HDL-C, triglycerides, total cholesterol, weight, BMI, waist circumference, markers of glucose metabolism, inflammation, cognition and psychopathology	6 and 12 weeks	Randomisation process not described. Possible selection bias and loss to follow up. Moderate sample size.

Table 6-6: Quality Assessment of literature retrieved through the systematic search, using the CASP (Critical Appraisal Skills Programme) checklist for RCTs

CASP question:	Vincenzi
Did the trial address a clearly focused issue?	Yes
Was the assignment of patients to treatments randomised?	Yes, although the randomisation process is not described
Were patients, health workers and study personnel blinded?	Not known
Were the groups similar at the start of the trial?	Yes
Aside from the experimental intervention, were the groups treated equally?	Yes
Were all of the patients who entered the trial properly accounted for at its conclusion?	Yes
How large was the treatment effect?	20% reduction in LDL-C and 18% reduction in total cholesterol in individuals taking statins over a 12 week period
How precise was the estimate of the treatment effect?	Precise
Can the results be applied in your context?	Yes
Were all the clinically important outcomes considered?	Yes
Are the benefits worth the harms and costs?	Not known

7 Discussion

7.1 Key findings

This systematic review identified a single small RCT seeking to evaluate the effectiveness of statins in people with SMI, which found that a 12 week course of pravastatin significantly lowered total cholesterol and LDL-C compared to placebo. The search also identified a number of trials that were terminated due to recruitment problems, which suggests that operating a statins trial in patients with SMI can be challenging. At least one study was not published due to negative findings, which might result in publication bias. I assessed evidence from non-randomised studies and identified four relevant studies. However, only one study compared patients who received statin therapy to patients who did not: this study provided some evidence that statins are effective in people with SMI, but was limited by non-random allocation into study groups and lack of adjustment for confounders, the choice of statin (rosuvastatin), small sample size, the single site recruitment, and a relatively short duration of follow-up.

The study authored by Vincenzi is the first randomised and placebo-controlled study examining statin prescribing in individuals with SMI and the results are therefore important. However, this study is a pilot, has a modest sample size, no evidence of blinding, and a relatively short duration of follow up. At six weeks the study identified a decrease in LDL-C of 28%, which is on a par with national guidance that attributes decreases of 29% to 40mg pravastatin (Joint Formulary Committee, 2012). However, the results from Vincenzi's study suggest that by 12 weeks the decrease in LDL-C was reduced to 20%, which raises concerns about the long-term effectiveness of statin therapy on lipid modification. Such findings could be compatible with declining statin medication adherence between 6 and 12 weeks after baseline; although estimates of adherence were not reported by the authors. By contrast, the study by De Hert indicated that rosuvastatin may result in larger absolute and relative reductions in lipid concentrations in people with SMI. However, although covariates measured at baseline did not differ between comparison arms within the study, the mechanism determining statin prescribing was not made explicit and the study arms could therefore differ with respect to unmeasured confounding. Individuals with SMI who received 10mg rosuvastatin had a 49% decrease in LDL-C relative to untreated individuals, which is similar to the 43% decrease in LDL-C observed in RCTs examining individuals without mental illness (De Hert M. et al., 2006;Law et al., 2003).

Of the four non-randomised studies that were identified through the search, all were limited by relatively small sample sizes, and three included no statin unexposed comparison arm. Despite these limitations, the level of concordance between study estimates is striking: total cholesterol was reduced in all groups that were prescribed a statin by 25-38%, LDL-C by 46-52% (except in the clozapine naïve arm of the Landry study, which was reduced by 19%), triglycerides by 35-53% and levels of HDL-C were increased by 4.3-16%. However, these estimates must be treated with caution as there is potential for residual confounding and the sample size was generally small, which leaves these studies vulnerable to chance findings. Furthermore, it was not possible to calculate 95% CIs for all of these estimates because the standard error of the difference in lipid concentration between baseline and the study end were not reported. The effect estimates from these studies have not been combined because each study selected different patient groups, which may not respond in the same way to statin therapy. In addition, the overlap between the studies authored by De Hert and Hanssens, makes combining these estimates as independent observations inappropriate.

The key finding of this review is the lack of evidence on the long-term effectiveness of statins in people SMI. Although there is some evidence of lipid modification with pravastatin and rosuvastatin therapy there is a lack of information on statins (such as atorvastatin) which are most commonly prescribed for primary prevention of CVD in the UK. Furthermore, it is unclear how reductions in lipid concentrations over a three month period may translate into long term prevention of CVD events in people with SMI, and some suggestion that benefits seen may reduce over time, perhaps due to problems with adherence. Thus there is a gap in the evidence-base for assessing the effectiveness of statins in people with SMI, which has important implications for clinical and cost-effective CVD prevention in this patient group.

7.2 Evaluation of search methodology

I aimed to identify studies that investigated the effectiveness of statins on CVD risk in people with SMI. My search strategy incorporated a comprehensive set of subject headings and free text terms that were grounded in the domains of a clear and focussed research question. The resulting strategy was executed in a broad and complementary set of scientific, clinical and trials data sources with each of the search terms tailored to fit the indexing system of each database.

I developed the search strategy by cross-referencing subject headings derived from the research question against terms indexed to four studies that were previously identified

as relevant, which helped to gauge whether the search strategies were working correctly. Further quality checks were undertaken by investigating which of the four studies were captured in each search and establishing (where relevant) why a particular reference was not included.

The combined results from the search included all four of the non-randomised studies, suggesting that the criteria were appropriate. However, not all of the individual database searches included all four of the key studies. For example the Landry study was not captured in the search executed in PsycInfo, and further investigation established that the paper was indexed to a term for “Drug Therapy” rather than “statin” (or a synonym). In light of this, I evaluated four possible options; 1) include ‘drug therapy’ as a key word in the statins domain of the research question, 2) merging the domains 1 and 2 (CVD risk and statins) into a single domain, 3) including “lipid-lowering medications”, which was the only statin equivalent term in the title of the paper as a free text term or 4) leaving the strategy in its current form. I tested the impact on the results of applying options 1 or 2 and established that with either search conducted in PsychInfo, approximately 2000 additional results would be obtained, which was not pragmatic given the available resources. Option 3 was successful in finding the Landry study in the search, however, the free text term was extremely specific and inclusion of this term in the search seemed illogical, particularly given that it did not result in any of the other key articles being retrieved by the search. I therefore opted to leave the search in its current form. This decision may have resulted in missing some studies of relevance: however, it is unlikely that any randomised studies would have been missed because trials registries were also searched separately.

7.3 Implications for this thesis regarding the effectiveness of statins for prevention of CVD in people with SMI

This systematic review examined the effectiveness of statins for primary prevention of CVD amongst people with SMI and did not identify any information on CVD events, mortality or long term statin use in people with SMI. However, two small studies provide some limited evidence that statin therapy may be associated with significant reductions in total cholesterol (relative decreases of 11% and 35% for pravastatin and rosuvastatin, respectively) and LDL-C (relative decreases of 20% and 49% for pravastatin and rosuvastatin, respectively) over 12 weeks in 60-100 individuals with SMI. In addition, several RCTs have failed to run to completion due to recruitment problems. These findings suggest that a large scale study to evaluate the long term impact of statin prescribing, particularly on CVD outcomes, is needed.

Chapter 3 : Exploring the Effectiveness of Statins in Primary Care: Description of THIN Data and Quality

1 Chapter content

The previous chapter evaluated the evidence-base for statin prescribing for primary prevention of cardiovascular disease (CVD) in people with severe mental illness (SMI) and highlighted the need for research on long term statin use and estimates of the impact on CVD events and mortality. This chapter provides the justification for using data from The Health Improvement Network (THIN) to explore the real-world effectiveness of statins in people with SMI. The first part of this chapter outlines the requisite features of a data source for examining this research question and the rationale for selecting an observational study design over experimental options. The subsequent parts of the chapter focus on the data source and outline the mode of data capture as well as case definitions for the research question. The final part of the chapter considers data quality, including both the ascertainment and accuracy with which the population, intervention, comparison group and outcome for this research question can be identified.

2 Requisite features of a data source to investigate the effectiveness of statins on CVD events in people with SMI

Investigating the effectiveness of statins on CVD events in people with SMI requires a dataset which meets a variety of standards including: providing accurate information on a sufficient number and rate of CVD events, and availability of minimum set of variables including mental health diagnoses, the presence and timing of statin exposure and CVD events. To provide an indication of the necessary scale, the most recent Cochrane systematic review of statins for the primary prevention of CVD meta-analysed data on 56,934 individuals from 19 randomised controlled trials (RCTs) with a minimum duration of 18 months (Taylor et al., 2013). In addition, any study must have a high level of internal and external validity in order to obtain unbiased estimates that are representative of people with SMI diagnoses who would be eligible for treatment with a statin.

2.1 Advantages and disadvantages of observational data relative to data from experimental study designs for investigating effectiveness

"At its best a trial shows what can be accomplished with a medicine under careful observation and certain restricted conditions. The same results will not invariably or necessarily be observed when the medicine passes into general use."

Austin Bradford Hill, 1984 (Horton, 2000)

A randomised study design is usually considered the gold standard of evidence for evaluating the optimal impact - and thereby reflecting efficacy (The Cochrane Collaboration, 2015) - of one treatment over another; including no treatment. This is because randomisation ensures that treatment allocation is not associated with baseline characteristics. However, large and long-running randomised studies are extremely expensive, can be vulnerable to selection bias and may apply eligibility criteria that result in a study population that does not reflect the clinical population of interest (Gilbody et al., 2002). In the case of statins RCTs, many studies have excluded people who were perceived as being less likely to comply with treatment: but in reality these individuals may form part of the target patient group (Beishuizen et al., 2005;Nakamura et al., 2006;Knopp et al., 2006;Baldassarre et al., 2000). This issue is demonstrated by the exclusion of those with mental illness from many of the major statin trials, as described in Chapter 2 section 2.2 earlier.

Non-participation in psychiatric (and non-psychiatric) trials also can result in selecting a study population that is not representative of the target group: non-participation is associated with poorer physical and mental health (Haapea et al., 2007) and differences in attitudes to health (Woodall et al., 2011). The PRIMROSE (Chapter 1, section 7) trial is an ongoing cluster-randomised trial of usual care versus a tailored intervention package that aims to increase physical medication adherence and promote lifestyle modification amongst people with SMI. A number of randomised studies outlined in the previous chapter (Chapter 2 section 6.2) were terminated due to recruitment issues; thereby demonstrating the difficulties of recruitment. Despite employing a range of service-user led initiatives to increase patient engagement, recruitment has also been a challenge for PRIMROSE and, on average, more than 12 individuals were approached for every participant who was enrolled during the early waves of recruitment (Burton A., Personal Communication, 21/5/2015). There were two main drivers at work: a high rate of non-participation and - amongst individuals who were willing to participate - the proportion who met the eligibility requirements (cholesterol >5mmol/L plus one of: diabetes, body mass index (BMI) >30kg/m^2, current

smoker or hypertension) was lower than anticipated. One possible explanation for these factors is that people who were willing to participate in the study may have had both a better relationship with their General Practitioner (GP) and had better management of CVD risk relative to non-participants.

Observational data sources using routinely collected data (such as GP records) may be less prone to selection bias than trials because such systems often work on an opt-out basis and do not require formal consent. However, the comparability of treatment groups in observational studies may be compromised when the exposure is not randomly assigned, which will bias the results if confounding is not adequately controlled. There are methods that can help to reduce bias in observational studies of effectiveness: a detailed discussion of these factors is outlined in the next chapter with reference to studies investigating statins (Smeeth et al., 2009;Danaei et al., 2013;Hippisley-Cox and Coupland, 2010). Given the potential for RCTs to produce estimates of effectiveness (but not efficacy) that are skewed by selection bias, the vast time and cost implications of such studies and the difficulties in recruitment seen in several studies in my systematic review of registered trials (Chapter 2 section 6.2), there is a strong argument for using observational data for producing the first estimates of the effectiveness of statins for primary prevention of CVD in people with SMI.

2.2 Primary care databases in the UK

This section of the chapter justifies the use of primary care data for investigating statin prescribing to individuals with SMI in terms of size, availability and data content and describes the scope of available data sources for the United Kingdom (UK).

The provision of physical healthcare to individuals with SMI has been flagged as an area of priority within UK primary care (National Institute for Health and Clinical Excellence, 2012). Each GP surgery maintains a register of all individuals with SMI and is financially incentivised to offer these individuals an annual physical health screen to guide appropriate intervention (lifestyle modification, preventative medication and/or continued monitoring) (National Institute for Health and Clinical Excellence, 2012).

Several large UK primary care data sources are available including the Clinical Practice Research Datalink (CPRD), THIN and QResearch (Gnani and Majeed, 2006). CPRD and THIN are the modern-day descendants of the Value Added Information Medical Products (VAMP) database, which was first set up in 1987. The original business model for the VAMP was to install computer systems and practice management software in GP offices across the UK with the intention of supporting both

administration and research: the offer of free software (at an estimated value of £25,000) incentivised practices to share anonymised data with the company (Garcia Rodriguez and Perez, 1998).

Since inception, the ownership and name for the VAMP have changed, but the mechanism for data capture continues through the roll-out of Vision software, which is used by both the CPRD and THIN. There remains an overlap of about 60% of the GP surgeries contributing data to both the CPRD and THIN (Cai et al., 2012;Carbonari et al., 2015), whereas QResearch obtains data from practices using different software (EMIS) (Ogdie et al., 2012). Several studies assessing the development and performance of clinical risk scores across the three databases have reported a high level of similarity; suggesting that the research implications of selecting one database over another may be modest (Collins and Altman, 2009;Collins and Altman, 2010;Collins and Altman, 2012;Reeves et al., 2014;Lewis et al., 2007).

THIN will be the data source for this research. A full licence is available via the Research Department of Primary Care and Population Health, UCL and a range of existing work on SMI (Petersen et al., 2014;McCrea et al., 2015;Osborn et al., 2011;Hayes et al., 2011;Hardoon et al., 2013;Osborn et al., 2013) and/or CVD risk (Garcia Rodriguez et al., 2000;Ogdie et al., 2015;Walters et al., 2014;de la Iglesia et al., 2011;Gunathilake et al., 2010) has used this data source.

3 THIN database

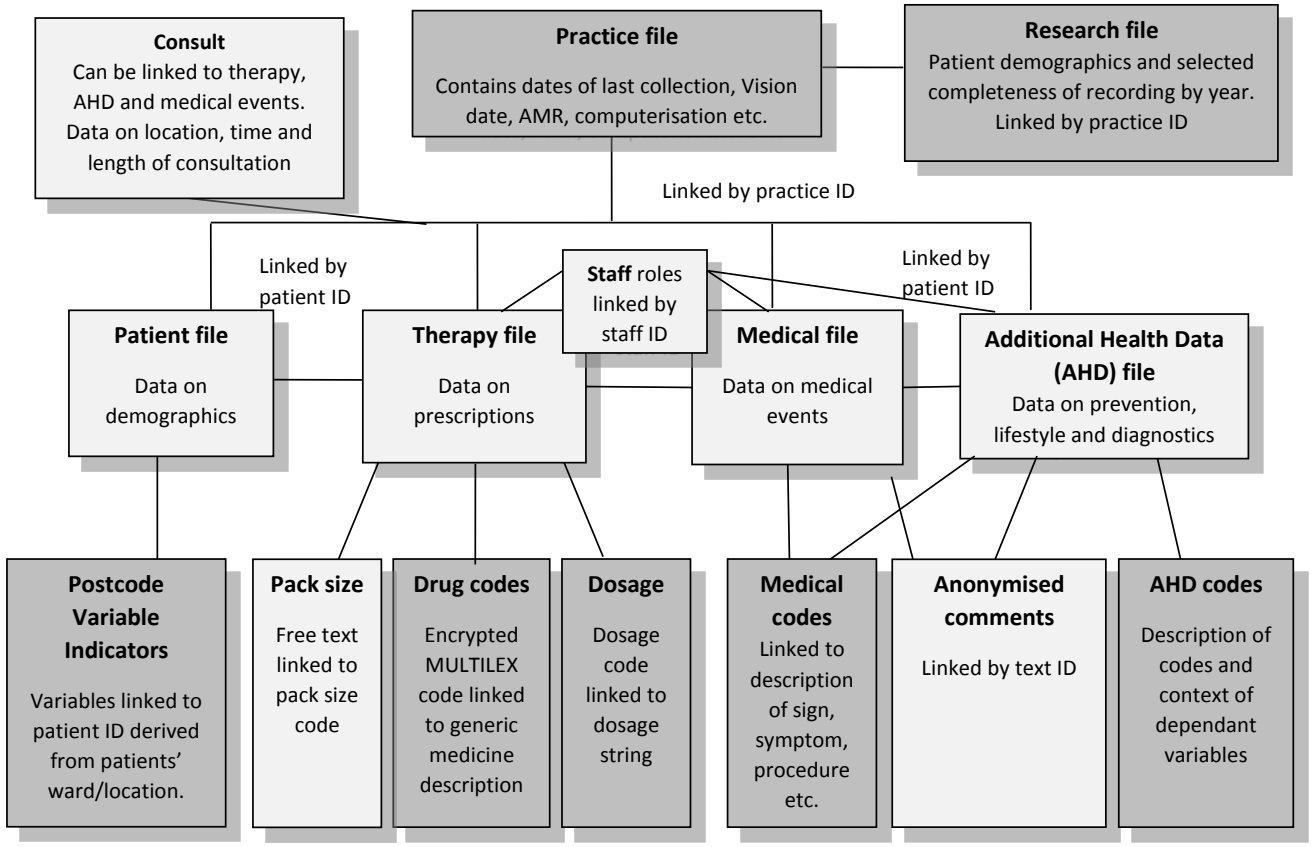
The next section of the chapter provides background information on THIN, which is used as the data source for my work investigating statin prescribing to individuals with SMI (outlined in Chapters 5 and 6).

3.1 Data Capture

Data held in THIN database are generated through information that is entered by the GP for the purposes of clinical management. Data capture is efficient, unobtrusive and enables longitudinal follow up. Data for the most recent year (2013) captures information from 587 practices covering 5.7% of the UK population (i.e. 12,374,853 patients contributing 85,803,247 person years of data) (IMS Health, 2015). Previous work with THIN data has identified a cohort of approximately 13,000 individuals with a diagnosis of schizophrenia and 10,000 with bipolar disorder (Hardoon et al., 2013;Osborn et al., 2011;Osborn et al., 2015).

The file structure and data content of THIN are outlined in Figure 3-1. Data are primarily recorded as medical codes, free text comments, drug codes for prescribed medications (based on the British National Formulary (BNF)(Joint Formulary Committee, 2012)), referrals and additional health information such as laboratory test results and biometrics. In addition, information from letters – such as hospital discharge letters – can be captured as scanned attachments or entered either as medical codes or free text comments. Medical codes are recorded using the Read clinical classification, which is a hierarchical system that was first developed in the 1980s for the purpose of providing a comprehensive and dynamic system for coding disease, clinical history, symptoms, examinations, findings and diagnostic procedures (Chisholm, 1990;Dave and Petersen, 2009). Read codes have been mapped to other coding systems including the international classification of diseases, injuries and causes of death (ICD9) and OPCS-4 surgical operations and procedure codes (Chisholm, 1990;Stuart-Buttle et al., 1996).

Figure 3-1: File structure for THIN redrawn from THIN Data Guide for Researchers (CSD Medical Research UK, 2011)



Standardised annual rates of all-cause mortality for practices reporting to THIN were evaluated against expected counts estimated using national deaths data in combination with the age and sex structure of the practice. The comparison of these estimates was used to establish the earliest date of acceptable mortality reporting (AMR) (Maguire et al., 2009). After the date of AMR there is much greater assurance of data quality; particularly when combined with other measures of reporting quality such as acceptable computer usage (ACU)(Horsfall et al., 2012). The ACU date marks the earliest time point at which a practice entered an average of two or more therapy records, one medical record and one data item into the additional health record per patient per year (Horsfall et al., 2012).

THIN data document the care initiated by, or relayed to, the GP and thus reflect real world treatment decisions and health outcomes as reported by the GP. Because almost all (98.5%, which excludes members of the armed forces, prisoners and illegal immigrants) of the usually resident population are eligible to register with a GP, primary care patients are roughly representative of the whole UK population. Conversely, certain groups - such as homeless people – who are more likely to have mental health conditions are less likely to be registered and may therefore be under-represented in studies of primary care.

I used an extract of data from THIN to form the dataset for the studies in this thesis, as described in Section 3.2 below, and in Chapters 5 and 6 following.

3.2 Case definitions

This section describes the definitions for terms applied to Chapter 5 (investigating patterns of CVD screening and statin prescribing in people with and without SMI - Thesis Objective 4) and Chapter 6 (investigating the impact of statin prescribing on CVD events - Thesis Objective 5). Read code and drug code lists were compiled using standard methods (Dave and Petersen, 2009). Where possible pre-existing code lists developed by The THIN Team at the Research Department of Primary Care and Population Health were used as the starting point for developing each code list.

Full code lists for all case definitions are included in the appendix; section 20.

3.2.1 GP surgery inclusion criteria

GP surgeries were included in the studies outlined in Chapters 5 and 6 if they had at least three years of data recorded and a list size of at least 2000 patients. Practices were excluded if less than 80% of their patients had a record of Townsend score for

deprivation in order to restrict the data to practices that are likely to report higher quality data. Townsend score for the quintile of deprivation is the most completely recorded socio-economic metric available in THIN; this measure is based on the deprivation score assigned to the enumeration district (areas of approximately 150 households) for a patient's address, according to census data for 2001. The Townsend score is expressed as national quintiles of deprivation reflecting unemployment, overcrowding, home and car ownership (Townsend et al., 1986).

3.2.2 SMI diagnoses

The code list used to identify individuals with SMI included 209 individual Read codes, which have been applied to other studies undertaken in THIN (Osborn et al., 2015;Osborn et al., 2011;Hayes et al., 2011). Individuals were classified as having a diagnosis of SMI if they had a Read code recorded in their medical records indicating schizophrenia, schizoaffective disorder or bipolar disorder recorded at any time during or prior to the study period. Search words (and truncated synonyms such as schizo*) were used to compile the Read code list. In addition, Read codes that started with *E1* and *Eu* (mental disorders) were reviewed for relevant terms that were missed by the initial word search. Code lists were reviewed by a clinician for irrelevant codes (e.g. depression without psychosis), which were excluded. Terms for SMI included:

Schizophrenia: *schizophrenia, schizoaffective, paranoid schizophrenia*

Bipolar disorder: *bipolar affective, psychotic depression, hypomanic psychoses, manic depressive, manic disorder, manic psychoses*

Individuals with other types of psychosis, or who only had a record indicating that they were on the SMI register, were not included in the study. This was because the clinical presentation of individuals with other types of psychosis is less well characterised than bipolar disorder or schizophrenia and could be too diverse to form a meaningful group. For example, the distribution of the age at diagnosis for other psychoses was more skewed towards older individuals than the age at which schizophrenia and bipolar disorder is typically diagnosed. This group may therefore differ both in terms of mental health and risk factors (such as older age) for CVD. Search words (and truncated synonyms such as psychos*) were used to compile the Read code list that was used to identify people with other psychoses or who were listed on the SMI register, but did not have a specific SMI diagnosis included the following terms:

Other SMI: *non-organic psychoses, oneirophrenia, affective psychoses, depressive psychoses, paranoid states, reactive psychosis*

SMI register: *severe mental illness register, national service framework mental health*

3.2.3 CVD events

CVD events were identified from Read codes held in the medical records: CVD events were classified according to whether the Read code described a new (incident) or pre-existing (prevalent) condition as well as the type of condition (myocardial infarction (MI), unstable angina, angina, haemorrhagic stroke, ischaemic and unspecified stroke, transient ischaemic attack (TIA), surgery, unspecified coronary heart disease (CHD) or unspecified CVD). Records of death that were associated with a CVD diagnosis were identified from Read codes held in the cause of death field (*1016500000*) in the additional health records. In addition, Read codes for CVD that were recorded after the date of death were assumed to reflect fatal CVD events.

The code list used to identify individuals with CVD included 408 Read codes, which have been applied to other studies examining CVD risk in THIN (Osborn et al., 2015;Osborn et al., 2011). Search words (and truncated synonyms such as atheroscler*) were used to compile the Read code list. In addition Read codes that started with *G3, G6*, *Gy* (circulatory system diseases) and *7* (operations, procedures and sites) were reviewed for relevant terms that were missed by the initial word search. Code lists were reviewed by a clinician for irrelevant codes, which were excluded.

Terms for identifying CVD included:

MI: *myocardial infarct, MI, myocardial infarction, myocardial ischaemia, acute Q-wave infarct, acute non-Q wave infarct, anteroseptal infection, anterolateral infection, anteropical infraction, acute papillary muscle infarction, acute atrial infarction, subendocardial infarction, Dressler's syndrome, ECG* AND *infarction*, *acute ischaemic heart disease, heart attack, post infarction pericarditis, thrombosis – coronary, coronary thrombosis, mural thrombosis*

Unstable angina and acute coronary syndrome: *coronary thrombosis not resulting in myocardial infarction, ACS, stenocardia, unstable angina, crescendo angina, subendocardial ischaemia, coronary artery spasm, preinfarction syndrome, impending infarction, refractory angina, worsening angina, acute coronary syndrome, acute coronary insufficiency, acute and subacute ischaemic heart disease, microinfarction of heart, angina at rest, transient myocardial infarction*

Angina: *stable angina, angina pectoric, angina on effort, Prinzmetal's angina, angina control, syncope angina, chronic ischaemic heart disease, nocturnal angina, angina*

decubitus, status anginosus, new onset angina, angina, chronic coronary insufficiency, chronic myocardial ischaemia, post infarct angina

Haemorrhagic stroke: *bulbar haemorrhage, intracerebral haemorrhage, capsule haemorrhage, cerebellar haemorrhage, cortical haemorrhage, non-traumatic intracranial haemorrhage, pontine haemorrhage, basal nucleus haemorrhage*

Ischaemic and unspecified stroke*: unspecified occlusion or stenosis of cerebral arteries, cerebral infarction, lateral medullary syndrome, stroke, basilar artery occlusion, brainstem infarction, Wallenberg syndrome, carotid artery occlusion, carotid artery syndrome, precerebral artery occlusion, vertebral artery occlusion, cerebral embolism, cerebral artery syndrome, infarction of basal ganglia, pure sensory lacunar syndrome, right sided CVD, left sided CVD amaurosis fugax, subclavian steal syndrome*

TIA: *transient cerebral ischaemia, transient ischaemic attack, TIA, intermittent cerebral ischamia*

Surgery: *angioplasty, operations on coronary artery, replacement* AND *coronary artery*, *bypass* AND *coronary artery*, *connection* AND *coronary artery*, *exploration of coronary artery, repair of coronary artery, stent* AND *coronary*, *anastomosis* AND *coronary, Endarterectomy* AND *coronary, percut transluminal coronary thrombolysis,*

Unspecified CHD: *ischaemic, coronary vessel disease, coronary artery disease, atherosclerotic heart disease, atherosclerotic cardiovascular disease, CHD*

Unspecified CVD: *cerebrovascular disease, cerebral artery syndrome, cardiovascular disease, stenosis of precerebral arteries, vertebrobasilar insufficiency, basilar artery syndrome, CVD, cerebral atherosclerosis, cerebral ischaemia*

3.2.4 Statin prescriptions

Statin prescriptions were identified from therapy records corresponding to drug codes for statins outlined in Chapter 2.12 (lipid-modification) of the BNF (Joint Formulary Committee, 2012) and by searching for generic drug names including the term “statin”. Code lists were reviewed by a clinician for irrelevant codes (e.g. mycostatin), which were excluded.

Terms for identifying statin medication included:

Statin: **statin, fluvastatin, simvastatin, rosuvastatin, cerivstatin, atorvastatin, pravastatin, lipitor, lescol, lipostat, crestor, zocor*

Individuals were classified as statin users if they had one or more records indicating that a statin was prescribed. The date of the first prescription was used to estimate the start of statin treatment. The last date of prescribed statin medication was calculated as the date of the last statin prescription plus the estimated duration of the last prescription. The estimated duration of prescriptions was derived as follows:

It was assumed that plausible values for the duration of each statin prescription should lie within the range 7-112 days, with the most common duration (obtained from the BNF) anticipated as 28 days (Joint Formulary Committee, 2012). Information on the duration of prescription is held in several fields in THIN. The *number of days* for which the prescription was issued was the preferred data source because this directly captured the intended duration of treatment. However, approximately 95% of statin records for the cohort held null values and therefore additional information from *pack size description* and *prescription quantity* was used to estimate treatment duration where the *number of days* of medication was not recorded. *Prescription quantity* was highly completed (<0.05% null values) but contained an unmarked mixture of the number of packs and tablets. By contrast, *pack size* was poorly completed but sometimes included an unambiguous description of the medication quantity (e.g. “28 tablets once daily”).

Where the *number of days* of medication was not reported (or was outside the range 7-112 days) values for the duration of treatment were derived as follows. Plausible information on the *pack size* description was used in combination with the *prescription quantity*: for plausible values of *pack size* (7-112 days) and *prescription quantity* (1-6 packs) the *pack size* was multiplied by the *prescription quantity*. Where information from other fields was not available plausible values (7-112 days) of *prescription quantity* were used to estimate the duration of treatment. Finally, remaining records with an estimated duration of less than 7 days or more than 112 days (<0.5%) were replaced with a duration of 28 days, which was the median derived from the observed data.

3.2.5 Conventional CVD risk factors

Data on conventional CVD risk factors (smoking status, height, weight, BMI, diabetes, systolic and diastolic blood pressure, treatment for hypertension, total cholesterol and high density-lipoprotein cholesterol (HDL-C)) in combination with age and gender are

likely to be the greatest predictors of both statin prescribing and future CVD events. This is because this information is used by clinicians to estimate a CVD risk score for an individual patient (D'Agostino et al., 2008). CVD risk scores that are calculated by the GP are not routinely captured in THIN data, meaning that it is necessary to estimate the risk score using available information on CVD covariates.

Data on CVD risk factors were identified in line with other studies undertaken in THIN (Osborn et al., 2015;Marston et al., 2014;Freemantle et al., 2013;Osborn et al., 2011;Walters et al., 2014):

Age in years: calculated as (date of interest minus the date of birth (held in adult patient records as *year of birth*)) divided by 365.25

Gender: held in the patient records (*sex*)

Smoking status: Read codes held in either the additional health records (*1003040000*) or the medical records were used as follows to classify an individual's smoking status for a given record:

> **Current smokers**: *1372.00, 1373.00, 1374.00, 1375.00, 1376.00, 137..11, 8CAg.00, 8CAL.00, E251.00, E251000, E251100, E251z00, 137H.00, 137J.00, 137P.00, 137P.11, 137Q.00, 137R.00, 137V.00, 1372.11, 137b.00, 137C.00, 137c.00, 137d.00, 137f.00, 137g.00, 137G.00, 137h.00, 137M.00, 8H7i.00, 8HTK.00, 9N2k.00, 9N4M.00, 67A3.00, ZG23300, ZV4K000, 8I2I.00, 8I39.00, ZRBm200, ZRBm211, 137Y.00, 6791.00*
>
> **Ex-smokers:** *1377.00, 1378.00, 1379.00, 137A.00, 137B.00, 137F.00, 137K.00, 137N.00, 137O.00, 137S.00, 137T.00, 13p4.00*
>
> **Never smokers:** *1371.00, 1371.11*
>
> **Smoking cessation:** Prescriptions recorded in the therapy records were used to indicate smokers attempting to quit (i.e. transition from current to ex-smoker status) and included the following generic drug names: *nicotine, varenicline, menthyl valerate and quinine, buproprion.*

Weight: Records of weight (and the associated unit of measurement, e.g. kilograms) were identified from the additional health records (*1005010200*)

Height: Records of height (and the associated unit of measurement, e.g. centimetres) were identified from the additional health records (*1005010100*) and retained for measurements taken at or after the age of 21 years

BMI: BMI was estimated as weight in kilograms divided by height in metres squared

Diabetes: Records indicating diabetes were identified using additional health records (*1009100000, 1020000004, 1001400327, 1001400140 and 1009120000*)**,** which indicate checks in people with a diagnosis of diabetes (e.g. for diabetic retinopathy) or diabetes medication. Read codes held in the medical records indicating the following conditions were also used to identify people with diabetes.

Diabetes: *diabetic, diabetes, insulin, referral to diabetologist, diabetology, IDDM, NIDDM,*

In addition Read codes that started with *C1* (endocrine, nutrition, metabolic and immunity disorders) were reviewed for relevant terms that were missed by the initial word search. Code lists were reviewed by a clinician for irrelevant codes, which were excluded.

Systolic and diastolic blood pressure: Records of blood pressure (and the associated unit of measurement; mmHg) were identified from the additional health records (*1005010500*).

Antihypertensive medication: Records indicating treatment with antihypertensive medication was identified as drugs listed in Chapter 2.2.1 (thiazides and related diuretics), 2.5.5.1 (angiotensin-converting enzyme inhibitors), 2.5.5.1 (angiotensin-II receptor agonists), 2.6.2 (calcium-channel blockers) and 2.4 (beta-adrenoceptor blocking drugs) of the BNF (Joint Formulary Committee, 2012).

Total cholesterol concentration and HDL-C: Records of cholesterol concentration (and the associated unit of measurement) were identified from the additional health records (total cholesterol; *1001400017* and HDL-C; *1001400031*).

3.2.6 Estimating CVD risk

CVD risk scores were estimated in THIN using published Cox proportional hazards regression coefficients for men and women participating in the Framingham Heart Study (D'Agostino et al., 2008) in combination with the formula:

$$\hat{p} = 1 - S_o(t)^{\exp(a)} \text{ where } a = \sum_{i=1}^{p} \beta_i X_i - \sum_{i=1}^{p} \beta_i \bar{X}_i$$

Where $S_0(t)$ is 10 year baseline survival, β*i* is the estimated regression coefficient outlined in the appendix (Table 19-1 and Table 19-2), X*i* is the log of the value of the *i* th risk factor for continuous variables, $\bar{X}_i$ is the associated mean value and p is the number of risk factors. Further detail including mean values for the Framingham cohort and worked examples for calculating CVD risk are outlined in the original paper (D'Agostino et al., 2008).

3.2.7 Psychiatric medication

Individuals who were prescribed antipsychotics, antidepressants or mood stabilizers were identified using code lists for the following generic drug names:

Antipsychotics

First generation: *benperidol, chlorpromazine, chlorprothixene, droperidol, flupentixol, fluphenazine, fluspirilene, haloperidol, levomepromazine, loxapine, pericyazine, perphenazine, pimozide, pipotiazine, promazine, thiopropazate, thioproperazine, thioridazine, trifluoperazine, trifluperidol, zuclopenthixol*

Second generation: *amisulpride, aripiprazole, asenapine, clozapine, olanzapine, oxypertine, paliperidone, quetiapine, remoxipride, risperidone, sertindole, sulpiride, zotepine*

Mood-stabilisers

carbmazapine, lamotrigine, lithium, sodium valproate

Antidepressants

Monoamine-oxidase inhibitor: *iproniazid, isocarboxazid, moclobemide, phenelzine, tranylcypromine, trifluoperazine*

Selective serotonin re-uptake inhibitor (SSRI): *citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline*

Tricyclic: *amitriptyline, amoxapine, bolvidon, butriptyline, clomipramine, desipramine, dosulepin, dothiepin, doxepin, imipramine, iprindole, lofepramine, maprotiline, merital, mianserin, nomifensine, nortriptyline, perphenazine, protriptyline, sinequan, tofranil, trazodone, trimipramine, viloxazine, zimelidine*

Other: *agomelatine, duloxetine, flupentixol, l-tryptophan, mirtazapine, nefazodonem, reboxetine, tryptophan, venlafaxine*

Defining predominant antipsychotic type

In the main study (Chapter 6) the predominant type of psychiatric medication was investigated during baseline. Individuals who were prescribed multiple types of antipsychotic during baseline were classified by the drug with the greatest number of prescriptions. Manual review of data for 20 individuals suggested that the method of classification described above was an appropriate measure of the predominant drug type. A possible exception was for antipsychotic drugs delivered by depot injection (which facilitates slow-release of the medication), where some misclassification may have occurred for individuals who received a mixture of tablets and depot injections and where both the type and treatment duration of prescription differed. However, this scenario is likely to be relatively uncommon and is most likely to reflect periods of transition from treatment with orally administered second generation drugs to depot injection of first generation drugs (or *vice versa*). In addition, psychiatric medication issued outside primary care settings (particularly hospital outpatient clinics issuing and monitoring clozapine) may be under recorded in primary care prescribing data (The NHS Information Centre, 2011).

3.2.8 Healthcare Factors

Annual face-to-face consultation rate in primary care was used as a measure of healthcare utilisation, types of consultation included consultations both within surgery opening hours and out of hours. Face to face consultations were identified from the following consultation codes: nursing home visits were not included.

Face to face consultations: *walk-in centre (consultation code 034), night visit, practice (006), emergency consultation (018), clinic (001), community clinic (100), surgery consultation (009), acute visit (011), out of hours, non-practice (008), home visit (027), out of hours, practice (007), night visit (110), co-op surgery consultation (036), co-op home visit (037), follow-up/routine visit (003)*

3.2.9 Comorbidity

Having one or more comorbid conditions is likely to result in more frequent GP consultations and thereby increases the opportunities available for GPs to prescribe a statin. Statin prescribing is also likely to be more common amongst patients who have a condition that is associated with increased risk of CVD. Comorbid diagnoses and conditions that were identified from the literature as of potential relevance included familial hypercholesterolaemia, hypothyroidism, cancer (by diagnosis type), heavy drinking, diabetes, chronic obstructive pulmonary disease (COPD), asthma, chronic kidney disease (CKD) and atrial fibrillation. In addition, individuals who were prescribed drugs that are used for lipid modification but are not statins (e.g. fibrates) during baseline were identified using a drug code list derived from Chapter 2.12 (lipid-modification) of the BNF.

Read codes held in the medical records were also used to identify people with the following conditions:

Hypothyroidism: *hypothyroidism, cretinism, Pendred's syndrome, Goitrous cretin, myxoedema, thyroid deficiency, thyroid insufficiency, acquired atrophy of thyroid*

Cancer (broad description of diagnosis type – see appendix (section 20.17) for detailed break-down): *neoplasm (not otherwise specified), dermatological, gastro-intestinal, metastasis, haematological, chest, respiratory, bone, central nervous system*

COPD: *COPD, chronic obstructive pulmonary disease, chronic obstructive airways disease, chronic bronchitis, bronchiolitis obliterans, emphysema, Sawyer-Jones syndrome*

Asthma: *asthma, hyper-reactive airways disease, status asthmaticus, allergic bronchitis*

CKD: *chronic kidney disease (stages 3-5), CKD (stages 3-5), chronic renal disease, chronic renal impairment*

Atrial fibrillation: *atrial fibrillation*

Heavy drinking: review of additional health records (*1003050000*) and the associated units for drinking habits indicating consumption of ≥28 (women) and 35 (men) units per week. In addition, the following Read codes were used to identify heavy drinkers.

Heavy drinkers: *alcohol intake above recommended sensible limits, binge drinker, moderate drinker, non-dependent alcohol abuse, alcoholic hepatitis, chronic hepatitis, hepatic failure, liver failure, alcohol amnestic syndrome, alcohol dependence, alcohol problem drinking, alcohol withdrawal, alcohol-induced chronic pancreatitis, alcoholic dementia, alcohol sclerosis of liver, alcoholics anonymous, alcoholic psychoses, portal cirrhosis, chronic alcoholic syndrome, harmful alcohol use, heavy drinker, hepatic failure, Laennec's cirrhosis, recurrent hepatitis, toxic hepatitis, toxic liver, Wernicke's,*

Read codes indicating "history of alcoholism" or "ex-alcoholic" were not included.

Familial hypercholesterolaemia: Read codes indicating *familial hypercholesterolaemia* and/or a record of total cholesterol concentration >7.5mmol/L was used to identify people with possible familial hypercholesterolaemia (National Institute for Health and Clinical Excellence, 2008a). Further evaluation of the strengths and limitations of this definition are outlined in the discussion (Chapter 7, section 9.6).

Non-statin lipid modification: review of therapy records for all drugs outlined in Chapter 2.12 of the BNF (Joint Formulary Committee, 2012) excluding all drugs previously identified as statins (see Section 3.2.4)

3.2.10 Economic and Social Factors

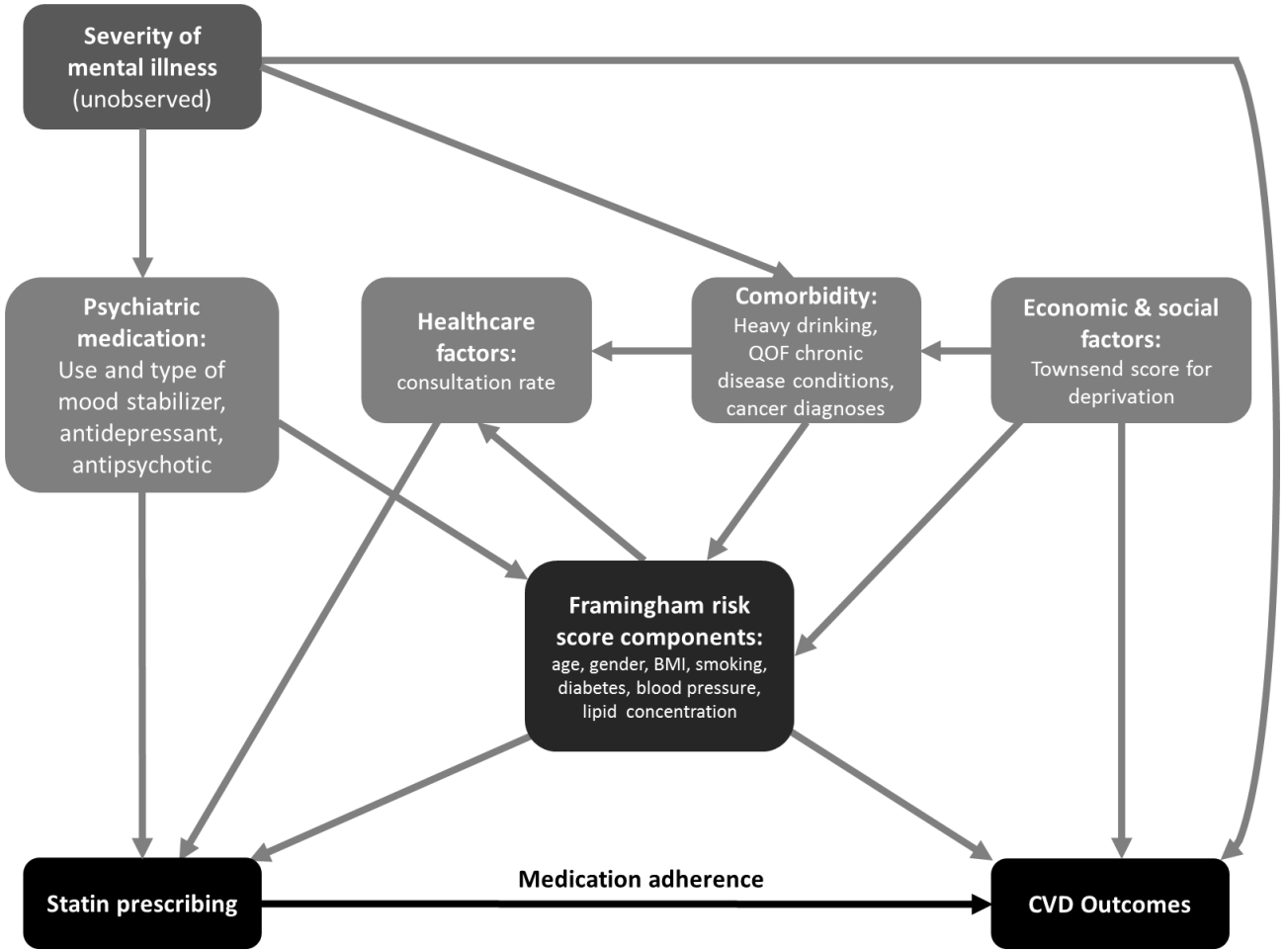
Townsend score (held in patient records within THIN) has been shown to be correlated with an individual's health status (Adams et al., 2005). Other potentially relevant economic and social factors – such as household income and employment - are not recorded in THIN. Information on ethnicity is captured in primary care data, but is infrequently and inconsistently recorded for patients registered prior to 2006 (Mathur et al., 2014). However, recording increased dramatically following the introduction of the Quality and Outcomes Framework (QOF) in 2004 (National Institute for Health and Clinical Excellence, 2012).

3.2.11 Summary of the availability of data in THIN

Chapter 1 introduced key factors identified from the literature that are associated with both statin prescribing and CVD events in people with SMI. Many, but not all, of the factors identified in Chapter 1 are recorded in THIN: Figure 3-2 outlines key data on the relationship between statin prescribing and CVD in primary care, and the likely direction of causal associations given information from the literature. Relative to the causal network outlined in Figure 5-1 of Chapter 1, information on several factors

(severity of mental illness, genetics, ethnic group and some lifestyle factors for such as diet and physical activity) is not systematically recorded in THIN, meaning that it is not possible to fully account for differences in the distribution of these characteristics in individuals prescribed a statin relative to non-statin users. However, because these factors are associated with other measured variables – for example psychiatric medication is likely to be correlated with severity of mental illness – residual confounding should be somewhat reduced. In addition, some information – such as economic and social factors – is imperfectly reflected in the information that is available in THIN, meaning that it will not be possible to fully adjust for these confounders. A discussion of the strengths and limitations of the information captured in THIN and the likely impact on the study results is outlined in Chapter 7.

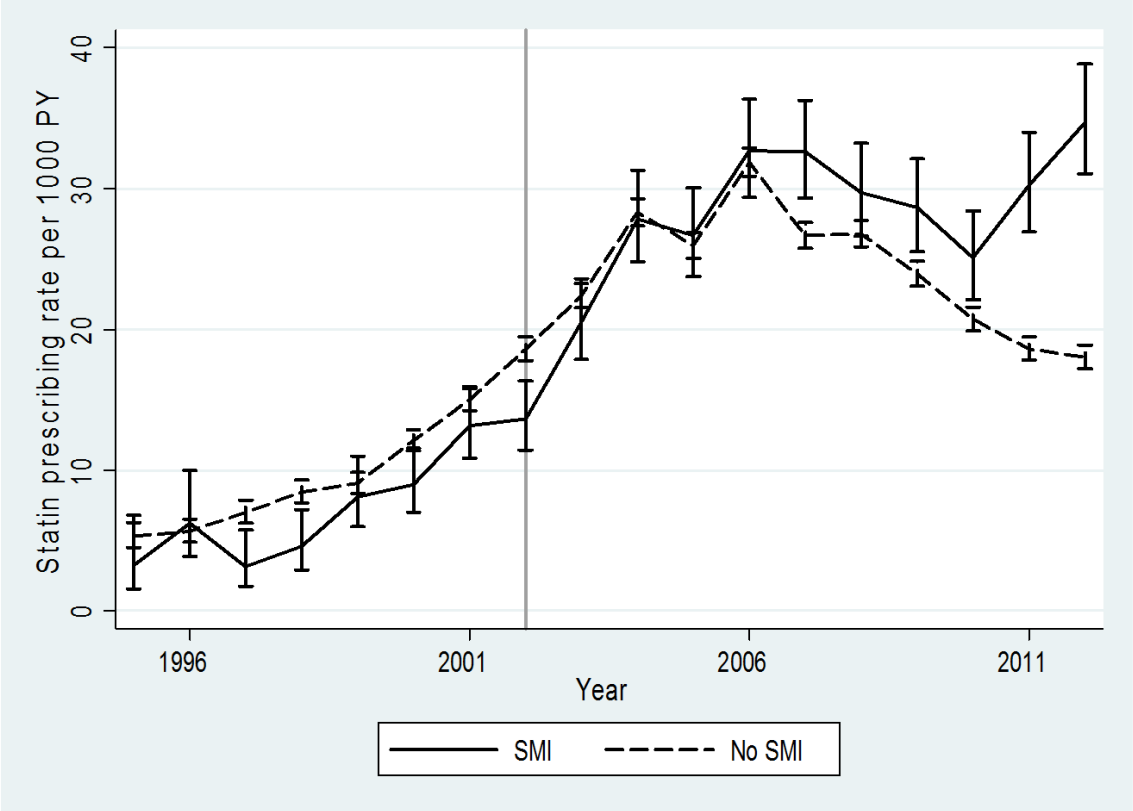
Figure 3-2: Causal diagram for the relationship between statin prescribing in primary care and CVD events in people with SMI



4 Time period for the studies outlined in this thesis

Preliminary investigations showed that the rate of statin prescribing for primary prevention was very low prior to 2002 (Figure 4-1 – vertical grey line indicates the calendar year 2002) with the total number of new prescriptions being issued annually to approximately 10,000 individuals with SMI being less than 100 prior to 2002. Chapters 5 and 6 therefore use data on statin prescribing for the time period 1st January 2002 to 31st December 2012.

Figure 4-1: Rates of statin prescribing (per 1000 person years) for primary prevention of CVD in people with and without SMI between 1995 and 2012



5 Data Quality

"if you put into the machine wrong figures, will the right answers come out?"

Charles Babbage, *Passages from the Life of a Philosopher (Babbage, 1864)*

The next section of this chapter considers the quality of data captured in primary care databases including THIN. Primary care databases offer significant opportunities for analyses that can inform public health policy and practice. However, the results of such analyses can only be as good as the underlying data. Validity and completeness are two key aspects of data quality, which are often quantified using estimates of sensitivity, specificity, negative and positive predictive values (Goldberg et al., 1980). These measures do not provide information about data quality *per se*, but rather on the performance of a test either in isolation (sensitivity and specificity) or within a given population (negative and positive predictive values). Analyses of primary care data rely upon methodological tests applied by researchers to identify specific conditions using drug and medical codes, free text searching or other more complex algorithms. These tests are not perfect and are subject to measurement error arising at the level of the test, GP recording and the original observation (including medical diagnostics). For example, if individuals with SMI are identified through using a list of Read codes to find cases, some individuals with SMI may be missed if the code list used by the researcher omits the Read code for a given condition or, alternatively, if the diagnosis was entered as free text only.

Validation studies aim to estimate the degree of measurement error for key study components such as the outcome and exposure by comparison with a "gold standard". For primary healthcare data, the gold standard often includes patient notes held at the GP practice, additional questionnaires or other linked datasets. Validation of the outcome and exposure under investigation is particularly important because inaccuracies in these measurements has the potential to introduce substantial uncertainty and may bias the results.

5.1 How valid are data from UK primary care databases?

This section of the chapter describes the validity of primary care databases - including THIN – and evaluates published evidence on the validity of case definitions applied to the studies outlined in Chapters 5 and 6. Further discussion of the implications of these aspects of data quality is outlined in Chapter 7; section 9.

A systematic review of CPRD validation studies identified 212 publications that investigated 357 separate validations of 183 diagnoses (Herrett et al., 2010). The majority of these studies (>80%) measured validity against external data sources predominantly using a mixture of GP questionnaires, requests for copies of the medical records or comparison of disease rates. Across the breadth of conditions covered, 89% of cases with a diagnosis recorded in the database were confirmed by an internal or external data source. The range of confirmed diagnoses differed by disease category and method of validation (24-100%), but was at least 80% for all categories except diseases of blood and blood forming organs. The high level of confirmation of diagnoses provides evidence of a generally high positive predictive value, but the review found few studies that examined sensitivity, specificity or negative predictive values, which are important aspects of data quality. The lack of studies examining these aspects may be explained by the cost (estimated in 2009 as £70 per patient) of manually reviewing patient notes to confirm that non-cases are correctly classified. Furthermore, as only a subset of the GP surgeries that regularly contribute data to CPRD participate in additional research activities, the findings of existing validation studies may not be generalizable to all data providers (Herrett et al., 2010).

5.2 Data quality for the case definitions for the population (individuals with SMI), intervention (statin prescriptions) and outcomes (CVD and mortality) of this study

Systematic reviews of validation studies are relatively uncommon and I was unable to identify one specific to THIN. However, individual validation studies have been published for THIN and its precursor VAMP, for conditions that are the focus of this research question.

5.2.1 Population: people with SMI

Nazareth and colleagues assessed the accuracy of diagnoses of schizophrenia and non-affective psychosis in London practices that reported to VAMP in 1990. The study compared computerised diagnoses entered by GPs to written records to confirm two tiers of criteria (strict and broad) for a lifetime diagnosis. In addition, case note review was undertaken for all patients who did not have a diagnosis of schizophrenia, but who were prescribed antipsychotics. Finally, a further 8000 case notes for adults without a diagnosis or associated prescribing were reviewed for evidence of psychosis that was not captured in electronic records. The sensitivity of diagnoses recorded in VAMP for schizophrenia, non-affective psychosis and non-organic psychosis was 88-93% (strict

criteria) and 71-91% (broad criteria) with positive predictive values ranging from 71-91% (strict criteria) and 81-100% (broad criteria) (Nazareth et al., 1993).

More recently, Hardoon and colleagues estimated the incidence of SMI using THIN data. The incidence was 46.4 per 100,000 person years for combined diagnoses of SMI, and 9.2 and 15.0 per 100,000 person years for schizophrenia and bipolar disorder, respectively (Hardoon et al., 2013). These figures are similar to - but somewhat higher than - a recent meta-analysis which was outlined in Chapter 1 section 3 (Kirkbride et al., 2012). This difference may reflect lower ascertainment of hospital cases (the basis for many of the published estimates included in the meta-analysis) than primary care, as not all individuals require hospital care and people with SMI may be more likely to be registered with a GP than the general population.

These studies suggest a high degree of validity for diagnoses of SMI recorded in THIN; particularly schizophrenia and non-organic psychosis, for which estimates of sensitivity and specificity are known.

5.2.2 Exposure: receiving a statin prescription

I was unable to identify any published validation studies of statin prescribing in UK primary care databases, however, the process of prescribing should be well recorded because electronic data capture is an automated feature of issuing a prescription in a GP surgery. By contrast, it is less clear how prescribing translates into therapeutic exposure because individuals may not fill the prescription and/or take the medication.

Studies investigating all prescriptions issued by a sample of practices reporting to THIN suggest good correlation between prescribing and redemption of the prescription; 98% of CVD medications were dispensed as prescribed (The NHS Information Centre, 2011). However, some prescriptions – particularly those issued in hospital or during home visits – may not be fully captured. Estimates from the literature suggest non-adherence is relatively high for statins: one in six individuals do not fill their first statin prescription and long term estimates of statin medication compliance for primary prevention in the general population are approximately 50% (Naderi et al., 2012;Poluzzi et al., 2008;Cheetham et al., 2013;Halava et al., 2014).

In addition, it is possible to buy low dosage simvastatin over the counter without a prescription, meaning that these individuals may be misclassified as not being a statin user. However, because equivalent prescribed medication is much cheaper, misclassification arising due to over-the-counter statin use is unlikely to substantially impact upon the results. In addition, people with SMI are more likely than the general

population to be entitled to free or subsidised prescription costs making over the counter purchase of statins (at full price) an unfavourable choice.

5.2.3 Outcomes: CVD events and mortality

A systematic review of 55 validation studies of circulatory system conditions carried out using data confirmed that a median of 85.3% of diagnoses recorded in the CPRD could be verified by GP record request, algorithm or manual review. Information was not presented on specific CVD diagnoses such as MI or stroke (Herrett et al., 2010). To date, no systematic reviews of validation studies are available specifically for THIN data, however positive predictive values for individual CVD diagnoses (outlined below) appear comparable to CPRD and well established biological associations have been replicated for key CVD diagnoses in both databases (Lewis et al., 2007).

5.2.3.1 Fatal and non-fatal MI

Garcia-Rodriguez *et al*. undertook a two stage validation process of Read codes for fatal and non-fatal MI using THIN data. Fatal MI was defined as "*post-mortem evidence of fresh MI or a recent coronary artery occlusion or ante-mortem evidence of CHD in the absence of another cause of death or recorded CHD as the underlying cause of death*". Stage one of the validation process reviewed the computerised patient profile to exclude patients who were not admitted to hospital or those who were hospitalised in the previous month for a non-cardiac condition. Stage two obtained GP confirmation of the diagnosis in a random sample of 500 cases. The study team were able to confirm 85% and >95% of diagnoses at stage one and two, respectively. Non-cases of MI were not reviewed (Garcia Rodriguez et al., 2004;Garcia Rodriguez et al., 2008).

5.2.3.2 Ischemic cerebrovascular diagnoses

Ruigomez and colleagues undertook a three step validation process to confirm diagnoses of ischemic cerebrovascular diagnoses. Stage one was a manual review of computerised medical records (excluding free text) for cerebrovascular diagnoses and hospitalisation within two weeks. Stage two extended the manual review of computerised medical records to include free text of a random sample of 300 possible cases and 100 non-cases. Stage three reviewed full medical records and a GP questionnaire for randomly sampled potential cases and non-cases. Of 15397 individuals with a first cerebrovascular event in the study period, 4239 (28%) had a record that indicated hospitalisation within two weeks. During the first validation step 81% of 4239 possible cases were confirmed and 792 were excluded (including 336 where the event was haemorrhagic rather than ischaemic). Step 2 validated a sample

of possible cases and non-cases and suggested that 245/300 (82%) of cases were positive and that 88/100 (88%) non-cases were negative. The third validation step resulted in 138/161 (86%) confirmed cases and 50/61 (82%) confirmed non-cases. Positive predictive values varied by diagnosis type and were markedly lower for TIA than other diagnoses (Stage One: 60% for TIA versus 83% for stroke and 88% for unspecified cerebrovascular events. Stage Two: 74% for TIA versus 90% for stroke and 92% for unspecified cerebrovascular events) (Ruigomez et al., 2010).

5.2.3.3 Haemorrhagic stroke

Gaist *et al*. investigated the validity of primary diagnoses of non-traumatic haemorrhagic stroke, comprising intracerebral haemorrhage or subarachnoid haemorrhage. The study team reviewed electronic health records from THIN including free text comments to confirm that events were not: ischaemic, prevalent or induced by trauma. In addition, cases were excluded if the patient had a diagnosis of cancer, was hospitalised at the time of the event or subdural haemorrhage preceded the event. Further validation of 400 computer-detected cases was confirmed by GP questionnaire and review of anonymised medical records including use of computed tomography, magnetic resonance imaging, x-ray angiography or lumbar puncture (subarachnoid haemorrhage only). The review of computerised records resulted in the exclusion of 697 cases leaving 3633 potential cases (84%). The majority of exclusions reflected ischaemic diagnoses (35%), trauma (25%) or a diagnosis that could not be confirmed (16%). A further consequence of the review was that the date at which the event occurred was revised for 589 cases (19%): on average the true date of the event was believed to have occurred 13 days earlier than the date assigned to the initial Read code. Of the 400 computer detected computer cases that were validated by questionnaire and full medical record review, responses were available for 369: 251/306 (82%) were confirmed as cases and 56/63 probable non-cases (89%) were discarded (Gaist et al., 2013).

5.2.3.4 Combined fatal and non-fatal CVD events

I was unable to find any validation studies for combined fatal and non-fatal CVD events, including diagnoses of angina or unspecified CHD. This is of concern because these diagnoses may refer to less severe events or non-specific conditions that may be of lower diagnostic validity than outcomes such as MI. In particular, it may be difficult to determine whether the record refers to a pre-existing condition, or if the individual was truly free of the condition prior to the date at which the Read code was recorded.

5.2.4 All-cause mortality

A study investigating recording of all-cause mortality in THIN was able to confirm 99% of recorded deaths through additional contact with the GP surgery. The study examined deaths occurring within a one year period within in a subset of individuals who had a weight measurement taken between January 2002 and December 2008: the cohort comprised 142,082 individuals from 118 practices for which a total of 1,621 deaths were identified The study did not investigate the number of deaths that were not captured in THIN (Hall, 2009).

5.2.5 Cause of death

The study by Hall (Hall, 2009) also investigated recording of the cause of death and established that ascertainment of this information was much lower than for all-cause mortality. A cause of death was recorded in the form of Read codes for 47% of reported deaths and in free text for a further 17% (Hall, 2009).

5.2.6 Interpretation of validations studies for CVD events and mortality

These validation studies provide evidence that some types of CVD events recorded in THIN have a high positive predictive value and are therefore likely to provide a true indication of the presence (but not absence) of disease. In particular, diagnoses of MI were particularly well correlated with hospital admission and GP verification (positive predictive value >95%). The certainty with which diagnoses of stroke were recorded was more complex. Ischaemic stroke was poorly correlated with hospital admission: however, this may reflect long rehabilitation periods following stroke, which may make temporal linkage of the hospital admission to the CVD event more challenging. It is therefore possible that some unconfirmed diagnoses of ischaemic stroke may reflect more complex or severe CVD events. Records of haemorrhagic stroke were more highly correlated with admission to hospital. Furthermore, the majority of unconfirmed cases of haemorrhagic stroke reflected other types of (ischaemic) CVD events, which should not introduce bias if ischaemic and haemorrhagic events are examined in tandem.

Although the positive predictive values for records indicating MI or hospitalised stroke in THIN were generally high, estimates of sensitivity have not been estimated. Incomplete ascertainment of CVD outcome data may introduce bias into estimates of the effectiveness of statins if the sensitivity of recording differs between statin users and non-users (e.g. higher ascertainment of events amongst statin users is likely to under-estimate effectiveness).

External validation of all-cause mortality data from THIN suggests both a high sensitivity and specificity of recording. In addition, the application of measures – such as restricting data to time periods after the date of AMR or ACU – provides further assurance that data quality is high. By contrast, information on the cause of death is substantially incomplete, and the sensitivity of recording for specific causes of death (e.g. those relating to CVD diagnoses) is therefore likely to be low.

6 Summary and implications for this thesis

Data from THIN provide an efficient way of capturing information on a large number of individuals, who have been followed up over time, and are representative of the UK population. These data have the advantage of being passively collected through routine clinical practice and the study population may therefore be less vulnerable to selection bias than clinical trials. Conversely, because data are collected for the purposes of clinical management, data on important factors such as lipid profile or weight may not be recorded for all time points of interest.

Validation studies of THIN data suggest positive predictive values that are high (typically 80-90%), however, these values do not provide a full picture of data quality. With the exception of diagnoses of SMI – for which electronic data quality has been found to be high – few studies have investigated sensitivity or negative predicative values, which are indicators of ascertainment. Validity of the full range of CVD diagnoses is currently unknown. Although the positive predictive values of studies investigating specific subsets of CVD diagnoses are high (e.g. MI), some were achieved by applying rigid classification criteria (e.g. hospitalised ischaemic stroke), which are likely to compromise the (currently unknown) sensitivity with which cases can be identified.

All epidemiological studies need to balance a trade-off in sensitivity and specificity against the objectives and feasibility of the study. Because my main study investigates a relatively rare event in a population of limited size it is pragmatic to maximise detection of the outcome even though this is likely to result in a higher rate of false positives than more exhaustive criteria such as specifying an associated hospital admission. For this reason the CVD outcomes of interest will focus on combined MI and stroke, and (separately) all-cause mortality. The feasibility of investigating other types of CVD outcome which have not been validated (e.g. CHD) will also be investigated, although it is possible that such outcomes may be a source of bias. The

implications of the strengths and limitations of using data from THIN for the research questions investigated in this thesis are discussed in greater detail in Chapter 7.

Chapter 4 : Choice of study design to assess effectiveness of statins using routine primary care data

1 Chapter content

This chapter explores the strengths and limitations of different study designs used within observational data to explain the choice of study design selected for the main analysis (Chapter 6). I provide a brief introduction to the theory underpinning causal inference with observational data. Then I focus on the methodological theory that is central to both my research aim (estimating the effectiveness of statins for primary prevention of cardiovascular disease (CVD) in people with severe mental illness (SMI)) and the practical considerations that must be factored into selecting a viable study design. The main emphasis of the methodological theory tackles problems of confounding - particularly confounding by indication; where treatment allocation is related to the prognosis of future health outcomes - that are common to all observational studies investigating causal effect. I also focus on practical issues specific to routinely collected datasets, such as The Health Improvement Network (THIN), including handling missing covariate data. To aid discussion of these methodological and practical considerations, I describe and appraise the study designs of three published studies, which were central to the choice and development of the design for my main analysis. Finally, I describe the core features of the proposed study design for the main analysis of my thesis with reference to other possible methods.

2 Causal inference using observational data

Causal inference can be conceptualised using the Potential Outcomes Framework, which considers the possible outcomes experienced by the same individual – at the same time point – both in the absence and presence of the treatment (Rubin, 2005). For example, whether or not the choice to prescribe a statin or not to a specific patient on a given date results in a CVD event. In reality, experimental evidence can allow us to see only one potential outcome for an individual, where the other outcome/s experienced if a different treatment (or no treatment) had been administered remain unobserved (counterfactual). For this reason causal inference using data derived from real-life settings cannot examine the effects of a given treatment on a single individual

and must instead focus on estimating the average effect across equivalent individuals who receive different treatments.

Random assignment of treatment is the primary feature of randomised controlled trials (RCTs) and this process produces treatment groups that are similar at the point of randomisation. In the context of the Potential Outcomes Framework, randomisation ensures that treatment assignment is not associated with the counterfactual outcome and that the participants are therefore equivalent; this is formally termed *exchangeability*[2]. Exchangeability is important because under ideal conditions (e.g. no loss to follow-up) the differences in the outcomes observed between each trial arm are the same as the average difference in potential outcomes. In addition, the causal effect (of intervention versus control) is the same regardless of which group actually receives the intervention. Randomisation therefore forms the link between theory that examines potential outcomes for the same individual and experimental studies that compare average outcomes across equivalent groups of individuals.

Classical RCTs usually randomly assign individuals to one of two different treatment options (e.g. statin or placebo); such that 50% receive treatment and 50% receive placebo. This type of randomisation is described as marginal, because all individuals have an equal probability of receiving either treatment option. However, RCTs are not always marginally (unconditionally) randomised; instead, randomisation may be conditioned on one or more variables, which define the likelihood of receiving one treatment option over another. For example, an RCT examining the effect of statin therapy versus placebo on CVD events could choose to prioritise statin therapy for individuals with high CVD risk scores (defined as >20% over a ten year period) by randomly assigning 75% of high risk and 25% of low risk individuals to receive a statin. In this scenario, the statin arm will include three times more high risk individuals than the placebo arm and the groups therefore differ with respect to CVD risk both at the point of randomisation and their subsequent probability of future events. However – crucially - within strata of the conditioning variable (high/low CVD risk score) the groups are equivalent, which is termed *conditional exchangeability*[3]*.*

The conditionally randomised trial provides a helpful framework with which to consider how data from observational studies may be best analysed. However, obtaining

[2] Exchangeability can be written mathematically as $Pr[Y^a=1|A=1] = Pr[Y^a=1|A=0]$ where Y is a binary outcome, Y^a is the counterfactual outcome given the other treatment option, A denotes the administered treatment option.

[3] Conditional exchangeability can be written mathematically as $Pr[Y^a=1|A=1,L=1] = Pr[Y^a=1|A=0,L=1]$ where Y is a binary outcome, Y^a is the counterfactual outcome given the other treatment option, A denotes the administered treatment option and L denotes the conditioning variable.

accurate estimates of effectiveness using observational datasets remains a challenge, primarily because treatment allocation (such as statin prescribing) is clinically indicated and not random. This chapter aims to explore the study designs employed by existing observational studies that have estimated the effectiveness of statin therapy (versus no treatment) on CVD events and to evaluate the best study design to investigate primary CVD in people with SMI. The selection of comparable exposed and unexposed individuals is a key issue when using observational data to estimate effect and is important because failure to do so results in biased estimates. In order to choose comparable groups the selection process must go beyond considering *who* is treated to also account for the *timing* of treatment and follow-up. I outline the major features that epidemiological studies can use to improve the validity of the results (Gagne et al., 2012) and I have selected three studies (Hippisley-Cox and Coupland, 2010;Smeeth et al., 2009;Danaei et al., 2013) to help discuss the relative merits and shortfalls of different design features.

3 Confounding by indication

Confounding by indication describes the imbalance in characteristics between exposed and unexposed individuals, which results when treatment allocation (such as a statin prescribing) is clinically determined, associated with the prognosis and, therefore, not random. Treatment is therefore related to the risk of future health outcomes, such that direct comparison of the outcomes between exposure groups yields a biased result (Signorello et al., 2002). The challenges of confounding by indication are illustrated by a study using data from THIN to estimate the effectiveness of adding spironolactone to standard treatment with high dose loop diuretics on mortality in people with severe heart failure (Freemantle et al., 2013). Despite using the best available methods (including propensity score matching on a large range of characteristics), the study was unable to replicate hazard ratios (HRs) that were compatible with a major RCT; namely 0.70 (0.60-0.82). Instead, estimates from their observational study suggested a harmful effect of spironolactone; 1.32 (1.18-1.47). Discordance between these results may reflect residual confounding arising from aspects of the treatment allocation in clinical practice that were not measured or recorded within the observational dataset.

A common source of residual confounding within analyses of primary care data is the severity of the condition, which is often apparent to the GP but may not be well captured within the dataset. For example, in the case of the spironolactone study, although all study subjects had heart failure that was sufficiently severe to require treatment with high dose loop diuretics, reliable indicators of disease severity were not

available. By contrast, the GP will have examined the patient for symptoms (such as breathlessness, tiredness and ankle swelling) as well as using test results (including electrocardiogram, echocardiogram and blood tests for relevant biomarkers including natriuretic peptides) to guide treatment decisions (National Institute for Health and Clinical Excellence, 2010). Much of this information will not have been recorded in a way that could be factored into the analysis: for example, Doppler echocardiogram test results may include a measure of blood flow through the heart, but equivalent information is likely to be absent or incompletely captured (e.g. “Doppler studies abnormal”) in medical codes.

Although confounding by indication should always be of concern when estimating effectiveness with observational data, there are certain conditions under which this type of confounding can be better controlled. Routinely captured information describing the severity of the condition and well defined algorithms guiding the selection of treatment are likely to facilitate control of confounding by indication (Freemantle et al., 2013). This thesis focuses on primary prevention of CVD, a condition for which the risk of future events can be estimated in primary care using CVD risk scores such as Framingham or QRisk2 (Hippisley-Cox et al., 2008;D'Agostino et al., 2008). The risk score for a patient may help the GP decide on whether or not they should prescribe statin. Therefore, statin prescribing for primary CVD may be less prone to confounding by indication than conditions such as heart failure because information on components of the CVD risk score are captured in electronic health records. Furthermore, because annual CVD screening is recommended for people with SMI, data on CVD covariates are likely to be relatively well recorded for this patient group (Osborn et al., 2011).

4 Other types of confounding and bias

Bias may also arise when the timing of exposure or start of follow up is not equal across comparison groups: particularly when the comparison group is untreated because it may be unclear how the start of follow up should be defined. As confounding is a diverse and complex issue, I will outline the ways in which this type of bias may be reduced by discussing smaller subtopics: selecting appropriate comparison groups, new-user designs, as well as addressing differences in the characteristics of comparison groups and the importance of selecting a valid index date.

5 Selecting appropriate comparison groups for cohort studies

Comparison groups should be as similar as possible in all aspects except for the intervention under investigation. Identifying the exposed group (such as statin users) is usually relatively straightforward, but choosing an appropriate comparison group in a cohort study is often more complex as a large portion of the unexposed individuals (non-statin users) may not be eligible for treatment. For example, as CVD events are rare in people under the age of 30 years few people under that age would be prescribed a statin. Therefore, it would be more sensible to include people who are older than 30 years in a study examining drugs prescribed to manage CVD risk. Applying strict inclusion and exclusion criteria also increases the similarity between study subjects and may therefore help to produce more precise estimates of effect. However, it should be recognised that there is a trade-off between increasing the similarity of the study subjects and the generalisability of the results, which are specific to individuals who are comparable to the study population (McKee et al., 1999).

6 New-user study designs

New-user designs begin by follow-up of individuals from the time that they first initiate a given treatment and exclude individuals who started treatment before entry into the study (Ray, 2003). The major benefits of this approach are twofold: bias arising from inadequate control for factors that are changed by exposure (for example reductions in cholesterol following statin use) is avoided and the potential to miss outcomes arising soon after exposure is minimised.

The new-user approach is also advantageous when the effect of treatment is not fixed over time, but varies relative to the time of initiation. For example, the risk of coronary heart disease (CHD) in women using hormone replacement therapy (versus no treatment or placebo) is elevated amongst treated women during the first 2 years, but the risk is equivalent to that of non-users when a longer timeframe is considered (Ray, 2003). In this example, incident and prevalent users differ with respect to CHD risk and should not be combined. Another study comparing the results from a RCT of statins and approximately equivalent observational studies showed that including a greater proportion of prevalent users decreased the similarity of the observational estimates relative to the trial results (Danaei et al., 2012).

As part of a bigger study, Danaei and colleagues investigated the impact of statin prescribing on primary prevention of CHD in prevalent statin users versus individuals who were never prescribed a statin (Danaei et al., 2013). The authors calculated an

adjusted HR of 1.42 (1.16-1.73) suggesting a harmful effect of statins that is unlikely to be plausible given the results from RCTs (Taylor et al., 2013). This anomalous result is likely to reflect insufficient adjustment for confounders (such as cholesterol concentration) that are changed by statin use as well as selecting statin users who had a higher risk of CVD than individuals who had never been prescribed a statin. Furthermore, attempts to restrict the exposed group to long term users (e.g. individuals with persistent statin use over a 1 year period) may introduce selection bias because only individuals who have survived and adhered to the medication for at least a year (in this example) will be included in such a study (Danaei et al., 2013). By contrast, defining the exposed group (e.g. statin users) to include individuals with a minimum duration of treatment will exclude people who received a sub-clinical dosage of the intervention. This type of restriction has the advantage of conveying information about the likely impact of optimal treatment (and is therefore more likely to reflect efficacy (The Cochrane Collaboration, 2015)). However, this adds the disadvantage of tending to over-estimate the real-world impact of rolling out the intervention.

7 Addressing differences in the characteristics of comparison groups: propensity score matching and regression

As described above, in clinical practice many treatments are given based on the prescriber's judgement of future risk of adverse health outcomes. This means that direct comparison of treated and untreated individuals is likely to generate biased results, often with treatment appearing to be harmful (Freemantle et al., 2013) because of imbalances in the risk profiles of the comparison groups. For example, it is likely that people who are prescribed a statin will be at higher risk of CVD risk than people who are not prescribed a statin. Possible solutions to this imbalance include adjusting for confounding variables, although this may not resolve imbalances in confounders that have not been measured and which may have influenced either clinician or patient preferences for a given treatment. For example, information on diet and physical activity is not systematically captured in primary care data, but these factors are likely to influence the choice of different options for managing CVD risk for a given patient. Other routinely recorded variables, such as body mass index (BMI) and blood pressure, may provide an indication of some unmeasured factors and can therefore help to reduce unmeasured confounding.

Matching can help to remove imbalances in measured confounders that make up the matching criteria and may also produce comparison groups that are more similar in terms of related - but unmeasured - indicators. For example, by matching on age,

gender, socio-economic status and level of comorbidity it *may* be possible to achieve comparison groups that are more similar in terms of other unmeasured characteristics (e.g. specific aspects of lifestyle). In the event that it is feasible i) to capture all confounding, and ii) to identify unexposed individuals, it becomes possible to estimate an unbiased estimate of effect. However, increasing the number of matching variables reduces the availability of suitable comparison individuals and can quickly become unworkable: for example, applying 10 age categories, two gender categories, five binary diagnosis categories, five binary drug therapies and five cost-of-care categories results in 102,400 potential groups ($10x2x2^5x2^5x5$). Exhaustive matching therefore becomes impossible and may dramatically reduce the number of individuals who can be included in the study, thereby negatively impacting upon sample size and generalisability (Seeger et al., 2007).

Another potential method for addressing imbalances in measured confounders without the need for such complex matching criteria is the propensity score. A propensity score is an estimate of an individual's probability of receiving a treatment given the distribution of their measured covariate data (Rosenbaum and Rubin, 1983). The propensity score can thereby be used as the sole criterion for matching (to select) or adjusting (to balance) comparison groups with respect to their indication for treatment. Instead of matching on all of the individual component variables, the propensity score simplifies the matching process as it does not require a perfect match on each variable and enables a greater portion of individuals to be included in the study. Propensity scores are increasingly used in observational studies because – within strata of the propensity score – individuals are similar (*exchangeable*) in terms of the *observed* variables that constitute the propensity score. Although using a propensity score to adjust for differences measured confounding can be beneficial, bias can still arise due to unmeasured confounding (Bosco et al., 2010).

Despite the increasing popularity of using propensity scores in observational studies, the methodology does not appear to outperform traditional regression methods. A systemic review that compared results from observational studies that adjusted for confounding using a propensity score and (separately) traditional regression concluded that both methods gave similar results (Shah et al., 2005). The effect estimates calculated using traditional regression and propensity score methods were highly concordant (kappa = 0.79 (0.65–0.92)), with propensity scores producing estimates that were, on average, 6% closer to the null (Shah et al., 2005). Furthermore, specific estimates for the effectiveness of statins (versus no treatment) for primary prevention of coronary heart disease (CHD) found almost identical HRs and confidence intervals

derived from either traditional regression or propensity score methods (0.89 (0.73-1.09) and 0.88 (0.72-1.08), respectively) (Danaei et al., 2012).

8 Selecting a valid index date

Another source of bias within observational studies arises when the timing of exposure or follow up differs between comparison groups. This type of bias is problematic where a treated group is compared to an untreated group; as it may be unclear how the start of follow-up should be defined for the untreated individuals. The selection of a valid index date is even more important if it forms part of the criteria used to define a baseline period in which time-varying confounders are measured (e.g. cholesterol measured in the twelve months prior to the index date). Methods to support selecting a valid index date for comparison individuals who did not receive treatment include choosing a date (often randomly) within the time period during which they were eligible to receive treatment (Seeger, 2014;Seeger et al., 2007;Hernan et al., 2008).

9 Approaches for handling missing data

Some covariate data in primary care records are not complete. In particular, cholesterol concentration (estimated from a blood sample) may be measured in line with national policies - including health checks offered to individuals with risk factors such as diabetes - or when clinically indicated. Cholesterol data are therefore unobserved within a given calendar year for a substantial proportion of individuals (ranging from >80% prior to 2002 to <40% after 2010 (Chapter 5)). Local testing policies may also impact upon the ascertainment of data such as cholesterol concentration. For example, total cholesterol concentration is universally measured to determine the lipid profile of a blood sample; however, the high density-lipoprotein cholesterol (HDL-C) fraction is not measured by all NHS clinical laboratories. The proportion of missing data is therefore generally higher for HDL-C than total cholesterol. Other partially observed data include blood pressure, weight, height and smoking status. Unlike cholesterol, this information is often collected at the time of patient registration ((Marston et al., 2014), Chapter 5 section 7.1.2), and also on regular basis for people with long-term conditions such as diabetes, CVD and SMI (National Institute for Health and Clinical Excellence, 2012). However, for people without chronic conditions these health indicators are not routinely recorded at regular time points after registration.

9.1 Types of missing data

There are three assumptions regarding the type of missingness within partially observed data, which have important implications for the likely viability of strategies such as complete case analysis (where data are restricted to records with fully obsereved covariate data) or imputation for missing handling data (Sterne et al., 2009).

9.1.1 Data are Missing Completely At Random (MCAR):

MCAR describes data where missingness of a variable *Y* is independent of both values of *Y* and the fully observed covariate *X*, such that individuals with missing data do not differ systematically from those with fully observed data. This type of missingness is the only scenario when performing a complete case analysis will consistently yield unbiased results (although complete-case analysis of datasets with very low proportions of missing data is unlikely to give strongly biased results).

9.1.2 Data are Missing At Random (MAR):

If *Y* is MAR, missingness is independent of values of *Y* but associated with covariate *X* and missing at completely at random after conditioning on *X*. For example, in a dataset comprising age (fully observed) and blood pressure (partially observed) missing values of blood pressure may increase with older age, but be MCAR within individuals who are the same age. However, without knowing the values of the missing data it is not possible to prove whether the assumption of MAR is correct. It may, however, be reasonable to assume data are MAR and impute missing values using an imputation model that explains the pattern of missingness.

9.1.3 Data are Missing Not At Random (MNAR):

In the event that the pattern of missing data for *Y* is associated with the value of *Y* (e.g. missing low values of blood pressure), then the type of missingness is not random (MNAR) and – even after conditioning on covariate *X* – would be difficult to handle without additional information on the value of *Y*.

A practical implication of clinically indicated data collection is that the distribution of observed and missing data is likely to be associated with other factors such as patient characteristics and calendar time; for example, reflecting changes in screening policy. This pattern of missingness is not compatible with data being MCAR and must instead be assumed to reflect data that are MAR or MNAR. Multiple imputation can be used to handle data that are MAR, although the success of this method is dependent on

specifying an imputation model that that incorporates variables (such as the presence of diabetes) that explain the pattern of missingness (Sterne et al., 2009). I explore patterns of missing CVD data in Chapter 5 and evaluate if it is plausible that data were MAR in Chapter 7.

There are a range of methods available for handling missing data including complete case analysis or other *ad hoc* missing data methods (Carpenter and Kenward, 2013). However, when correctly implemented, multiple imputation performs better than these methods because it becomes possible to analyse data that are MAR for all individuals and also provides more accurate measures of the uncertainty around the effect estimate (Sterne et al., 2009). There is a growing selection of tools to help impute missing data in longitudinal datasets, including the Stata *MI* (*Multiple Imputation*) suite of commands and *twofold FCS* (*fully conditional specification*) algorithm, which have been developed and tested using CVD data extracted from THIN (Nevalainen et al., 2009;Welch and Bartlett, 2013).

Multiple imputation results in many (typically 5-10) copies of the imputed dataset and can be challenging to combine with some methods for controlling confounding: for example, propensity scores. This is because each of the imputed datasets comprise different estimates of the unobserved value. Current methods for combining multiple imputation and propensity score matching are imperfect, although strategies such as incorporating missing data patterns into the score or randomly selecting one possible score per patient have been attempted (Hayes and Groner, 2008). By contrast, methods for undertaking regression analysis with multiple imputed datasets are well established and feasible using standard statistical software packages such as Stata, R or SAS.

10 Summary

Confounding (by indication) and missing data pose major challenges for the use of observational data for causal inference. However, there are a range of techniques to aid the selection of appropriate comparison groups and to undertake analyses that account for differences in the characteristics and follow up time that can help to reduce confounding. Methods for handling missing data are rapidly advancing but are not yet fully compatible with propensity score matching. However, methods for undertaking traditional regression analysis with an imputed dataset are now well developed and supported in most statistical software packages.

11 Methods for analysing observational data to estimate the causal effects of statins: three case studies in populations without SMI

I will now outline three studies (Boxes 1-3 and Table 11-1) that have used different methodological approaches (namely matching with propensity score adjustment, multivariable regression and a series of staggered cohort studies) to estimate causal effects of statins using large primary care databases. These studies have been highly influential on my choice of study design and also provide a useful frame of reference for explaining how the design and methods of my proposed study have developed.

Box 1

Title: Smeeth, L., Douglas, I., Hall, A., Hubbard, R., Evans, S. Effect of statins on a wide range of health outcomes: a cohort study validated by comparison with randomized trials *Br J Clin Pharmacol* 2008 67(1): 99-109

Aim: to replicate the Heart Protection Study using part of a cohort that was analysed to identify the pleiotropic (cholesterol-independent) effects of statins using data from THIN.

Methods: Data were extracted for individuals aged 40-80 years who had a diagnosis of atherosclerosis (before or within the study period) and contributed data between January 1995 and December 2006. Due to the high CVD risk amongst this group, the first 12 months of follow-up after the index date was excluded from the analysis. People with a history of MI or stroke, or a previous statin prescription prior to the index date (statin initiation or randomly generated start date) were excluded. The outcomes examined were time to fatal or non-fatal MI or stroke, and all-cause mortality. Imbalances in the characteristics of exposed and unexposed individuals were minimised by adjusting for a propensity score for being prescribed statin and imposing tight matching criteria: up to five non-statin users were selected from the same practice and matched to each statin user on the basis of sex and five-year age band. The dates of registration also had to be compatible, with registration occurring at least 12 months prior to the index date. Additionally, all individuals needed to consult the GP during the 6 months before or after the index date. In the primary analysis individuals were analysed according to their exposure status at the index date; regardless of later changes in exposure (starting or stopping statin therapy). A sensitivity analysis investigated the impact of curtailing follow up time for individual's whose exposure status changed after the index date.

Results: Adjusted HRs and 95% CI for mortality, MI and stroke were 0.78 (0.74, 0.82), 0.86 (0.76, 0.97) and 0.86 (0.77, 0.97), respectively. The sensitivity analysis investigating changes in exposure after the index date did not produce significantly different results to the main analysis.

Conclusions: The study identified similar effect sizes for statin prescribing on mortality, MI and stroke to the Heart Protection study.

Box 2

Title: Hippisley-Cox, J., Coupland, C., Unintended effects of statins in men and women in England and Wales: population based cohort study using the QResearch database *BMJ* 2010 20;340:c219

Aim: To quantify the unintended effects of statins according to type, dose, and duration of use, using a large UK primary care database (QResearch).

Methods: Data were extracted for an open cohort of new statin users and previously unexposed individuals who were aged 30-84 years. The exposure status of these individuals was defined by whether or not each individual was prescribed a statin over the course of the study period of 6.5 years (1 January 2002-30 June 2008). Entry into the cohort occurred at either the earliest start date (the latest of: January 2002, registration plus twelve months, 30th birthday) for non-statin users or on the date of the first statin prescription after the earliest start date for statin users. A range of outcomes (cataract, fracture, cancer (by type: breast, prostate, lung, colon, melanoma, oesophageal, gastric, renal), liver dysfunction, venous thromboembolism, dementia, rheumatoid arthritis, Parkinson's disease, acute renal failure, myopathy) were studied, and the number needed to treat or harm (NNT/NNH) was calculated for each of these outcomes. Multiple imputation was used to replace missing values for BMI and smoking status, which were used in the main analysis. Analyses were stratified by gender and adjusted for a range of variables including age, BMI, Townsend score, smoking status and the presence of treatment or conditions such as cancer, hypertension or depression. Where appropriate, non-linear functions of continuous variables were included in the models as fractional polynomials.

Results: Data describing the characteristics of exposed and unexposed individuals in the cohort at baseline are presented in the publication. These data appear to show imbalances in some baseline characteristics such as age, gender, comorbidity and the presence of liver function test results between statin users and non-users. Statins were associated with increased risk of myopathy, cataract, acute renal failure and liver dysfunction and reduced risk of oesophageal cancer, but not associated with the other outcomes under investigation. A dose-response effect was apparent for liver dysfunction and acute renal failure.

Conclusions: The results suggest that statins are associated with greater risk of myopathy, cataract, acute renal failure and liver dysfunction, and a reduced risk of oesophageal cancer, in comparison to no statin exposure.

Box 3

Title: Danaei G., Rodriguez G., Cantero O., Logan R., Hernan M., Observational data for comparative effectiveness research: an emulation of randomised trials to estimate the effect of statins on primary prevention of CHD *Stat Methods Res*. 2013 22(1): 70-96

Aim: To mimic recruitment into a series of non-randomised cohort studies (termed "trials" by the authors) of statins that run at staggered intervals using primary care data from THIN.

Methods: Individuals aged 55-84 years who had not been prescribed a statin during the prior 24 months were eligible for inclusion in one or more "trials" that were initiated each month over an 83 month period. Each month a new "trial" enrolled individuals who either i) were prescribed a statin during that month (to form the exposed cohort) or ii) did not initiate statin therapy that month (the unexposed comparison group). Thus a total of 83 distinct "trials" were developed and pooled using the robust sandwich estimator (to account for the same individuals being incorporated in several "trials"). Individuals who stopped being prescribed a statin entered later "trials" after a 24 month washout period from the last day of statin therapy. The authors explored the impact of using different measures of treatment effectiveness and efficacy (akin to the intention to treat, per protocol and as-treated analyses often incorporated into RCTs) and they applied a variety of methods for reducing confounding (statistical adjustment for confounders, propensity score inverse probability weighting).

Results: The fully adjusted HR for the effect of statins on CHD in the main intention to treat analysis was 0.89 (0.73, 1.09), whereas the unadjusted estimate was 1.37 (1.14, 1.66). Fully adjusted results from per protocol and as-treated analyses were 0.86 (0.59, 1.27) and 0.73 (0.50, 1.06), respectively. Comparison of prevalent statin users versus never users yielded a HR of 1.31 (1.04, 1.66). The main intention to treat analysis did not exclude any follow up time, however, a sensitivity analysis undertaken by the authors showed that when between 3 and 12 months of follow up time was excluded the effect estimate for statin prescribing and CHD was protective with a 95% confidence interval that excluded one.

Conclusions: The authors show that an effect estimate that is compatible with the results from randomised controlled trials can be calculated by emulating a trial with observational data, although the confidence intervals around these estimates were wide (e.g. 0.50 to 1.06). They also show that comparison of prevalent statin users and never users results in a biased estimate of effect.

Table 11-1: Key characteristics of three observational studies investigating the effects of statin therapy

First author	Smeeth	Hippisley-Cox	Danaei
Title	*Effect of statins on a wide range of health outcomes: a cohort study validated by comparison with randomized trials*	*Unintended effects of statins in men and women in England and Wales: population based cohort study using the QResearch database*	*Observational data for comparative effectiveness research: an emulation of randomised trials to estimate the effect of statins on primary prevention of CHD*
Objective	To assess the effect of statins on a range of health outcomes and to replicate the Heart Protection Study	To quantify the unintended effects of statins according to type, dose, and duration of use	To test the limitations of a study design that aims to emulate a series of randomised controlled trials of statins
Study design	Prospective open cohort study using routinely collected data	Prospective open cohort study using routinely collected data	Series of prospective staggered cohort studies ("trials") using routinely collected data
Population	Individuals aged 40-80 years between January 1995 and December 2006 who were registered with a THIN practice and had a diagnosis of atherosclerosis: 30,024 statin initiators and a matched sample of 53,598 non-initiators	Individuals aged 30-84 years registered with GP surgeries reporting to the QResearch database: 225,922 statin initiators and 1,778,770 non-initiators	Individuals aged 55-84 years in the year 2000 who were registered with a THIN practice and had no prior history of CHD or other specified conditions. Individuals were excluded if they had a prescription for a statin in the 24 months prior to enrolment: 13,599 new initiators of statins and 831,201 non-initiators
Intervention	Receiving a prescription of simvastatin, atorvastatin, pravastatin, rosuvastatin, fluvastatin or cerivastatin at any point during follow up	Receiving a prescription of simvastatin, atorvastatin, pravastatin, rosuvastatin or fluvastatin at any point during follow-up	Any statin prescription during the one month exposure period at the start of each "trial".
Comparison	No statin prescription at or before the index date	No statin prescription during follow-up	No statin prescription during the one month exposure window at the start of each "trial"
Primary Outcome/s	First recorded occurrence of MI, stroke or death	First recorded occurrence of CVD, moderate or serious myopathic events	First recorded occurrence of MI or death from CHD
Follow-up	Median 4.4 years plus a 12 month washout period post index date	Maximum duration of 6.5 years	Average: 26 months (initiators) and 30 months (non-initiators)

12 Development of the study design to estimate the effectiveness of statins for primary prevention of CVD events in people with SMI

This section of the thesis documents how the study design that I implemented in the main analysis (Chapter 6) was influenced – and is justified - by the strengths and weaknesses of each of the three case studies led by Smeeth (Box 1 (Smeeth et al., 2009)), Hippisley-Cox (Box 2 (Hippisley-Cox and Coupland, 2010) and Danaei (Box 3 (Danaei et al., 2013)).

12.1 Considerations around propensity scores and matching

My initial plans for my study design were strongly influenced by the methods of Smeeth and colleagues. They used a propensity score in combination with judicious eligibility and matching criteria to select statin exposed and unexposed individuals with atherosclerosis who were free of CVD at baseline and did not have a prior statin prescription. However, I believe that the success of Smeeth's study is in part due to the large pool of individuals (30,024 statin initiators and 53,598 people who did not initiate treatment) included in the study which thus enabled the use of restrictive eligibility criteria. For my study, achieving an adequate sample size was likely to be more difficult because the prevalence of schizophrenia and bipolar disorder is relatively low and yields a population of around 24,000 individuals (including only 3,000 that were prescribed a statin) in THIN.

To assess the feasibility of replicating a study similar to that undertaken by Smeeth – within a population of individuals with a diagnosis of SMI - I examined the number of people registered with each GP surgery by strata of gender and age-band that received or did not receive a statin prescription during the study period. As the pool of individuals with SMI is much smaller than the population used by Smeeth, I investigated wider strata of age-band (10 years versus 5 years): these broader strata would not be sufficient to balance differences in age-related CVD risk between exposed and unexposed individuals, but were useful for exploring the feasibility of using more precise matching criteria. The results of these exploratory analyses suggested that, on average, for each person who was prescribed a statin, there were 3.2 individuals of the same 10-year age band and gender within the same practice who were not prescribed a statin. This ratio of possible matches for statin users and non-users (3.2 when using 10-year age bands) was less than 5, which is usually considered optimal in terms of efficient gains in power (Hennessy et al., 1999). Therefore,

matching individuals on the basis of narrower age bands (e.g. 5 years), gender and practice was unlikely to yield sufficient numbers of suitably matched individuals and would be even further reduced by restricting matching to individuals with compatible dates of registration at their practice. In addition, because the majority of prescribing occurred during the latter part of the study period (Chapter 3, section 4), the ratio of unexposed to exposed individuals decreased substantially over the study period and it became progressively more difficult to find appropriate matches for exposed individuals. I therefore concluded that it was not possible to replicate Smeeth's methods within a population of people with SMI in THIN.

Smeeth's study is well designed and is successful in reproducing the results of the Heart Protection Study, however, there are some aspects of the design where modifications could be considered. The eligibility and matching criteria (GP practice, gender, 5-year age-band and time of registration) are used in combination with a propensity score, which in turn was used to adjust (not match) for differences in the scores of exposed and unexposed individuals. However, the authors had to make some assumptions regarding missing data in order to define some of the variables in the propensity score; which may have misclassified some individuals. For example, in Smeeth's study cholesterol was dichotomised into individuals with dyslipidaemia versus no record of dyslipidaemia, which will include many individuals who were not tested. Whilst this practice is common and generally accepted for symptomatic conditions, it is probably less appropriate for measures such as dyslipidaemia that are not usually apparent without testing and do not have a well-defined high risk threshold. The proportion of individuals who did not have available data on cholesterol was not reported in Smeeth's study. However, other research using data from THIN suggests an annual incidence rate for cholesterol monitoring of 7% in adults aged 40 rising to 23-25% in 60-80 year olds during the period 1999-2008, meaning that in a given year data were missing for 75-93% of individuals (Welch, 2012). As the prevalence of dyslipidaemia in the general population aged 40 years or more is in the region of 50-70% (Townsend et al., 2012), it is possible that a significant minority of those who had not had their cholesterol monitored were misclassified as having normal lipids in this study.

I considered - at length - the possibility of developing a propensity score for being prescribed a statin in my main analysis and using this to select statin users and non-users with SMI who were matched within strata of the propensity score. This method was particularly appealing because - within matched strata of the propensity score - estimates of effect for individuals who received treatment (termed Average Treatment

effect on the Treated (ATT)) are equivalent to the treatment effect in both treated and untreated individuals (termed Average Treatment Effect (ATE)) (Austin, 2011;Austin, 2008;Austin et al., 2007). These stratum-specific estimates can be weighted to reflect the whole population and pooled to estimate the ATE for the whole study population (Imbens, 2004). However, as described previously (section 9.1.3), it is not currently possible to use propensity score matching with multiple imputation and I was unable to find any satisfactory means of combining these methods within the literature.

Multiple imputation helps to reduce selection bias because the analysis is not restricted to individuals with complete data (Sterne et al., 2009). Methods for handling missing data were a particular priority in my study because of the likely associations between missing data and statin prescribing, physical (including CVD risk) and mental health. In addition, the limited size of the study population and relatively large amount of missing data add further justification for using multiple imputation in preference to other methods for handling data. Furthermore, multiple imputation has been successfully implemented to investigate CVD risk in individuals with SMI (Osborn et al., 2015). For these reasons I shifted my attention to study designs that used standard regression methods, which have been shown to produce similar effect estimates to using a propensity score, as described in the section 7 above.

12.2 Considerations around selection of exposed and unexposed individuals

One example of a study that uses multiple imputation in combination with regression methods is the study by Hippisley-Cox and Coupland. This study is strong in many respects, particularly in terms of the application of a new-user design, handling unobserved data (on BMI and smoking status) and the use of regression to adjust for differences in a large range of baseline confounders. However, the way in which statin exposure is defined may have introduced some bias.

The study by Hippisley-Cox and Coupland examined a relatively long time period (6.5 years), with a new statin prescription at any point during this period leading to the classification of an individual as exposed. This way of selecting exposed and unexposed groups of individuals could have the unintended effect of identifying people who are systematically different because the design requires individuals who were not prescribed a statin to remain free of statin prescriptions throughout the whole study period (6 years). Indeed in Hippisley-Cox's study, the unexposed individuals appear to be more healthy at baseline (i.e. less likely to require a statin) than exposed individuals. Imbalances in baseline characteristics are particularly apparent for: age (mean 57

years amongst exposed and 42 among unexposed) and the proportion with a liver function test (58.1% among exposed and 9.1% among unexposed), as well as a generally higher prevalence of comorbid conditions such as type two diabetes (21.1% in the exposed group versus 1% in the unexposed) (Hippisley-Cox and Coupland, 2010).

Selecting index dates for individuals is difficult when no placebo or other intervention is provided, and is particularly important if it defines a baseline period in which time-varying confounders are measured (e.g. blood pressure measured in the six months prior to the index date). In their study, Hippisley-Cox and Coupland defined the date of entry as follows: non-statin users: earliest start date (after January 2002, registration plus 12 months, 30th birthday etc.), statin users: first statin prescription date. However, this leaves the study vulnerable to bias arising from the relatively earlier entry of non-statin users into the study; because statin user entry is delayed until the first prescription after the earliest start date.

Because statin users must be alive and event free in the period before they receive a statin, this creates an "*immortal time period*" before the index date – that is excluded from the study for statin users but not non-statin users. This is problematic because an event (and the associated follow-up time) that occurs during the "*immortal time*" can only contribute to the unexposed cohort (overestimating the event rate in the unexposed arm), even though the individual is later prescribed a statin (Suissa, 2007). In instances when exposed and unexposed study populations are analysed in their entirety, or equally sampled, it is possible to correct the biased rate in the unexposed study group by including the "*immortal time*" for the statin users in the denominator. However, in studies where the exposed and unexposed populations are not equally sampled, this may introduce bias that is larger than that arising from excluding the "*immortal time*" preceding the index date (Rothman and Suissa, 2008).

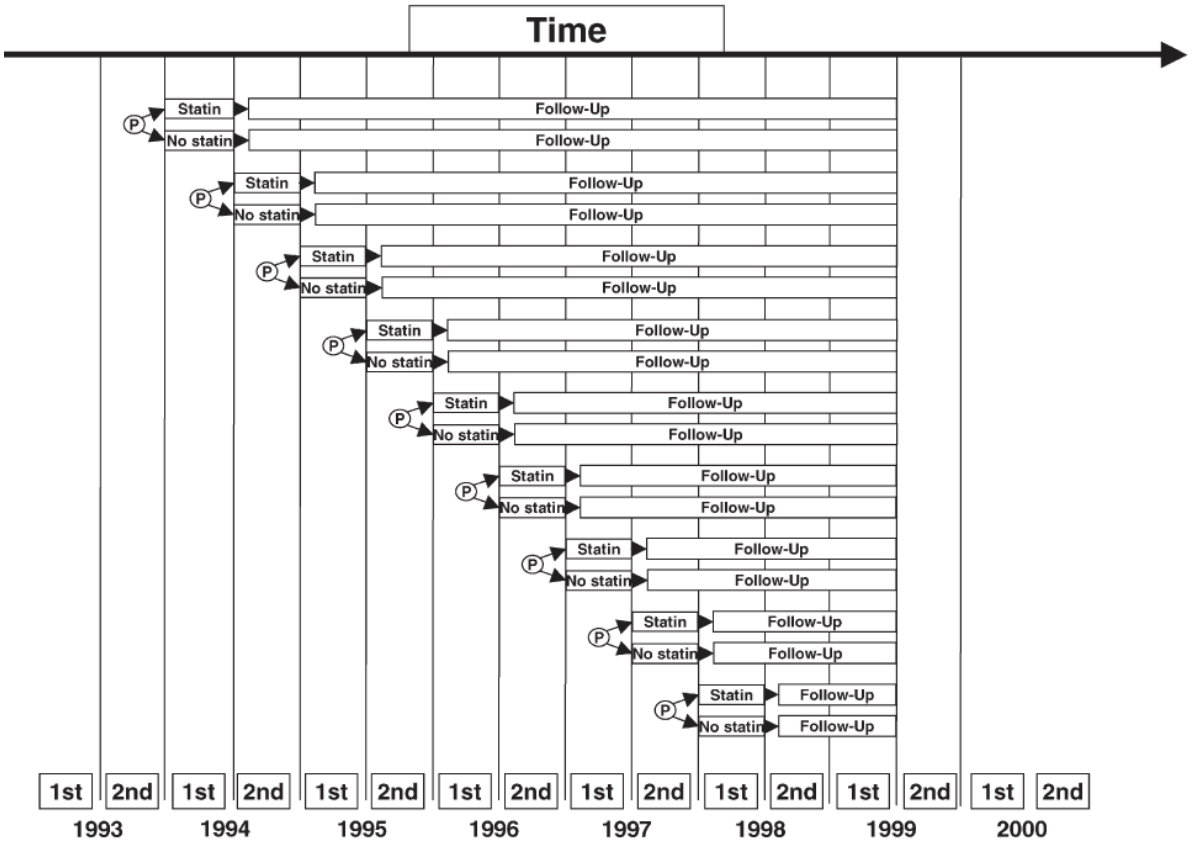
It is difficult to determine the extent to which confounding by indication – and any impact arising from differences in the entry of exposed and unexposed individuals into the cohort – may have impacted upon the results of this study. It is likely that defining statin exposure on the basis of prescriptions over the whole study period will tend to select a non-statin user group that is relatively healthier than statin users: and this scenario is compatible with the imbalance in CVD covariates reported by the authors. However, these imbalances may be largely addressed in the analysis through the application of multivariable regression (as undertaken by the authors) to adjust for differences in measured covariates. By contrast, it is likely that the misclassification of the unexposed "*immortal time*" for individuals in the statin arm will have contributed to

an over-estimation of the event rate in the unexposed arm, thus biasing the results away from the null, although it is unclear what the possible magnitude of bias might be.

12.3 Considerations around the timing of exposure and follow-up

Methods that impose equivalent times of entry for both exposed and unexposed individuals may help to reduce bias and confounding: Seeger, Kurth and Walker used this approach to examine the effectiveness of statins (Seeger et al., 2007). The authors stratified the study into six month blocks of time and looked at whether statins were prescribed during each time block to determine an individual's exposure status (Figure 12-1). Individuals were followed-up from either the index prescription date, or (for unexposed individuals) a random date within the six month time-window until censoring or an event. An *intention-to-treat* approach was used to analyse the data such that all individuals irrespectively of whether statin exposure later changed (e.g. prescribing stopped) were analysed according to statin prescribing at the index date. The authors used these time criteria in conjunction with propensity matching and "*candidacy*" requirements, with the latter requiring all individuals to have dyslipidaemia recorded in the prior six months (Seeger et al., 2007).

Figure 12-1: Study design incorporating a series of staggered cohorts (used with permission)(Seeger, 2014)



Danaei and Hernan have recently proposed a new kind of study design that uses a similar approach – ensuring that the start of follow-up time is balanced across the two exposure groups – to the study developed by Seeger and colleagues. Danaei's study analyses data on a series of staggered cohorts that are initiated at one month intervals in order to imitate multiple non-randomised trials. The authors divided the study period into one month windows of time in which all individuals initiating a statin that month were defined as exposed and all other individuals were unexposed: all individuals with statin prescription in the prior two years were excluded. The study population was then followed-up from the start of the one month window until a first CVD event or censoring occurred.

Using a series of staggered cohorts enables unexposed individuals from previous cohorts to form the study population for future cohorts, as well as allowing newly eligible individuals to be added into subsequent studies. The multiple staggered cohorts that are unique to this design have several advantages over other study types: the selection of exposed and unexposed individuals was done at the same time point but, by having multiple staggered cohort studies, an individual's exposure status to statins could vary over time. Allowing the exposure status to change at different time

points has some advantages over alternative strategies such as conditioning on future exposure or using a long baseline time period to define exposed and unexposed individuals. Both these scenarios potentially introduce bias because the unexposed individuals can never become exposed (and are therefore likely to differ to unexposed individuals), which may lead to selecting a healthier set of unexposed individuals as was demonstrated by the differences in baseline characteristics in the study by Hippisley Cox and Copeland.

The method developed by Danaei should theoretically make it possible to select an unexposed group that is more similar to the exposed group than other study designs exemplified by Hippisley-Cox and Smeeth. Furthermore, this design makes the selection of an index date for unexposed individuals straightforward (as the start of the trial is the same for both exposed and unexposed individuals) and should avoid introducing "*immortal time*" bias. However, it should be stressed that issues of confounding by indication are not fully addressed by the introduction of multiple staggered cohorts alone. Other methods are required to correct inevitable differences in measured baseline confounders for exposed and unexposed individuals.

On balance, the study design developed by Danaei and Hernan appears pragmatic for use with my dataset from THIN as the design aims to reduce selection bias, makes good use of the data and overcomes the problem of selecting an index date for unexposed individuals and is compatible with multiple imputation to estimate unobserved covariate data. However, this study design does not offer a perfect solution and the limitations of the methodology are further evaluated in the discussion chapter (Chapter 7).

13 Summary of the proposed study design

A detailed specification of the study design that I chose to address my main research question is given in Chapter 6.

In summary, the effectiveness of statins for primary prevention of CVD events in people with SMI will be investigated using a study design that most closely resembles the methods used by Danaei.

14 Exploratory work and next steps

In preparation for undertaking the main study, I performed two exploratory studies to investigate patterns of CVD screening and statin prescribing in individuals with and

without SMI (Chapter 5). I investigated patterns of CVD screening to better understand patterns of missing covariate data and thereby inform the imputation model used in the main analysis (Chapter 6). In addition, I investigated patterns of statin prescribing to people with and without SMI, in order to support comparison with results – such as those estimated by Smeeth and Danaei - for people without SMI. Analyses of both CVD screening and statin prescribing are also of public health interest, because they provide an indication of the uptake of physical health checks and whether statin prescribing is comparable amongst people with and without SMI.

Chapter 5 : Exploring patterns of CVD screening and statin prescribing in primary care to individuals with SMI

1 Chapter content

This chapter examines patterns of screening for prevention of cardiovascular disease (CVD) and statin prescribing in individuals with and without severe mental illness (SMI) using data from The Health Improvement Network (THIN). In addition to assessing the impact of health policy on the uptake of CVD screening, this work is important because it characterises the pattern of missing CVD covariate data. These patterns of missing data are used to inform the imputation model that supports the later phases of my PhD work investigating the effectiveness of statin prescribing. In this chapter I first introduce background information on the clinical care pathway, fundamental policies and key publications regarding CVD screening and statin prescribing in primary care in the United Kingdom (UK) for individuals with and without SMI. I then describe the rationale for the study and outline the study aims and objectives. These objectives focus on different parts of the clinical care pathway, namely i) uptake of physical health checks and ii) rates of statin prescribing; with a focus on people who have been screened and therefore have CVD covariate data recorded. This second part of the study is also extended to evaluate whether the rate of statin prescribing differs in people with and without SMI after either stratifying on, or adjusting for differences, in estimated CVD risk scores between these groups. The results and limitations of these studies are discussed with reference to published literature. Finally the implications of the study results are outlined with respect to the planning of the main analysis and for policy and practice.

This work was peer-reviewed and subsequently accepted for presentation at the following conferences (associated abstracts are outlined in the appendix, section 23):

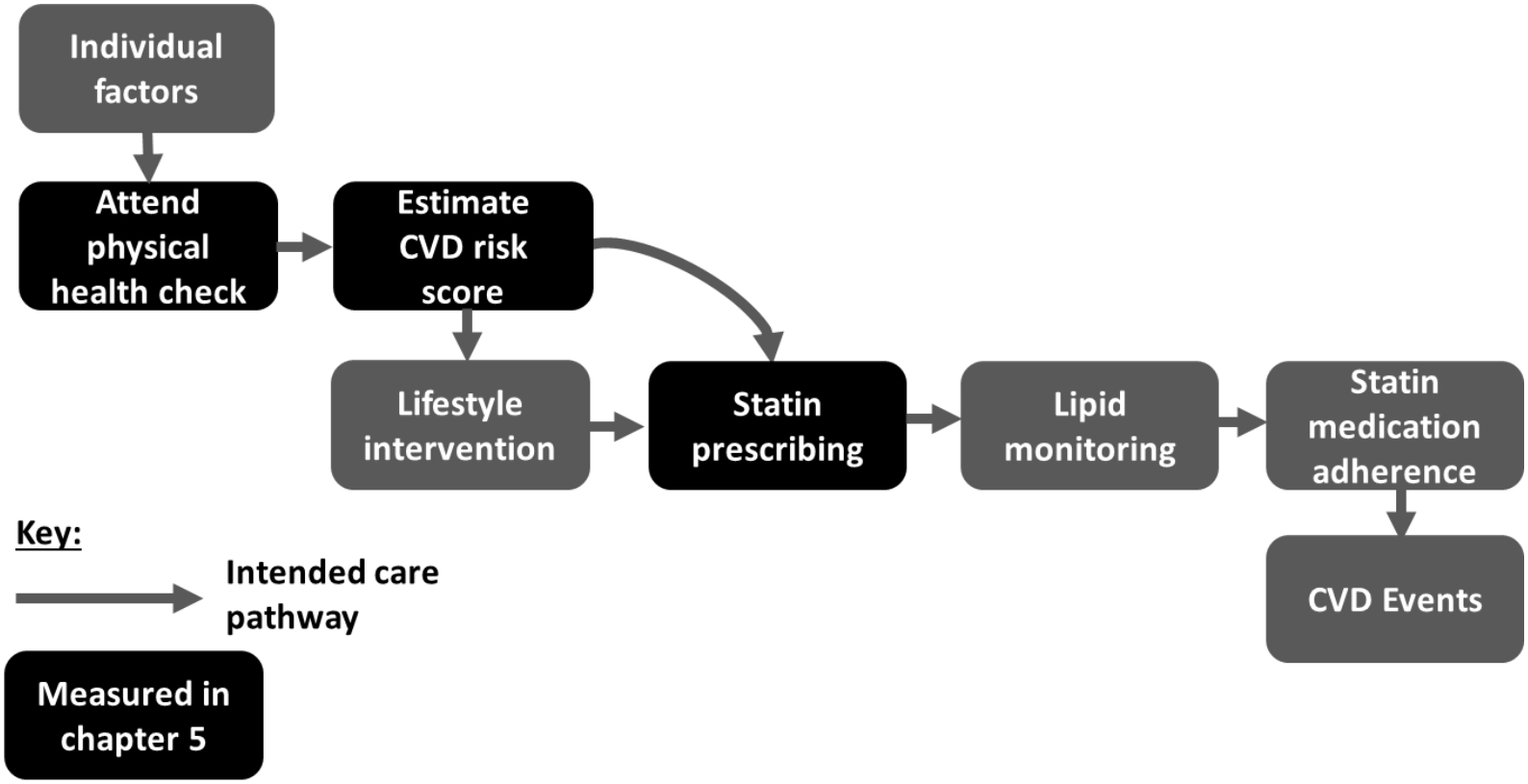
- Primary Care Mental Health Annual Conference (March 2014 - Exeter): poster presentation
- UK Society of Academic Primary Care (SAPC) annual conference (July 2014 - Edinburgh) where it received the 2014 SAPC Travel Award to present an extended version of the original oral presentation at the North American Primary Care Research Group Annual Conference (November 2014 – New York)

- International Society for Pharmaco-Epidemiology Annual Conference (October 2014 - Taipei): oral presentation (Blackburn et al., 2014a)

2 CVD screening and statin prescribing: UK primary care policies

Primary prevention of CVD in primary care settings is initiated through a multi-step process, in which a physical health check is used to screen and identify people who are likely to benefit from interventions to manage CVD risk (Figure 2-1).

Figure 2-1: Clinical care pathway for CVD screening and statin prescribing for primary prevention of CVD in UK primary care

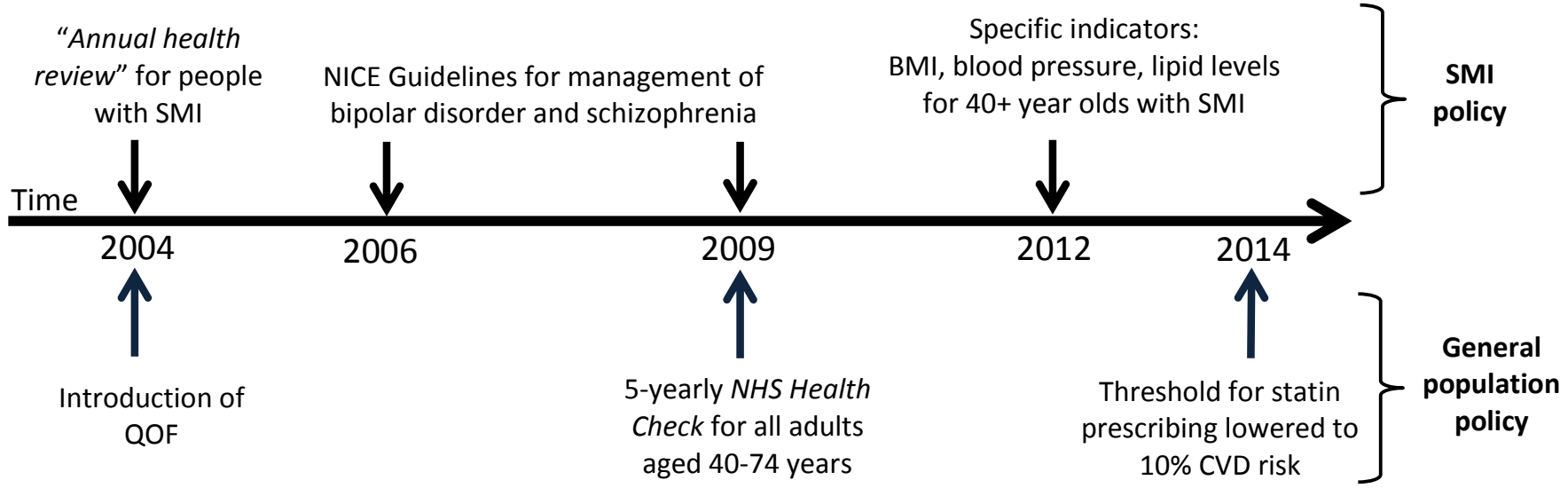


A physical health check aims to facilitate estimation of a CVD risk score - such as Framingham (D'Agostino et al., 2008) or QRisk2 (Hippisley-Cox et al., 2008) - by measuring the information that is needed to calculate an individual's risk of developing CVD over a ten year period. In the case of the Framingham risk score, this information is age, gender, diabetes, smoking status, blood pressure, use of medication for hypertension and either body mass index (BMI) or total cholesterol and high density-lipoprotein-cholesterol (HDL-C) concentration in combination (as outlined in Chapter 3 section 3.2.6). Other risk scores – including QRisk2 – may also use additional information on ethnicity, geographical region, family history of CVD, chronic kidney disease (CKD) and rheumatoid arthritis ((Hippisley-Cox et al., 2008)). In addition, both Framingham and QRisk2 risk scores include information on the presence of atrial fibrillation, which is associated with a three-fold greater risk of stroke but has a low prevalence (<0.5%) amongst people without pre-existing CVD (DeWilde et al., 2006). Online interfaces to calculate an individual's risk score are freely available (e.g. http://qrisk.org/) and have also been integrated into software - such as Vision – that is routinely used by General Practitioners (GPs). Within Vision software CVD risk scores are automatically estimated using the most recently recorded patient data available (Abegunde, 2010).

According to national guidelines, "high" CVD risk has historically been defined as a ≥20% likelihood of having a CVD event over a 10 year period (National Institute for Health and Clinical Excellence, 2008b), but was re-defined in July 2014 to a ≥10% risk over a 10 year period (National Institute for Health and Clinical Excellence, 2014b)). Both sets of guidelines acknowledge that people with SMI may have additional risk factors (e.g. smoking more heavily) relative to the general population and that risk scores may therefore underestimate risk: however, they do not explicitly define bespoke guidance for statin prescribing to people with SMI.

Recent policy developments are outlined in Figure 2-2.

Figure 2-2: CVD screening and prescribing policy developments in individuals with SMI and the UK general population.



QOF; Quality and Outcomes Framework, NICE; National Institute for Health and Clinical Excellence

In 2004 the Quality and Outcomes Framework (QOF) was implemented, and this strategy helped to promote annual physical health checks for people on the SMI register (National Institute for Health and Clinical Excellence, 2006;National Institute for Health and Clinical Excellence, 2009). However, financial incentives for GPs to measure specific components of the physical health check (blood pressure, BMI, diabetes, cholesterol and smoking status) were not implemented until 2012 (National Institute for Health and Clinical Excellence, 2012). These policy interventions have been associated with increased uptake of physical health checks in people with SMI (Osborn et al., 2011): however, the absolute uptake of screening remains low, with estimates suggesting that around one third of people with schizophrenia received a full health check in 2012 (Royal College of Psychiatrists, 2014). In the general population, the NHS Health Check was introduced in 2009 and advocates offering a similar physical health check to all adults aged 40-74 years on a five-yearly basis (Department of Health, 2015). The NHS Health Check includes measuring blood pressure, BMI, diabetes, cholesterol and smoking status (National Institute for Health and Clinical Excellence, 2012).

2.1 CVD screening in people with SMI

The provision of physical health checks to people with SMI in the UK has been explored using primary care data from THIN for the period 2000-2007 (Osborn et al., 2011). The study compared the completeness of recording of CVD covariates in 18,696 patients with SMI (primarily diagnoses of schizophrenia, bipolar disorder or schizoaffective disorder) and 95,512 gender and five-year age-band frequency matched comparison patients without a SMI diagnosis. Annual incident rate ratios (IRRs) (adjusted for age, sex, Townsend score for deprivation, consultation rate and whether the patient was newly registered) derived from the study showed that recording of BMI, total cholesterol, blood pressure and glucose monitoring all increased over time and that the gap in uptake between people with and without SMI reduced during the study period. There were some important differences by age: in the most recent time period in the study (2007) the rate of uptake was approximately equal in patients aged 18-59 years with and without SMI, whereas the rate amongst older patients with SMI was 20-35% lower than people without SMI (Osborn et al., 2011).

2.2 Statin prescribing to individuals with SMI

In the UK, statins are one of three major groups of pharmacological interventions for reducing CVD risk in and are considered to be cost-effective for primary prevention in high risk individuals in the general population (Taylor et al., 2013). At present, little is

known about patterns of statin prescribing to individuals with SMI and how this compares with the general population. I was unable to find any studies investigating the provision of statin therapy specifically for primary prevention of CVD in people with SMI. However, a meta-analysis of three studies examining statin prescribing for a mixture of primary and secondary prevention of CVD found that people with SMI were almost 40% less likely to access statin therapy than people without mental illness (odds ratio (OR) 0.61 (0.39-0.94)) (Mitchell et al., 2012).

3 Rationale for investigating CVD screening and statin prescribing in individuals with and without SMI

The risk of CVD morbidity and associated mortality is much higher amongst people with schizophrenia and bipolar disorder relative to individuals without SMI: those aged between 50 and 74 have approximately two-fold risk (IRR 1.86 and 95% CI 1.63-2.12) (Osborn et al., 2007a) and improved management of CVD risk is needed. Historically, there has been substantial inequality in the uptake of physical health checks to older people with SMI (Osborn et al., 2011) and under-provision of interventions for disease prevention (Mitchell et al., 2012). Statins are clinically and cost-effective for preventing CVD in the general population, however, the uptake of statin therapy for primary prevention of CVD in people with SMI is not known.

I set out to characterise differences in statin prescribing patterns in people with and without SMI for two reasons: i) to evaluate the viability of using estimates of statin effectiveness in the general population as an external validity check for the later phases of my PhD research. ii) To inform the development of the imputation model used to develop the dataset for the main analysis investigating the effectiveness of statins.

4 Aim

This chapter aims to explore patterns of CVD risk screening and to describe differences in the prescribing of statins to people with and without SMI who do not have a pre-existing CVD condition.

4.1 Objectives

1) Investigate the rate of physical health checks and describe how rates differ in people with and without SMI

2) Investigate rates of statin prescribing in people who have been prescribed a statin for the first time
3) **i)** Describe how rates of new statin prescribing differ in people with and without SMI within a given timeframe
   ii) Amongst people who have had a CVD screen, investigate whether the rate of statin prescribing differs in people with and without SMI after accounting for differences in estimated CVD risk

5 Methods:

5.1 Data Source

THIN was the data source for this study: an extended description of the database and indicators of the reliability of the data are outlined in Chapter 3.

5.2 Inclusion and exclusion criteria

A retrospective cohort study was developed: data for all GP surgeries were extracted for people with a diagnosis of schizophrenia or bipolar disorder (case definitions outlined in Chapter 3 and code lists included in the appendix; section 20) for the period 1st January 2002 to 31st December 2012. Ten times as many comparison individuals from the same practice who did not have a SMI diagnosis were frequency-matched by age (±5 years at study start) and gender to individuals with SMI. People were excluded from the comparison cohort if they had a diagnosis of bipolar disorder, schizophrenia, other type of non-organic psychosis or had a record indicating that they were on the SMI register.

Inclusion Criteria: people aged 30-99 years old who; i) were permanently registered with the GP practice (Patflag A and C) ii) consulted their GP within the study period and iii) had data reported after practice acceptable mortality rate (AMR) and acceptable computer usage (ACU) dates (further detail outlined in Chapter 3 section 3.2).

Exclusion Criteria: people who; i) had a diagnosis of CVD prior to the start of the study ii) were prescribed a statin prior to start of the study.

Entry into the study was at the latest of:

i) 1st January 2002
ii) 30th birthday
iii) date of registration plus 6 months

iv) date of practice AMR or ACU (Horsfall et al., 2012;Maguire et al., 2009)

Exit from the study occurred at the earliest of:

i) 31st December 2012
ii) 100th birthday
iii) out of practice transfer
iv) first statin prescription
v) first CVD event
vi) death

Individuals were not eligible to enter the study until six months after the date of registration: this was in order to exclude people with prevalent diagnoses of CVD or who were continuing statin treatment from when they were registered with another general practice. I used this cut-off based on another study which demonstrated that incidence rates for the majority of acute conditions – including MI – stabilize within six months of the date of registration (Lewis et al., 2005).

People below the age of 30 years were not included in the cohort because the risk of CVD is very low and because UK policy for management of CVD focuses on people aged 40 and above. In addition, the majority of people who develop SMI are diagnosed before the age of 30 (Kirkbride et al., 2012) and diagnoses may be missed or less accurate at substantially younger ages. The upper age limit (100 years) should help exclude people with erroneously recorded age and to ensure that the cohort age range is representative of those with SMI.

Additional criteria for objectives 3i and 3ii: It was necessary to apply extra inclusion criteria for objectives 3i and 3ii, which investigated statin prescribing to individuals within the time period 1st January 2007-31st December 2012. The time period (2007-2012) was selected because UK policy introduced in 2009 advocates offering an NHS health check to the general population aged 40-74 on a five-yearly basis and it would therefore be anticipated that everyone in the target population should be offered a health check over the course of a six year period. By contrast, people with SMI should be offered a health check annually. In addition, objective 3ii restricted the cohort to people aged 30-74 years for whom a full CVD screen had been undertaken. A full CVD screen was defined as one or more records of: weight or lipids (total cholesterol and HDL-C) and blood pressure within the 6 year period 1st January 2007-31st December 2012, plus at least one adult record of height and smoking status recorded before the end of follow-up. People aged 75 years and older were excluded from the cohort data

analysed for objective 3ii because Framingham risk scores can only reliably be calculated for people aged 30-74 years (D'Agostino et al., 2008).

Study variables (Chapter 3 section 3.2 and appendix; section 20)

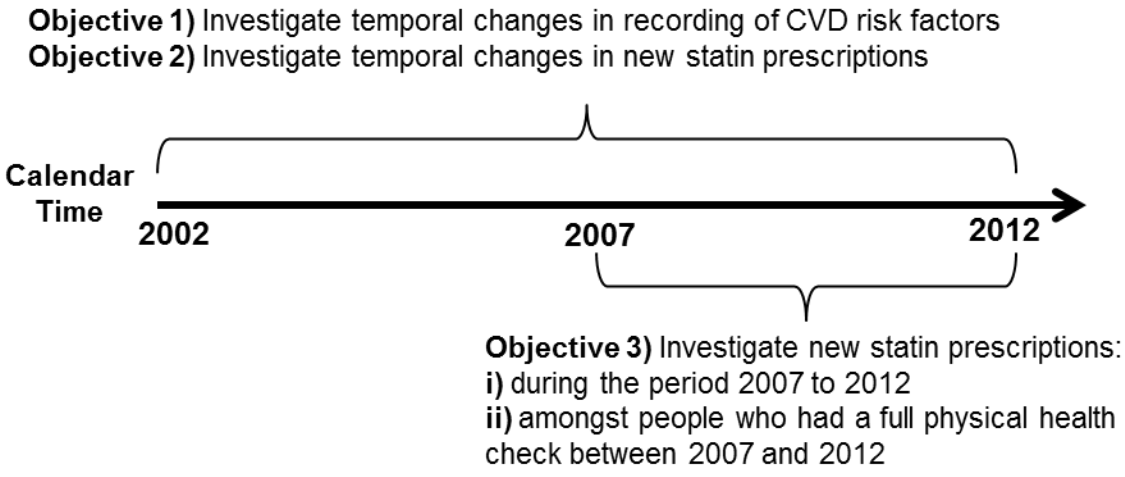
- **Core individual data:** age, sex and Townsend score for deprivation
- **CVD risk covariates:** blood pressure, weight, height, total and HDL-C concentration, diabetes and smoking status
- **Presence of SMI**: Read codes for bipolar disorder or schizophrenia
- **Exposure to statins:** one or more statin prescriptions

Data on covariates such as blood pressure were included for each individual from the twelve months prior to entering the study until the end of follow up. The distribution of categorical and continuous variables was compared using χ^2 and Mann-Whitney tests respectively, with the latter selected on the basis that data were not required to have a normal distribution (which was important because the values of covariates such as cholesterol cannot be negative and therefore tend to have a distribution that is skewed towards higher values).

6 Analysis

Figure 6-1 presents an overview of the time periods investigated for each of the three objectives, which are outlined in greater depth in the following text.

Figure 6-1: Overview of the time periods investigated by different parts of the analysis



Objective 1) Temporal changes in the recording of CVD risk factors in people with and without SMI (2002-2012)

Annual rates of the recording of CVD risk factors were calculated separately for each year by dividing the number of people with one or more recorded physical health indicators (height, weight, blood pressure, cholesterol, smoking status) in the 12 month period by the total number of people who were under follow up during the same calendar year. Four separate age groups (30-39, 40-59, 60-74, 75-99 years), which are compatible with age groups targeted by policies for the general population or people with SMI, were considered. Wilson's method (Brown et al., 2001) was used to calculate 95% confidence intervals (CI) that were bounded within 0 and 1 in order to estimate the proportion who had a physical health check.

New patient registration is a key time point for capturing information on health indicators (Marston et al., 2014): the proportion of people who had a measurement of weight, blood pressure, cholesterol or smoking status recorded in primary care was calculated for each calendar year from the time of registration. This method was repeated for people with and without SMI who were newly registered in three years (2005, 2007 or 2010) that were selected to cover a broad cross-section of time after the introduction of QOF.

The uptake of a full physical health screen was assessed. A full physical health screen was defined as at least one adult record of smoking status (during follow-up) plus one or more records within a given calendar year of:

- Systolic blood pressure

And one of:

- Total cholesterol and HDL-C (laboratory CVD risk score)
- BMI (office CVD risk score)

The proportion screened was estimated by dividing the number of people in the 12 month period with data for these covariates by the total number of people who were under follow-up during the same calendar year. Measuring smoking status should be part of the CVD screening process, however, I dropped the requirement for an annual record because smoking status appeared to be routinely collected at the time of patient registration rather than annually (see Figure 7-7).

Objective 2) Temporal changes in rates of new statin prescriptions to people with and without SMI (2002-2012)

Annual rates of new statin prescriptions were calculated by dividing the number of people with a first statin prescription in a given 12 month period by the total person-time at risk during the same period. Data were analysed by age-group (30-39, 40-59, 60-74, 75-99 years).

Objective 3i) Investigate differences in the rate of new statin prescriptions to people with and without SMI (2007 to 2012)

Poisson regression models were used to calculate IRRs separately for the four age groups (30-39, 40-59, 60-74, 75-99 years) for the period January 1st 2007 to December 31st 2012, with new statin prescriptions as the outcome. Likelihood ratio testing was used to assess evidence of an association between statin prescribing and SMI in a model that was adjusted for Townsend quintile of deprivation, gender and age in five year age bands (to account for additional confounding by age).

Objective 3ii) Investigate the rate of new statin prescriptions amongst people who had a full physical health check between 2007 and 2012

Estimated 10 year CVD risk was calculated for each individual using records from January 1st 2007 to December 31st 2012. CVD covariates for each individual were pooled from all time points that preceded statin prescribing between 2007 and 2012: where multiple measurements were available for the same patient, the mean of these values was calculated to contribute to the risk score. The method used to estimate CVD risk scores is outlined in the section 3.2.6 of Chapter 3.

Estimated CVD risk was used to stratify individuals into risk strata of 5-percentile intervals (<5%, 5-9%, 10-14% etc.) between 0-29% and 10-percentile intervals thereafter. The proportion of people who were prescribed a statin during the study period was calculated for the each of the SMI cohorts within strata of CVD risk and plotted against the proportion of people who were prescribed a statin.

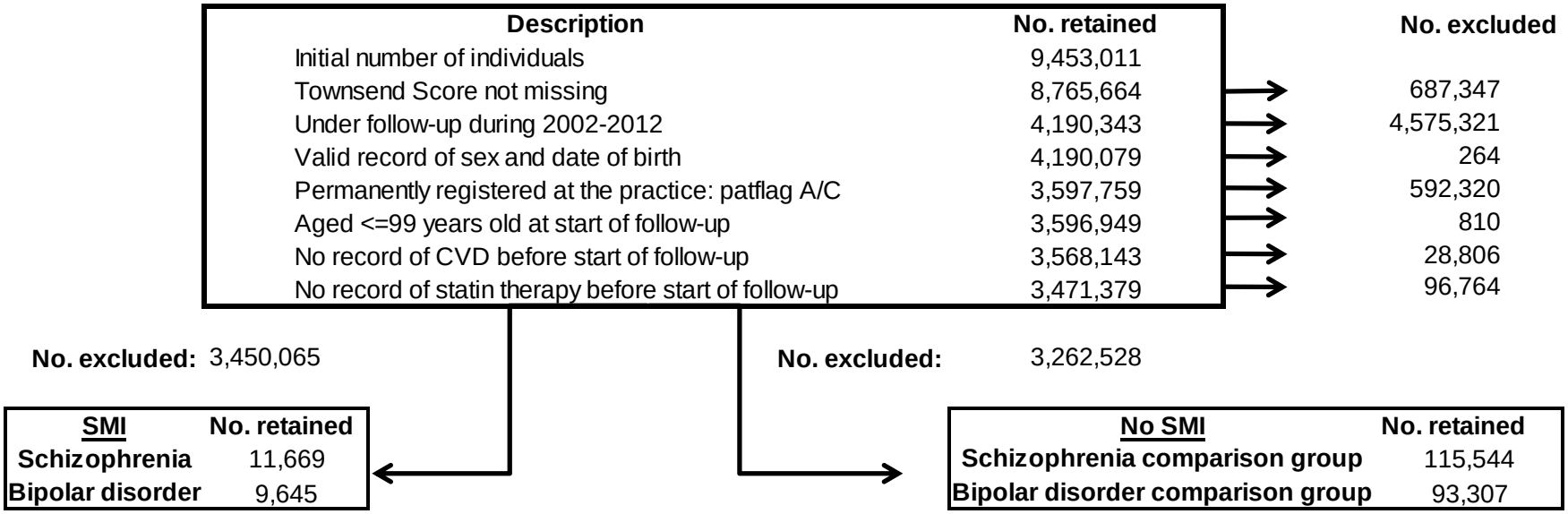
Evidence for differences in the rate of statin prescribing to people with and without SMI was formally tested using Poisson regression models that were adjusted for estimated CVD risk. Preliminary analysis of the proportion of people who were prescribed a statin plotted against estimated CVD risk suggested a non-linear relationship that could be modelled using restricted cubic splines (Harrell, 2001) and further illustrated in previous work that I have undertaken (Blackburn et al., 2014b). Splines are a collection of linear

and cubic functions joined at one or more breakpoints, which are termed knots. This analysis used a restricted cubic spline with three knots (placed at recommended intervals of 10th, 50th and 90th percentiles (Harrell, 2001)) that was incorporated into Poisson regression models for the rate of new statin prescribing in people with and without SMI. The spline variables were calculated using the Stata package *mkspline2* and the fit of the spline to the underlying data was checked by visualising the spline using *postrcspline* (Buis, 2009). Likelihood ratio testing was used to assess evidence of an interaction between SMI and the spline terms for CVD risk.

7 Results

A flowchart outlining case numbers for people included and excluded from the study is outlined in Figure 7-1. A total of 11,669 people with a diagnosis of schizophrenia and 9,645 people with a diagnosis of bipolar disorder were identified for inclusion in the study between January 1st 2002 and December 31st 2012. A total of 115,544 and 93,307 age and gender frequency-matched people who did not have a SMI diagnosis formed the comparison groups for the schizophrenia and bipolar cohorts, respectively.

Figure 7-1: Dataflow for data extraction for people with and without SMI



The median duration of follow up was shorter amongst people with SMI. People with a diagnosis of schizophrenia were followed up for an average of 4.2 years (interquartile range (IQR): 1.8-7.9 years) versus 5.3 (IQR: 2.3-9.6) in the comparison group. People with a diagnosis of bipolar disorder were followed up for an average of 4.5 years (IQR: 1.9-8.5) versus 5.6 years (IQR: 2.4-10.0) in the comparison group.

7.1 Objective 1) Temporal changes the recording of physical health checks

7.1.1 Separate components of the CVD risk score

The proportion of people who had at least one measurement per year for weight, blood pressure, total cholesterol or HDL-C-concentration increased substantially over the study period (

Figure 7-2 to Figure 7-9) for the period 1st January 2002 to 31st December 2012). The next section describes the recording of physical health checks in over calendar time for each of the components of the Framingham risk score. In general, the rate of uptake of physical health checks has increased since 2002 both for people with and without SMI: however, the magnitude of increase has been greater amongst people with SMI. Stratifying uptake by age (30-39, 40-59, 60-74, 75-99 years) and type of SMI (schizophrenia or bipolar disorder) has highlighted differences in the rate of recording of physical health measures between sub-groups.

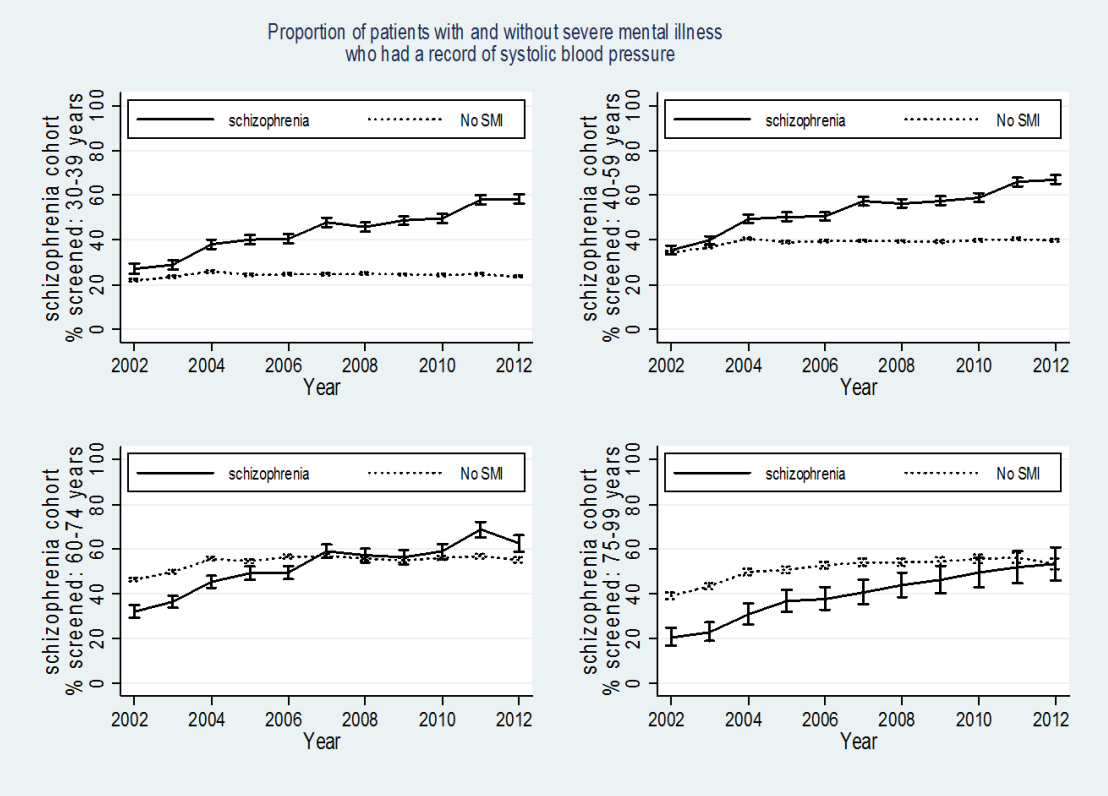
7.1.1.1 Blood pressure

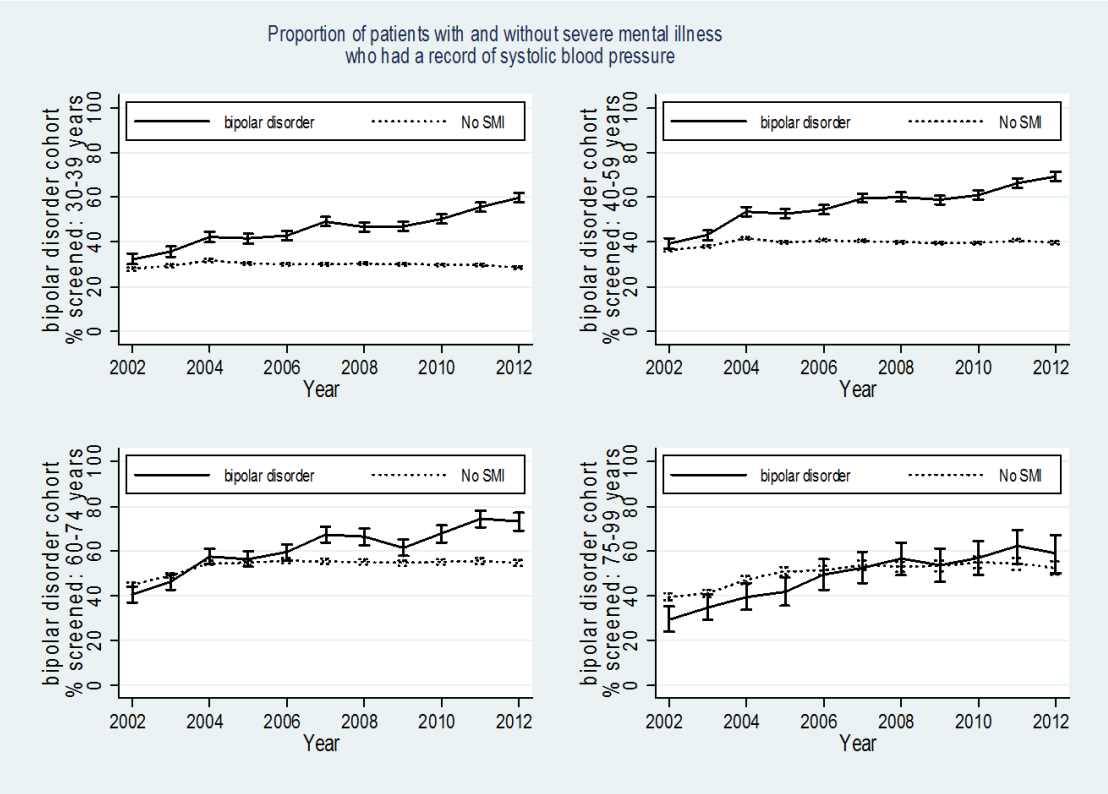
Amongst people with a diagnosis of SMI, 25-40% had a blood pressure measurement taken in 2002 an uptake increased over time to 60-75% in 2012 (

Figure 7-2). During the same time period the uptake of blood pressure monitoring in people without SMI started at a similar level (20-40% in 2002) and remained fairly constant in people aged 30-39 and 40-59 years; but rose by approximately 10% in people aged 60-74 and 75-99 years.

The proportion of people who had a record of systolic blood pressure recorded within each calendar year between 2002 and 2012 was consistently highest amongst people aged 30-39 and 40-59 years who had a diagnosis of SMI than people without SMI. The rate of uptake of blood pressure measurements occurred more slowly amongst people over 60 years of age and only reached comparable levels in the oldest age group (75-99 years) amongst people with and without SMI after 2012.

Figure 7-2: Annual measurement of blood pressure recorded in people with schizophrenia (above) or bipolar disorder (below) compared to people without SMI



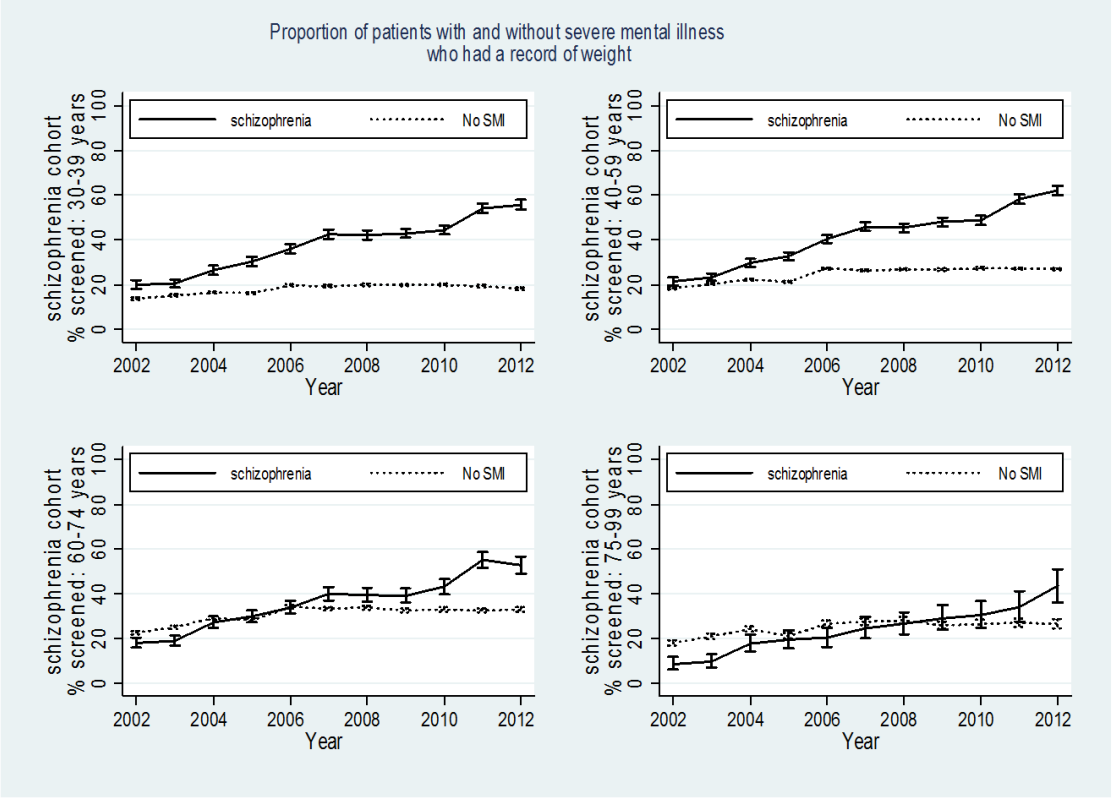


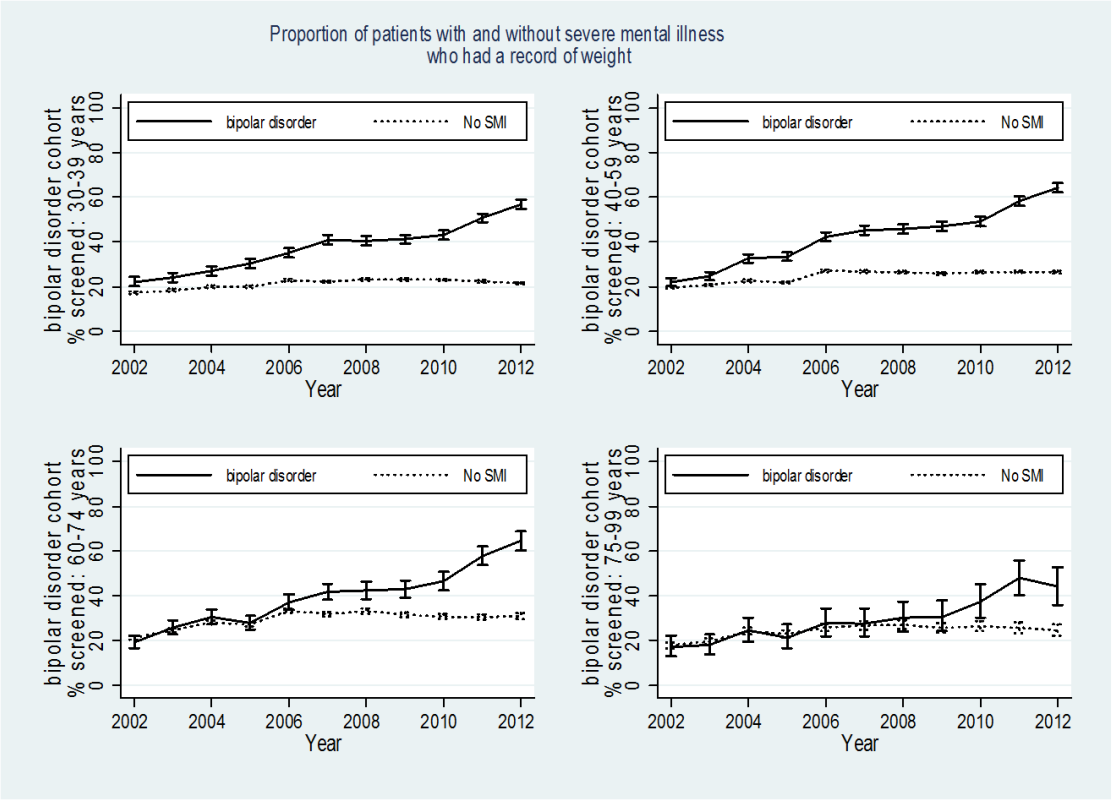
7.1.1.2 Weight

Amongst people with SMI, approximately one fifth had a weight measurement taken in 2002 compared to 50-60% in 2012 (Figure 7-3). During the same time period the uptake of weight monitoring in people without SMI was at a similar level (15-20% in 2002) and increased by approximately 10% between 2002 and 2006 and remained at relatively constant levels thereafter.

The proportion of people who had a record of weight was consistently highest amongst people aged 30-39 and 40-59 years with a diagnosis of SMI. The rate of uptake of weight monitoring was slower amongst people over 60 years of age and only reached comparable levels in the oldest age group (75-99 years) amongst people with and without SMI after 2006.

Figure 7-3: Annual measurement of weight recorded in people with schizophrenia (above) or bipolar disorder (below) compared to people without SMI





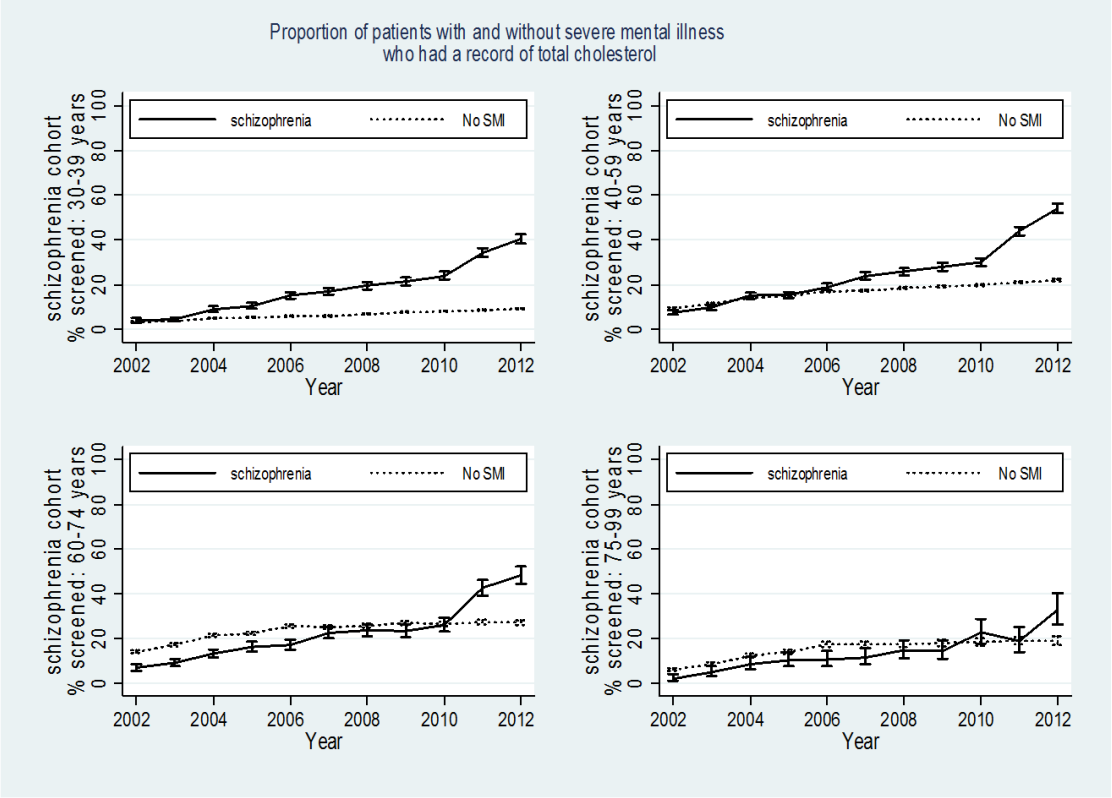
7.1.1.3 Total cholesterol

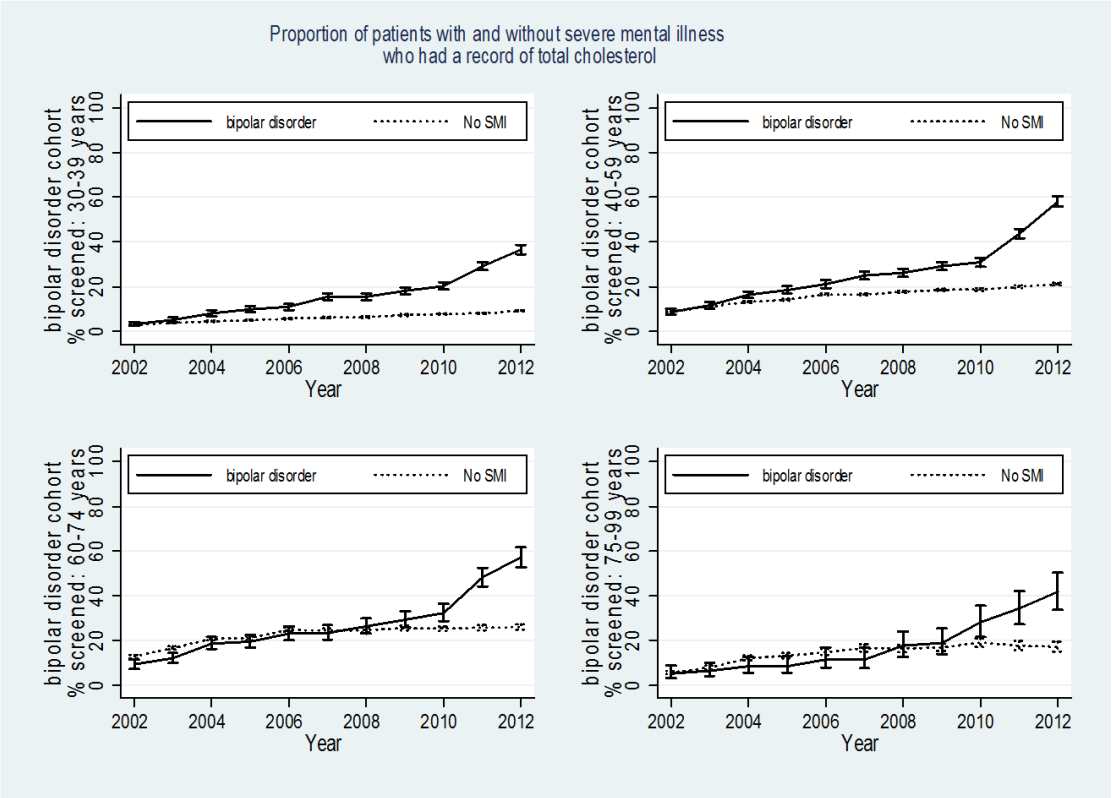
The uptake of total cholesterol monitoring in people with SMI increased markedly between 2002 and 2012 from no more than 10% in 2002 to 30-60% in 2012 (Figure 7-4). The rate of annual cholesterol monitoring increased most sharply in people with SMI between 2010 and 2012 and uptake approximately doubled during this time period. Total cholesterol monitoring also increased in people without SMI, but at a slower and smoother rate: in 2002 approximately 10% had a total cholesterol measurement taken, increasing to 20-25% by 2012.

Patterns of cholesterol monitoring were generally similar for both SMI groups; however, uptake amongst people with schizophrenia appeared to lag behind people with bipolar disorder. This trend was particularly evident for the oldest age group (75-99 years) for which levels of cholesterol monitoring in people with and without SMI reached comparable levels in 2009 for the bipolar disorder cohort and 2011 for the schizophrenia cohort.

Cholesterol monitoring during 2012 was more common amongst people with SMI than those without for all age groups: absolute uptake was greatest in people aged 40-74 years with the largest relative increase in the youngest age group (30-39 years).

Figure 7-4: Annual measurement of total cholesterol recorded in people with schizophrenia (above) or bipolar disorder (below) compared to people without SMI

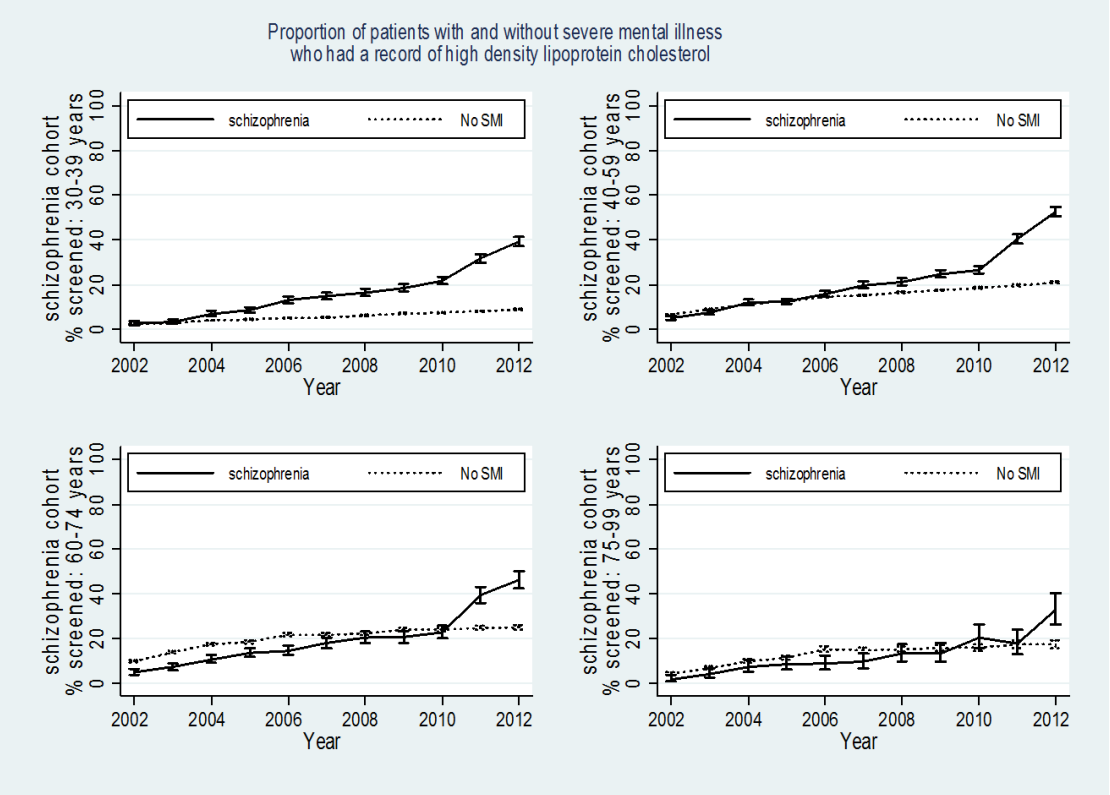


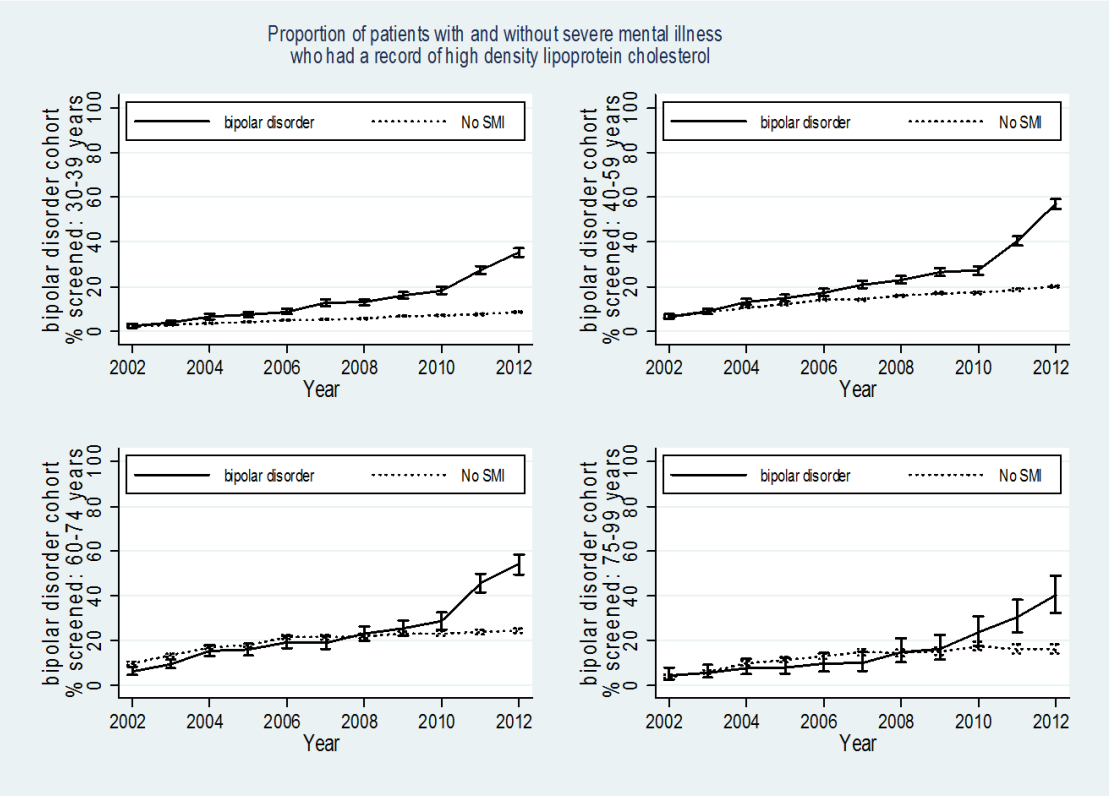


7.1.1.4 HDL-C

HDL-C testing (Figure 7-5) followed a very similar pattern to total cholesterol monitoring, although uptake of HDL-C monitoring was consistently slightly (2-5%) lower than for total cholesterol.

Figure 7-5: Annual measurement of high density lipoprotein-cholesterol recorded in people with schizophrenia (above) or bipolar disorder (below) compared to people without SMI

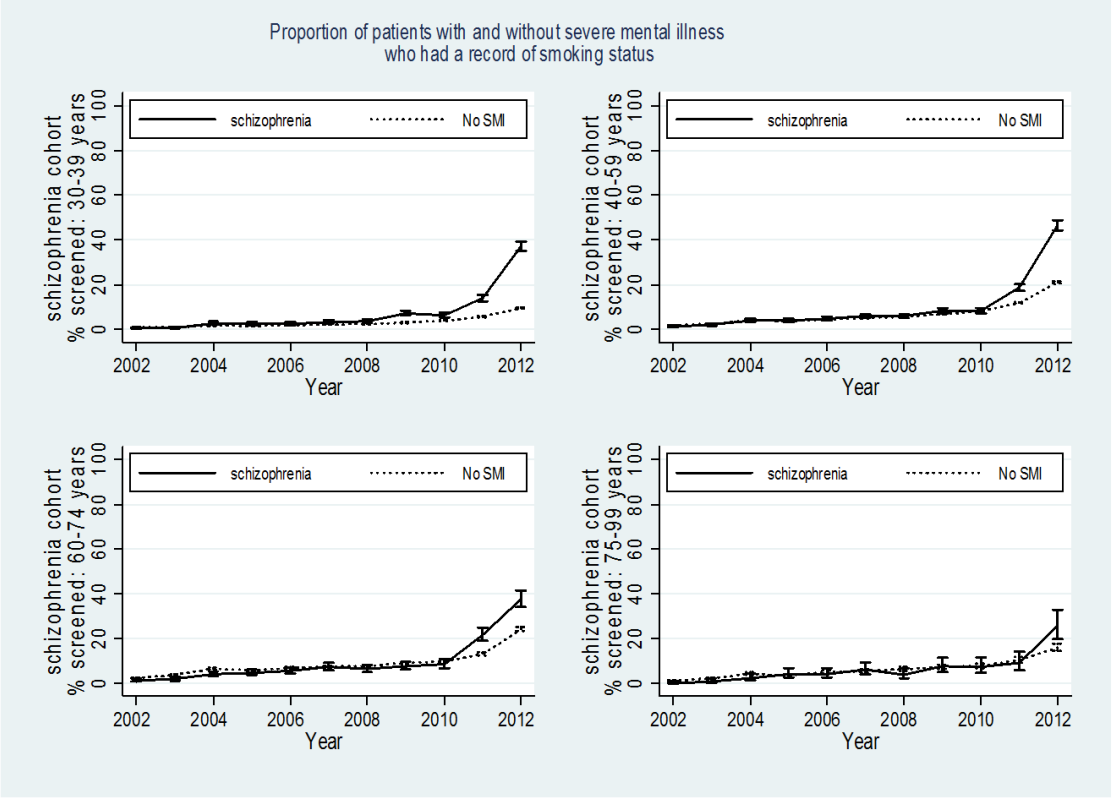


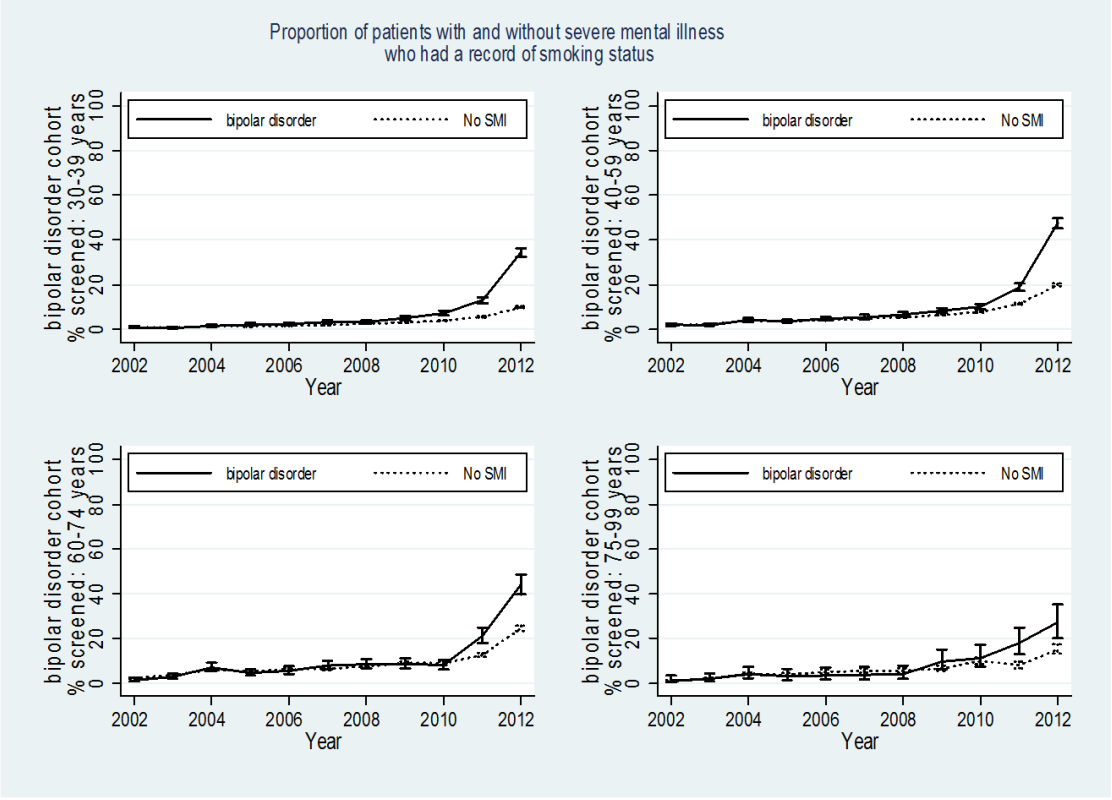


7.1.1.5 Smoking

The pattern of recording suggests that only a minority (<20%) of people had smoking status recorded each year between 2002 and 2010 (Figure 7-6). However, the proportion of people who had smoking status recorded in 2011 and 2012 was substantially higher: up to 50% amongst people with SMI and 10-20% amongst people without SMI.

Figure 7-6: Annual measurement of smoking status recorded in people with schizophrenia (above) or bipolar disorder (below) compared to people without SMI

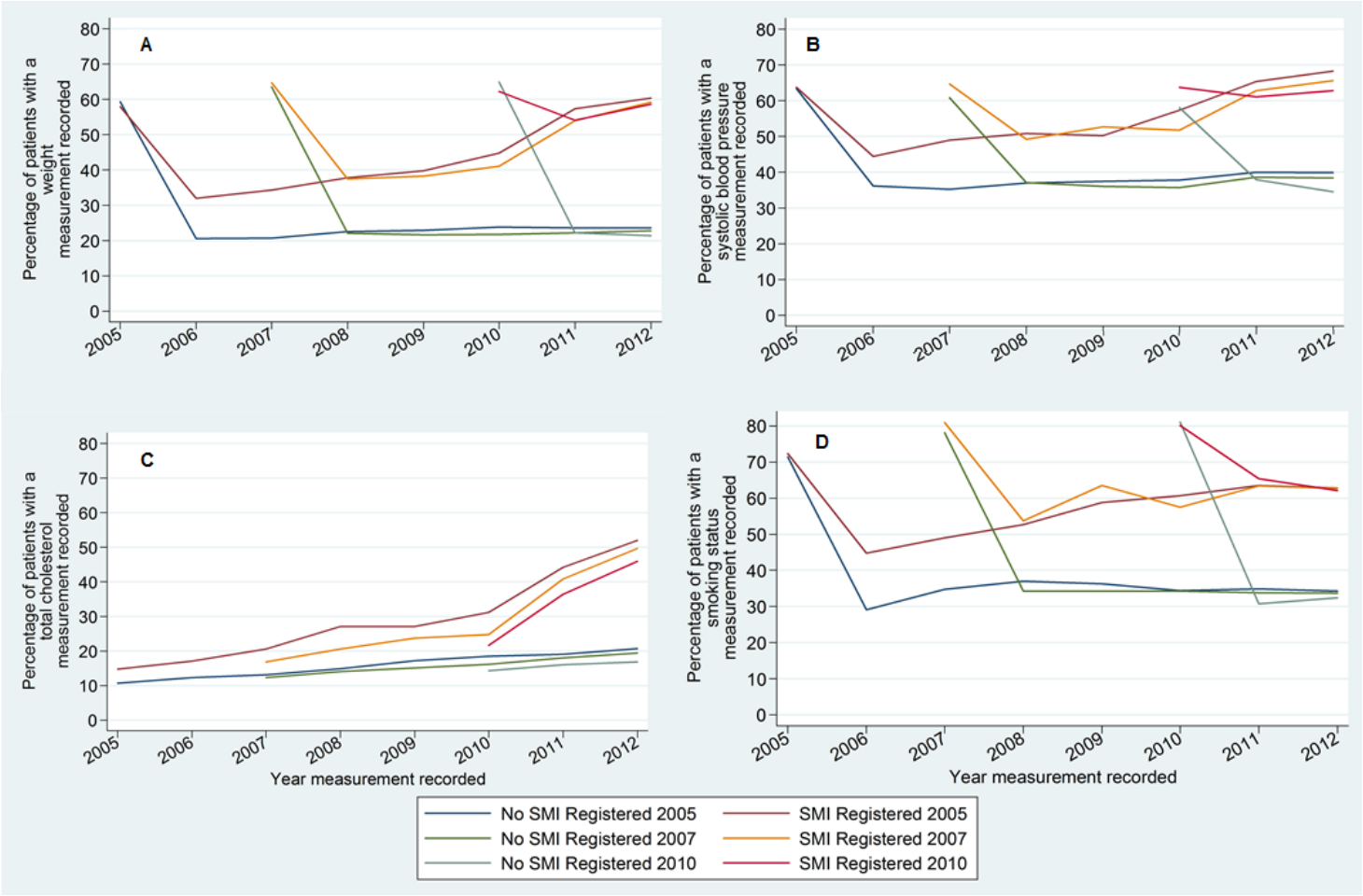




7.1.2 Recording of physical health data relative to the time of registration

Figure 7-7 confirms that the recording of physical health data on weight, blood pressure and smoking status was most complete in the year of registration, and that amongst people with SMI, the completeness of this information improved year on year. The figures also show that at the time of registration, people with or without SMI had approximately equal levels of recording. However, after the year of registration people with SMI were more likely to have physical health measurements recorded than people without SMI.

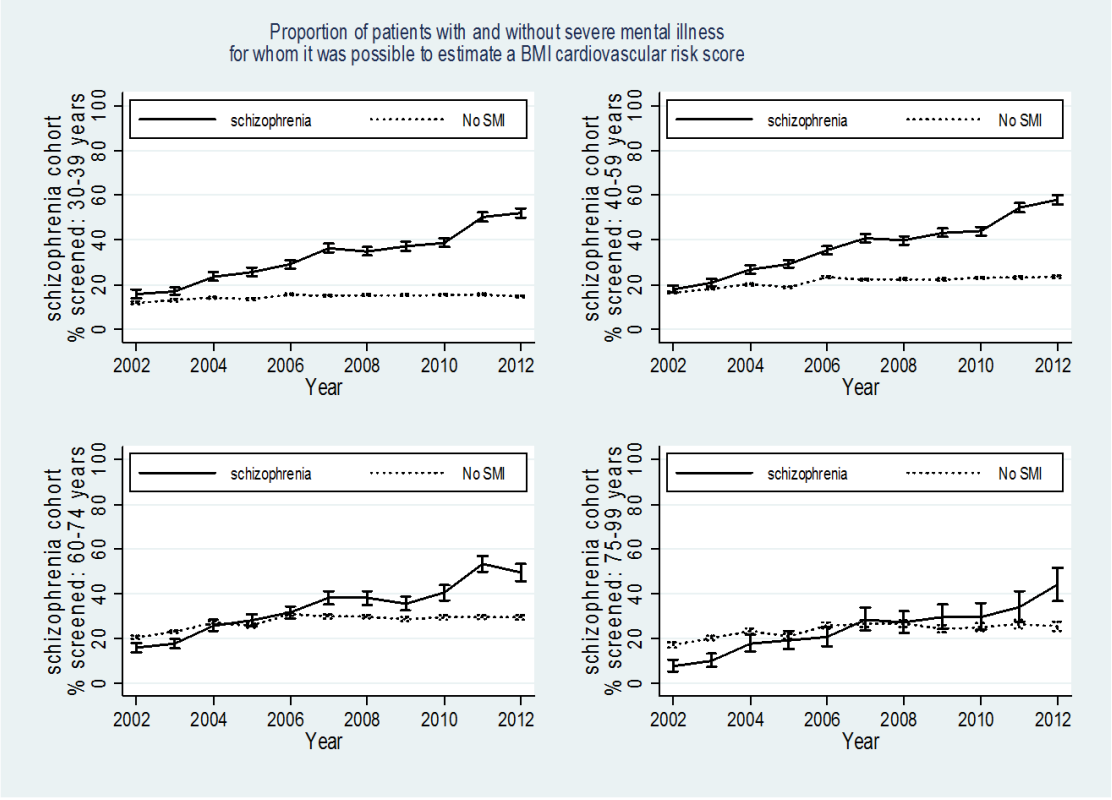
Figure 7-7: The proportion of people with or without SMI who had one or more records of (clockwise from top left); A) weight, B) systolic blood pressure, C) total cholesterol or D) smoking status, per calendar year following registration



7.1.3 Combinations of components of the CVD risk score

The proportion of people who had measurements for the collection of covariates needed to estimate the office version of the 10 year Framingham CVD risk score for a given year is outlined in Figure 7-8. Over the study period, the proportion of people for whom a CVD risk score could be estimated (using BMI) increased amongst people with SMI from <20% in 2002 to 50% of people aged 30-39 years, 60% aged 40-59 years, 50-60% aged 60-74 years and approximately 40% aged 75-99 years in 2012.

Figure 7-8: Annual recording of the set of covariates required to estimate BMI CVD risk in people with schizophrenia (above) or bipolar disorder (below) compared to people without SMI



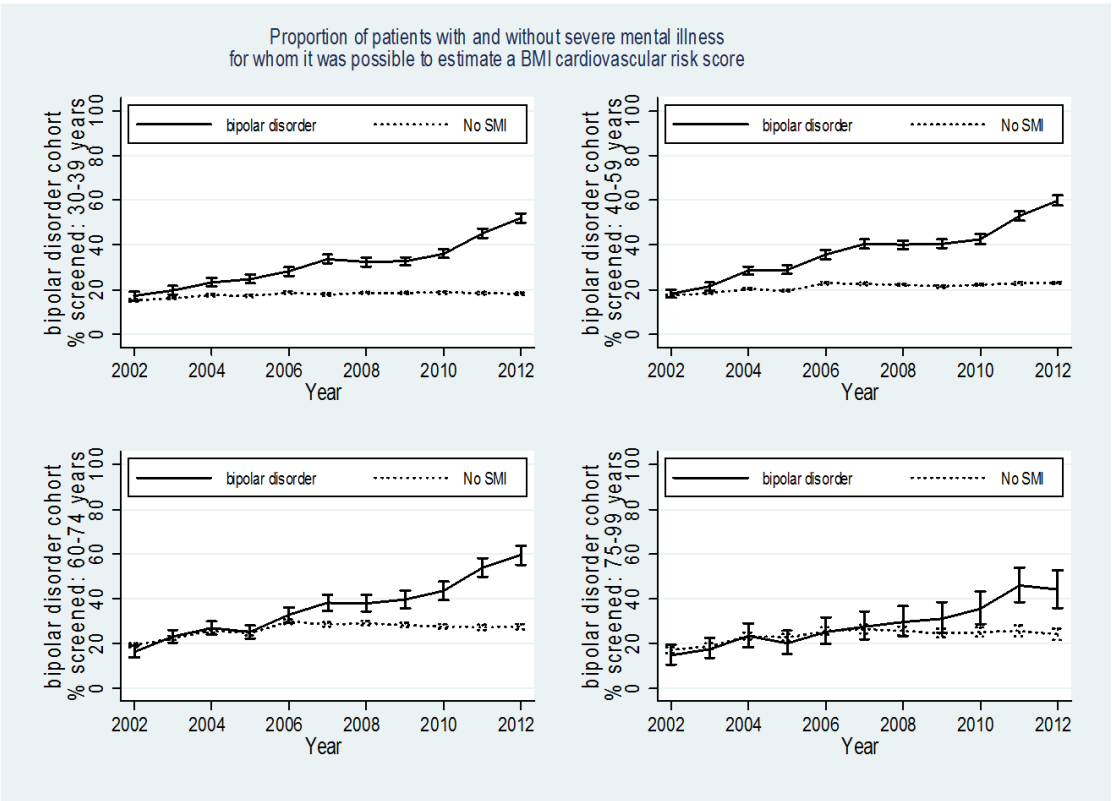
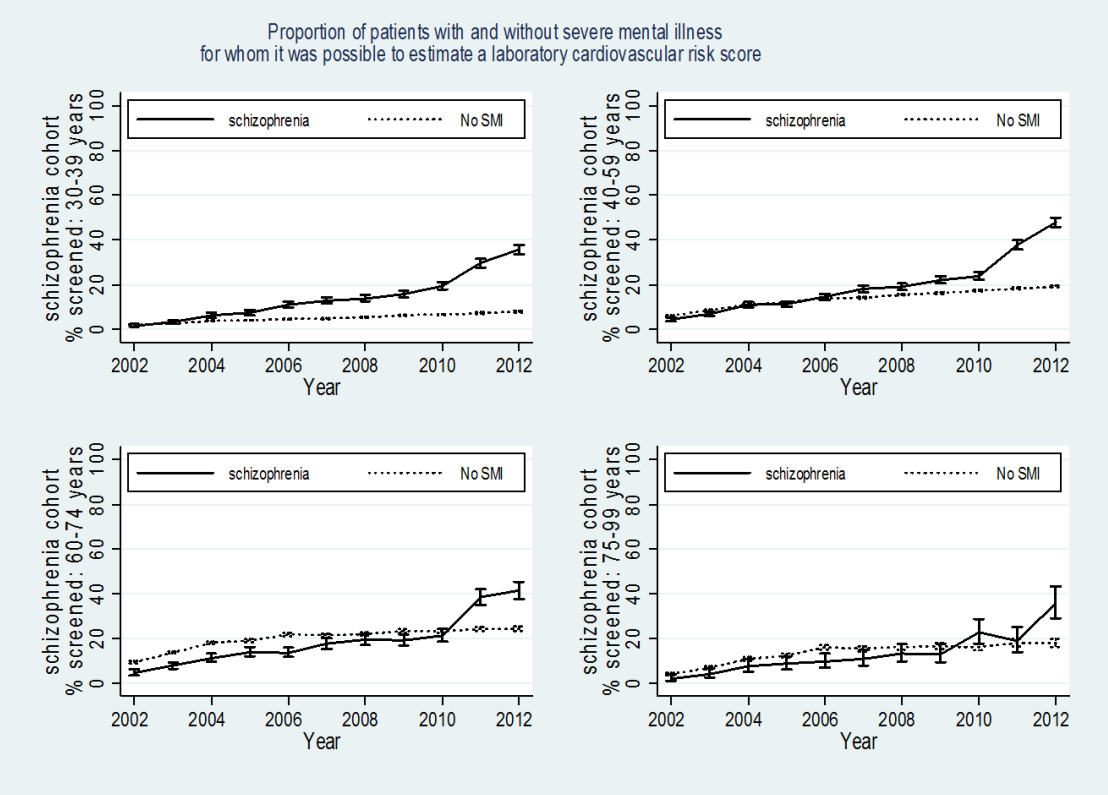
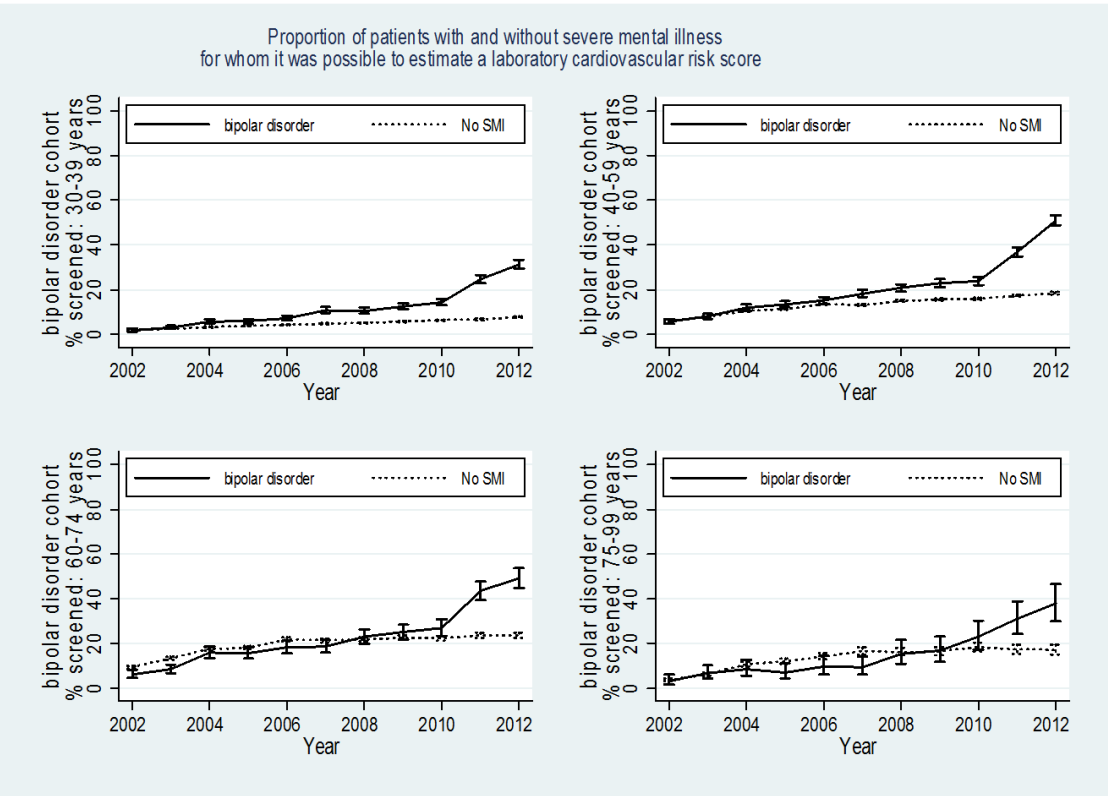


Figure 7-9 outlines proportion of people who had measurements for the collection of covariates needed to estimate the laboratory version of the 10 year Framingham CVD risk score for a given year. Over the course of the study period the proportion of people for whom a CVD risk score could be estimated (using lipid measurements) increased amongst people with SMI from <10% in 2002 to 30-35% of people aged 30-39 years, 50% aged 40-59years, 40-50% aged 60 in 2012.

Figure 7-9: Annual recording of the set of covariates required to estimate laboratory CVD risk in people with schizophrenia (above) or bipolar disorder (below) compared to people without SMI

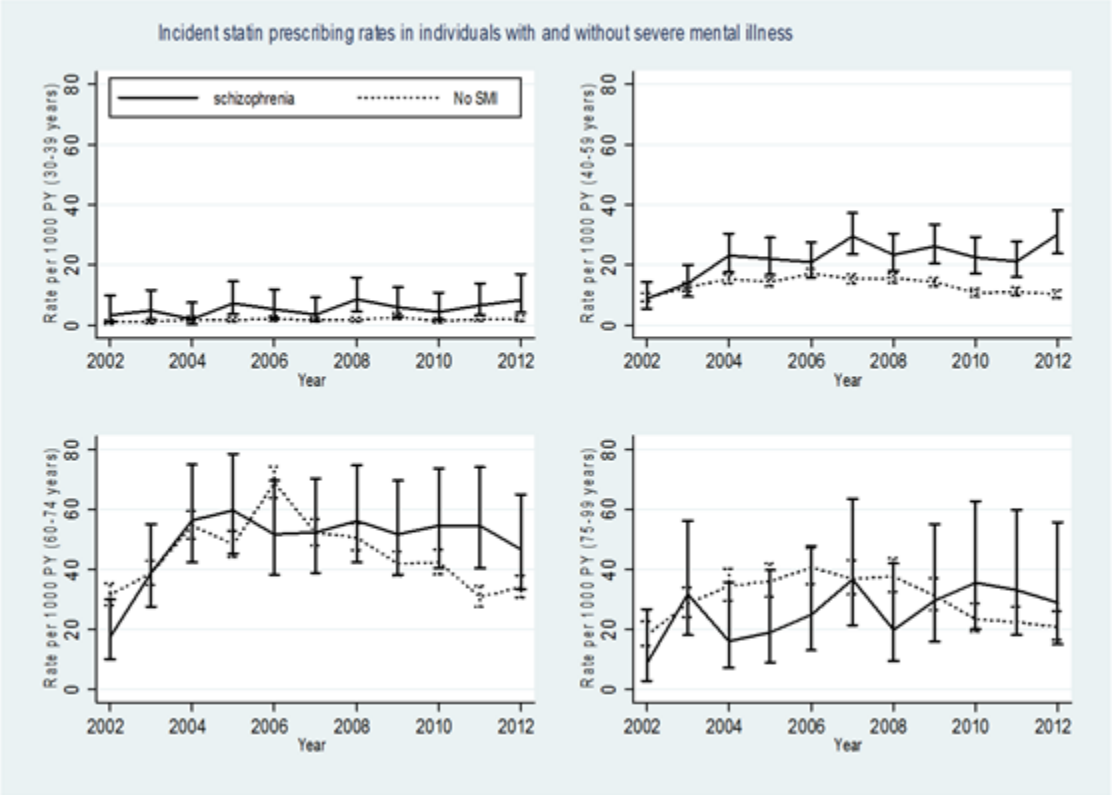


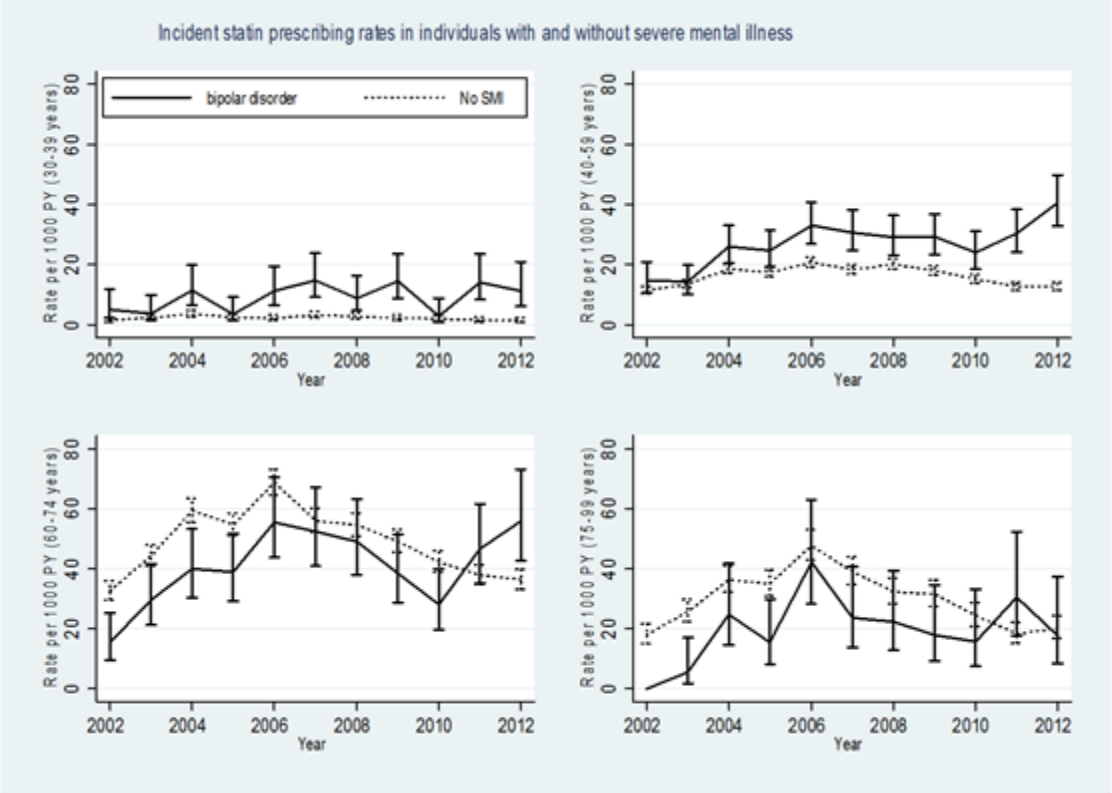


7.2 Objective 2: Temporal changes in new statin prescriptions (January 2002- December 2012)

Figure 7-10 outlines the rate of new statin prescribing by age group to people with and without SMI for the period January 2002 to December 2012. During this period rates were relatively static in people aged 30-39 years and 40-59 years, with an increase in prescribing between 2010 and 2012 amongst those with SMI, but not those without SMI. Prescribing rates were higher amongst people aged 30-39 years and 40-59 years who had a diagnosis of SMI than comparison people without SMI. The rate of prescribing was highest amongst people aged 60-74 years: for this age group prescribing rates peaked in 2006 for people with and without SMI. There was substantial overlap in the rate of statin prescribing for people with and without SMI who were aged 60-74 years or 75-99 years.

Figure 7-10: the rate of statin prescribing (per 1000 person years) in people with schizophrenia (above) or bipolar disorder (below) compared to people without SMI for the period 2002-2012





7.3 Objective 3) Investigate differences in new statin prescriptions to people with and without SMI (2007 to 2012)

7.3.1 Characteristics of the cohort:

A total of 8,779 people with a diagnosis of schizophrenia and 7,690 people with a diagnosis of bipolar disorder and ten times as many people without SMI (87,709 and 76,846, respectively) were identified for inclusion in the study between 2007 and 2012 (Table 7-1). Table 7-1 describes the characteristics of the cohort for the period 2007-2012. People with SMI were more likely to have a higher level of deprivation, larger BMI, and a greater proportion had diabetes and were smokers ($p<0.001$ in all instances). Mean cholesterol concentration was similar in people with and without bipolar disorder ($p=0.8$) and slightly lower ($p<0.001$ for a difference of 0.1mmol/L) in people with schizophrenia relative to those without SMI; which reflects lower HDL-C concentration amongst people with SMI ($p<0.001$ for a difference of 0.1mmol/L in both cohorts). Mean systolic blood pressure was lower in people with SMI ($p<0.001$ for a difference of 4mmHg in both cohorts).

Table 7-1: Summary statistics for people with a diagnosis of schizophrenia or bipolar disorder compared to age and gender frequency matched people without a SMI: data for the period 2007-2012

Characteristic		n=8,779		n=87,709		n=7,690		n=76,846	
		Schizophrenia	(%)	No SMI	(%)	Bipolar disorder	(%)	No SMI	(%)
Age at study start (years)	30-39	2,521	(29)	25,249	(29)	2,538	(33)	25,414	(33)
	40-59	3,859	(44)	38,816	(44)	3,507	(46)	35,104	(46)
	60-74	1,657	(19)	16,395	(19)	1,131	(15)	11,251	(15)
	75-99	742	(8)	7,249	(8)	514	(7)	5,077	(7)
Median age at start in years [IQR]		48.5	[38.5-61.5]	48.5	[38.5-61.0]	45.8	[37.5-57.5]	45.5	[37.1-57.5]
Sex	Males	5,176	(59)	51,721	(59)	3,031	(39)	30,266	(39)
Townsend score for deprivation	1	997	(11)	18,629	(21)	1,465	(19)	18,957	(25)
	2	1,207	(14)	17,487	(20)	1,444	(19)	16,905	(22)
	3	1,734	(20)	18,698	(21)	1,665	(22)	16,491	(21)
	4	2,323	(26)	17,651	(20)	1,726	(22)	14,420	(19)
	5	2,518	(29)	15,244	(17)	1,390	(18)	10,073	(13)
Diabetes	Yes	812	(9)	4,614	(5)	579	(8)	3,546	(5)
Smoker	Yes	4,725	(54)	25,519	(29)	3,505	(46)	21,037	(27)
	Not recorded	156	(2)	3,352	(4)	71	(1)	2,192	(3)

Table 7-1 continued

Characteristic	n=8,779		n=87,709		n=7,690		n=76,846	
	Schizophrenia	(%)	No SMI	(%)	Bipolar disorder	(%)	No SMI	(%)
Mean cholesterol (mmol/L)	5.4	(1.1)*	5.5	(1.1)*	5.5	(1.1)*	5.5	(1.1)*
Not recorded	3,174	(36)	47,455	(54)	2,587	(34)	43,267	(56)
Mean HDL-C (mmol/L)	1.3	(0.4)*	1.4	(0.4)*	1.4	(0.4)*	1.5	(0.4)*
Not recorded	3,693	(42)	51,950	(59)	3,011	(39)	46,979	(61)
Mean SBP (mmHg)	129	(15)*	133	(16)*	128	(15)*	131	(16)*
Not recorded	1,137	(13)	21,452	(24)	759	(10)	16,623	(22)
Mean BMI (kg/m^2)	27.7	(5.9)*	27.1	(5.3)*	27.8	(5.6)*	27.0	(5.5)*
Not recorded	1,943	(22)	35,712	(41)	1,409	(18)	29,746	(39)

*Figure in brackets indicates standard deviation rather than percentage. IQR; inter-quartile range, SBP; systolic blood pressure. Where multiple measurements were available for the same individual, the mean (continuous variables) or mode (categorical variables) was retained in the dataset.

7.3.2 Differences in new statin prescriptions to people with and without SMI (2007 to 2012)

The crude rate and incidence rate ratios (adjusted for sex, five-year age-band and Townsend score for deprivation) for new statin prescribing during the period 2007-2012 are outlined in Table 7-2.

Table 7-2: IRRs for new statin prescriptions in people with and without SMI between 2007 and 2012: results from multivariable Poisson regression models

SMI type	Age group (years)	SMI		No SMI		Adjusted IRR		
		Crude rate	95% CI	Crude rate	95% CI	aIRR*	95% CI	p value
Schizophrenia	30-39	10.51	(8.09-13.7)	2.13	(1.78-2.55)	4.48	3.25-6.19	<0.001
	40-59	32.57	(29.6-35.9)	16.40	(15.8-17.1)	1.87	1.68-2.08	<0.001
	60-74	48.30	(42.9-54.3)	51.04	(49.3-52.8)	0.91	0.80-1.02	0.114
	75-99	31.21	(24.9-39.1)	37.63	(35.5-39.9)	0.79	0.62-1.00	0.049
Bipolar disorder	30-39	7.65	(5.67-10.3)	1.91	(1.61-2.31)	3.85	2.70-5.49	<0.001
	40-49	25.07	(22.4-28.0)	12.82	(12.2-13.4)	1.87	1.65-2.11	<0.001
	60-74	59.72	(52.7-67.6)	44.38	(42.5-46.3)	1.32	1.16-1.51	<0.001
	75-99	34.81	(27.0-44.8)	36.79	(34.2-39.5)	0.92	0.71-1.20	0.531

* IRRs for statin prescribing and SMI adjusted for 5-year age-band, gender and Townsend score for deprivation

The absolute rate of new statin prescribing in people with SMI ranged from 8 per 1000 person-years in 30-39 years olds to 60 per 1000 person-years in 60-74 years olds. Amongst people without SMI, rates of new statin prescribing were comparatively lower in younger people and similar or slightly higher in older people.

After adjusting for 5 year age band, gender and Townsend score, IRRs for statin prescribing during the period 2007 to 2012 were significantly higher amongst people with a diagnosis of bipolar disorder than comparison people for all but the oldest age group (75-99 years), for which there was no evidence of a difference in prescribing rate (p=0.5). The greatest relative difference in prescribing rate was for people aged 30-39 years, where rates were 3-4 fold higher in people with bipolar disorder than comparison people (adjusted IRR of 3.9 (2.7-5.5), p<0.001). Relative rates of prescribing to people with bipolar disorder were approximately doubled amongst people aged 40-59 years (adjusted IRR of 1.9 (1.7-2.1), p<0.001) and 30% higher for people aged 60-74 years (adjusted IRR of 1.3 (1.2-1.5), p<0.001), relative to comparison people without SMI (Table 7-2).

A similar – but more pronounced - pattern of prescribing was evident for people with a diagnosis of schizophrenia (Table 7-2), for whom relative rates of prescribing were nearly five-fold higher amongst people aged 30-39 years (adjusted IRR of 4.5 (3.3-6.2), p<0.001) and almost doubled in people aged 40-59 years (adjusted IRR of 1.9 (1.7-2.1), p<0.001). Rates of prescribing were equivalent in people aged 60-74 years with schizophrenia compared to those without SMI (adjusted IRR of 0.9 (0.8-1.0), p=0.1). However, there was evidence of significantly lower rates of statin prescribing to people with schizophrenia in the oldest age group (75-99 years), relative to people without SMI (adjusted IRR of 0.8 (0.6-1.0)).

7.3.3 Amongst people who have had a CVD screen, investigate whether the rate of statin prescribing differs in people with and without SMI after accounting for differences in estimated CVD risk (2007-2012)

A total of 8,037 people with a diagnosis of schizophrenia and 7,176 with a diagnosis of bipolar disorder (and 80,460 and 71,769 comparison people, respectively) who were aged between 30 and 74 years of age were identified for the period 2007 to 2012 (link back to Table 7-1).

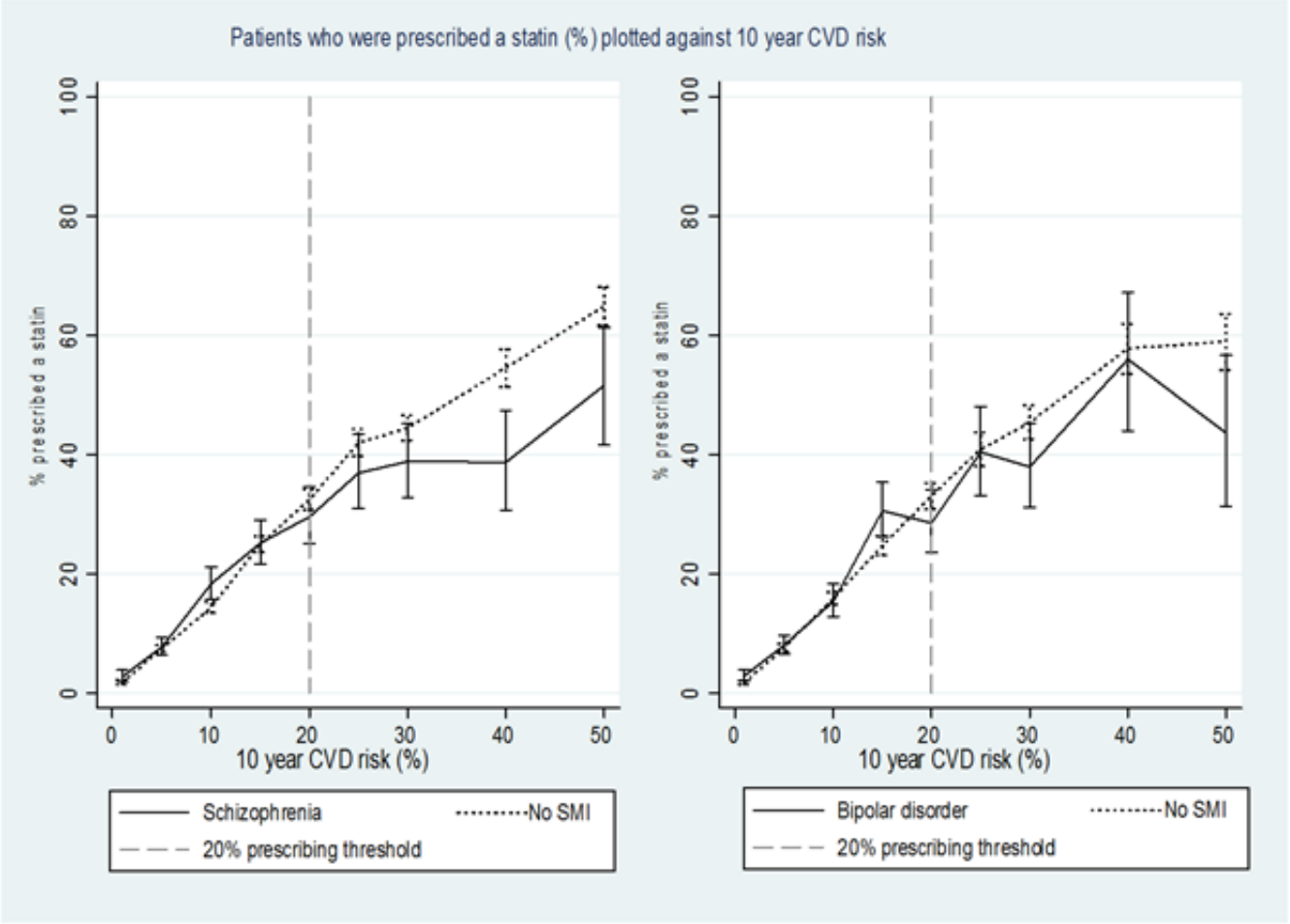
Due to missing data, it was only possible to estimate CVD risk scores for a total of 9034 (59%) people with SMI (schizophrenia: 4,697 (58%) or bipolar disorder: 4,337 (60%)) and 58,153 (38%) without SMI. Of these, 20% (1775 of 9034) with SMI and

23% (13,380 of 58,153) without SMI had a CVD risk score of 20% or greater (p<0.001). A total of 37% (651 of 1,775) of people with SMI who had a risk score of 20% or higher were prescribed a statin, which compares to 43% (n=5,748 of 13,380) in people without SMI (p<0.001).

Figure 7-11 outlines the relationship between estimated CVD risk and the proportion of people who were prescribed a statin aged 30-74 years (and who had sufficient data to estimate CVD risk using the lipid version of the Framingham equation).

The proportion of people who were prescribed a statin at risk scores below 20% (which was the recommended threshold for statin prescribing at the time of data collection) was similar for people with and without SMI. However a lower proportion of people with high risk scores - and who had schizophrenia - prescribed a statin relative to people without SMI. For example, for people who had a risk score in excess of 40%, 39% (95% CI: 31-47) with schizophrenia (n= 50 of 129) were prescribed a statin versus 55% (95% CI: 51-58) without SMI (n= 520 of 952).

Figure 7-11: the proportion of people who were prescribed a statin, by 10 year CVD risk (%)



IRRs for new statin prescription show that, after adjusting for estimated CVD risk score, the rate of prescribing did not differ significantly between people with or without SMI. The adjusted IRRs were 0.97 (95% CI; 0.90-1.05) for people with schizophrenia and 1.00 (95% CI; 0.92-1.10) for bipolar disorder, relative to comparison people. Further detail regarding the spline model is outlined in the appendix; section 22.

8 Discussion

8.1 Key results

The key findings of this study are that annual rates of CVD screening in people with SMI are now at or above equitable levels relative to people without SMI. Despite these improvements, there were many people (40-60%) who had insufficient physical health data recorded to estimate a CVD risk score. The increased rate of CVD screening has been accompanied by increases in statin prescribing in people with SMI – particularly those aged 40-59 and 60-74 years – relative to people without SMI. However, the oldest people (75-99 years) with schizophrenia remain less likely to be prescribed a statin relative to people without SMI.

8.2 Uptake of physical health checks amongst people with and without SMI

The recording rate of covariates used to estimate 10 year CVD risk has rapidly increased over time (particularly after the introduction of QOF), with the greatest rise seen amongst people with SMI who were aged 30-59 years. However, uptake of physical health checks is not universal and a substantial proportion (40-60% depending on age group and type of CVD risk score) of people with SMI had insufficient data to estimate CVD risk. However, it should be noted that the uptake of physical health checks during the period 2007-2012 was relatively lower in people without SMI.

The results of this study echo findings from the National Audit of Schizophrenia, which found that two thirds of people with a diagnosis of schizophrenia were not given a full physical health check during the 12 month period ending in 2013 (Royal College of Psychiatrists, 2014). Few studies have investigated the uptake of physical health checks in people who do not have a pre-existing CVD condition and

who have a SMI diagnosis: the results from this chapter are novel, but comparison with other studies is limited.

Osborn *et al*. used primary care data from THIN to investigate differences in the rate of physical health checks between January 2000 and December 2007 in people with and without SMI who did not have an existing CVD condition (Osborn et al., 2011). My study and the work by Osborn *et al*. use similar methodologies and have the same data source (although the study by Osborn applied additional criteria – such as a date range for confirming the diagnosis of SMI - to define the study population): it is therefore unsurprising that the overall patterns of screening are similar. However, the results I have presented in this chapter are more contemporary and assess the collective availability of health parameters required to estimate CVD risk, not just individual factors.

Two other studies have sought to estimate differences in uptake of physical health checks for people with SMI, relative to people without SMI. Roberts *et al*. examined the proportion of patients registered at 22 UK GP practices who had six health parameters (blood pressure, weight, cholesterol, smoking status, alcohol consumption and family history of heart disease) recorded between April 1998 and December 2000. The study found that patients with a diagnosis of schizophrenia were approximately half as likely have a record of blood pressure or cholesterol concentration compared to age- and gender-matched patients from either the general population or the asthma register. In comparison to asthma patients (but not the general population patient sample), people with schizophrenia were much less likely (OR: 0.37, p=0.001) to have had smoking status recorded (Roberts et al., 2007). Direct comparison to my study is difficult because the time periods are different: however, there is agreement from both studies that physical health measurements have historically been less frequently provided to people with SMI, although my results show marked improvement in more recent years.

A different study (Hardy et al., 2013) opted to use people with a diagnosis of diabetes as the comparison group for people with SMI. The study team undertook a retrospective audit of the uptake of full physical health checks (defined as measurement of blood pressure, BMI, blood glucose or HbA1c and cholesterol within a 15 month period) across five primary care centres in Northampton between September 2009 and August 2010. People with SMI were identified through the register or from prescribing records for antipsychotic medication. People with diabetes were identified through the Quality Management Analysis System (which

determines payment of GP surgeries as part of the national contract). The study found that 21% of people with SMI received a full health check (with recording of individual components varying between 63% (blood pressure) and 35% (HbA1c/blood glucose)). This compared to 96% of patients with diabetes receiving an equivalent screen, thus giving a crude odds ratio of 90.4 (95% CI: 64.5-126.6) that favoured screening in diabetic patients relative to people with SMI.

The same study investigated the distribution of full physical health checks by age and found that this proportion increased with advancing age amongst people with SMI: 16-35 years; 11%, 36-55 years; 22% and 56 years+; 31% (n=386) (Hardy et al., 2013). Whilst this result appears at odds with my findings of lower rates of screening amongst older people with schizophrenia, there are several factors that may explain these differences. In particular, Hardy *et al*. did not exclude people with pre-existing CVD. Although it is not possible determine the proportion of people with an existing CVD diagnosis from the publication, physical health checks are more frequently carried out amongst people with a CVD diagnosis, and CVD diagnoses are more frequent in older people.

The results of my study suggest that disparities in the provision of physical health checks have decreased over time such that people with SMI are now more likely to be screened than those without this condition. However, despite these improvements, there are many people for whom it is not possible to estimate CVD risk. I identified age as being associated with uptake of health checks: younger people with SMI were more likely to be screened than older people. This study has enabled me to explore patterns of physical health checks and to develop an understanding of some of the mechanisms (such as new patient registration) through which physical health data are collected. These factors will be essential for more detailed exploration of unobserved (i.e. missing) covariate data that will support development of a multiple imputation model used in the main analysis regarding the effectiveness of statins in people with SMI.

8.3 Rates of new prescriptions of statins to people with and without SMI

Rates of new statin prescriptions have fluctuated over time and after 2010 were more frequently prescribed to people with SMI than comparable people without SMI. Age was strongly associated with the likelihood of receiving a new statin prescription, with prescribing rates amongst younger people (aged 30-59 years) with

SMI being twice as high as rates in the comparison group. By contrast, older adults (60-99 years) with schizophrenia (but not bipolar disorder) had reduced rates of prescribing, which were 9% lower than for comparison people.

In my study, the frequency with which new statin prescriptions were issued was much higher (2-5 times) in younger people with SMI than comparison people without SMI. However, rates of new statin prescribing were the same or lower in older people with SMI, with significant disparity in prescribing for people with schizophrenia. Although inequalities in the provision of statins to older people with schizophrenia have (to the best of my knowledge) not been investigated elsewhere, it is recognised that older people with a mental health condition are at risk of greater inequality in other forms of health provision (Karim et al., 2005;Davies, 2011;Lawrence and Kisely, 2010;Green and Benzeval, 2013). However, it is difficult to interpret the clinical implications of lower rates of statin prescribing to the over 75s because the guidance on statin prescribing at the time of the data collection was unclear for this age group (National Institute for Health and Clinical Excellence, 2008b).

Amongst the subset of people for whom a CVD risk score could be calculated (assumed to be those who participated in screening), the proportion who received a statin increased with increasing estimated risk. After taking into account estimated CVD risk score, there was no evidence that rates of new statin prescribing differed between people with or without SMI who had been screened: this suggests that the increased frequency of statin prescribing in people with SMI is proportionate to the higher CVD risk of the group. This could suggest that the decision-making process governing statin prescribing after a physical health check is similar regardless of SMI status. However, my results may not reflect trends at time points earlier than 2007.

In addition, the descriptive analysis of CVD risk and statin prescribing amongst people who were screened indicated that the proportion of people with high CVD risk who were prescribed a statin was lower amongst people with a diagnosis of schizophrenia than people without SMI. Although this difference was not statistically significant across the whole spectrum of CVD risk, the discrepancy in prescribing could warrant further investigation. Amongst people with SMI who had a CVD screen, only a minority (37%) of those with an estimated risk of 20% or higher were prescribed a statin, which suggests a concerning level of under-treatment. However, this figure is broadly similar to figures for the general population (Wu et al.,

2013;Artac et al., 2013) and is likely to reflect both GP and patient perceptions and preferences for cardiovascular management.

In addition, other studies have indicated that lower provision of statins to people with SMI may be at least partly driven by GP prescribing preferences. A recent study randomly assigned one of three sets of vignettes to all GPs in a single region in Scotland (Macklin and Morrison, 2011). Each vignette set outlined details for two patients with a CVD risk score of 20% (using the Joint British Hypertension Society Risk Calculator), which differed only in terms of each patient's status as having; type 1 versus type 2 diabetes, schizophrenia versus epilepsy, or being retired versus unemployed. The results (obtained from 56/133 GPs initially approached) showed that 37% of GPs surveyed recommended prescribing statins to an individual with schizophrenia, which was similar to individuals with epilepsy (31%). This figure was markedly lower than for individuals with diabetes (type 1 diabetes (88%) versus type 2 diabetes (85%)), but similar for people who were not working (retired (33%) versus unemployed (23%)) (Macklin and Morrison, 2011).

8.4 Limitations of the study

The low proportion of high risk people who were prescribed a statin in this study may reflect some important limitations:

8.4.1 Imperfect replication of the risk score estimated by the GP

Vision software has a built-in application that estimates a patient's CVD risk score based on risk factors that have been measured at recent time points (Abegunde, 2010): however, this estimate is not routinely captured in THIN data. Although there are designated Read codes for estimated CVD risk, these fields were not well populated and I therefore opted to calculate risk scores from available data held in other parts of each electronic patient record (as described in Chapter 3). As a result, my estimates of CVD risk might differ to scores calculated by the GP in real life, since a number of risk algorithms are available (Hippisley-Cox et al., 2010;Conroy et al., 2003;D'Agostino et al., 2008) as well as different criteria for selecting covariate data. In particular, risk scores estimated by GP software packages do not routinely restrict measurements to those taken within a specific time period (e.g. the 6 year calendar period used in my study) but will default to using the most recently recorded measurements.

The Framingham Risk score (which I used in this study) tends to overestimate CVD risk in European populations (Brindle et al., 2003), which may have contributed to the apparently low levels of statin prescribing to people at and above the 20% threshold. I considered using the QRISK2 algorithm (Hippisley-Cox et al., 2008) to estimate CVD risk; however, this was not possible because full details of the algorithm (coefficients and baseline population risk) were not freely available at the time of undertaking the study.

8.4.2 Use of lifestyle modification

National guidelines for lipid management recommend that people with raised CVD risk should try to modify their lifestyle through changes to diet and physical activity before initiating a statin (National Institute for Health and Clinical Excellence, 2008b). However, these recommendations are not routinely recorded in primary care data such as THIN. It is therefore possible that people with high CVD risk who were not prescribed a statin were advised by their GP to change aspects of their lifestyle such as diet.

8.4.3 Use of other lipid modifying drugs

This study has focused on statins and has not considered other types of lipid-modifying drugs. Although statins account for over 90% of pharmacological interventions for lowering cholesterol in the UK (Wu et al., 2013), other drugs such as fibrates, may be used for lipid modification (Joint Formulary Committee, 2012). Later work will include an indicator denoting people who were prescribed non-statin lipid modifying drugs, which will be incorporated into multiple imputation and analysis models.

8.4.4 Contraindications for statin prescribing

I did not exclude people with a contraindicating condition such as acute liver disease, although this is unlikely to substantially impact upon my results (as the number of people to whom this applies is likely to be low). However, it will be necessary to exclude people with contraindicating conditions from the main analysis of my PhD work regarding the effectiveness of statins in people with SMI.

8.4.5 Missing data on covariates

I was only able to estimate risk scores for a subset of people (59% with SMI and 38% without SMI) who were under follow up during the period January 2007-

December 2012. Risk scores were estimated for all people who had covariate data on blood pressure, smoking status, total cholesterol and HDL-C during the during the six year period and were therefore assumed to have received a full CVD screen. However, it is important to note that people for whom it was possible to estimate a risk score are not likely to be representative of people with missing covariate data. In particular, it was not possible to estimate CVD risk scores for the majority of people without SMI, which may reflect both differences in screening policy in people with and without SMI (e.g. annual screening in people with SMI versus five yearly screening in the general population aged 40-75 years).

8.5 Implications for my work on estimating the effectiveness of statins in people with SMI (Chapter 6)

The results of this study indicate the importance and potential value of imputing missing CVD covariate data in order to select statin exposed and unexposed people with similar CVD risk scores. In addition, this study identified strong temporal trends in missing covariate data and statin prescribing. The design selected for the main study (estimating the effectiveness of statins – Chapter 6) stratifies people into a series of cohorts on the basis of whether or not they were prescribed a statin within a given calendar period. Because this approach explicitly selects people within the cohort on the basis of time it may therefore be well suited to analysing datasets - such as this one - where patterns of both prescribing and missing data are associated with calendar time.

This study found that over half of people who had physical health measurements that indicated high ten-year CVD risk (>20%) were not prescribed a statin. Plausible reasons for these people not being prescribed a statin include the patient declining to be treated with a statin, or trying lifestyle modification first. In addition, the GP may not have directly estimated the CVD risk score and were therefore unaware that the patient's risk score was above the prescribing threshold. Furthermore, the presence of contra-indicating conditions (such as liver disease or terminal illness) may preclude prescribing. This latter reason highlights the importance of applying rigorous inclusion and exclusion criteria in addition to incorporating confounding variables that are predictive of statin prescribing patterns. The main analysis will include covariate information on a much more extensive range of confounders, and should therefore be more able to adjust for differences in the characteristics of people who were prescribed a statin, relative to statin non-users (thereby decreasing the likelihood of confounding by indication).

In April 2014 the QOF target for measuring cholesterol for primary prevention of CVD was retired, thus removing the financial incentive for monitoring this physical health parameter (National Institute for Health and Clinical Excellence, 2012). Although measuring cholesterol in people who have been prescribed statin therapy is still considered to be best practice (National Institute for Health and Clinical Excellence, 2014b), the loss of the QOF target is likely to reduce rates of annual cholesterol monitoring. It is currently unclear what impact (if any) this will have on individual patients, but decreased completion of primary care data seems likely. For this reason, the current dataset from THIN (up to 2014) is likely to provide the most complete dataset regarding cholesterol concentration and therefore makes the timing for investigating the effectiveness of statins with primary care data optimal.

8.6 Implications for policy and practice

These results suggest that the observed higher rate of statin prescribing to people with SMI relative to people without SMI is proportionate given differences in CVD risk between the two groups. However, the results also suggest that high risk and older people with schizophrenia may potentially be an undertreated group. However, although current guidelines advocate statin prescribing to older people, previous guidance (in place at the time of data collection) did not promote prescribing to people aged over 75 years (National Institute for Health and Clinical Excellence, 2014b;National Institute for Health and Clinical Excellence, 2008b). In addition, older people - especially those with SMI - may be more difficult to both access and engage in preventative therapies. It may therefore be necessary to consider different approaches for improving the physical care of this demographic, for example through opportunistically undertaking physical checks in secondary care or during visits by community mental health staff.

Chapter 6 : The effectiveness of statins for primary prevention of CVD in people with SMI: a staggered cohort study in THIN

1 Chapter content

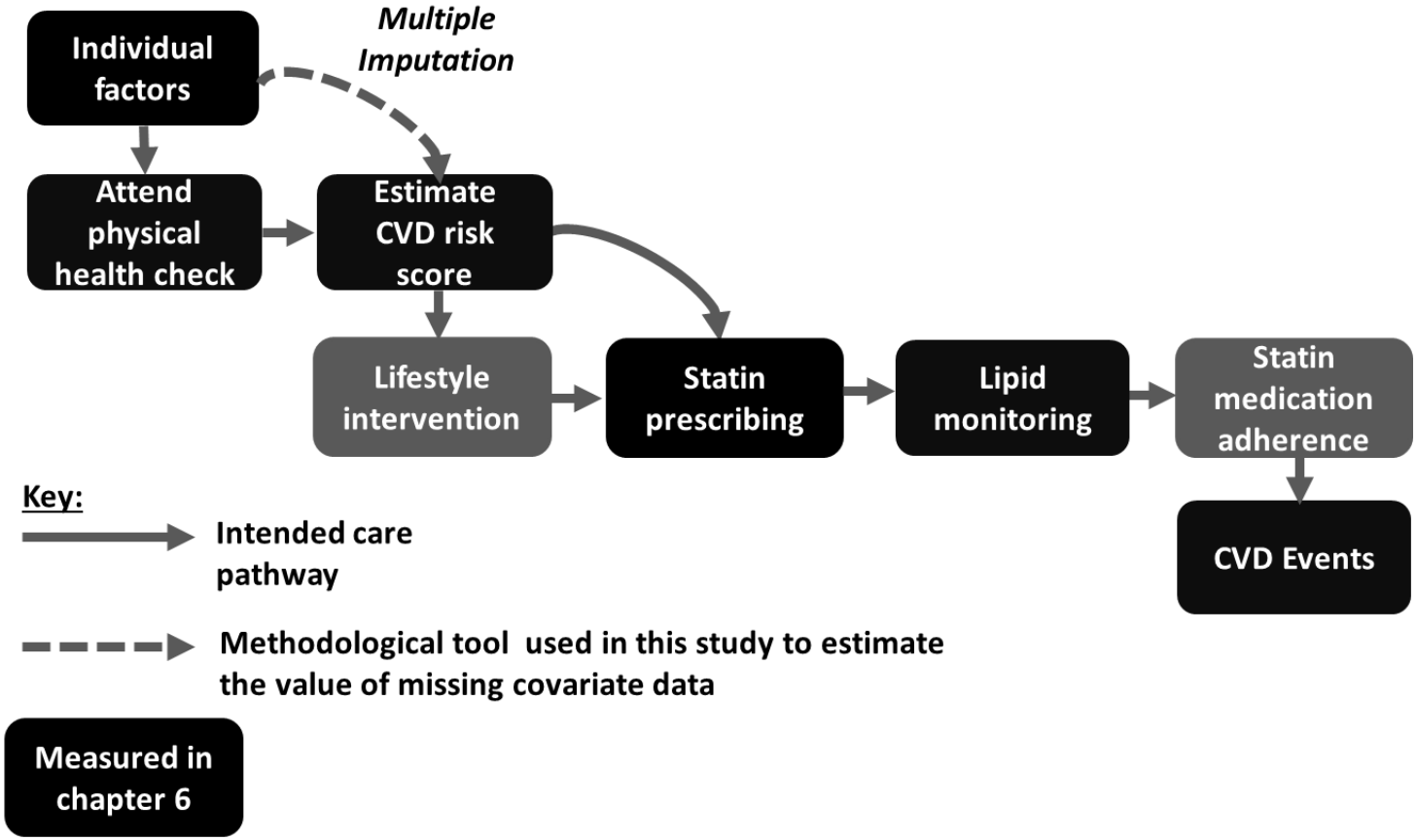
This chapter builds on material presented elsewhere in the thesis. Chapter 2 evaluated the evidence-base for statin prescribing for primary prevention of cardiovascular disease (CVD) in people with severe mental illness (SMI). It also identified a need for research investigating the impact of statin prescribing on CVD events and over longer periods of time. Chapters 3 and 4 detail the rationale for selecting the data source (The Health Improvement Network (THIN)), case definitions and type of methodology (staggered cohort study), respectively. The results of chapter 5 described the scale and temporal distribution of missing data on CVD covariates and confirmed that statins are prescribed with increasing frequency to individuals with SMI. This chapter outlines the method and results for the main analysis investigating the effectiveness of statins for primary prevention of CVD in people with SMI. The primary outcome was combined first myocardial infarction (MI) and stroke events. The secondary outcomes were all-cause mortality, MI, stroke and change in total cholesterol concentration at 1 and 2 years after the index date. I describe the key results and interpret the main findings with reference to published literature and the likely limitations of the study. Finally, I suggest some preliminary conclusions, which are discussed in greater depth in Chapter 7.

This work has been submitted for presentation at the UK Public Health England Applied Epidemiology Scientific Conference 2016 (March 2016 - Warwick). The associated abstract is outlined in the appendix; section 24.1.

2 Statin prescribing for primary prevention of CVD in people with SMI

Figure 2-1 outlines the clinical care pathway for CVD screening and statin prescribing in UK primary care.

Figure 2-1: Clinical care pathway for CVD screening and statin prescribing in UK primary care



Chapter 5 examined the processes that occur upstream of statin prescribing and identified that statins are now more frequently prescribed to people aged 30-74 years with SMI than comparable individuals without SMI. The results from chapter 5 also highlighted that in 2012 40-60% of individuals with SMI did not attend an annual physical health check. Furthermore, of the people for whom it was possible to estimate a CVD risk score, only a minority (37%) with risk scores at or above the recommended clinical threshold (≥20% over a 10 year period) were prescribed a statin. These findings are of significance to this study because:

- people who attended a physical health check may not be representative of those who did not attend

- people who were prescribed a statin may not be representative of those who were not prescribed a statin; even amongst the subset of people who were screened and had a high CVD risk score

In practical terms the implication of these findings are that restricting the analysis to people with fully observed covariate data (i.e. a complete case analysis) may produce biased results that are not representative of the full SMI population. This is because people with and without fully observed covariate data may differ with respect to characteristics such as severity of mental illness and their preference for taking a statin (factors which are imprecisely described by data from THIN). Furthermore, national policy identifies people with SMI as a population that is at high risk of developing CVD and for whom statin prescribing should be considered. This chapter therefore focuses on the association between statin prescribing and CVD events in all individuals with SMI, rather than only those who attended an annual physical health check.

The importance of multiple imputation as a method for estimating unobserved values of CVD covariates was emphasised in Chapter 4 section 9. Multiple imputation is likely to offer the best available method to facilitate extending the analysis beyond the subset of people with complete covariate data. This is because multiple imputation uses the correlations within the observed covariate data to determine the underlying distribution from which imputed values are estimated (Sterne et al., 2009).

3 Rationale for investigating the effectiveness of statins in people with SMI

The evidence-base for statin prescribing for primary prevention of CVD in people with SMI was outlined in Chapter 2. In brief, randomised controlled trials (RCTs) have shown statins to be cost-effective for managing dyslipidaemia and preventing CVD events in high risk people (recently defined for the UK as ≥10% risk of CVD over a ten year period, but historically 20%: Chapter 5 section 2) (National Institute for Health and Clinical Excellence, 2014b;Gutierrez et al., 2012;Baigent et al., 2005;Lazar et al., 2011;Taylor et al., 2013). However, people with SMI are under-represented in statins trials and the effectiveness of statins may differ relative to the general and trial populations due to increased CVD risk, antipsychotic exposure and potentially lower medication adherence.

4 Aim

This study aims to estimate the effectiveness of statins in reducing CVD events in people with SMI.

Objectives:

To compare people with SMI who did (statin users), or did not (statin non-users), receive a statin prescription and to estimate the effect of statin prescribing on:

1) combined first MI and stroke **(primary outcome)**
2) combined first MI and stroke within clinically relevant sub-groups
3) all-cause mortality
4) first MI
5) first stroke
6) change in total cholesterol concentration 1 and 2 years after the index date

5 Methods:

This section describes the methods applied to the study: the rationale and justification of these methods was discussed in detail in Chapter 4.

5.1 Data Source

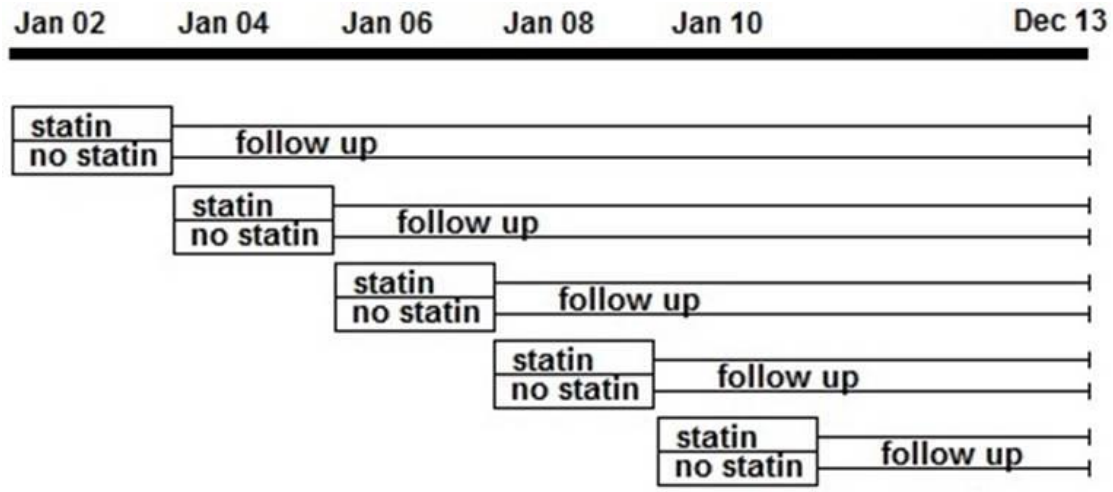
The data source for this study is THIN: an extended description of the database, all case definitions and indicators of the reliability of the data were outlined in Chapter 3.

5.2 Study design

5.2.1 Overview:

The effect of statin prescribing on CVD events in people with SMI was evaluated using pooled data from five cohort studies in THIN that were initiated at two year intervals from 1st January 2002 to 1st January 2010 (Figure 5-1). Each cohort study started with a twenty-four month exposure window (the duration of which was identified through exploratory work), in which the presence or absence of at least one statin prescription was used to classify an individual as a statin user or non-user (respectively) for that time period. Statin users and non-users were re-defined at the start (twenty-four month exposure window) of each subsequent cohort, meaning that an individual could contribute data to both statin user and non-user study groups.

Figure 5-1: diagrammatic representation of the staggered cohort study design



The duration of the exposure window (twenty-four months) was selected on the basis of exploratory work that investigated both the width of the confidence intervals (CI) around the effect estimate for the crude association between statin prescribing and CVD events and the feasibility of imputing missing data for each cohort.

Possible exposure windows of 6, 12 and 24 months were investigated, which would correspond to a study design comprising 20, 10 or 5 cohorts, respectively.

In this study the term "case" is used to refer to statin users and non-users who were under follow-up. Given that each individual could contribute data to more than one cohort the total number of cases under follow-up across all five cohorts is larger than the total number of individuals.

5.2.2 Inclusion and exclusion criteria for each staggered cohort

A series of retrospective cohort studies were developed. Data for all GP surgeries were extracted for people with a diagnosis of schizophrenia or bipolar disorder (Chapter 3 section 3.2) for the period 1st January 2002 to 31st December 2013.

Inclusion Criteria: people aged 40-84 years who; i) were permanently registered with the GP practice (Patflag A and C) ii) consulted their GP within the study period and iii) have data reported after practice acceptable mortality rate (AMR) and acceptable computer usage (ACU) dates (Horsfall et al., 2012;Maguire et al., 2009) (Chapter 3 section 3.2).

Exclusion Criteria: individuals who; i) had a diagnosis of CVD (Chapter 3 section 3.2) prior to the start of the study, ii) had been prescribed a statin in the twenty-four months prior to the start of the study or iii) had a statin contraindicating condition (terminal illness, raised liver enzymes or dementia) recorded before the start of the study. Full code lists for these conditions are outlined in the appendix; section 20.

> **Terminal illness** was defined as Read codes held in medical records relating to the following conditions: *terminal illness – late stage, last days of life, terminal care, palliative care, GSF supportive care, Liverpool care pathway, end of life advanced care plan, terminal care, end of life care,*
>
> **Raised liver enzymes** was defined as: 3x the upper limit of the reference ranges for either alanine transaminase (ALT) or aspartate aminotransferase (AST) as indicated in addition health records (*1001400006* and 1001400007, for ALT and AST respectively). The threshold would ideally be defined using local reference ranges specific to the testing laboratory, but this approach was not pragmatic so general criteria were applied to exclude individuals with high threshold values. For ALT and AST the current upper limits of the reference ranges for NHS Camden are 33 and 31 IU/L, respectively. These

values were inflated by 25% and multiplied by 3 to give highly conservative values of 124 (ALT) and 116 IU/L (AST) for exclusion. These individuals were excluded because statins are contraindicated for people with elevated liver enzymes (Joint Formulary Committee, 2012).

Dementia was defined as Read codes held in medical records relating to the following conditions: *Alzheimer's, dementia, other senile and presenile organic psychoses, presbyophrenic psychosis, senile psychosis,*

Entry into the study was at the latest of:

v) Index date (see Section 5.3.1)
vi) 40th birthday
vii) date of registration plus 12 months
viii) date of practice AMR or ACU

Exit from the study occurred at the earliest of:

vii) 31st December 2013
viii) out of practice transfer
ix) first CVD event
x) death

Individuals were not eligible to enter the study until 12 months after the date of registration. This was to ensure that people were under follow-up though-out the baseline period of 12 months (in which covariate data were measured – Chapter 3 section 3.2) but also exclude people with prevalent diagnoses of CVD and prevalent statin users (Lewis et al., 2005).

Individuals below the age of 40 years were not included in the cohort because the CVD event rate in this age group is very low. The upper age limit (84 years) for people entering the cohort at baseline was applied because – at the time of data collection – guidance regarding initiation of statin prescribing to people aged older than 75 years was unclear and prescribing practice was likely to be inconsistent. However, once statin medication has been initiated there is no upper age limit at which discontinuing medication is advised, therefore no upper age limit was used to define follow-up.

The latest date that an individual could exit the cohort was 31st December 2013, which was selected because this date marked the most current data available at the time and allowed a two year period after the last possible index date (31st December 2011) to capture CVD and total cholesterol outcome data.

5.3 Study variables

5.3.1 Index date

Statin users: Individuals who initiated a statin within the two year exposure period began follow-up on the day of their first statin prescription (the index date).

Statin non-users: For individuals who did not receive a statin prescription (Chapter 3 section 3.2) during the two year exposure period, the index date was a randomly selected day within the two year exposure period and within the follow up time of the individual.

In the main analysis individuals were analysed on the basis of statin prescribing at the index date regardless of any subsequent changes in use (e.g. initiating a statin after the exposure period, or discontinuation of prescribing) and is broadly analogous to "intention to treat" analyses of trial data.

5.3.2 Study outcomes

Primary outcome: first MI or stroke (combined MI, haemorrhagic and ischaemic or unspecified stroke) (Chapter 3 section 3.2)

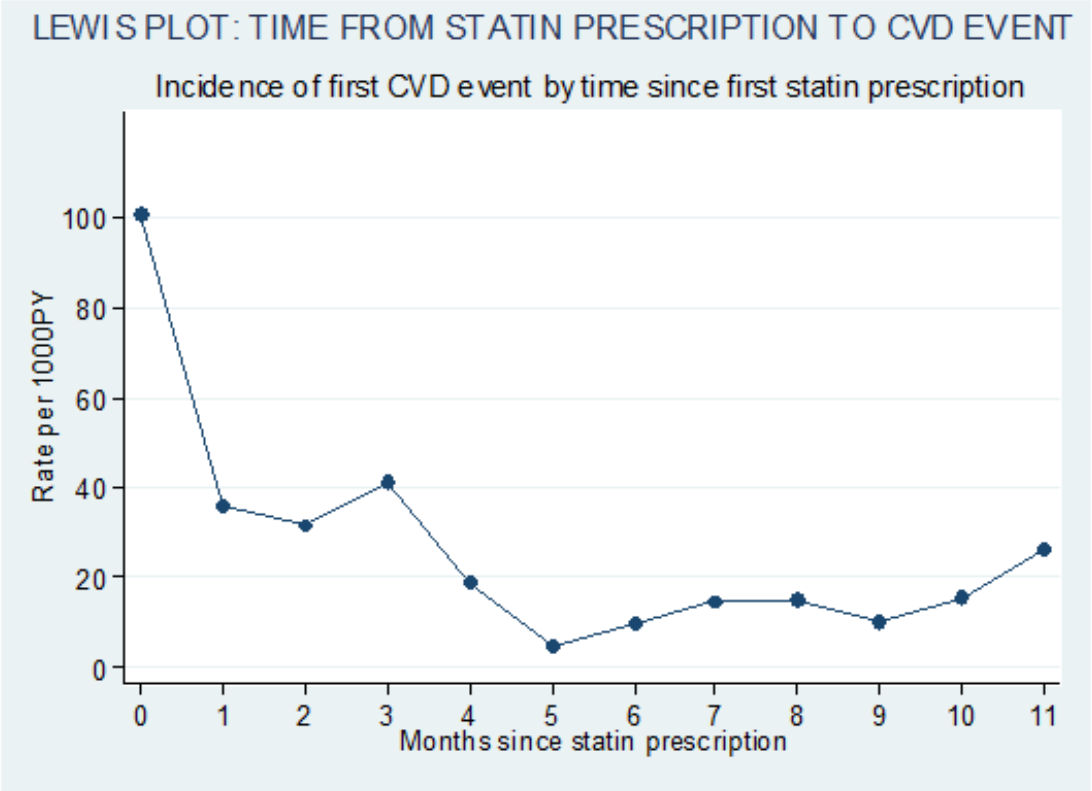
Secondary outcomes: all cause-mortality, MI, stroke, change in total cholesterol concentration 1 and 2 years after the index date (Chapter 3 section 3.2)

Chapter 3 introduced literature that aimed to assess the validity of CVD diagnoses recorded in THIN. These studies indicated reasonable confidence in diagnoses of MI, stroke and all-cause mortality, but considerable uncertainty for other types of coronary heart disease (CHD) diagnoses (including angina and unstable angina), transient ischaemic attack (TIA) as well as unspecified diagnoses of CVD. For this reason preliminary work for this study examined temporal trends by sub-groups of CVD diagnoses to assess whether there was any indication that prevalent diagnoses of CVD might be recorded. On the basis of this work and published validation studies other types of CHD diagnoses were not included as an outcome measure in this study.

Exclusion of misclassified CVD events: Statin users and non-users who had a CVD event recorded within three months of the index date were excluded. This was primarily to exclude individuals for whom statins were prescribed as secondary prevention: i.e. prescriptions after a CVD event, but where the CVD event date may have been incorrectly recorded in the patient's notes such that the event appears to occur immediately after the index date. This scenario may arise when a GP is notified of the CVD event via a discharge letter from secondary services, or at the point at which the patient obtains a statin prescription.

An exclusion period of three months after the index date was selected on the basis that the rate of CVD events in individuals who were prescribed a statin was very high at time points close to the index date (Figure 5-2). The rate of CVD events amongst statin users fell and fluctuated less after three months, suggesting that this was the minimum period that should be excluded. Discussion with clinicians also suggested that three months was a plausible length of time for the GP to be formally notified of a CVD event and to update the electronic health record.

Figure 5-2: The rate of CVD events in statin users relative to the date of first statin prescription



Change in total cholesterol concentration in the 1 and 2 years after the index date: The impact of statin prescribing on lipid modification is of interest both as an

intermediate outcome for CVD risk reduction and as an indicator of statin medication adherence. In this analysis lipid modification was only investigated amongst people with complete baseline covariate data (i.e. complete case analysis) in order to avoid imputing either the outcome (total cholesterol concentration at 1 and 2 years after the index date) or total cholesterol concentration at baseline; which is likely to be strongly correlated with cholesterol outcomes at 1 and 2 years.

5.3.3 Covariates

Data on all covariates were measured for each individual during the 24 month baseline period prior to entering the study and are summarised in Table 5-1: a proposed causal diagram and case definitions were outlined in Chapter 3 section 3.2.

Covariates were: age, sex**,** type of SMI, blood pressure, weight, height, total cholesterol and high density lipoprotein-cholesterol (HDL-C) concentration, diabetes, smoking status**,** Townsend score, antihypertensive use, non-statin lipid modification, heavy drinking, familial hypercholesterolaemia, hypothyroidism, chronic kidney disease (CKD), chronic obstructive pulmonary disease (COPD), asthma, atrial fibrillation, predominant antipsychotic, mood stabilizing drug, anti-depressant drug, annual consultation rate, cancer diagnosis, health authority region.

Table 5-1: Variables considered for inclusion in the imputation and analysis models

	Variable	Value
Fully observed	Index date	Date
	CVD event	MI or stroke
	Date of death	Date
	Time to event	Nelson–Aalen estimates
	Statin prescriptions	Type and date prescribed
	Start date	Date
	End date	
	5 year age band	5 year age band (between 40 and 84 years)
	Sex	Male / Female
	SMI type	Bipolar disorder / Schizophrenia
	Diabetes	No/Yes at or before baseline
Partially observed	Total cholesterol	Mean during baseline (mmol/L)
	HDL-C	
	Systolic blood pressure	Mean during baseline (mm/Hg)
	Diastolic blood pressure	
	Weight	Mean during baseline (kilograms)
	Height	Adult height (centimetres)
	Smoking status	Never, Ex, Current
	Townsend score	1-5 (5=most deprived)

Table 5-1 continued

	Variable	Value
Fully observed	Antihypertensive	
	Non-statin lipid modification	
	Heavy drinking	
	Familial hypercholesterolaemia	
	Hypothyroidism	No/Yes at or before baseline
	CKD	
	COPD	
	Asthma	
	Atrial fibrillation	
	Predominant antipsychotic	No/Yes and generation (first or second) during baseline
	Mood stabilizing drug	No/Yes and class (lithium, valproate, carbamazepine, lamotragine) during baseline
	Anti-depressant drug	No/Yes and class (SSRI, tricyclic, monoamine oxidase inhibitor, other) during baseline
	Annual consultation rate	Quartiles of consultation rate during baseline
	Cancer diagnosis	No/Yes and type in 5 years before the index date
	Health authority	A-M including Scotland, Northern Ireland and Wales

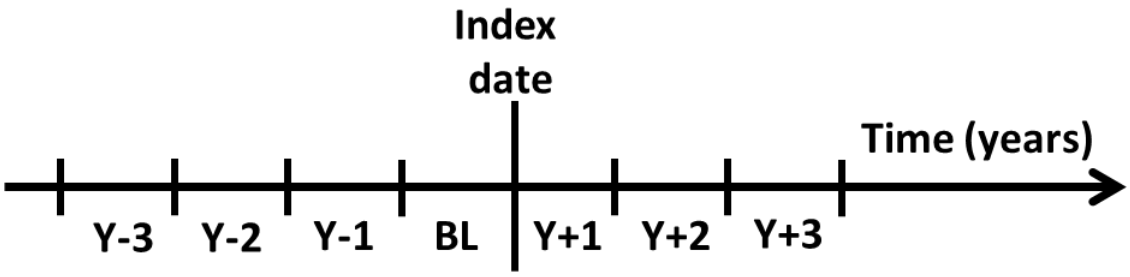
Shaded cells indicate essential variables or covariates; non-shaded cells are additional covariates

5.4 Multiple imputation of unobserved covariate data

Complete cases: Individuals were defined as complete cases if they had a record of systolic blood pressure, weight and total cholesterol concentration measured in the 12 months before the index date in addition to a record of height (at age 21 years or older) and smoking status recorded at any time point.

Imputation of missing data: Unobserved covariate data were estimated using multiple imputation to generate ten imputed datasets for the full study population. The *MI suite* of commands in Stata was used to estimate missing covariate data and analyse the imputed datasets. Data were separately imputed by gender in each of the five cohorts because CVD risk differs markedly between men and women, even after accounting for other factors such as age (Osborn et al., 2015). The imputation model used mean time-varying data for each year from three years either side of the index date to estimate unobserved records for the baseline period (twelve months before the index date) (Figure 5-3).

Figure 5-3: Temporal relationships between the index date, baseline year (BL), and imputation variables (up to three years before (Y-3) and after (Y+3) the index date).



Final imputation model: *MI chained* (Stata version 12) was used to produce 10 imputed datasets for each cohort. The imputation model included measurements of total cholesterol, blood pressure, height and weight in log form.

Variables being imputed: log of cholesterol concentration at baseline and at +/-3 years, log of height, log of weight at baseline and +/-3 years, log of systolic blood pressure at baseline and +/- 3 years, Townsend score, smoking status. Although only baseline measurements were included in the analysis model (see section 6) a chained equations approach was used to impute data for the three years either side of baseline immediately prior to estimating missing baseline values.

Fully observed variables: statin exposure at the index date, CVD event indicator, Nelson-Aalen estimates, indicators for statin prescribing at 1 and 2 years after the index date, sex, SMI diagnosis and baseline estimates of: 5 year age-band, diabetes status, heavy drinking, antihypertensive use, non-statin lipid modifying drug use, anti-depressant use, antipsychotic use and type/generation of antipsychotic, mood stabilizing drug use, quartiles of annual consultation rate, cancer diagnosis, hypothyroidism, familial hypercholesterolaemia, CKD, COPD, health authority region. Further detail regarding the specification of these variables is included in Table 5-1 and Chapter 3 section 3.2.

5.4.1 Developing and checking the specification of the multiple imputation model

Initial exploratory analyses confirmed that each of the covariates identified from the literature (Table 5-1) was associated with missing data and/or the observed data value.

Requirements of the imputation model specification: The selection of a multiple imputation model to estimate unobserved covariate data for use in the final analysis was constrained by several factors that are specific to the study design and the research question. These factors were that:

i) the imputed dataset should support estimation of the office version of the Framingham risk score (described in detail in Chapter 3 section 3.2.6); with the ideal dataset allowing estimation of the laboratory version of the Framingham risk score
ii) the same combination of variables should be included in the imputation model for each of the 5 time periods (cohorts)
iii) the imputation model should incorporate essential variables on statin exposure, CVD outcomes (both the event indicator and time component) and all other variables included in the final analysis model (White et al., 2011).

5.4.1.1 Developing the imputation model

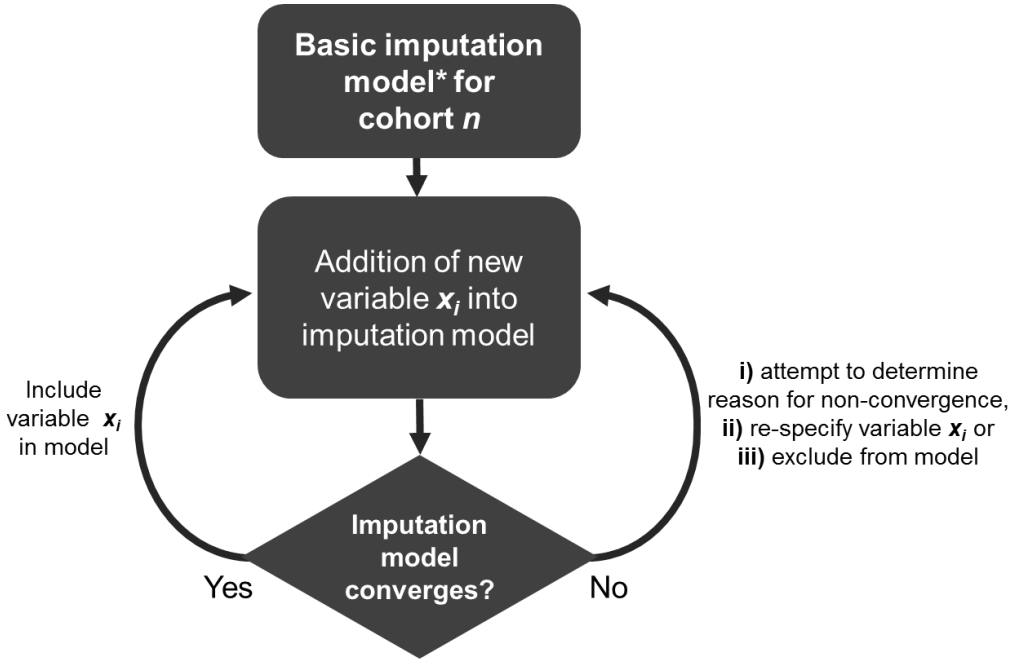
Figure 5-4 describes the process used to specify the imputation model. The imputation model was developed using a forwards elimination approach starting with a basic model incorporating essential variables. Additional variables were added to this model in order of anticipated importance for patterns and values of

missing data. Where the addition of a variable resulted in failure of the imputation model to converge it was omitted. The proportion of missing data for variables included in the Framingham risk score (Chapter 3 section 3.2.6) increased over time (Chapter 5 section 7.1): it was therefore anticipated that the earliest time periods would limit the complexity of the imputation model, relative to more recent data. For example, HDL-C was recorded for less than 5% of individuals in 2002, but was available for over 60% of individuals in 2012. Similarly the pattern of recording for smoking status had changed over time such than in earlier years only current smokers had a record, whereas never- and ex-smoking statuses were much more commonly recorded for recent time points. The basic imputation model was therefore developed using data from the earliest cohorts and then applied to data from later cohorts.

Essential variables in the imputation model: The process outlined in Figure 5-4 started with a basic imputation model for each cohort, which included the following essential variables: age (in 5 year bands), statin prescribing at the index date and 1 and 2 years after the index date, diabetes status, systolic blood pressure, total cholesterol concentration, height, weight, smoking status, CVD events and the associated Nelson-Aalen cumulative hazard function estimate (White and Royston, 2009). Time varying indicators marking whether an individual was prescribed a statin at one and two years after the index date were added to the imputation model. This improved the potential of the model to impute cholesterol concentration correctly at time periods after baseline in response to the initiation or cessation of statin therapy after the index date.

Additional variables in the imputation model: Other variables (termed $\boldsymbol{X_i}$ in Figure 5-4) that were identified from the literature as being correlated with CVD events and statin therapy were sequentially added to the model in order of anticipated importance. The order of importance was specified as follows: HDL-C, diastolic blood pressure, Townsend score, antihypertensive use, heavy drinking, non-statin lipid modifying drug use, antipsychotic use, antidepressant use, mood stabilising drug use, hypothyroidism, familial hypercholesterolaemia, consultation rate during baseline, cancer diagnoses, antipsychotic type and generation, CKD, COPD, asthma, atrial fibrillation, health authority region.

Figure 5-4: Flowchart for the process of developing the imputation model



Review imputed values and – if the imputed values are plausible given the observed data - repeat the process for cohort *n+1* once all variables (x_i) have been added to the model

Cohort n denotes the cohort which was initiated at the earliest calendar time period (i.e. January 2002-December 2003).

Cohort n+1 denotes the next cohort in the sequence (e.g. January 2004-December 2005).

The **basic imputation model*** incorporated essential variables as follows: age (in 5 year bands), statin prescribing at the index date and 1 and 2 years after the index date, diabetes status, blood pressure, total cholesterol concentration, height, weight, smoking status, CVD events and the associated Nelson-Aalen cumulative hazard function estimate.

Each **additional variable (x_i)** was added in the following order: HDL-C, diastolic blood pressure and Townsend score for deprivation, antihypertensive use, heavy drinking, non-statin lipid modifying drug use, antipsychotic use, antidepressant use, mood stabilising drug use, hypothyroidism, familial hypercholesterolaemia, quartiles of consultation rate during baseline, cancer diagnoses, antipsychotic type and generation, CKD, COPD, asthma, atrial fibrillation, health authority region.

Data on smoking status was difficult to impute as a time-varying variable and resulted in an imputation model that was incompatible (unstable at >3 imputations) with each of the other essential variables in the model. Smoking status was therefore imputed as a time-fixed variable in which the highest recorded smoking status (ordered as never<ex-smoker<current smoker) for each individual was retained in the dataset. Whilst this definition of smoking is fairly satisfactory for individuals classed as never and ex-smokers, it may overestimate CVD risk for individuals classified as current smokers who later stopped smoking. However, manual review of records for ex-smokers suggested that many had a mixture of current and ex-smoker records, which is indicative of multiple failed cessation attempts and thus reflects a CVD risk profile that is more similar to a smoker than a non-smoker. The mode of classification used is further justified by the practical advantage that the resulting imputation model was highly stable and could support the inclusion of all other essential variables.

Imputing HDL-C was not possible for early time periods (the model did not converge), reflecting a very low proportion of people that had a measurement of HDL-C recorded (e.g. 5% in 2002). However, given information on other covariates such as total cholesterol concentration, height and weight, imputed values of HDL-C near the start of the study would be unlikely to be informative because data were missing for 95% of individuals. Because it was not possible to impute HDL-C, the laboratory version of the Framingham risk score could not be estimated from the imputed dataset, instead CVD risk profile was reported using the office version of the Framingham risk score.

Imputation model checking: The standard output (example outlined in the appendix sections 25 and 26) obtained from execution of *MI impute* in Stata was checked for any indication of model instability or misspecification. The plausibility of imputed values for total cholesterol, height, weight, systolic blood pressure and smoking status were carefully assessed for each cohort and across the full dataset (all five cohorts) as follows:

- Data that were imputed in log form were back-transformed in order to make assessment of the biological plausibility of these values easier to determine

- The range and distribution of imputed values was assessed relative to the observed (complete) data; particular attention was given to values of total

cholesterol at baseline and other time points

- Complete and imputed data were also investigated by estimating CVD risk scores within strata of age (40-59, 60-69, 70-74, 75-84 years) and gender. In addition, the coefficients obtained for regression of estimated risk score on (continuous) age in years (separately for men and women) was used as a further means of gauging the compatibility of the complete and imputed datasets

- Multivariable regression models (output included in the appendix; Table 8 and Table 9) were used to assess the similarity of correlations within complete and imputed datasets between each of the variables included in the main analysis and statin prescribing or CVD events for the association. These associations were also useful for sense-checking complete and imputed data for well-established correlations such as increasing CVD risk and advancing age

6 Analysis

Descriptive analysis: the characteristics of statin users and non-users were described using data for the complete cases and the imputed dataset. Observed and imputed cholesterol data at 1 and 2 years after the index date were investigated but these variables were not incorporated into the final analysis models. However, these estimates are of interest because change in cholesterol concentration is an intermediate outcome for CVD and may be indicative of statin medication adherence.

Calculating average treatment effect: Data for each of the five cohort studies were pooled to obtain average causal effect estimates for the whole study period. Incident rate ratios (IRRs) for the association between statin prescribing and combined MI and stroke were estimated using a Poisson regression model with receipt of a statin prescription as the exposure and first MI or stroke event as the outcome: follow up time was used as an offset. As the same individual could be included in more than one cohort it was necessary to combine the effect estimates using the 'robust sandwich estimator' to calculate conservative estimates of variance.

In addition to calculating the crude IRR, the Poisson model was adjusted for a panel of essential (SMI condition, age, gender, diabetes status, blood pressure, BMI, total cholesterol concentration, smoking status and year of cohort initiation) and additional covariates. Additional covariates were added to the analysis model in order of their perceived importance as confounders of the causal association between statin use and CVD events. The order was as follows: antihypertensive drug use, psychological drug use (antipsychotics, antidepressant and mood stabilizer use), consultation rate, Townsend score and comorbid conditions (familial hypercholesterolaemia, non-statin lipid modification, CKD, COPD, hypothyroidism, heavy drinking, asthma, atrial fibrillation, cancer). The pooled dataset was reviewed to understand what impact each of the essential covariates and all additional variables in the final model had on the crude effect estimate and were presented as a Forest plot.

Systolic blood pressure and total cholesterol were included in the analysis model on their original scale (mmHg and mmol/L, respectively): however, the full multivariable model was reviewed for evidence of improved specification (using Wald tests and reviewing the effect estimates and associated standard error) after including these variables in log form. In addition, the impact of substituting age bands with different transformations of age (continuous or log of age) and the inclusion of an interaction term between age and sex was assessed for the complete case analysis by reviewing the effect estimates and using likelihood ratio testing. Evidence of improved model specification through the inclusion of transformed variables and interaction terms in the complete case analysis was used to guide the development of the imputation model.

Calculating cohort-specific estimates of effect: Data for each cohort were analysed separately to calculate crude and adjusted effect estimates for statin prescribing and combined MI and stroke for each time period.

Secondary outcomes: all-cause mortality, fatal and non-fatal stroke, fatal and non-fatal MI, cholesterol concentration 1 and 2 years after the index date: The primary analysis was repeated for: all-cause mortality (any record of death), first stroke (haemorrhagic or ischaemic stroke) and first MI to identify whether the effectiveness of statins was substantially altered for each of these outcomes.

Changes in total cholesterol concentration measured during the 1 and 2 years after the index date (i.e. 1-365 or 366-730 days after the index date, respectively) were

evaluated for statin users and non-users in individuals with complete data at baseline. For this analysis, linear regression models with total cholesterol at one or two years after the index date were developed using the same array of covariates as for the main analysis. Change in cholesterol as an outcome for individuals who did not have complete data was not assessed because the imputation model was developed to impute covariate rather than outcome data.

Sub-group analyses: Sub-group analyses were conducted by repeating the main analysis (primary outcome of combined MI and stroke) within strata of: high 10 year CVD risk (≥10%, ≥15%, ≥20% and ≥25%) at baseline, gender and type of SMI (bipolar disorder or schizophrenia). In order to increase the similarity of risk scores between statin users and non-users individuals with the top 5% (by gender) of CVD risk scores were excluded from the CVD risk analysis.

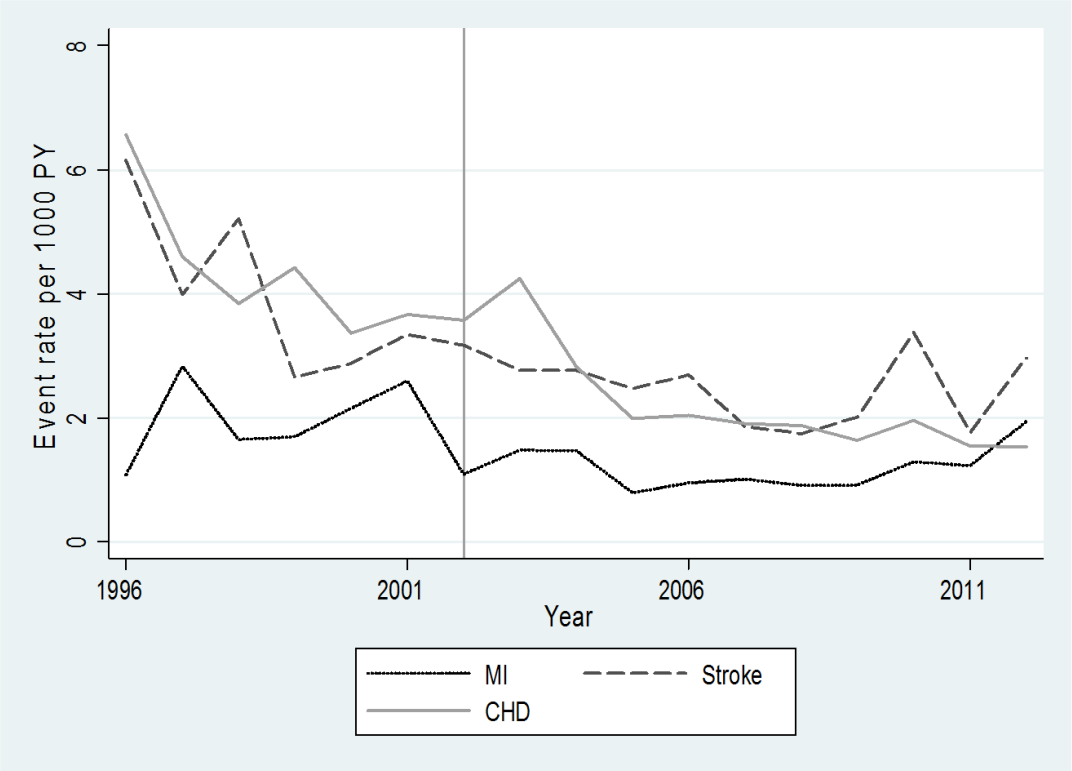
7 Results

7.1 Exploratory work

7.1.1 Selecting the CVD outcomes included in the study

Figure 7-1 shows the rate of first CVD events by type (MI, stroke or CHD excluding MI) over time. The grey vertical line indicates the calendar year 2002 (the start of the first staggered cohort study). There was moderate variation in the rate of first CVD events over time. Although not conclusive, the peak in CHD diagnoses in 2003 could potentially be indicative of a catch-up exercise (i.e. recording prevalent CVD diagnoses) in anticipation of the introduction of the Quality and Outcomes Framework (QOF) in 2004.

Figure 7-1: CVD event rate (per 1000 person years) in people with SMI by type of CVD diagnosis



The grey vertical line indicates the calendar year 2002

7.1.2 Selecting the duration of the exposure window

An exposure window of 24 months was required for the imputation model to be compatible with data for each of the cohorts. This was because the imputation model would not converge for some of the cohorts when a shorter exposure window (of 6 or 12 months) was specified, which is likely to reflect issues of perfect prediction arising from the small number of CVD events within sub-groups of statin use and gender (White et al., 2011).

7.2 Descriptive results

7.2.1 Study population

A total of 16,854 individuals with a diagnosis of schizophrenia or bipolar disorder from five cohorts spanning from January 2002 to December 2011 were included in the pooled dataset. On average each individual was included in 2.7 cohorts such that data for a total of 45,830 cases (total statin users and non-users under follow-up) were available for analysis (Table 7-1). The majority of individuals (96%)

contributed data to the statin non-users arm of at least one cohort and a total of 2913 (17%) people were prescribed a statin during the study period.

The complete case analysis was conducted on a subset of 6915 cases, which had data on all essential covariates during the baseline period (reflecting 5321 individuals who contributed data to an average of 1.3 cohorts: (Table 7-1)).

Table 7-1: Summary of the number of cases and individuals in the study population, classified by statin exposure

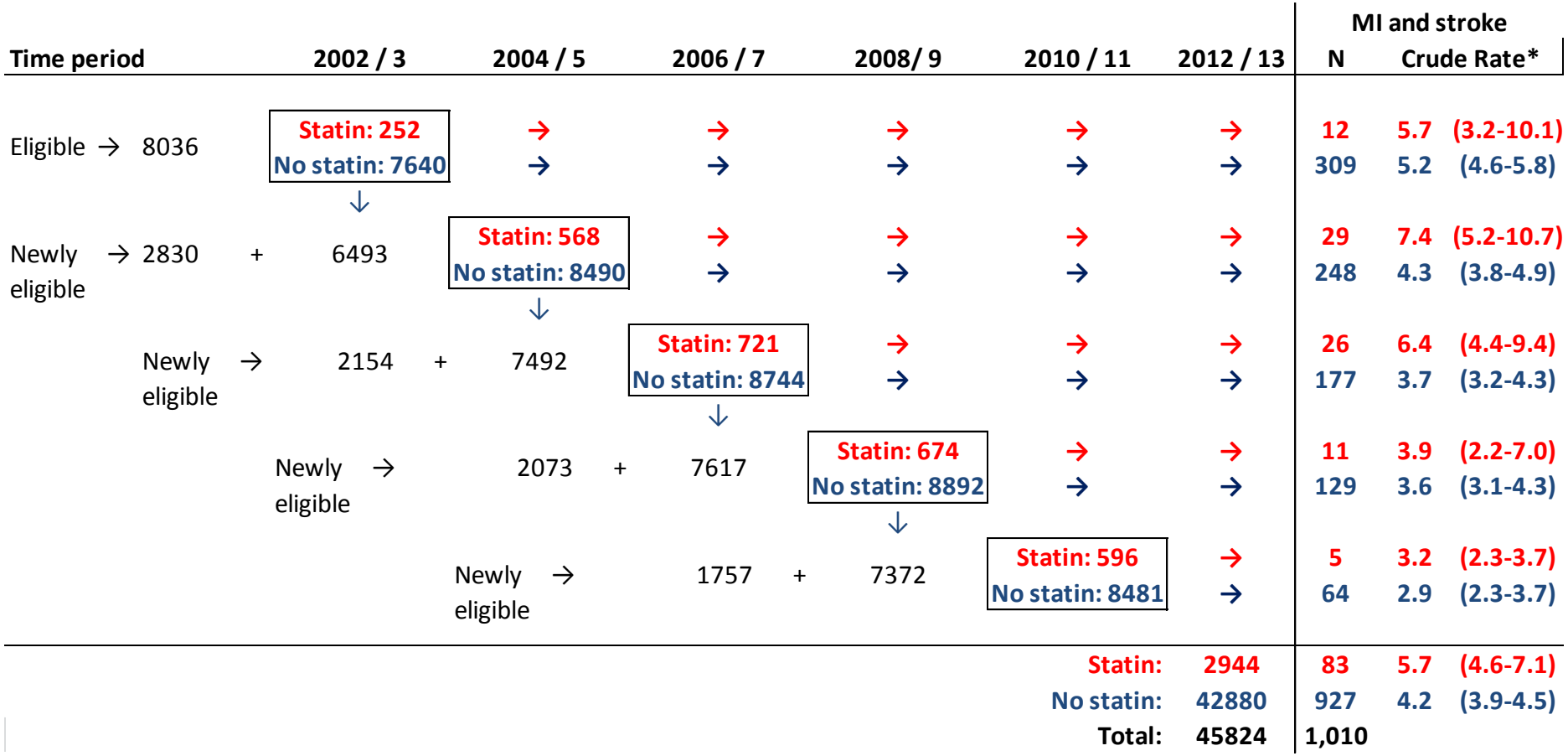
Subset of data		Total	Statin Users		Statin non-users	
Full population	**Total cases under follow-up***	45,824	2,944	6%	42,886	94%
	People**	16,850	2,913	17%	16,098	96%
	Mean cohorts per person	2.72	1.01		2.66	
Complete cases	**Total cases under follow-up***	6,915	1,714	25%	5,201	75%
	People**	5,321	1,706	32%	4,017	75%
	Mean cohorts per person	1.30	1.00		1.29	

***Total cases under follow up describes the number of statin users and non-users that were included in the pooled datasets derived from combining cohorts for different time periods.
****Because the same individual could be included as both a statin user and non-user (at different time points) the combined percentage of people who were statin users or statin non-users exceeds 100%.

Of the 2,944 statin prescriptions issued at the index date, 2,938 (83%) were for simvastatin, 395 (13%) for atorvastatin and the remaining 111 (4%) for pravastatin (n=46), rosuvastatin (n=45), fluvastatin (n=16) or cerivastatin (n=4).

The number of statin users and non-users and the associated event rate for MI and stroke that were included in each of the five cohort studies is outlined in Figure 7-2 describes the flow of individuals between adjacent cohorts (e.g. 6,493 individuals who were statin non-users in 2002/3 were included in the 2004/5 cohort in addition to 2,830 newly eligible individuals).

Figure 7-2: Flowchart of statin users and non-users contributing data to each of the five cohorts in the full population



***Crude event rates (and associated 95% CI) per 1000 person-years**

Table 7-2 reports the number and rate of events within each cohort separately for MI and stroke.

Table 7-2: The number and rate of events within each cohort for MI and stroke in the full population

Time period	Exposure at index date	MI			Stroke		
		N	Crude Rate*		N	Crude Rate*	
2002/3	Statin	4	1.9	(0.7-5.0)	8	3.8	(1.9-7.5)
	No statin	108	1.8	(1.5-2.2)	201	3.4	(2.9-3.9)
2004/5	Statin	10	2.6	(1.4-4.8)	19	4.9	(3.1-7.6)
	No statin	88	1.5	(1.2-1.9)	160	2.8	(2.4-3.3)
2006/7	Statin	11	2.7	(1.5-4.9)	15	3.7	(2.2-6.2)
	No statin	59	1.2	(1.0-1.6)	118	2.5	(2.1-3.0)
2008/9	Statin	5	1.8	(0.7-4.3)	6	2.5	(1.0-4.7)
	No statin	41	1.2	(0.8-1.6)	88	2.1	(2.0-3.0)
2010/11	Statin	1	0.6	(0.1-4.5)	4	2.5	(1.0-6.8)
	No statin	20	0.9	(0.6-1.4)	44	2.0	(1.5-2.7)
All cohorts	Statin	31	2.1	(1.5-3.0)	52	3.6	(2.7-4.7)
	No statin	316	1.4	(1.3-1.6)	611	2.8	(2.5-3.0)
	Total	347			663		

*Crude event rates (and associated 95% CI) per 1000 person-years

7.2.2 Characteristics of the study population

Table 7-3 describes the baseline characteristics of statin users and non-users included in the complete case and full population analyses.

Of note, total cholesterol concentration at baseline differed in statin users and non-users for both the complete cases (6.2 and 5.3mmol/L in statin users and non-users, respectively) and those with imputed data (6.4 and 5.4mmol/L in statin users and non-users, respectively). Values of total cholesterol recorded in the year after statin initiation were reduced by 1.7mmol/L (27%) in both the observed and imputed datasets. By contrast, amongst statin non-users total cholesterol recorded in the year after the index date was decreased by 0.08mmol/L (1%) in the observed data and 0.02mmol/L in the imputed dataset (0.4%).

The distribution of estimated CVD risk scores was different for statin users and non-users, with baseline risk being higher (on average) for statin users. The characteristics of the full study population (investigated using imputed data) were similar to the complete cases; however, the proportion of individuals with diabetes was much higher in the subset with complete data (22% versus 8% in statin non-users and 45% versus 35% in statin users). As diabetics are in general more intensively monitored in primary care, this difference was anticipated. Table 7-3 outlines estimated CVD risk scores within strata of age-band and gender and Figure 7-3 depicts histograms of the distribution of the risk scores for statin users and non-users.

In addition to differences in CVD risk score, the number of face-to-face consultations during baseline differed for statin users and non-users: on average statin users consulted more frequently. Statin users were also relatively more likely to be more deprived, be prescribed an antihypertensive, antidepressant and to have familial hypercholesterolaemia (for which statin therapy is indicated). There were smaller absolute differences for the proportion of statin users and non-users who were prescribed mood stabilisers, non-statin lipid modifying drugs or who had a diagnosis of asthma, COPD, atrial fibrillation, cancer, hypothyroidism, CKD or being a heavy drinker (Table 7-3).

Table 7-3: Characteristics of the study population at baseline

	Characteristic at baseline	Complete cases				Full population			
		Statin -	IQR	Statin +	IQR	Statin -	IQR	Statin +	IQR
	Total cases under follow-up*	5201		1714		42886		2944	
	Bipolar	50%		49%		51%		50%	
	Median age (years)	55	(48, 64)	58	(50, 65)	54	(47, 64)	59	(51, 67)
	Male	47%		51%		45%		48%	
	Diabetes (yes)	22%		45%		8%		35%	
	Median Sys BP (mmHg)**	131	(120, 141)	136	(125, 147)	130	(120, 141)	137	(126, 148)
	Median BMI**	28	(25, 33)	30	(26, 34)	27	(24, 31)	30	(26, 34)
	Median cholesterol conc (mmol/L)**	5.3	(4.7, 6.0)	6.2	(5.5, 7.1)	5.4	(4.8, 6.2)	6.4	(5.6, 7.2)
	Smoker**	58%		65%		55%		61%	
	Median BMI CVD risk score								
Women	**40-49 years**	6	(4, 10)	10	(7, 16)	5	(4, 7)	10	(6, 14)
	50-59 years	11	(8, 15)	19	(12, 26)	10	(7, 14)	17	(11, 24)
	60-74 years	20	(13, 30)	29	(19, 42)	17	(12, 25)	25	(17, 38)
	75-84 years***	34	(23, 49)	36	(27, 56)	26	(18, 36)	34	(24, 48)
Men	**40-49 years**	14	(10, 20)	20	(15, 28)	12	(9, 16)	19	(14, 26)
	50-59 years	26	(18, 35)	33	(23,42)	22	(16, 30)	32	(22,41)
	60-74 years	41	(29, 55)	47	(35, 59)	36	(26, 47)	45	(34, 57)
	75-84 years***	58	(45, 71)	62	(48, 80)	49	(39, 63)	58	(48, 79)

Table 7-3 continued	Characteristic at baseline	Complete cases				Full population			
		Statin -	%	Statin +	%	Statin -	%	Statin +	%
	Total cases under follow-up*	5201		1714		42886		2944	
Annual consultation rate	**<4**	630	12%	150	9%	10906	25%	322	11%
	4-6	1024	20%	323	19%	9310	22%	568	19%
	7-12	1679	32%	561	33%	11506	27%	942	32%
	>13	1868	26%	680	40%	11158	26%	1112	38%
Antipsychotic use	**None**	1926	37%	649	38%	20061	47%	1178	40%
	First generation	1091	21%	384	22%	8932	21%	630	21%
	Second generation	2184	42%	681	40%	13886	32%	1136	39%
Townsend score	**1 (least deprived)**	813	16%	238	14%	7280	17%	448	15%
	2	823	16%	253	15%	7419	17%	462	16%
	3	987	19%	336	20%	8653	20%	595	20%
	4	1278	25%	380	22%	9731	23%	626	21%
	5 (most deprived)	1214	23%	469	27%	9101	21%	755	26%
	Not recorded	86	2%	38	2%	969	2%	58	2%
Year of cohort	**2002**	268	5%	98	6%	7752	18%	285	10%
	2004	592	11%	336	20%	8718	20%	605	21%
	2006	1024	20%	453	26%	8901	21%	747	25%
	2008	1387	27%	427	25%	8994	21%	697	24%
	2010	1930	37%	400	23%	8521	20%	610	21%

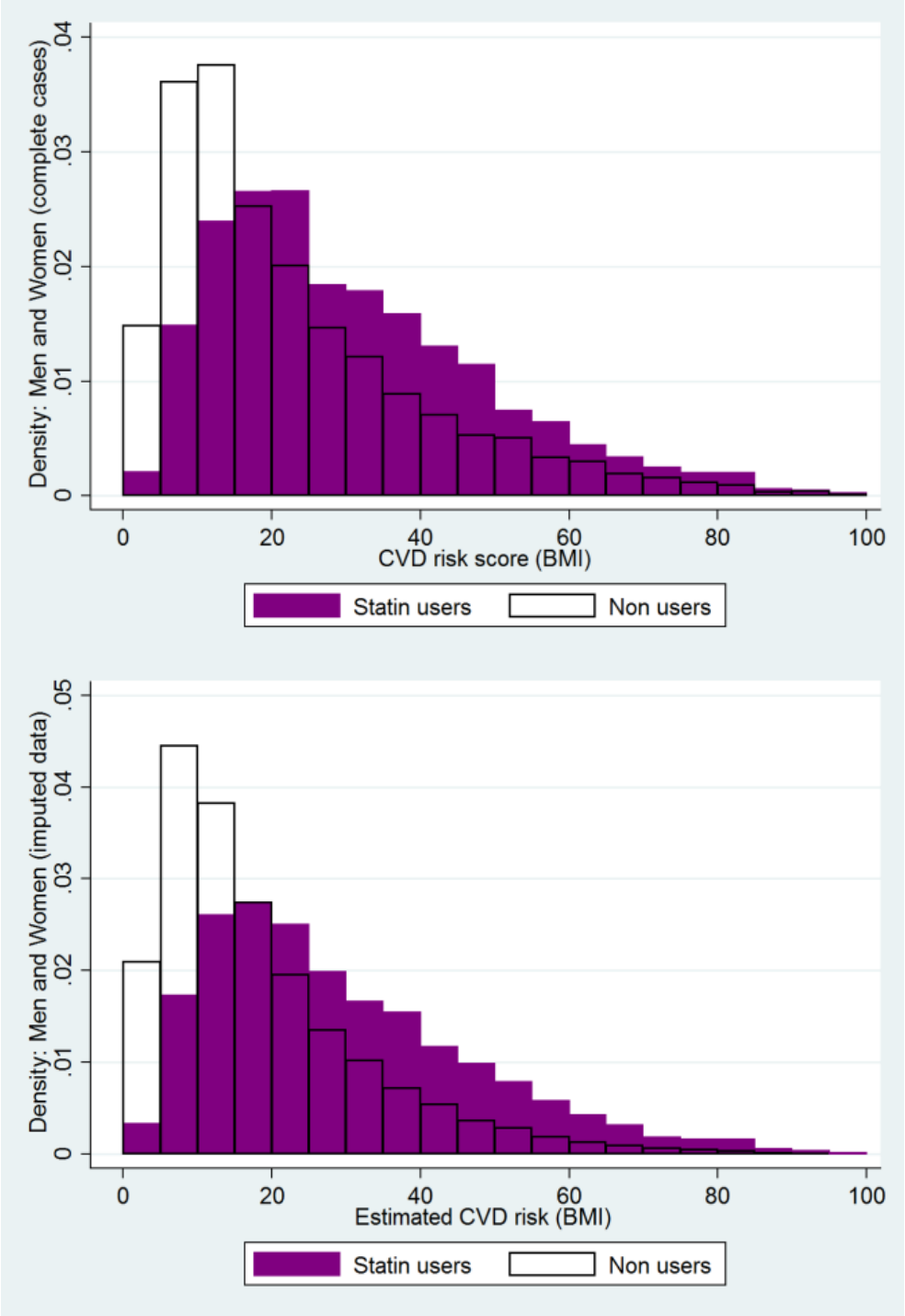
Table 7-3 continued	Characteristic at baseline	Complete cases				Full population			
		Statin -	%	Statin +	%	Statin -	%	Statin +	%
	Total cases under follow-up*	5201		1714		42886		2944	
Antihypertensive use	**(yes)**	1201	23%	1065	62%	5685	13%	961	33%
Antidepressant use	**(yes)**	2156	41%	801	47%	17252	40%	1371	47%
Mood stabiliser use	**(yes)**	1815	35%	538	31%	13166	31%	922	31%
Asthma	**(yes)**	596	11%	211	12%	4387	10%	336	11%
COPD	**(yes)**	224	4%	85	5%	1300	3%	132	4%
Familial hypercholesterolaemia	**(yes)**	38	0.7%	173	10%	77	0.2%	302	10%
Atrial fibrillation	**(yes)**	59	1.0%	16	0.9%	406	1.0%	41	1.4%
Cancer diagnosis in past year	**(yes)**	80	2%	22	1.2%	607	1.4%	39	1.3%
Hypothyroidism	**(yes)**	47	0.9%	21	1.2%	342	0.8%	34	1.2%
CKD	**(yes)**	424	8%	102	6%	1398	3%	188	6%
Heavy drinker	**(yes)**	933	18%	293	17%	5994	14%	469	16%
Non-statin lipid modification	**(yes)**	66	1.3%	34	2%	196	0.5%	51	2%

*****Total cases under follow up describes the number of statin users and non-users that were included in the pooled datasets derived from combining cohorts for different time periods

**Denotes variables where unobserved baseline values were imputed in the full population dataset

***Framingham risk score not validated for individuals aged >74 years

Figure 7-3: Distribution of CVD risk scores (top: complete cases and below: full population)

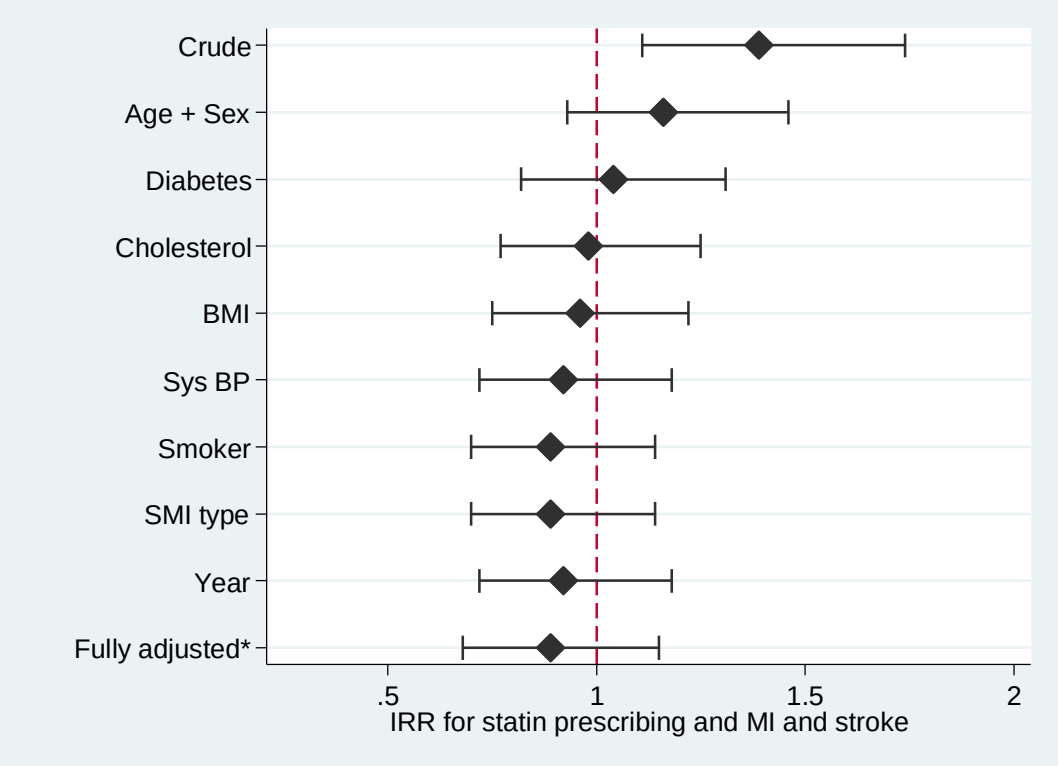


CVD risk scores in the full population were estimated using imputed values of blood pressure, BMI and smoking status where these values were not recorded during baseline.

8 Average treatment effect of statin prescribing on MI and stroke

The crude rate of first MI and stroke per 1000 person-years of follow-up was 5.74 (4.62, 7.11) in statin users and 4.17 (3.91, 4.45) in statin non-users (Figure 7-2, previous) in the full population. The impact of adding covariates to the model is outlined in Figure 8-1. The crude IRR for the association between statin prescribing and MI and stroke events was 1.39 (1.11, 1.74) for the full study population: the addition of all essential covariates to the model reduced the IRR to 0.92 (0.89, 1.18). This estimate were further reduced to 0.89 (0.68, 1.15) after adjustment for all additional covariates. Inclusion of transformed versions of continuous variables (age, total cholesterol, systolic blood pressure, BMI) in the model did not have a marked impact upon the effect estimates or associated 95% CI for the association between statin prescribing and MI and stroke events.

Figure 8-1: Crude and adjusted IRRs for statin prescribing and MI and stroke



*Fully adjusted model baseline covariates: age and sex, diabetes, total cholesterol concentration**, BMI**, systolic blood pressure**, smoking status**, SMI type, year of cohort start, antihypertensive use, antidepressant use, consultation rate, antipsychotic use and type, mood-stabiliser use, Townsend score, asthma, COPD, hypothyroidism, CKD, atrial fibrillation, familial hypercholesterolaemia, heavy drinking, non-statin lipid modification, cancer, hypothyroidism.

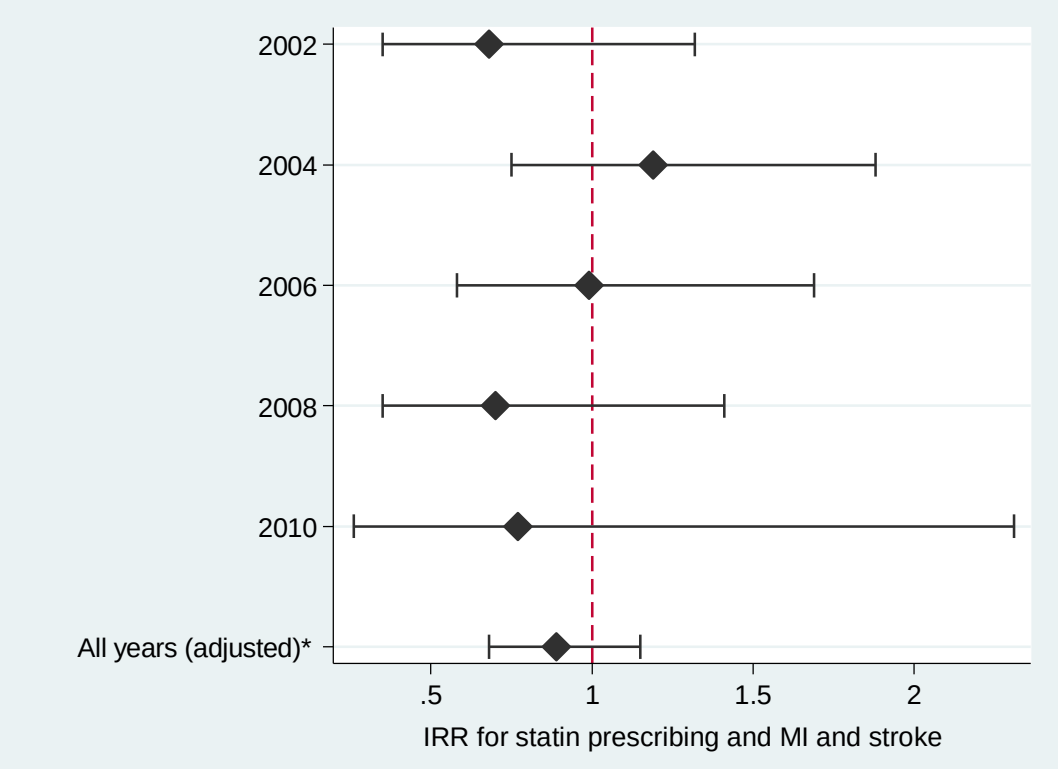
**Denotes variables where unobserved baseline values were imputed

The fully adjusted IRR for the primary outcome (0.89) suggests that statin prescribing may be associated with a 10% reduction in the rate of first MI and stroke in people with SMI. However, because the 95% CI around the point estimate were wide (0.68-1.15), there is insufficient evidence to conclude that the lower rate of CVD events amongst statin users could not have arisen by chance.

8.1 Cohort-specific effects of statin prescribing on MI and stroke

Fully adjusted IRRs for the association between statin prescribing and MI and stroke are outlined for each of the five cohorts and for the pooled dataset in Figure 8-2. Although there was some variation in the point estimates for a given cohort (which ranged from 0.68 in 2002 to 1.19 in 2004), the associated 95% CI were wide and there were no outliers with respect to the pooled result for all years.

Figure 8-2: Adjusted IRRs for statin prescribing and CVD events for each of the cohort studies



*Fully adjusted model baseline covariates: age and sex, diabetes, total cholesterol concentration**, BMI**, systolic blood pressure**, smoking status**, SMI type, year of cohort start, antihypertensive use, antidepressant use, consultation rate, antipsychotic use and type, mood-stabiliser use, Townsend score, asthma, COPD, hypothyroidism, CKD, atrial fibrillation, familial hypercholesterolaemia, heavy drinking, non-statin lipid modification, cancer, hypothyroidism.

**Denotes variables where unobserved baseline values were imputed

8.2 Secondary outcomes:

8.2.1 Average treatment effect of statin prescribing on all-cause mortality

The crude rate of all-cause-mortality per 1000 person-years of follow-up was 19.6 (17.4, 22.0) in statin users and 19.3 (18.7, 19.8) in statin non-users in the full population. The crude IRR for the association between statin prescribing and all-cause mortality was 1.02 (0.90, 1.14) and was reduced to 0.89 (0.78, 1.02) after adjusting for all covariates.

8.2.2 Average treatment effect of statin prescribing on first MI

The crude rate of first MI per 1000 person-years of follow-up was 2.14 (1.51, 3.05) in statin users and 1.42 (1.27, 1.59) in statin non-users in the full population. The crude IRR for the association between statin prescribing and first MI was 1.51 (1.04, 2.18) and was reduced to 0.75 (0.48, 1.15) after adjusting for all covariates.

8.2.3 Average treatment effect of statin prescribing on first stroke

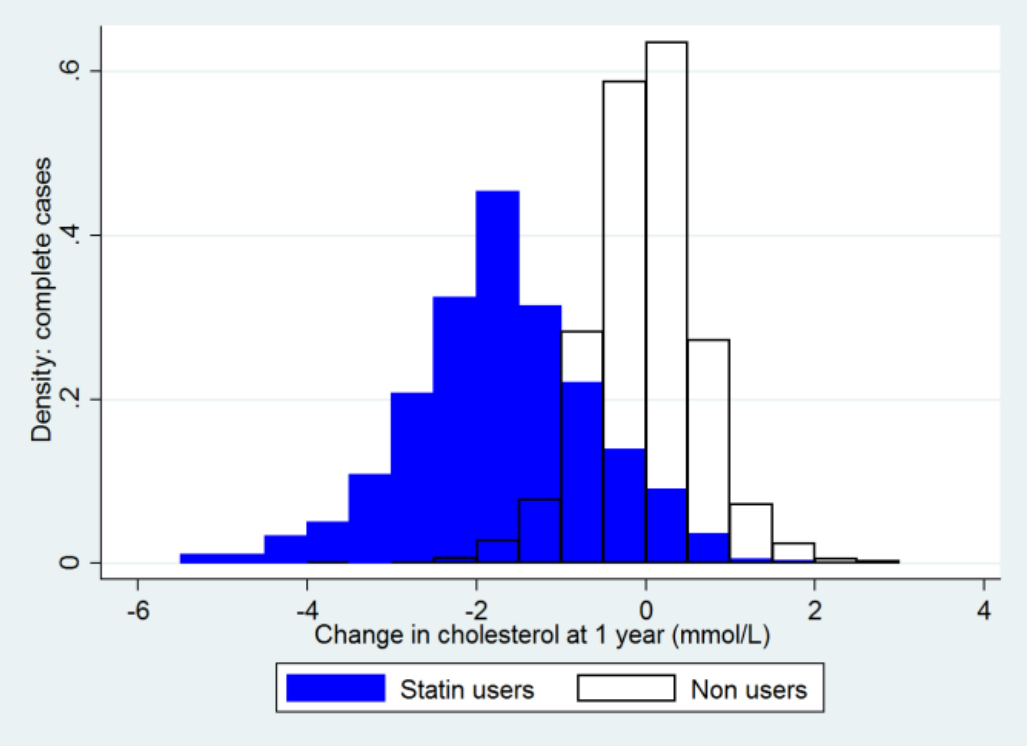
The crude rate of first stroke per 1000 person-years of follow-up was 3.60 (2.74, 4.72) in statin users and 2.75 (2.50, 2.98) in statin non-users in the full population. The crude IRR for the association between statin prescribing and first stroke was 1.31 (0.99, 1.74) and was reduced to 0.96 (0.68, 1.15) after adjusting for all covariates.

8.2.4 Change in total cholesterol and 1 and 2 years after the index date in complete cases

A total of 82% and 73% of the 1714 statin users had measurements of total cholesterol recorded within the 1 and 2 years after the index date, respectively. By comparison, 55% and 69% of statin non-users had a measurement of cholesterol recorded within the 1 and 2 years after the index date, respectively. Mean total cholesterol at baseline was almost 1mmol/L lower in statin non-users than statin users.

On average, the total cholesterol concentration of individuals who were prescribed a statin was decreased by 1.7mmol/L at both 1 and 2 years after the index date: mean cholesterol concentration at 1 and 2 years did not substantially change in individuals who were not prescribed a statin (Figure 8-3).

Figure 8-3: Change in total cholesterol concentration (mmol/L) at 1 year after the index date



In statin users total cholesterol was decreased by 1.7mmol/L (27%) from baseline concentrations of 6.3 to 4.6mmol/L at both 1 and 2 years after baseline (Table 8-1). By contrast, amongst statin non-users mean total cholesterol in each individual was slightly decreased by 0.1mmol/L (2%) from baseline concentrations of 5.4mmol/l to 5.3mmol/L at both 1 and 2 years after baseline.

Table 8-1: summary statistics for change in total cholesterol within 1 and 2 years of the index date

Group	Description of metric	Baseline	1 year	2 years
Statin non-users	Number under follow-up	5201	2865	3002
	Mean cholesterol concentration mmol/L (SD)	5.4 (1.0)	5.3 (1.0)	5.3 (1.0)
	Change from baseline mmol/L (%)	--	-0.1 (-2%)	-0.1 (-2%)
Statin users	Number under follow-up	1714	1409	1253
	Mean cholesterol concentration mmol/L (SD)	6.3 (1.2)	4.6 (1.0)	4.6 (1.1)
	Change from baseline mmol/L (%)	--	-1.7 (-27%)	-1.7 (-27%)

A linear regression model for the crude change in cholesterol by statin exposure confirmed that statin use was associated with a 1.7mmol/L (95% CI; 1.6, 1.7) decrease in cholesterol concentration, relative to non-users at both 1 and 2 years after the index date. The fully adjusted model produced lower estimates of 1.3mmol/L (95% CI; 1.2, 1.4) and 1.2mmol/L (95% CI; 1.1, 1.3) decreases at 1 and 2 years after the index date, respectively.

In the fully adjusted model statin use was the most important predictor of change in cholesterol concentration at both time points (coefficients of -0.36 and -0.41 at 1 and 2 years, respectively). A range of other variables were more weakly associated with change in cholesterol (model outputs outlined in the appendix; Table 6 and Table 7): including baseline cholesterol concentration, age, gender, and presence of familial hypercholesterolaemia, diabetes, non-statin lipid modification, type of antipsychotic used and hypothyroidism.

8.3 Sub-group analyses

8.3.1 Average treatment effect of statin prescribing on MI and stroke in the subgroup of cases at high risk of CVD

Within the subset of cases with estimated 10 year CVD risk scores indicating high risk the fully adjusted IRRs for statin prescribing and first MI and stroke were as

follows: ≥10% CVD risk score; 0.93 (95% CI; 0.69, 1.26), ≥15%; 0.90 (95% CI; 0.67, 1.21), ≥20%; 0.82 (95% CI; 0.59, 1.13) and ≥25%; 0.73 (95% CI; 0.52, 1.05).

8.3.2 Average treatment effect of statin prescribing on MI and stroke within strata of gender

Fully adjusted IRRs for the association between statin prescribing and first MI and stroke within strata of gender were as follows: men; 0.96 (95% CI; 0.65, 1.42) and women; 0.84 (95% CI; 0.58, 1.20).

8.3.3 Average treatment effect of statin prescribing on MI and stroke within strata of mental illness type

Fully adjusted IRRs for the association between statin prescribing and first MI and stroke within strata of mental illness type were as follows: schizophrenia; 0.85 (95% CI; 0.60, 1.20) and bipolar disorder; 0.89 (95% CI; 0.60, 1.32).

9 Complete case analysis

A parallel set of results to those presented for the full population are outlined in the appendix (Table 9) for complete cases. Fully adjusted IRRs for the association between statin prescribing and combined MI and stroke were 0.88 (95% CI; 0.58, 1.36). Estimates for the association between statin prescribing and secondary outcomes were as follows: 1.02 (95% CI; 0.82, 1.27) for all-cause mortality, 0.85 (95% CI; 0.49, 1.48) for stroke and 0.93 (95% CI; 0.47, 1.83) for MI.

10 Key results

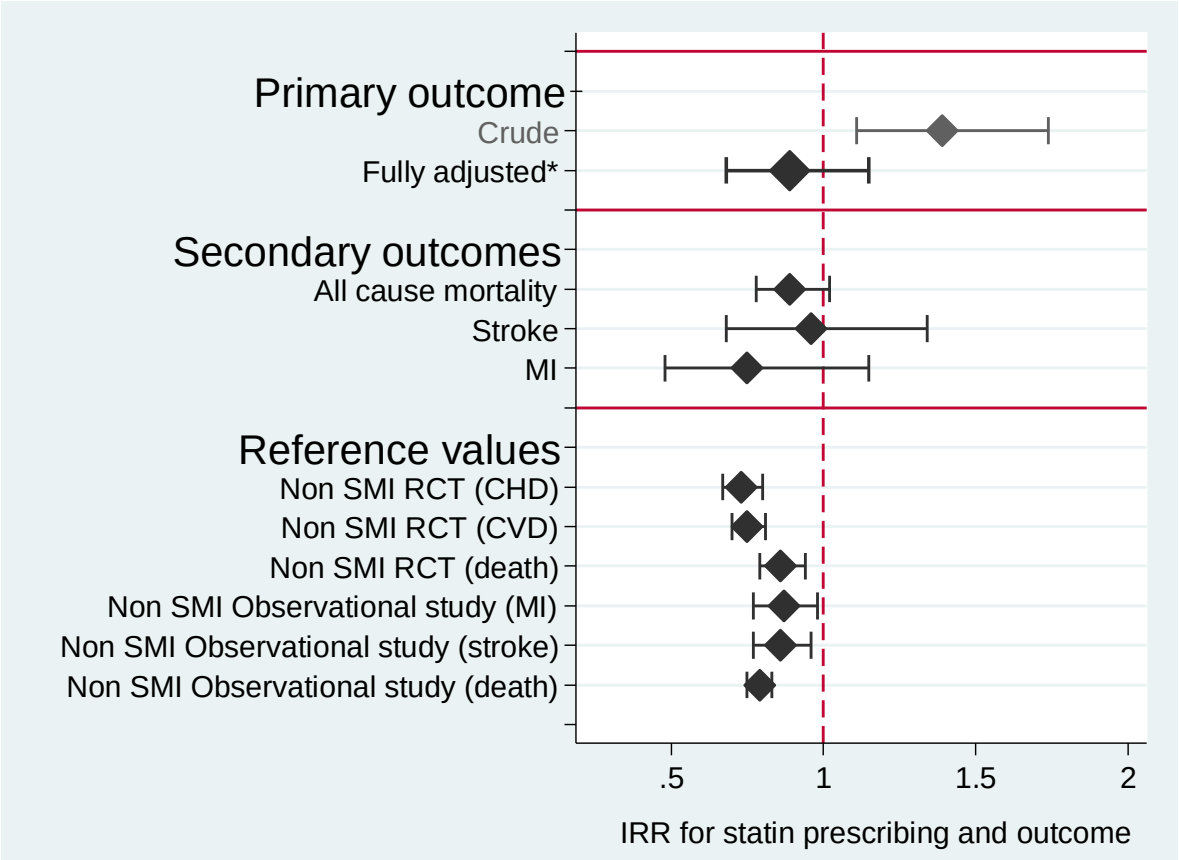
The results from this study provide consistent evidence that statin prescribing to people with SMI may be beneficial, with statistically significant reductions in total cholesterol (of 1.2mmol/L for up to 2 years, $p<0.001$) and non-significant reductions in the rate of combined MI and stroke (0.89; 95% CI; 0.68-1.15) and all-cause mortality (0.89 with 95% CI; 0.78, 1.02).

11 Comparison with the literature

Figure 11-1 summarises key results for statin prescribing and the rate of MI, stroke and all-cause mortality derived from this study relative to published estimates from meta-analysis of RCTs (outlined in Chapter 2) (Taylor et al., 2011) and

observational studies of the general population without SMI (outlined in Chapter 4) (Smeeth et al., 2009).

Figure 11-1: Summary of the key results for the association between statin prescribing and the rate of MI, stroke and all-cause mortality derived from this study relative to reference values



Reference values derived from published estimates. **Non SMI RCT** (Taylor et al., 2011): **CHD**; 0.73 (0.67, 0.80) n=48049, **CVD**; 0.75 (0.70, 0.81) n=23805, **death**; 0.86 (0.79, 0.94) n=48060. **Non SMI observational study** (Smeeth et al., 2009): **MI**; 0.87 (0.77, 0.98) n=61291, **stroke**; 0.86 (0.77, 0.96) n=71564, **death**; 0.79 (0.75, 0.83) n=83622.

11.1 MI and stroke

The fully adjusted IRRs for the association between statin prescribing and the rate of MI and stroke were 0.89 (0.68, 1.15). This point estimate is similar to that derived from observational studies in the general population (MI; 0.87 (0.77, 0.98), stroke; 0.86 (0.77, 0.96), CHD; 0.89 (0.73, 1.09)) (Smeeth et al., 2009;Danaei et al., 2013). Additional analyses within sub-groups of people with a high risk of CVD, by gender and type of mental illness all resulted in consistent and broadly comparable estimates of effect.

The point estimates (but not the 95% CI) suggest a protective effect of statin prescribing on stroke (0.96) and MI (0.75), with a larger potential magnitude of effect on MI. The interpretation of these results is further evaluated in the context of published validation studies (outlined in Chapter 3) in the discussion chapter (Chapter 7).

11.2 All-cause mortality

The point estimate from this study for the association between statin prescribing and all-cause mortality in the full population was 0.89 (95% CI; 0.78, 1.02). For purposes of comparison with five-year mortality in RCTs, this IRR can be expressed as an adjusted odds ratio of 0.92 (95% CI; 0.79, 1.07); which is broadly similar to the results obtained from the meta-analysis of RCTs in the general population, notably 0.86 (95% CI; 0.79, 0.94) (Taylor et al., 2013). However, it should be noted that direct comparison of these estimates requires caution because the duration of follow-up varied in my study whereas the trials included in the meta-analysis were of fixed length (usually 5 years). The IRR is therefore the more appropriate measure of effect. Furthermore, the proportion of participants who died in the trials was almost half that of my study population: the mortality rate reported in the meta-analysis was: statin group; 4.4% and placebo; 5.1% (Taylor et al., 2013). In the current study 9.6% of statin users and 10% of statin non-users died. By contrast, the observational study by Smeeth and colleagues identified a greater reduction in statin-associated mortality (IRR of 0.79 (0.75, 0.83)), which may reflect generally higher frequencies of death in their study; particularly in statin non-users (21% of statin non-users died compared to 11% of statin users) (Smeeth et al., 2009).

11.3 Impact of statins on total cholesterol

Statin use was associated with a mean decrease in total cholesterol concentration at 1 and 2 years after the index date of 1.3 and 1.2mmol/L respectively (equivalent to a 20-21% decrease from the index date), after adjusting for differences in the baseline characteristics of statin users and non-users. RCTs with a minimum of six months of follow up in people without SMI have identified a similar net decrease in total cholesterol of 1.05mmol/L (95% CI; 0.76, 1.35), with variation between difference types and dosage of statin (Taylor et al., 2013). The estimates from my study lie between those obtained from published studies in people with SMI: to date, only two studies that incorporate a statin non-user arm have been published (Chapter 2). These both were small with short follow-up (12 weeks). The non-

randomised study compared changes in lipid levels during a 12 week period in 52 individuals taking 10mg rosuvastatin daily and 48 individuals not taking statins: total cholesterol concentration was decreased by an additional 2.9mmol/L (35%) in statin users (De Hert M. et al., 2006). The RCT of 60 individuals randomised to receive 40mg pravastatin daily or no statin for a 12 weeks reported smaller decreases in total cholesterol of 0.5mmol/L (11%) in statin use. The study also examined changes in cholesterol at 6 weeks after baseline and established that the reduction in total cholesterol was greater at 6 weeks than 12 weeks, which may indicate issues with the long term effectiveness of statins (Vincenzi et al., 2014).

The cholesterol reduction observed in this study lies approximately at the mid-point between the two published studies. This result is not unexpected given 20-40mg simvastatin (the most commonly prescribed statin within the population investigated by my study) has an intermediate level of cholesterol-lowering activity relative to 10mg rosuvastatin and 40mg pravastatin when tested in the general population over a period of 1-3 years (Weng et al., 2010). My results provide the first evidence that medication adherence amongst individuals with SMI is sustained at sufficient levels to reduce cholesterol concentration by over 1mmol/L for up to 2 years. However, an important limitation of this finding is that the results apply only to individuals who had complete data at baseline and who had one or more measurements of total cholesterol recorded in the 2 years after the index date. Although the ascertainment of cholesterol outcome data was good for statin users (73-82%) it is likely that unobserved cholesterol measurements may not be missing at random as individuals who are less compliant may be less willing to have a blood test. In addition, outcome data were less available for statin non-users (55-57%) and may also be missing not at random, although it is well established from other trials of statins that cholesterol concentration is unlikely to change substantially in the control arm.

12 Statistical power and sample size

It is possible to calculate a crude estimate[4] of the standard error arising due to Poisson counting error alone in this study using the number of events amongst statin users. Given the number of MI (n=31) and stroke (n=52) events amongst statin users the results would be likely to be null unless the point estimate for the IRR was smaller than 0.65 (MI), 0.73 (stroke) or 0.78 (combined MI and stroke). On the same basis, estimates for the 95% confidence interval for all-cause mortality (given 284 deaths amongst statin users) are unlikely to yield significant results unless the point estimate for the IRR was less than 0.88.

These figures are based on minimum estimates of the standard error within the study: RCTs carried out in high risk individuals without SMI suggest that reductions of up to 25% in MI or stroke are attributable to statins. The sample size for my study was therefore unlikely to yield statistically significant results for MI and stroke (either combined or separately). However, the study is likely to have been sufficiently powered to detect a statistically significant effect of statin prescribing on all-cause mortality at an equivalent level to previous observational studies of people without SMI who have diagnosed atherosclerosis (0.79, 0.75-0.83) (Smeeth et al., 2009) and from RCTs of people without SMI (0.86, 0.79, 0.94) (Taylor et al., 2013).

13 Control of confounding

The use of observational data for studies that compare treated and untreated arms is likely to result in comparison groups that differ in terms of their risk for the condition being medicated. Although this study employed strategies to increase the comparability of statin user and non-user groups (for example by excluding individuals with contraindications for statin therapy) the profiles of statin users and non-users differed at baseline; with statin users having greater CVD risk and a crude MI and stroke event rate. These baseline differences were anticipated and their impact was greatly reduced by using a multivariable regression model that adjusted for a wide range of confounding variables that were known to be associated with both prescribing and CVD outcomes. However, this approach can

[4] The minimum standard error of IRR is driven by Poisson counting error, which is equal to the square root of the mean (estimated as the number of events in statin users). The half width of the 95% CI around its central limit can therefore be estimated as 1.96 multiplied by the square root of the mean divided by the mean. For example, there were 31 cases of MI in statin users, the half width of the 95% CI can therefore be estimated as 1.96*(√31/31) = 0.35 (or 35%)

only reduce bias arising from differences in measured confounders: the results are therefore likely to be biased to some extent by residual confounding arising from unmeasured factors such as the severity of mental illness. Nevertheless, the point estimates for combined (0.89) and separate MI (0.75), stroke (0.96) and all-cause mortality (0.89) in the full population provide evidence that the impact of confounding by indication has been minimised.

14 Role of missing data

The results of statin effectiveness on CVD outcomes described by this study have focused on data for the full population with imputed values of covariate data (on blood pressure, total cholesterol, smoking status, weight and height) where these measurements were unobserved at baseline. Results for the full population have been given greater prominence because of concerns that data on complete cases might not be representative: although it is reassuring to note that results from the complete case analysis were similar to the full population for the primary outcome (0.88 (95% CI; 0.58, 1.36) and (0.89; 95% CI; 0.68-1.15), respectively). Application of multiple imputation improved the precision of the estimate, which reflects the inclusion of all cases in the analysis.

Individuals who were not prescribed a statin but who had complete baseline data made up only a small proportion (12%) of total statin non-users included in the full analysis. Furthermore, the unadjusted rates of CVD events and mortality in statin users and non-users (summarised in the appendix; Table 25) indicate important differences between individuals with and without full covariate data at baseline. It was therefore important to extend the analysis beyond individuals for whom complete data was available. Comparison of complete and multiple imputed datasets suggests that the imputation model appeared to be functioning well in terms of generating plausible values, particularly with respect to unobserved values of cholesterol in statin users and non-users at time points after the index date. Some misspecification of the model is inevitable, however, because a minority of potentially important variables, such as the severity of mental illness, are not recorded. The absence of these variables weakens the legitimacy of assuming that data are missing at random, although it should be noted that proxies such as psychiatric medication use may help to capture comparable information.

Full consideration of the impact of missing data and the strengths and limitations of the strategies that I have implemented in this analysis are reviewed with reference

to patterns of physical health screening (Chapter 5) in the discussion chapter (Chapter 7).

15 Conclusions

The results from this study provide evidence that the potential impact of statin prescribing to people with SMI may have a magnitude of effect that is similar to the general population. This study identified statistically significant reductions in total cholesterol (of 1.2mmol/L up to 2 years, $p<0.001$) and non-significant reductions in the rate of combined MI and stroke (0.89; 95% CI; 0.68-1.15) and all-cause mortality (0.89 with 95% CI; 0.78, 1.02). There was no evidence of strong effect modification within strata of clinical sub-groups (by SMI type, gender or people with high CVD risk).

Chapter 7 : Discussion

"It is clear that patients with schizophrenia and other mental disorders are not accessing adequate treatment for their cardiovascular diseases. What is less clear is the level at which these patients are being failed by the system – whether somatic disorders are not being recognized, cardiovascular drugs are not being prescribed, or patients are not taking the drugs… …we suspect that all these mechanisms may be at work but our data are not able to address this question."

(Laursen et al., 2013)

1 Chapter Content

This quote describes a snapshot of psychiatric cardiovascular medicine as it was in September 2012 at the start of my PhD and – by chance – the time at which Thomas Laursen and colleagues submitted their manuscript (from which the quote is derived) to the journal. My thesis did not set out to answer these questions specifically but they provide a framework with which to position and discuss the findings of this thesis. This chapter discusses my research findings in terms of the level at which inequalities in cardiovascular health may arise in people with severe mental illness (SMI) in the context of provision of physical health checks, statin prescribing and the effectiveness of statins for primary prevention of cardiovascular disease (CVD). As part of this evaluation I summarise the major findings of this thesis and the evidence as it was at the time of embarking upon the work. I then discuss the broader interpretation of these findings and evaluate their significance in relation to each other and the literature – including evidence that has recently been published. I also explore whether individuals with the greatest physical health needs are engaged in CVD screening, which was not central to my research objectives but has important implications for the interpretation of the results. I weigh up the strengths and weaknesses of the research undertaken and reflect upon how these factors limit the findings. Finally I appraise the contribution made by my PhD research to the evidence-base, and discuss the implications for policy and future research.

2 Summary of key findings

This thesis aimed to explore the effectiveness of statins for primary prevention of CVD in people with SMI by examining the following objectives (Chapter 1 section 9):

1. Evaluate the evidence-base for statin prescribing for prevention of CVD in people with SMI (Chapter 2)

2. Describe the strengths and limitations of using UK primary care data to investigate the impact of statin prescribing on CVD in people with SMI (Chapter 3)

3. Explore methods to reduce confounding and handle missing data to support estimates of effectiveness derived from primary care data (Chapter 4)

4. Investigate the uptake of CVD screening and statin prescribing in UK primary care amongst people with and without SMI (Chapter 5)

5. Estimate the effectiveness of statin prescribing in UK primary care for prevention of CVD in people with SMI (Chapter 6)

6. Discuss the collective interpretation of the findings from these objectives and their significance in terms of policy, practice and research (Chapter 7)

The major findings were that statin prescribing was associated with statistically significant reductions in total cholesterol of 1.2mmol/L (with 95% confidence intervals (CI) of 1.1-1.3) for up to 2 years. The reduction in total cholesterol is coherent and consistent with the non-significant reductions in the estimate of the rate of combined myocardial infarction (MI) and stroke and all-cause mortality observed amongst statin uses in the main analysis: incident rate ratios (IRRs) of 0.89 (95% CI; 0.68-1.15) for MI and stroke and 0.89 (95% CI; 0.78, 1.02) for all-cause mortality.

Earlier phases of the research outlined in this thesis investigated the uptake of CVD screening and statin prescribing in UK primary care amongst people with and without SMI. This work established that current provision of CVD screening and statin prescribing is increasingly accessed by individuals with SMI, relative to people without SMI. However, although the provision of CVD screening has improved markedly over time, uptake is not universal and in 2012 over 40% of people with SMI did not attend an annual physical health check. Older people with schizophrenia were identified as a group among whom statins were prescribed inequitably relative to people without SMI, and under-treatment may be an issue.

3 A disadvantaged starting point: SMI and the social determinants of health

The association between premature death and SMI has been documented for over a century, with the role played by lifestyle, healthcare access and medication in individuals with psychosis being explored in more recent decades (De Hert et al., 2011a;De Hert et al., 2011b;Felker et al., 1996). The relationship between SMI and CVD is driven by increased rates of conventional risk factors (such as smoking, poor diet and low levels of physical activity) in combination with factors specific to psychosis (such as diagnostic overshadowing, the side-effects of some types of antipsychotic medication and possible genetic associations) that may exacerbate physical health conditions or delay their diagnosis. However, the source of these factors is deeply rooted in the social determinants of health including social gradient, stress, social exclusion and unemployment, which are adversely associated with both mental and physical health (World Health Organization, 2003). In other words, SMI and social disadvantage are inextricably linked and it is important to recognise that treating downstream physical health conditions is unlikely to fully rectify this disadvantaged starting point.

Nevertheless, the burden of CVD amongst individuals with SMI is considerable and at least partly avoidable. The risk of CVD events is at least doubled amongst people with schizophrenia and bipolar disorder, with a further doubling of the subsequent risk of death following a CVD event relative to those without similar mental health conditions (De Hert et al., 2011a;De Hert et al., 2011b;Osborn et al., 2007a;Nordentoft et al., 2013). Approximately one third (Brown et al., 2010) of the 13-30 year deficit in life expectancy experienced by people with SMI relative to the general population has been attributed to CVD (Lahti et al., 2012;Tiihonen et al., 2009;Hennekens et al., 2005;Colton and Manderscheid, 2006), making this condition a prime target for reducing health inequalities in people with SMI. Effective interventions for primary prevention of CVD are therefore needed to improve the physical health prognosis for people with SMI.

4 Uptake of physical health checks

Policy in the United Kingdom (UK) has evolved to better manage physical health conditions in individuals with schizophrenia and bipolar disorder: SMI registers were established at general practice-level in 2003 and financial incentives introduced

thereafter for providing physical health checks to people on the register (National Institute for Health and Clinical Excellence, 2006;National Institute for Health and Clinical Excellence, 2009;National Institute for Health and Clinical Excellence, 2012). Since the introduction of these measures, the proportion of individuals with schizophrenia or bipolar disorder who had one or more physical health parameters recorded in primary care has risen each year and the level of disparity relative to individuals without SMI has declined (Osborn et al., 2011). However, the latest published data (for the year 2007) suggested that individuals with SMI who were over the age of 60 years were significantly less likely than those without SMI to have a physical health check (Osborn et al., 2011).

Thesis Objective 4 - outlined in Chapter 5 section 7.1 - provided an extension to the study published by Osborn and colleagues by investigating the recording of CVD covariates both in isolation and in combinations that support the estimation of CVD risk using scores such as Framingham (D'Agostino et al., 2008). This work established that the increasing uptake of physical health checks reported by Osborn and colleagues has continued such that individuals aged 30-39 and 40-59 years with SMI are now more likely to have measurements of blood pressure, total cholesterol, weight and smoking status recorded than individuals without a comparable mental health condition who were of the same age and gender. The uptake of physical health screening in adults aged 60-74 and 75-99 years with an SMI diagnosis has also increased over time to reach a greater level than similar individuals without mental illness. Rates of screening amongst the oldest people with SMI were much slower to improve and only reached comparable levels to people without SMI between 2008 and 2010. These results provide new assurance that CVD monitoring in people with SMI now occurs at levels that are at least equivalent to similar people without SMI and mark substantial progress given the historic disparity in screening. However, the uptake of CVD screening amongst people with SMI is not universal: in 2012 over 40% of individuals aged 30-74 and almost 60% aged 75-99 years did not have sufficient measurements recorded in their electronic health records to support estimation of CVD risk. This is of particular concern as it is unclear whether participation in screening is inversely correlated with health needs: I return to this issue later in this chapter.

5 Provision of statin prescribing for primary prevention of CVD

Health assessments are a check point at which interventions for improving physical health can be implemented. These assessments measure individual CVD risk factors and allow an individual's likelihood of developing CVD to be estimated over a given timeframe. CVD risk is estimated in general practice using a range of algorithms including the Framingham Risk Score (recommended until 2014) (D'Agostino et al., 2008) and QRisk (Hippisley-Cox et al., 2008) and estimated risk is used to guide clinical management. Individuals found to be at high risk of CVD (defined as 20% risk over a ten year period until 2014 and 10% thereafter) should be managed using lifestyle modification either alone or – if insufficient progress has been made towards reducing CVD risk - in combination with pharmacological interventions. Statins form the mainstay of these pharmacological interventions and are prescribed on the basis of CVD risk rather than lipid concentration alone (National Institute for Health and Clinical Excellence, 2008b;National Institute for Health and Clinical Excellence, 2014b). The primary pharmacological action of statins inhibits the synthesis of low density lipoprotein cholesterol (LDL-C), thereby slowing the deposition of lipids onto blood vessel walls and gradually reducing the lipid core of existing plaques (Maron et al., 2000). In addition, statins have anti-inflammatory properties that are beneficial in preventing CVD through a mechanism that is independent of the pathway that reduces LDL-C concentration (Antonopoulos et al., 2012). Some researchers have reported that these anti-inflammatory properties may also be beneficial for reducing symptoms of psychosis and statins are therefore a potential target for new therapies for psychosis itself (Vincenzi et al., 2014). The role of statins for primary prevention of CVD in people with SMI has been the particular focus of this thesis because statin use is clinically and cost effective in the general population but the evidence-base for people with SMI was unclear (Taylor et al., 2013).

Thesis Objective 4 - outlined in Chapter 5 section 7.2 - investigated the uptake of statin prescribing in UK primary care in individuals with and without SMI. This work is important because the impact of increased CVD screening on interventions such as statin prescribing was not previously known. These results provide the first evidence that, in recent years, the rate of statin prescribing is 21% lower in the oldest individuals (75-99 years) with schizophrenia, relative to controls without SMI. This is despite evidence that those with schizophrenia in this age group are being

screened at least as often as their counterparts without SMI, suggesting that this difference is not explained by a difference in older people with schizophrenia attending for screening; for example due to negative symptoms of schizophrenia. By contrast, the results for people with bipolar disorder and younger individuals with schizophrenia suggest that statins are prescribed to at a similar or higher rate to individuals who do not have an SMI diagnosis.

Amongst the subset of people who had all component parts of the physical health check measured within a six-year period there was no evidence of a difference in the rate of statin prescribing to people with or without SMI after adjusting for estimated CVD risk score (Chapter 5, section 7.3). However, although not statistically significant, descriptive work for the relationship between CVD risk and statin prescribing amongst screening participants suggested that a small number of individuals with schizophrenia who had high CVD risk (exceeding 30%) were less likely to receive a statin than people without SMI who had a comparable CVD risk score. This result is not conclusive but may justify further investigation to evaluate evidence for a high-risk and undertreated group for whom preventative care is inadequate.

6 What is known about the effectiveness of statins for primary prevention of CVD in people with SMI?

Thesis Objective 1 (Chapter 2) aimed to evaluate the evidence-base for statin prescribing for prevention of CVD in people with SMI. Evidence in support of statin prescribing for the general population is almost exclusively derived from randomised controlled trials (RCTs) of statins (Taylor et al., 2013). This evidence-base was not readily transferable to people with SMI because this population was excluded from many of the original trials of statins and may differ in terms of CVD risk profile, antipsychotic exposure and statin medication adherence.

To establish what was known about the effectiveness of statins for primary prevention of CVD in people with SMI I undertook a systematic review of published literature and registered trials; which revealed a paucity of evidence. The systematic review did not identify any information on CVD events, mortality or long term statin use in people with SMI. However, the search did find two studies that included both statin user and non-user comparison groups (De Hert M. et al., 2006;Vincenzi et al., 2014), and three other single arm studies have also been published (Ojala et al., 2008;Landry et al., 2008;Hanssens et al., 2007). In addition, three trials were

registered but not published: two were terminated due to recruitment problems and the remaining study was completed and had negative results (Brar, J. Personal Communication, 23/4/2012).

The two studies with comparison groups provide evidence from observational (De Hert M. et al., 2006) and experimental (Vincenzi et al., 2014) study designs and show that statin therapy is associated with significant reductions in total cholesterol and LDL-C over the course of a 12 week period. The magnitude of the decrease differed substantially between the two studies. Total cholesterol was decreased by 11% (0.5mmol/L) in the trial of 40mg pravastatin versus placebo and 35% (2.9mmol/L) in the observational study of 10mg rosuvastatin. LDL-C was decreased by 20% (0.6mmol/L) with pravastatin and 49% (2.0mmol/L) with rosuvastatin, most likely reflecting differences in the biological activity of the statins investigated and lipid concentrations at baseline. One of the studies measured lipid fractions at both 6 and 12 weeks after randomisation of pravastatin or placebo and reported that reductions in total cholesterol and LDL-C waned between these two time points, thus raising concerns over the long term effectiveness and medication adherence to statin therapy (Vincenzi et al., 2014).

7 Are statins effective for primary prevention of CVD in people with SMI?

Thesis Objective 5 (Chapter 6) aimed to estimate the effectiveness of statin prescribing in UK primary care for prevention of CVD in people with SMI. The main analysis investigated CVD outcomes in people who were prescribed a statin during a given two-year period and compared them to people who were not prescribed a statin. Statin use was associated with a mean decrease in total cholesterol concentration at 1 and 2 years after the index date of 1.3 and 1.2mmol/L, respectively (equivalent to a 20-21% decrease from the index date), after adjusting for differences in the baseline characteristics of statin users and non-users. This result is consistent with results from RCTs in people without SMI (Taylor et al., 2013) and with the two studies identified by the systematic review (outlined above) (De Hert M. et al., 2006;Vincenzi et al., 2014).

The primary outcome was combined incident MI and stroke, which was non-significantly reduced by 11% (IRR 0.89; 95% CI; 0.68-1.15) in the main analysis. The rate of all-cause mortality was also non-significantly reduced (0.89 with 95% CI; 0.78, 1.02) amongst statin users relative to non-users. These estimates are broadly

similar to those from other observational studies (MI; 0.87 (0.77, 0.98), stroke; 0.86 (0.77, 0.96), CHD; 0.89 (0.73, 1.09)) (Smeeth et al., 2009;Danaei et al., 2013) and RCTs (CHD; 0.73 (0.67, 0.80), CVD; 0.75 (0.70, 0.81)) (Taylor et al., 2013). The point estimates for MI, stroke and all-cause mortality identified in the main study are coherent with the decrease in total cholesterol concentration that was attributable to statin use: all confirm a cardio-protective effect of statins that is broadly similar to the effect of statins in the general population (Danaei et al., 2013;Smeeth et al., 2009).

Changes in cholesterol concentration are on the causal pathway between statin prescribing and CVD events, and are the endpoint for many trials because differences in continuous outcomes are more efficiently measured relative to binary events such as mortality (Campbell et al., 1995). Furthermore, trials of very long duration or sample size would be required to examine mortality. Other studies have shown that the impact of statin prescribing on CVD events increases with extended use: reductions of 0.6mmol/L of total cholesterol are associated with a 7% decrease in ischaemic heart disease during the first two years of therapy and >20% decreases thereafter (Law, 2003). The decreased total cholesterol concentrations attributed to statin therapy in people with SMI are therefore likely to translate into long term clinically meaningful reductions in CVD.

8 Possible correlation between severity of mental illness and CVD risk

It important to consider the possibility that - even though statin prescribing appears to be effective for lowering intermediate CVD outcomes – the current clinical pathway for CVD screening and statin prescribing may not adequately reach people with SMI who are at high risk of CVD. Individuals with SMI are as likely to take up the offer of CVD screening as people without a comparable mental health diagnosis (Osborn et al., 2003). However, it is not clear whether there is any correlation between the severity of mental illness and willingness to participate with CVD screening amongst people with SMI. Studies investigating physical health screening for other types of conditions have reported lower participation amongst individuals requiring the highest level of mental health support (Werneke et al., 2006).

If a similar association (i.e. decreasing engagement with increasing severity of mental illness) exists for cardiovascular health then individuals with poorer mental health could be less likely to be screened, be prescribed a statin and could also

have worse CVD outcomes. In such case, results from the complete case analysis would not be generalizable to the subset of people with the poorest health because missing covariate data could be indicative of poorer mental and physical health. A similar pattern is evident for the general population, where uptake of primary care health checks is inversely correlated with modifiable CVD risk (i.e. people with missing data are more likely to have poorer health), thus limiting the benefits of screening (Waller et al., 1990;Artac et al., 2013). This pattern of uptake is described by the Inverse Care Law and has been observed in many areas of healthcare (Hart, 1971).

The existence of a sizable group of high risk individuals who were not engaged in CVD screening might be indicated by results from the imputed data analysis suggesting greater effectiveness of statins relative to the complete case analysis. This was not borne-out by results for the primary outcome, which had very similar point estimates in both the full population and in the complete case analysis: 0.89 (95% CI; 0.68-1.15) versus 0.88 (95% CI; 0.58-1.36). However, comparison between the rate of all-cause mortality among non-statin users in the full population (crude rate of 19.3 (18.7-19.8) per 1000 person years) and complete cases (16.8 (15.1-18.6) per 1000 person years) could potentially be compatible with the existence of an unscreened subgroup of high risk individuals; although the magnitude of difference is relatively small. A potential barrier to identifying a hypothetical population of high risk individuals with missing covariate data is insufficiently accurate or precise imputed data values, which could result in biased effect estimates and wide 95% CIs. The relevance of a group of individuals who have a high level of CVD risk but are not engaged in screening is discussed further in the Policy and Research Implications sections at the end of this chapter.

9 Discussion of the strengths and weaknesses of the work presented in this thesis (relating to Objectives 2 and 3)

9.1 Use of observational data

The strengths and limitations of using an observational study design over experimental options such as an RCT were outlined in Chapter 3 section 2.1. The analyses presented in this thesis have drawn upon electronic patient records which provide longitudinal data on a large and representative cohort of individuals with a diagnosis of SMI or comparable individuals without SMI. THIN data are a record of

healthcare interactions and the care that was actually delivered and, as such, are an excellent resource for investigating the uptake of physical health checks and statin prescribing in UK primary care. By contrast, investigating the causal effect of statins is more challenging with this type of data. One consequence of analysing data where statin assignment is not random is that the association between being prescribed the drug and the risk of future CVD events is confounded. Nevertheless, the point estimates for statin prescribing derived from the main analysis suggest acceptable control of confounding, although some bias due to unmeasured confounders such as diet and severity of mental illness was unavoidable.

9.2 Misclassification bias

The Framingham risk score was used as a means of estimating the absolute risk of CVD for an individual. In the main analysis risk scores were used for the purpose of assessing differences in the CVD risk profiles of statin users and non-users only, and were not used to address any imbalances. By contrast, in the study investigating statin prescribing amongst the subset of individuals who had all components of the physical health check recorded within a six year period, risk scores were used to adjust for differences in CVD risk between individuals with and without SMI (Chapter 5 section 7.3). Since the start of my PhD new work in this area has established that CVD risk scores that incorporate factors specific to mental illness have superior discrimination to the Framingham risk score (Osborn et al., 2015). A practical implication of this research for my work is that CVD risk scores may underestimate risk in individuals with SMI relative to people without similar mental health conditions.

For example, risk scores specific to individuals with SMI may include information on psychiatric medication, which are not included in the Framingham risk score (Osborn et al., 2015). Furthermore, there is likely to be misclassification of information on some factors such as smoking, which are included in the Framingham risk score as a binary indicator (smoker/not a smoker). Because individuals with SMI are known to smoke more heavily than smokers in the general population (Williams and Foulds, 2007;Williams and Ziedonis, 2004;Dixon et al., 2007) the risk of smoking-related morbidity (including CVD) will tend to be under-estimated for this group. It is therefore possible that the equivalent patterns of statin prescribing, attained after adjusting for estimated CVD risk, may translate into under-provision in real terms because CVD risk is under-estimated in people with SMI, relative to people without SMI.

9.3 Missing data

The potential for missing data to bias the results of the main study was described in Chapter 3 sections 3.2.11 and 5.2.6, and Chapter 5 section 9. Covariate data that were either partially or entirely missing were a limitation of the data source and have strongly shaped the choice of study design. Factors such as diet, severity of mental illness and genetics (e.g. familial hypercholesterolaemia), which may be associated with both statin prescribing and the risk of CVD events (as described in Chapters 1 and 3), are not directly captured by the data held in THIN. However, it is likely that some – but not all - of the causal effect of these factors is correlated with information on traditional CVD covariates (including lipid profile and body mass index (BMI)) or related characteristics such as psychiatric medication and comorbidity. However, adjusting for a greater number of covariates can have unintended consequences and increases the risk of over-adjustment. In this study over-adjustment is likely to be most problematic for variables that are associated with medication adherence and therefore lie on the causal pathway between statin prescribing and CVD events (Schisterman et al., 2009). In this type of scenario over-adjustment usually biases results towards the null (Rothman and Greenland, 1998). For this reason the variables included in the main analysis model were added sequentially and the impact on the IRR was carefully reviewed (Chapter 6 section 8): there was no evidence that one or more variables were associated with inflating either the point estimate or associated 95% CI.

Some important factors – such as total cholesterol concentration – were not fully observed: the pattern of missingness had strong temporal correlations and was also associated with statin prescribing. The methods that I used to impute data in the main analysis were well adapted to these conditions because the staggered cohort design explicitly stratifies individuals on the basis of calendar time and statin exposure. This approach enables data for each time point (cohort) to be imputed separately but still incorporated time-varying data from three years before and after baseline in the imputation model. Review of the distribution of the values that were imputed, relative to values that were recorded, suggested that the model was well specified. However, some potentially important variables, such as GP surgery and high density lipoprotein-cholesterol (HDL-C) were not included in the imputation or analysis model. This was because it was not possible to develop an imputation model that included HDL-C (as outlined in Chapter 6) and because a multi-level multiple imputation model that accommodated clustering by GP surgery would be extremely computationally demanding and was therefore be impractical given the

need to impute data separately for each of the five cohorts. Despite these limitations, the approach used for handling missing data was carefully researched and implemented and offers distinct advantages over complete case analysis or *ad hoc* forms of imputation.

9.4 Study design

The primary purpose of undertaking an analysis using multiple imputed data for the whole population of individuals with SMI was to analyse data for which information on the outcome was available, but covariate data were missing. The advantages of this type of analysis relative to a complete case analyse are twofold: it is possible to analyse the full sample of data and to estimate the effect for the whole population, rather than a subset of potentially unrepresentative individuals. As a consequence, the study was able to estimate the average treatment effect of statin prescribing for all individuals with SMI aged 40-84 years. The average treatment effect is distinct from the effect in the treated and estimates the impact of treating the whole population rather than the impact in treated individuals. This estimate is now of particular value because current guidance states that statin prescribing should be considered for individuals aged 40-84 years with a QRisk score of 10% or above (National Institute for Health and Clinical Excellence, 2014b). To put this into context, in the main study that I undertook 94% of men aged over 40 years and 83% of women aged over 50 years had an estimated Framingham risk score that exceeded 10% and could therefore be eligible for statin prescribing.

A major disadvantage of the staggered cohort design is that it is more complex to understand than other study designs. However, in essence, the design of each cohort (illustrated in Figure 5-1 of Chapter 6) is simple: 1) individuals with a prior diagnosis of CVD or statin exposure in the 2 years before baseline are excluded, 2) exposure is defined on the basis of whether or not a statin is prescribed during the baseline period and 3) follow-up begins at the start of the baseline period and ends at first CVD event or censoring (out-of-practice transfer, death or the end of the study period). Nevertheless, once several cohorts are considered, it quickly becomes difficult to visualise the dataflow.

A further weakness of the methodology is that it does not appear to be possible to do a formal sample size calculation which correctly accounts for the inclusion of the same individual in multiple cohorts. Arguably, a sample size calculation is not essential for undertaking a database study, because no additional resource is

expended – nor is patient burden increased - by using a larger subset of the dataset, so it is often reasonable to analyse as many records as possible. However, in the event of obtaining marginal or non-significant results (as was the case for the primary outcome in my study), a sample size calculation enables assessment of whether or not the result is likely to be due to chance and can therefore be useful for directing future work.

In my study I overcame this problem by crudely estimating the half-width of the 95% CI using the minimum estimate of standard error for the number of events in statin users (Chapter 6 section 12). Although not precise (in part because the normal distribution was used to estimate the Poisson distribution), these estimates suggested that the study was underpowered to detect an effect size of less than 22% for combined MI and stroke and 12% for all-cause mortality, which are similar effect sizes to those from RCTs in people without SMI (Taylor et al., 2013). There is no straightforward solution for increasing the sample size for this study. However, possible approaches are extending the dataset (for example by combining with other data sources) and/or confirming the validity of other types of CVD outcomes are outlined in the Methodological Implications section at the end of this chapter.

9.5 "Intention to treat" analytical approach

The main analysis adopted an analytical approach that was akin to an "intention to treat" analysis in an RCT, which was pragmatic given that the study aimed to estimate the actual (rather than optimal) impact of prescribing. However, selection of the statin user group on the basis of one or more statin prescriptions at the index date has an important bearing on the results because prescribing and medication usage are not equivalent. For instance, some individuals will not fill the prescription at the pharmacy and others will pick up the medication but not take it as directed. In addition, it has been possible to buy low dose statin therapy (simvastatin 10mg) over the counter in the UK for about a decade. It is therefore possible that some individuals may have started statin therapy independently of their GP, although these numbers are likely to be low because the additional costs of over-the-counter medication are borne by the patient. Non-compliance with treatment (for both statin users and non-users) may therefore have impacted upon the results. The most common scenario for non-compliance is likely to be statin users not taking medication (and therefore being under-medicated), although statin drop-in (i.e. prescriptions made after the index date) and over-the-counter purchase of

simvastatin may also occur. All these scenarios are likely to attenuate the measurable impact of statin prescribing.

Medication adherence is often highlighted as a source of differences in effectiveness between observational studies and RCTs, with trials usually expected to yield greater estimates of effect than equivalent observational studies. For example, a meta-analysis evaluating non-adherence to statin therapy estimated that one year after initiating statin therapy approximately half of patients participating in observational studies were compliant compared to 90% in RCTs (Lemstra et al., 2012). These differences in adherence are usually attributed to selection bias (arising at the time of enrolment) and the combined impact of additional monitoring that is carried out as part of the trial and because RCTs usually aim to recruit a clinically similar group with less complex health needs than the target patient group in clinical practice. To date, there is relatively little research on physical health medication adherence in individuals with SMI and there are no published studies for statin adherence. It is therefore not possible to evaluate whether statin medication adherence in people with SMI is likely to differ substantially relative the general population, although the comparable reduction in total cholesterol at 1 and 2 years after the index date provides tentative evidence that adherence may be broadly similar to the general population.

9.6 Inclusion and exclusion criteria

Case definitions and the justification of the criteria used in each of the analyses described in this thesis were outlined in Chapter 3 (section 3.2). The inclusion and exclusion criteria applied to the main study as a consequence of these case definitions were selected with the purpose of optimising the number of people who were potentially eligible for statin therapy for primary prevention of CVD. This approach was pragmatic given the limited study population size, relatively low rate of CVD events and desire to ensure that the results were generalizable to the whole SMI population.

However, there were some aspects of the inclusion and exclusion criteria which, with the benefit of hindsight, were not ideal. Of note, the main study did not exclude people with familial hypercholesterolaemia, which is a limitation because the clinical pathway for statin prescribing and prognosis for this condition is distinct from that of routine primary CVD prevention (National Institute for Health and Clinical Excellence, 2008a). However, this decision reflected uncertainty around identifying

people with possible familial hypercholesterolaemia, which was determined on the basis of Read codes or a total cholesterol concentration of >7.5mmol/L, which reflects national guidance for the general population, but may be a less reliable indicator of the condition amongst people with SMI because this group is at greater risk of antipsychotic-associated dyslipidaemia (Chapter 1 section 5.3).

The inclusion of people with familial hypercholesterolaemia (according to the definition used in this study) is not likely to substantially impact upon estimates of the effectiveness of statins because the true prevalence of familial hypercholesterolaemia is low (~0.2%) (Marks et al., 2003) and statistical adjustment was made for differences in the presence of this condition and baseline total cholesterol concentration. However, it should be noted that people classified as having familial hypercholesterolaemia in this study were over-represented amongst statin users (10% versus 0.2%, although the absolute number of cases in both groups was small: 379 (0.8%)).

9.7 CVD outcomes

This study investigated a relatively uncommon primary outcome (MI and stroke) in a population of limited size and therefore was a trade-off between maximising the quality or quantity of CVD endpoints. I investigated the feasibility of including coronary heart disease (CHD) events in the primary outcome (with MI and stroke) but was concerned that this might result in including misclassified prevalent cases, potentially reflecting the introduction of the Quality and Outcomes Framework (QOF) (National Institute for Health and Clinical Excellence, 2012). For this reason I chose to select only outcomes that were known to have a high level of validity (indicated by positive predictive value: Chapter 3 section 5.2.3). The advantage of this approach is that it was possible to obtain plausible and informative point estimates from the study, but this gain in validity was made at the expense of decreased precision.

Summary of findings:

The final section of this thesis summarises the collective interpretation of the results and how these findings could feed into health policy and future research. The implications of this work are presented in the context of the questions raised by Laursen and colleagues in 2012 (quote at start of chapter) that relate to the level at which inequalities in cardiovascular health among people with SMI arise.

10 At what level do inequalities in cardiovascular health arise in people with SMI?

This thesis aimed to evaluate the effectiveness of statins for primary prevention of CVD in people with SMI. The collective body of work examines the processes that occur upstream of primary CVD diagnoses, which include CVD screening and statin prescribing. Investigating patterns of screening and statin prescribing through comparison of individuals with and without SMI offers two major benefits. Firstly, by increasing our understanding of the level at which inequalities in cardiovascular health to people with SMI may arise. Secondly, by characterising patterns of missing data and statin prescribing, thus informing the design of the final study of effectiveness and enabling the results to be interpreted with respect to estimates for the general population.

Results from the screening study show that substantial improvements have been made with increased CVD screening in people with SMI: the proportion of individuals who did not have physical health information recorded has declined from 90% to 40% over a ten year period. This marks a substantial improvement in uptake of physical health checks following the introduction of QOF, but suggests that many people with SMI are not yet engaged in CVD screening. Amongst the subset of people who were screened, statin prescribing was broadly equivalent to individuals with and without SMI who had similar levels of CVD risk. However, because risk scores may not adequately capture CVD risk in individuals with SMI, it is possible that current patterns of prescribing to screened people do not reflect (but under-estimate) cardiovascular need. In other words, although absolute levels of CVD screening and prescribing were higher amongst individuals with SMI, provision may still be suboptimal relative to people without SMI.

My work provides the first evidence that statin prescribing is associated with a 20% reduction in total cholesterol concentration at two years after the first statin

prescription – which is important because it demonstrates longer term medication use than had been previously reported. However, it was not possible to satisfactorily quantify the effectiveness of statins in preventing CVD events; partly because the number of events amongst statins users was small and the 95% CI were therefore too wide to rule out a null effect. Similarly, although the main study was likely to be adequately powered to detect a statin-associated reduction in all-cause mortality at a similar level to that observed in RCTs, I did not identify a reduction that was significant at the 5% level. Crude estimation of the width of the half CI around the point estimate identified from the main analysis did however confirm that the upper limit of the 95% CI was likely to be limited by sample size (Chapter 6 section 12). These results provide good evidence that statin prescribing is associated with meaningful reductions in total cholesterol concentration and that prescribing is not adversely associated with CVD events or all-cause mortality. In conjunction with published evidence on the long term impact of reductions in total cholesterol concentration (Law et al., 2003), it is likely that statins have a broadly similar level of effectiveness in people with and without SMI. However, further evidence is required to confirm precise estimates of the magnitude of effect on CVD events.

Collectively, these results suggest advances in CVD management for people with SMI. However, there is scope for improvement: annually, over 40% of individuals with SMI had insufficient information recorded in their electronic patient record to estimate CVD risk. Furthermore, there was some indication that older individuals may be less frequently prescribed a statin than people without SMI. Other individuals – particularly those with schizophrenia – did participate in physical health checks and had records indicating high CVD risk and eligibility for statin therapy, but were not prescribed a statin. This observation may reflect unawareness of the patient's risk score by the GP or some resistance towards statin therapy on the part of the clinician and/or patient.

11 Methodological implications

This study highlighted the limitations and opportunities for using primary care data to investigate less common events within a relatively small patient group. My study was challenged by a relatively low rate of validated CVD outcomes in the SMI population and more research in this area is needed. More precise estimates of effectiveness of statins on preventing MI, stroke and all-cause mortality could be obtained by pooling data from several primary care databases including THIN, Clinical Practice Research Datalink (CPRD) and QResearch. Alternatively, the use

of linked primary and secondary care data could assist with the validation of CVD events (for example confirming which CHD events resulted in a hospital admission) and thereby produce more precise estimates for CVD events and statin prescribing.

I needed to design a study which was compatible with multiple imputation and that was appropriate for investigating treatment versus no treatment. Although the study design appears to have functioned well, there was an important trade-off in terms of the ease with which the results can be communicated relative to traditional study designs. A preferable approach (as outlined in Chapter 4) might have been to integrate methods for improving covariate balance between statin users and non-users (e.g. propensity score matching) and multiple imputation. At present we lack the methods to combine these features and further investment in this area of research could facilitate the use of more accessible study designs.

12 Policy implications

12.1 Statin prescribing to people with SMI is likely to be beneficial

The statistically significant reductions in total cholesterol (of 1.2mmol/L) at 1 and 2 years after initiating a statin identified by this study provide evidence that statin prescribing is effective for lipid modification in people with SMI. In addition, this study identified non-significant reductions in CVD events and all-cause mortality. These results confirm that statins are not harmful with respect to CVD events or mortality and provide suggestive evidence that the long-term impact of prescribing to people with SMI may carry similar benefits to the general population (Law et al., 2003;Rahilly-Tierney et al., 2009;Penning-van Beest et al., 2007). On balance, the findings of this thesis therefore provide greater evidence to support the use of statin prescribing for primary CVD prevention in people with SMI.

The screening results outlined in this thesis observed substantial increases in the uptake of CVD screening in people with SMI, which were temporally associated with the introduction of QOF. This finding suggests that QOF has been successful in helping to reduce inequalities in the uptake of physical health checks between people with and without SMI. However, because the uptake of physical health checks amongst people with SMI is not universal, there remains some uncertainty regarding the effectiveness of the current clinical care pathway with respect to targeting people who would derive the greatest benefit from statin prescribing.

12.2 Improving the uptake of CVD screening amongst individuals with SMI

Health checks are an attractive and seemingly intuitive intervention to improve CVD prevention and management. However, the clinical and cost effectiveness of such schemes relies upon sufficient uptake amongst individuals with the capacity to benefit from interventions: reflecting CVD risk, willingness to engage in both screening and subsequent interventions, and the effectiveness of intervention. To date, the clinical and cost-effectiveness of CVD screening to individuals with SMI has not been evaluated (Tosh et al., 2010) and the value of similar strategies in the general population is contested (McCartney, 2013;Braillon et al., 2015).

NHS Health Checks were first introduced in 2008 to offer comprehensive 5-yearly physical health screening to all individuals in England aged 40-75 years. The scheme was implemented under the assumption that uptake would be at least 75%, whereas current estimates indicate that less than 50% participate (Dalton and Soljak, 2012;Artac et al., 2013). Advocates argue that health checks increase pharmacological management of CVD risk and result in significant reductions in blood pressure, cholesterol concentration and CVD risk scores; particularly in high risk patients (Lauritzen et al., 2014;Si et al., 2014). Critics emphasise the modest reductions in CVD risk factors (Si et al., 2014;Robson et al., 2015;Artac et al., 2013), which are driven by pharmacological management rather than changes in lifestyle (Jorgensen et al., 2014). A lack of evidence indicating reduced CVD morbidity or mortality (Krogsboll et al., 2012a;Krogsboll et al., 2012b), potential harms associated with screening (Gotzsche et al., 2014) and the multi-billion pound price tag associated with implementation (Braillon et al., 2015) cast further doubt on the value of NHS Health Checks. Worse still, there is suggestion of an inverse association between uptake and need (Waller et al., 1990;Bender et al., 2014;Krogsboll et al., 2012a;Krogsboll et al., 2012b), meaning that the scheme may widen health inequalities (Capewell and Graham, 2010).

Physical health checks amongst individuals with SMI focus on a high risk group with specific health needs and are therefore likely to result in greater health gains than less targeted schemes. However, health benefits may be achieved at the expense of greater inequality if the uptake of screening is inversely correlated with need. Results from Chapter 5 demonstrate that, whilst the provision of CVD screening has improved markedly over time, uptake is not universal. This is important because there was an indication that the rate of all-cause mortality was higher in the full

population of people with SMI than those who were screened. It is therefore possible that some people who do not participate in screening may have poor physical health. Although my study can only offer suggestive evidence on the physical health needs of individuals who did not have complete covariate data, the implication that individuals with particularly poor physical health are not participating in screening is concerning and needs further attention. Furthermore, whilst it appears that QOF has increased uptake of physical health checks amongst people with SMI, it is unclear what – if any – impact the recent removal of some QOF targets, particularly for cholesterol, may have on management of CVD and evaluation of this policy change is needed.

13 Research Implications

13.1 Identifying how participation in CVD screening to individuals with SMI can be increased

Preferences for different approaches to CVD prevention in people with SMI are complex and the acceptability of options such as monitoring by community mental health teams and blood tests may play a role in limiting the uptake of screening (Wright et al., 2006). Emerging evidence (Zomer et al., 2015) suggests that use of specific CVD risk scores for individuals with SMI may offer significant benefits in terms of better identifying those at high risk of CVD. Furthermore, as one of the SMI-specific CVD risk scores which was found to be cost-effective does not require a blood test, it may facilitate increased uptake of CVD screening (Osborn et al., 2015).

Recording the correct information for estimation of CVD risk may also hinder screening and can be facilitated by integrating tools that aid structured data capture with the primary care information system (Yeomans et al., 2014). At present there is no evidence to suggest an improved model for providing health checks to people with SMI. However, increased uptake might be achieved through improved implementation at GP surgeries (for example using tools to aid data capture and using risk scores that do not require a blood test) in addition to offering health checks within secondary care to the small but important minority of individuals who do not routinely access primary care (Reilly et al., 2012). Central to the success of such a strategy would be increased integration of physical and mental health teams to ensure that health checks result in appropriate action.

13.2 Prescribing statins to individuals with the greatest capacity to benefit

Although statin prescribing does appear to be effective for lipid modification for people with SMI and may therefore improve cardiovascular health, the current strategy for prescribing may miss some individuals at high risk of CVD; particularly individuals with schizophrenia. It is unclear what factors may be driving this process and further qualitative and quantitative work is required to better characterise individuals who are likely to be missed and to ascertain the types of intervention that are appropriate for this group of individuals. In addition, it may be possible to achieve greater benefits from statin prescribing through further studies to determine optimal timings and dosages for people with SMI. For example, given the earlier age of CVD onset within this group, it may be advantageous to explore whether starting pharmacological intervention in younger individuals is worthwhile.

My study identified that statins were prescribed to less than half of people who had all components of the physical health check recorded over a six-year period and had an estimated Framingham risk score of 20% or higher. This finding raises the question of why these individuals were not prescribed a statin. Perhaps the most likely explanation is that the GP had not actively estimated a risk score for the patient and was therefore unaware of the patient's potential eligibility for statin prescribing. There may therefore be a role for tailoring GP software to highlight when sufficient information is available to estimate a risk score (e.g. by including an alert in a visible but unobtrusive part of the patient's electronic health record), and whether this score is likely to be at or above the threshold for prescribing. However, given the vast burden of competing priorities that GP consultations must already address, further research is required to ascertain acceptable and effective forms for such prompts to take.

UK guidance promotes the role of lifestyle modification prior to initiating statin therapy, and it is likely that some of the high CVD risk individuals identified in my study were encouraged to consider this approach (National Institute for Health and Clinical Excellence, 2014b). However, given evidence from the general population (Jorgensen et al., 2014), it is likely that statin prescribing would offer CVD benefits over and above interventions that aim to change lifestyle. UK guidance advocates shared decision making between the patient and GP for statin prescribing (National Institute for Health and Clinical Excellence, 2008b;National Institute for Health and Clinical Excellence, 2014b): the absence of prescribing to eligible individuals may

therefore occur when one or both parties are reluctant to pursue this line of risk management.

Although, information arising from the decision process can theoretically be captured in free text held in electronic patient records, this information is likely to be infrequently available, difficult to interpret and was therefore not considered in my study. Further qualitative work is required to understand the extent and basis of resistance to statin medication on the part of both GPs and people with SMI. In particular, better understanding of whether the primary concerns relate to perceptions of side-effects, medication adherence or other health beliefs is needed.

It is likely that there are many individuals who – *if* able to implement and maintain lifestyle changes to lower cholesterol - would obtain greater benefit (including those that are not specific to CVD) than could be achieved through statin therapy alone. However, effective means of supporting lifestyle modification among people with SMI have not been established and further work is needed in this area (Burton et al., 2015). In particular, the results from the PRIMROSE RCT will help to provide a fuller picture of how statin therapy can be used to compliment strategies for improving medication adherence, stopping smoking, increasing physical activity and promoting healthy eating. In combination, these interventions will help to reduce the inequalities in CVD that are experienced by people with SMI.

14 Conclusions

The findings of this thesis are that the evidence to support statin prescribing for primary CVD prevention in people with SMI greatly outweighs the paucity of evidence that opposes prescribing to this group. This thesis provides new evidence to show that statin prescribing is associated with clinically relevant reductions in total cholesterol and that these reductions may translate into long term benefits in terms of CVD events and mortality. However, the results from this thesis do not provide conclusive evidence on the magnitude of effectiveness in people with SMI and this may have implications for the cost-effectiveness of statin therapy. Although there is good evidence to suggest that substantial progress has been made towards reducing inequalities in the uptake of physical health checks amongst people with SMI; uptake is not universal. For this reason, there remains some uncertainty regarding the effectiveness of the current clinical care pathway with respective to targeting people who would derive the greatest benefit from statin prescribing. Statin therapy is therefore a valuable component of care for primary prevention of CVD in

people with SMI. However, further policy intervention and research is required to ensure that statins are prescribed to individuals with the greatest capacity to benefit, which encompasses factors such as medication adherence and side-effects relative to other pharmacological or lifestyle interventions.

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16 Appendices:

17 Tailored literature search terms for each database

17.1 Search terms for querying MedLine

Domain 1) *("cardio*" mp.) OR ("metabolic*" mp.) OR ("lipid*" mp.) OR ("cholesterol*" mp.) OR (exp CVDs/) OR (exp Cholesterol/) OR (exp Lipids/) OR (exp Dyslipidemias/) OR (exp Hyperlipidemias/) OR (exp Metabolic Syndrome X/)*

Domain 2) *("Hydroxymethylglutaryl-CoA Reductase Inhibitor*" mp.) OR ("statin*" mp.) OR (exp Hydroxymethylglutaryl-CoA Reductase Inhibitors/)*

Domain 3) *("Bipolar" mp.) OR ("mania*" mp.) OR ("manic*" mp.) OR ("hypomanic*" mp.) OR ("psychotic" mp.) OR ("postpsychotic" mp.) OR ("post psychotic" mp.) OR ("schizoaffective" mp.) OR ("psychosis" mp.) OR ("psychoses" mp.) OR (exp Bipolar Disorder/) OR (exp Schizophrenia/) OR (exp Psychotic Disorders/) OR (exp Antipsychotic Agents/)*

Multipurpose search (mp.)=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier, exp = exploded term

17.2 Search terms for querying EMBASE

Domain 1) *(exp CVD/) OR (exp cholesterol/) OR (exp lipid/) OR (exp dyslipidemia/) OR (exp hyperlipidemia/) OR (exp metabolic syndrome X/) OR ("cardio*" mp.) OR ("metabolic*" mp.) OR ("lipid*" mp.) OR ("cholesterol*" mp.)*

Domain 2) *(exp hydroxymethylglutaryl coenzyme A reductase Inhibitor/) OR (exp "statin (protein)") OR ("Hydroxymethylglutaryl-CoA Reductase Inhibitor*" mp.) OR ("statin*" mp.)*

Domain 3) *(exp bipolar disorder/) OR (exp schizophrenia/) OR (exp psychosis/) OR (exp neuroleptic agent/) OR ("Bipolar" mp.) OR ("mania*" mp.) OR ("manic*" mp.) OR ("hypomani*" mp.) OR ("psychotic" mp.) OR ("postpsychotic" mp.) OR ("postpsychotic" mp.) OR ("rapid cycling") OR ("schizoaffective" mp.) OR ("psychosis" mp.) OR ("psychoses" mp.)*

Multipurpose search (mp.)=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, exp = exploded term

17.3 Search terms for querying PsycInfo

Domain 1) *(exp Cardiovascular Disorders/) OR (exp Cholesterol/) OR (exp Lipids/) OR (exp Lipid Metabolism Disorders/) OR (exp Metabolic Disorders/) OR (exp Metabolic Syndrome/) OR ("cardio*" mp.) OR ("metabolic*" mp.) OR ("lipid*" mp.) OR ("cholesterol*" mp.)*

Domain 2) *(exp "Statins") ("Hydroxymethylglutaryl-CoA Reductase Inhibitor*" mp.) OR ("statin*" mp.)*

Domain 3) *(exp Bipolar Disorder/) OR (exp Schizophrenia/) OR (exp Psychosis/) OR (exp Neuroleptic drugs/) OR ("Bipolar" mp.) OR ("mania*" mp.) OR ("manic*" mp.) OR ("hypomani*" mp.) OR ("psychotic" mp.) OR ("postpsychotic" mp.) OR ("post psychotic" mp.) OR ("rapid cycling" mp.) OR ("schizoaffective" mp.) OR ("psychosis" mp.) OR ("psychoses" mp.)*

Multipurpose search (mp.)=title, abstract, heading word, table of contents, key concepts, original title, tests & measures, exp = exploded term

17.4 Search terms for querying CINAHL

Domain 1) *(MH "CVD+") OR (MH "lipid+") OR (MH "cholesterol+") OR (MH "hyperlipidaemia+") OR cardio* OR lipid* OR cholesterol* OR dyslipid* OR hyperlipid* OR metabolic**

Domain 2) *(MH "statin") OR (Hydroxymethylglutaryl-CoA Reductase Inhibitor*) OR statin**

Domain 3) *(MH "bipolar disorder") OR (MH "schizophrenia") OR (MH "anti psychotic agents") OR bipolar OR mania* OR manic* Or hypomani* OR psychotic OR postpsychotic OR (post psychotic) OR (rapid cycling) OR schizoaffective OR psychosis OR psychoses*

MH = medical heading

17.5 Tailored literature search terms for querying NHS evidence

Domain 1) ((cardio*) OR (cholesterol*) OR (lipid*) OR (metabolic*))

Domain 2) ((statin*) OR ("Hydroxymethylglutaryl-CoA Reductase Inhibitor*"))

Domain 3) ((Bipolar) OR (mania*) OR (manic*) Or (hypomani*) OR (psychotic) OR (postpsychotic) OR ("post psychotic") OR ("rapid cycling") OR (schizoaffective) OR (psychosis) OR (psychoses))

Domain 4) Information type ='primary research'

18 Systematic review abstract submitted to SAPC

Title: Systematic review of the evidence for the effectiveness of statins for the primary prevention of cardiovascular disease in people with severe mental illness.

The Problem: Cardiovascular–related mortality and morbidity are twofold higher amongst individuals with severe mental illness (including schizophrenia and bipolar disorder) than the general population; thus highlighting the need for improved cardiovascular care for this group. Statins are a cost-effective means of preventing cardiovascular disease in the general population. However, the evidence-base for statin use in people with severe mental illness is unclear and may differ to the general population because of interaction with antipsychotic medication or patterns of medication adherence.

The Approach: We aimed to identify studies evaluating the impact of statin therapy on the primary prevention of cardiovascular disease in individuals with severe mental illness. A systematic search was conducted using five complimentary databases (EMBASE, MedLine, CINAHL, NHS Evidence, PsycInfo) and five major trials registries (CENTRAL, International Standard Randomised Controlled Trial Register, US National Institutes of Health service, UK National Institute for Health Research Register,UK Clinical Research Network study portfolio

database). Search terms included synonyms, free text and wildcard terms for: 1) cardiovascular disease, 2) statins and 3) severe mental illness. All results were independently screened for relevance by two reviewers.

Findings: A total of 1994 citations were screened to yield six potentially relevant registered trials and four non-randomised studies. Of the trials, one is currently recruiting, one has been completed but results are not yet available, three were terminated early with no available results and one has been completed, with negative results and has not been published. Of the four non-randomised studies, only one incorporated a statin unexposed comparison group: results from this study suggest that statins can produce meaningful reductions in total cholesterol (-35% (±6), $p<0.001$) and low density lipoprotein cholesterol (-49% (±8), $p<0.001$) in individuals with severe mental illness. However, the strength of these findings are limited by relatively small sample size (n=100) from a single centre, type of statin investigated (rosuvastatin) and short duration of follow up (3 months).

Consequences: There is an extremely limited pool of evidence assessing the effectiveness of statins in people with severe mental illness, with some evidence of publication bias, no results currently available from randomised controlled trials and only one study incorporating a statin-free comparison arm. Further evidence is required to support effective primary prevention of cardiovascular disease amongst individuals with severe mental illness.

19 Estimating CVD risk scores

Table 19-1: Published regression Coefficients for the laboratory version of the Framingham risk score for CVD (D'Agostino et al., 2008)

Variable	Coefficient
Women (10 year baseline survival: So(10)=0.95012)	
Log of age	2.32888
Log of total cholesterol	1.20904
Log of HDL cholesterol	−0.70833
Log of SBP if not treated	2.76157
Log of SBP if treated	2.82263
Smoking	0.52873
Diabetes	0.69154
Men (10 year baseline survival: So(10)=0.88936)	
Log of age	3.06117
Log of total cholesterol	1.1237
Log of HDL cholesterol	−0.93263
Log of SBP if not treated	1.93303
Log of SBP if treated	1.99881
Smoking	0.65451
Diabetes	0.57367

SBP; systolic blood pressure

Table 19-2: Published regression Coefficients for the desk version of the Framingham risk score for CVD (D'Agostino et al., 2008)

Variable	Coefficient
Women (10 year baseline survival: So(10)= 0.94833)	
Log of age	2.72107
Body mass index	0.51125
Log of SBP if not treated	2.81291
Log of SBP if treated	2.88267
Smoking	0.61868
Diabetes	0.77763
Men (10 year baseline survival: So(10)= 0.88431)	
Log of age	3.11296
Body mass index	0.79277
Log of SBP if not treated	1.85508
Log of SBP if treated	1.92672
Smoking	0.70953
Diabetes	0.53160

SBP; systolic blood pressure

20 Drug and Read Code Lists

20.1 SMI

Description (SMI)	Med Code	SMI Type
H/O: schizophrenia	1464.00	schizophrenia
H/O: manic depressive disorder	146D.00	bipolar
H/O: psychosis	146H.00	other
On national service framework mental health	9H6..00	register
On severe mental illness register	9H8..00	register
Non-organic psychoses	E1...00	other
Schizophrenic disorders	E10..00	schizophrenia
Simple schizophrenia	E100.00	schizophrenia
Schizophrenia simplex	E100.11	schizophrenia
Unspecified schizophrenia	E100000	schizophrenia
Subchronic schizophrenia	E100100	schizophrenia
Chronic schizophrenic	E100200	schizophrenia
Acute exacerbation of subchronic schizophrenia	E100300	schizophrenia
Acute exacerbation of chronic schizophrenia	E100400	schizophrenia
Schizophrenia in remission	E100500	schizophrenia
Simple schizophrenia NOS	E100z00	schizophrenia
Hebephrenic schizophrenia	E101.00	schizophrenia
Unspecified hebephrenic schizophrenia	E101000	schizophrenia
Subchronic hebephrenic schizophrenia	E101100	schizophrenia
Chronic hebephrenic schizophrenia	E101200	schizophrenia
Acute exacerbation of subchronic hebephrenic schizophrenia	E101300	schizophrenia
Acute exacerbation of chronic hebephrenic schizophrenia	E101400	schizophrenia

Description (SMI)	Med Code	SMI Type
Hebephrenic schizophrenia in remission	E101500	schizophrenia
Hebephrenic schizophrenia NOS	E101z00	schizophrenia
Catatonic schizophrenia	E102.00	schizophrenia
Unspecified catatonic schizophrenia	E102000	schizophrenia
Subchronic catatonic schizophrenia	E102100	schizophrenia
Chronic catatonic schizophrenia	E102200	schizophrenia
Acute exacerbation of subchronic catatonic schizophrenia	E102300	schizophrenia
Acute exacerbation of chronic catatonic schizophrenia	E102400	schizophrenia
Catatonic schizophrenia in remission	E102500	schizophrenia
Catatonic schizophrenia NOS	E102z00	schizophrenia
Paranoid schizophrenia	E103.00	schizophrenia
Unspecified paranoid schizophrenia	E103000	schizophrenia
Subchronic paranoid schizophrenia	E103100	schizophrenia
Chronic paranoid schizophrenia	E103200	schizophrenia
Acute exacerbation of subchronic paranoid schizophrenia	E103300	schizophrenia
Acute exacerbation of chronic paranoid schizophrenia	E103400	schizophrenia
Paranoid schizophrenia in remission	E103500	schizophrenia
Paranoid schizophrenia NOS	E103z00	schizophrenia
Acute schizophrenic episode	E104.00	schizophrenia
Oneirophrenia	E104.11	other
Latent schizophrenia	E105.00	schizophrenia
Unspecified latent schizophrenia	E105000	schizophrenia
Subchronic latent schizophrenia	E105100	schizophrenia
Chronic latent schizophrenia	E105200	schizophrenia
Acute exacerbation of subchronic latent schizophrenia	E105300	schizophrenia
Acute exacerbation of chronic latent schizophrenia	E105400	schizophrenia
Latent schizophrenia in remission	E105500	schizophrenia
Latent schizophrenia NOS	E105z00	schizophrenia
Residual schizophrenia	E106.00	schizophrenia
Restzustand - schizophrenia	E106.11	schizophrenia
Schizo-affective schizophrenia	E107.00	schizophrenia
Cyclic schizophrenia	E107.11	schizophrenia
Unspecified schizo-affective schizophrenia	E107000	schizophrenia
Subchronic schizo-affective schizophrenia	E107100	schizophrenia
Chronic schizo-affective schizophrenia	E107200	schizophrenia
Acute exacerbation subchronic schizo-affective schizophrenia	E107300	schizophrenia
Acute exacerbation of chronic schizo-affective schizophrenia	E107400	schizophrenia
Schizo-affective schizophrenia in remission	E107500	schizophrenia
Schizo-affective schizophrenia NOS	E107z00	schizophrenia
Other schizophrenia	E10y.00	schizophrenia
Cenesthopathic schizophrenia	E10y.11	schizophrenia
Atypical schizophrenia	E10y000	schizophrenia
Coenesthopathic schizophrenia	E10y100	schizophrenia
Other schizophrenia NOS	E10yz00	schizophrenia
Schizophrenia NOS	E10z.00	schizophrenia
Affective psychoses	E11..00	other
Bipolar psychoses	E11..11	bipolar
Depressive psychoses	E11..12	other
Manic psychoses	E11..13	bipolar
Manic disorder, single episode	E110.00	bipolar
Hypomanic psychoses	E110.11	bipolar

Description (SMI)	Med Code	SMI Type
Single manic episode, unspecified	E110000	bipolar
Single manic episode, mild	E110100	bipolar
Single manic episode, moderate	E110200	bipolar
Single manic episode, severe without mention of psychosis	E110300	bipolar
Single manic episode, severe, with psychosis	E110400	bipolar
Single manic episode in partial or unspecified remission	E110500	bipolar
Single manic episode in full remission	E110600	bipolar
Manic disorder, single episode NOS	E110z00	bipolar
Recurrent manic episodes	E111.00	bipolar
Recurrent manic episodes, unspecified	E111000	bipolar
Recurrent manic episodes, mild	E111100	bipolar
Recurrent manic episodes, moderate	E111200	bipolar
Recurrent manic episodes, severe without mention psychosis	E111300	bipolar
Recurrent manic episodes, severe, with psychosis	E111400	bipolar
Recurrent manic episodes, partial or unspecified remission	E111500	bipolar
Recurrent manic episodes, in full remission	E111600	bipolar
Recurrent manic episode NOS	E111z00	bipolar
Single major depressive episode, severe, with psychosis	E112400	other
Recurrent major depressive episodes, severe, with psychosis	E113400	other
Bipolar affective disorder, currently manic	E114.00	bipolar
Manic-depressive - now manic	E114.11	bipolar
Bipolar affective disorder, currently manic, unspecified	E114000	bipolar
Bipolar affective disorder, currently manic, mild	E114100	bipolar
Bipolar affective disorder, currently manic, moderate	E114200	bipolar
Bipolar affect disord, currently manic, severe, no psychosis	E114300	bipolar
Bipolar affect disord, currently manic,severe with psychosis	E114400	bipolar
Bipolar affect disord,currently manic, part/unspec remission	E114500	bipolar
Bipolar affective disorder, currently manic, full remission	E114600	bipolar
Bipolar affective disorder, currently manic, NOS	E114z00	bipolar
Bipolar affective disorder, currently depressed	E115.00	bipolar
Manic-depressive - now depressed	E115.11	bipolar
Bipolar affective disorder, currently depressed, unspecified	E115000	bipolar
Bipolar affective disorder, currently depressed, mild	E115100	bipolar
Bipolar affective disorder, currently depressed, moderate	E115200	bipolar
Bipolar affect disord, now depressed, severe, no psychosis	E115300	bipolar
Bipolar affect disord, now depressed, severe with psychosis	E115400	bipolar
Bipolar affect disord, now depressed, part/unspec remission	E115500	bipolar
Bipolar affective disorder, now depressed, in full remission	E115600	bipolar
Bipolar affective disorder, currently depressed, NOS	E115z00	bipolar
Mixed bipolar affective disorder	E116.00	bipolar
Mixed bipolar affective disorder, unspecified	E116000	bipolar
Mixed bipolar affective disorder, mild	E116100	bipolar
Mixed bipolar affective disorder, moderate	E116200	bipolar
Mixed bipolar affective disorder, severe, without psychosis	E116300	bipolar
Mixed bipolar affective disorder, severe, with psychosis	E116400	bipolar
Mixed bipolar affective disorder, partial/unspec remission	E116500	bipolar
Mixed bipolar affective disorder, in full remission	E116600	bipolar
Mixed bipolar affective disorder, NOS	E116z00	bipolar
Unspecified bipolar affective disorder	E117.00	bipolar
Unspecified bipolar affective disorder, unspecified	E117000	bipolar
Unspecified bipolar affective disorder, mild	E117100	bipolar

Description (SMI)	Med Code	SMI Type
Unspecified bipolar affective disorder, moderate	E117200	bipolar
Unspecified bipolar affective disorder, severe, no psychosis	E117300	bipolar
Unspecified bipolar affective disorder,severe with psychosis	E117400	bipolar
Unspecified bipolar affect disord, partial/unspec remission	E117500	bipolar
Unspecified bipolar affective disorder, in full remission	E117600	bipolar
Unspecified bipolar affective disorder, NOS	E117z00	bipolar
Other and unspecified manic-depressive psychoses	E11y.00	bipolar
Unspecified manic-depressive psychoses	E11y000	bipolar
Atypical manic disorder	E11y100	bipolar
Other mixed manic-depressive psychoses	E11y300	bipolar
Other and unspecified manic-depressive psychoses NOS	E11yz00	bipolar
Other and unspecified affective psychoses	E11z.00	other
Unspecified affective psychoses NOS	E11z000	other
Other affective psychosis NOS	E11zz00	other
Paranoid states	E12..00	other
Simple paranoid state	E120.00	other
Chronic paranoid psychosis	E121.00	other
Sander's disease	E121.11	other
Paraphrenia	E122.00	other
Shared paranoid disorder	E123.00	other
Folie a deux	E123.11	other
Other paranoid states	E12y.00	other
Paranoia querulans	E12y000	other
Other paranoid states NOS	E12yz00	other
Paranoid psychosis NOS	E12z.00	other
Other nonorganic psychoses	E13..00	other
Reactive psychoses	E13..11	other
Reactive depressive psychosis	E130.00	other
Psychotic reactive depression	E130.11	other
Acute hysterical psychosis	E131.00	other
Acute paranoid reaction	E133.00	other
Bouffee delirante	E133.11	other
Psychogenic paranoid psychosis	E134.00	other
Other reactive psychoses	E13y.00	other
Psychogenic stupor	E13y000	other
Brief reactive psychosis	E13y100	other
Other reactive psychoses NOS	E13yz00	other
Nonorganic psychosis NOS	E13z.00	other
Psychotic episode NOS	E13z.11	other
Other specified non-organic psychoses	E1y..00	other
Non-organic psychosis NOS	E1z..00	other
Schizotypal personality	E212200	schizophrenia
[X]Schizophrenia, schizotypal and delusional disorders	Eu2..00	schizophrenia
[X]Schizophrenia	Eu20.00	schizophrenia
[X]Paranoid schizophrenia	Eu20000	schizophrenia
[X]Paraphrenic schizophrenia	Eu20011	schizophrenia
[X]Hebephrenic schizophrenia	Eu20100	schizophrenia
[X]Disorganised schizophrenia	Eu20111	schizophrenia
[X]Catatonic schizophrenia	Eu20200	schizophrenia
[X]Catatonic stupor	Eu20211	schizophrenia
[X]Schizophrenic catalepsy	Eu20212	schizophrenia

Description (SMI)	Med Code	SMI Type
[X]Schizophrenic catatonia	Eu20213	schizophrenia
[X]Schizophrenic flexibilatis cerea	Eu20214	schizophrenia
[X]Undifferentiated schizophrenia	Eu20300	schizophrenia
[X]Atypical schizophrenia	Eu20311	schizophrenia
[X]Post-schizophrenic depression	Eu20400	schizophrenia
[X]Residual schizophrenia	Eu20500	schizophrenia
[X]Chronic undifferentiated schizophrenia	Eu20511	schizophrenia
[X]Restzustand schizophrenic	Eu20512	schizophrenia
[X]Simple schizophrenia	Eu20600	schizophrenia
[X]Other schizophrenia	Eu20y00	schizophrenia
[X]Cenesthopathic schizophrenia	Eu20y11	schizophrenia
[X]Schizophreniform disord NOS	Eu20y12	schizophrenia
[X]Schizophrenifrm psychos NOS	Eu20y13	schizophrenia
[X]Schizophrenia, unspecified	Eu20z00	schizophrenia
[X]Schizotypal disorder	Eu21.00	schizophrenia
[X]Latent schizophrenic reaction	Eu21.11	schizophrenia
[X]Borderline schizophrenia	Eu21.12	schizophrenia
[X]Latent schizophrenia	Eu21.13	schizophrenia
[X]Prepsychotic schizophrenia	Eu21.14	schizophrenia
[X]Prodromal schizophrenia	Eu21.15	schizophrenia
[X]Pseudoneurotic schizophrenia	Eu21.16	schizophrenia
[X]Pseudopsychopathic schizophrenia	Eu21.17	schizophrenia
[X]Schizotypal personality disorder	Eu21.18	schizophrenia
[X]Persistent delusional disorders	Eu22.00	other
[X]Delusional disorder	Eu22000	other
[X]Paranoid psychosis	Eu22011	other
[X]Paranoid state	Eu22012	other
[X]Paraphrenia - late	Eu22013	schizophrenia
[X]Sensitiver Beziehungswahn	Eu22014	other
[X]Paranoia	Eu22015	other
[X]Delusional misidentification syndrome	Eu22100	other
[X]Capgras syndrome	Eu22111	other
[X]Cotard syndrome	Eu22200	other
[X]Other persistent delusional disorders	Eu22y00	other
[X]Delusional dysmorphophobia	Eu22y11	other
[X]Involutional paranoid state	Eu22y12	other
[X]Paranoia querulans	Eu22y13	other
[X]Persistent delusional disorder, unspecified	Eu22z00	other
[X]Acute and transient psychotic disorders	Eu23.00	other
[X]Acute polymorphic psychot disord without symp of schizoph	Eu23000	other
[X]Bouffee delirante	Eu23011	other
[X]Cycloid psychosis	Eu23012	other
[X]Acute polymorphic psychot disord with symp of schizophren	Eu23100	other
[X]Bouffee delirante with symptoms of schizophrenia	Eu23111	other
[X]Cycloid psychosis with symptoms of schizophrenia	Eu23112	schizophrenia
[X]Acute schizophrenia-like psychotic disorder	Eu23200	other
[X]Brief schizophreniform disorder	Eu23211	other
[X]Brief schizophrenifrm psych	Eu23212	other
[X]Oneirophrenia	Eu23213	other
[X]Schizophrenic reaction	Eu23214	schizophrenia
[X]Other acute predominantly delusional psychotic disorders	Eu23300	other

Description (SMI)	Med Code	SMI Type
[X]Psychogenic paranoid psychosis	Eu23312	other
[X]Other acute and transient psychotic disorders	Eu23y00	other
[X]Acute and transient psychotic disorder, unspecified	Eu23z00	other
[X]Brief reactive psychosis NOS	Eu23z11	other
[X]Reactive psychosis	Eu23z12	other
[X]Induced delusional disorder	Eu24.00	other
[X]Folie a deux	Eu24.11	other
[X]Induced paranoid disorder	Eu24.12	other
[X]Induced psychotic disorder	Eu24.13	other
[X]Schizoaffective disorders	Eu25.00	schizophrenia
[X]Schizoaffective disorder, manic type	Eu25000	schizophrenia
[X]Schizoaffective psychosis, manic type	Eu25011	schizophrenia
[X]Schizophreniform psychosis, manic type	Eu25012	schizophrenia
[X]Schizoaffective disorder, depressive type	Eu25100	schizophrenia
[X]Schizoaffective psychosis, depressive type	Eu25111	schizophrenia
[X]Schizophreniform psychosis, depressive type	Eu25112	schizophrenia
[X]Schizoaffective disorder, mixed type	Eu25200	schizophrenia
[X]Cyclic schizophrenia	Eu25211	schizophrenia
[X]Mixed schizophrenic and affective psychosis	Eu25212	schizophrenia
[X]Other schizoaffective disorders	Eu25y00	schizophrenia
[X]Schizoaffective disorder, unspecified	Eu25z00	schizophrenia
[X]Schizoaffective psychosis NOS	Eu25z11	schizophrenia
[X]Other nonorganic psychotic disorders	Eu2y.00	other
[X]Chronic hallucinatory psychosis	Eu2y.11	other
[X]Unspecified nonorganic psychosis	Eu2z.00	other
[X]Psychosis NOS	Eu2z.11	other
[X]Manic episode	Eu30.00	bipolar
[X]Bipolar disorder, single manic episode	Eu30.11	bipolar
[X]Hypomania	Eu30000	bipolar
[X]Mania without psychotic symptoms	Eu30100	bipolar
[X]Mania with psychotic symptoms	Eu30200	bipolar
[X]Mania with mood-congruent psychotic symptoms	Eu30211	bipolar
[X]Mania with mood-incongruent psychotic symptoms	Eu30212	bipolar
[X]Manic stupor	Eu30213	bipolar
[X]Other manic episodes	Eu30y00	bipolar
[X]Manic episode, unspecified	Eu30z00	bipolar
[X]Mania NOS	Eu30z11	bipolar
[X]Bipolar affective disorder	Eu31.00	bipolar
[X]Manic-depressive illness	Eu31.11	bipolar
[X]Manic-depressive psychosis	Eu31.12	bipolar
[X]Mainc-depressive reaction	Eu31.13	bipolar
[X]Bipolar affective disorder, current episode hypomanic	Eu31000	bipolar
[X]Bipolar affect disorder cur epi manic wout psychotic symp	Eu31100	bipolar
[X]Bipolar affect disorder cur epi manic with psychotic symp	Eu31200	bipolar
[X]Bipolar affect disorder cur epi mild or moderate depressn	Eu31300	bipolar
[X]Bipol aff disord, curr epis sev depress, no psychot symp	Eu31400	bipolar
[X]Bipolar affect dis cur epi severe depres with psyc symp	Eu31500	bipolar
[X]Bipolar affective disorder, current episode mixed	Eu31600	bipolar
[X]Bipolar affective disorder, currently in remission	Eu31700	bipolar
[X]Other bipolar affective disorders	Eu31y00	bipolar
[X]Bipolar II disorder	Eu31y11	bipolar

Description (SMI)	Med Code	SMI Type
[X]Recurrent manic episodes	Eu31y12	bipolar
[X]Bipolar affective disorder, unspecified	Eu31z00	bipolar
[X]Severe depressive episode with psychotic symptoms	Eu32300	other
[X]Single episode of major depression and psychotic symptoms	Eu32311	other
[X]Single episode of psychogenic depressive psychosis	Eu32312	other
[X]Single episode of psychotic depression	Eu32313	other
[X]Single episode of reactive depressive psychosis	Eu32314	other
[X]Major depression, severe with psychotic symptoms	Eu32800	other
[X]Manic-depress psychosis,depressd,no psychotic symptoms	Eu33213	bipolar
[X]Recurrent depress disorder cur epi severe with psyc symp	Eu33300	other
[X]Endogenous depression with psychotic symptoms	Eu33311	other
[X]Manic-depress psychosis,depressed type+psychotic symptoms	Eu33312	bipolar
[X]Recurr severe episodes/major depression+psychotic symptom	Eu33313	other
[X]Recurr severe episodes/psychogenic depressive psychosis	Eu33314	other
[X]Recurrent severe episodes of psychotic depression	Eu33315	other
[X]Recurrent severe episodes/reactive depressive psychosis	Eu33316	other
[X]Affective psychosis NOS	Eu3z.11	other
[X]Hysterical psychosis	Eu44.14	other
[X]Symbiotic psychosis	Eu84314	other
Profile of mood states, bipolar	ZRby100	bipolar
Schizophrenic language	ZS7C611	schizophrenia
[V]Personal history of schizophrenia	ZV11000	schizophrenia
[V]Personal history of manic-depressive psy	ZV11111	bipolar
[V]Personal history of manic-depressive psy	ZV11112	bipolar

20.2 CVD

description (CVD)	MedCode	CVD Type	Incident
H/O: cerebrovascular disease	1477.00	CVD unspecified	n
H/O: cardiovascular disease	14A..00	CVD unspecified	n
H/O: myocardial infarct<60	14A3.00	MI	n
H/O: myocardial infarct>60	14A4.00	MI	n
H/O: angina pectoris	14A5.00	angina	n
H/O: CVA/stroke	14A7.00	ischaemic/unspecified stroke	n
H/O: CVA	14A7.11	ischaemic/unspecified stroke	n
H/O: stroke	14A7.12	ischaemic/unspecified stroke	n
H/O: heart disease NOS	14AA.00	CHD unspecified	n
H/O: TIA	14AB.00	TIA	n
H/O: Myocardial infarction in last year	14AH.00	MI	n
H/O: Angina in last year	14AJ.00	angina	n
H/O: Stroke in last year	14AK.00	ischaemic/unspecified stroke	n
H/O: Treatment for ischaemic heart disease	14AL.00	CHD unspecified	n
History of myocardial infarction	14AT.00	MI	n
H/O: CVS disease NOS	14AZ.00	CVD unspecified	n
ECG: myocardial ischaemia	322..00	MI	y
ECG:shows myocardial ischaemia	3222.00	MI	y
ECG: myocardial ischaemia NOS	322Z.00	MI	y
ECG: myocardial infarction	323..00	MI	y
ECG: old myocardial infarction	3232.00	MI	n

description (CVD)	MedCode	CVDType	Incident
ECG: antero-septal infarct.	3233.00	MI	y
ECG:posterior/inferior infarct	3234.00	MI	y
ECG: subendocardial infarct	3235.00	MI	y
ECG: lateral infarction	3236.00	MI	y
ECG: myocardial infarct NOS	323Z.00	MI	y
Angina control - good	662K000	angina	n
Angina control - poor	662K100	angina	n
Angina control - improving	662K200	angina	n
Angina control - worsening	662K300	angina	n
Angina control NOS	662Kz00	angina	n
Coronary artery operations	792..00	surgery	y
Coronary artery bypass graft operations	792..11	surgery	y
Saphenous vein graft replacement of coronary artery	7920.00	surgery	y
Saphenous vein graft bypass of coronary artery	7920.11	surgery	y
Saphenous vein graft replacement of one coronary artery	7920000	surgery	y
Saphenous vein graft replacement of two coronary arteries	7920100	surgery	y
Saphenous vein graft replacement of three coronary arteries	7920200	surgery	y
Saphenous vein graft replacement of four+ coronary arteries	7920300	surgery	y
Saphenous vein graft replacement of coronary artery OS	7920y00	surgery	y
Saphenous vein graft replacement coronary artery NOS	7920z00	surgery	y
Other autograft replacement of coronary artery	7921.00	surgery	y
Other autograft bypass of coronary artery	7921.11	surgery	y
Autograft replacement of one coronary artery NEC	7921000	surgery	y
Autograft replacement of two coronary arteries NEC	7921100	surgery	y
Autograft replacement of three coronary arteries NEC	7921200	surgery	y
Autograft replacement of four of more coronary arteries NEC	7921300	surgery	y
Other autograft replacement of coronary artery OS	7921y00	surgery	y
Other autograft replacement of coronary artery NOS	7921z00	surgery	y
Allograft replacement of coronary artery	7922.00	surgery	y
Allograft bypass of coronary artery	7922.11	surgery	y
Allograft replacement of one coronary artery	7922000	surgery	y
Allograft replacement of two coronary arteries	7922100	surgery	y
Allograft replacement of three coronary arteries	7922200	surgery	y
Allograft replacement of four or more coronary arteries	7922300	surgery	y
Other specified allograft replacement of coronary artery	7922y00	surgery	y
Allograft replacement of coronary artery NOS	7922z00	surgery	y
Prosthetic replacement of coronary artery	7923.00	surgery	y
Prosthetic bypass of coronary artery	7923.11	surgery	y
Prosthetic replacement of one coronary artery	7923000	surgery	y
Prosthetic replacement of two coronary arteries	7923100	surgery	y
Prosthetic replacement of three coronary arteries	7923200	surgery	y
Prosthetic replacement of four or more coronary arteries	7923300	surgery	y
Other specified prosthetic replacement of coronary artery	7923y00	surgery	y

description (CVD)	MedCode	CVDType	Incident
Prosthetic replacement of coronary artery NOS	7923z00	surgery	y
Revision of bypass for coronary artery	7924.00	surgery	y
Revision of bypass for one coronary artery	7924000	surgery	y
Revision of bypass for two coronary arteries	7924100	surgery	y
Revision of bypass for three coronary arteries	7924200	surgery	y
Revision of bypass for four or more coronary arteries	7924300	surgery	y
Revision of connection of thoracic artery to coronary artery	7924400	surgery	y
Revision of implantation of thoracic artery into heart	7924500	surgery	y
Other specified revision of bypass for coronary artery	7924y00	surgery	y
Revision of bypass for coronary artery NOS	7924z00	surgery	y
Connection of mammary artery to coronary artery	7925.00	surgery	y
Creation of bypass from mammary artery to coronary artery	7925.11	surgery	y
Double anastomosis of mammary arteries to coronary arteries	7925000	surgery	y
LIMA sequential anastomosis	7925011	surgery	y
RIMA sequential anastomosis	7925012	surgery	y
Double implant of mammary arteries into coronary arteries	7925100	surgery	y
Single anast mammary art to left ant descend coronary art	7925200	surgery	y
Single anastomosis of mammary artery to coronary artery NEC	7925300	surgery	y
LIMA single anastomosis	7925311	surgery	y
RIMA single anastomosis	7925312	surgery	y
Single implantation of mammary artery into coronary artery	7925400	surgery	y
Connection of mammary artery to coronary artery OS	7925y00	surgery	y
Connection of mammary artery to coronary artery NOS	7925z00	surgery	y
Connection of other thoracic artery to coronary artery	7926.00	surgery	y
Double anastom thoracic arteries to coronary arteries NEC	7926000	surgery	y
Double implant thoracic arteries into coronary arteries NEC	7926100	surgery	y
Single anastomosis of thoracic artery to coronary artery NEC	7926200	surgery	y
Single implantation thoracic artery into coronary artery NEC	7926300	surgery	y
Connection of other thoracic artery to coronary artery OS	7926y00	surgery	y
Connection of other thoracic artery to coronary artery NOS	7926z00	surgery	y
Transposition of coronary artery NEC	7927300	surgery	y
Exploration of coronary artery	7927400	surgery	y
Open angioplasty of coronary artery	7927500	surgery	y
Other specified other open operation on coronary artery	7927y00	surgery	y
Other open operation on coronary artery NOS	7927z00	surgery	y
Transluminal balloon angioplasty of coronary artery	7928.00	surgery	y
Percutaneous balloon coronary angioplasty	7928.11	surgery	y
Percut transluminal balloon angioplasty one coronary artery	7928000	surgery	y
Percut translum balloon angioplasty mult coronary arteries	7928100	surgery	y
Percut translum balloon angioplasty bypass graft coronary a	7928200	surgery	y
Percut translum cutting balloon angioplasty	7928300	surgery	y

description (CVD)	MedCode	CVDType	Incident
coronary artery			
Transluminal balloon angioplasty of coronary artery OS	7928y00	surgery	y
Transluminal balloon angioplasty of coronary artery NOS	7928z00	surgery	y
Other therapeutic transluminal operations on coronary artery	7929.00	surgery	y
Percutaneous transluminal laser coronary angioplasty	7929000	surgery	y
Percut transluminal coronary thrombolysis with streptokinase	7929100	surgery	y
Percut translum coronary thrombolytic therapy-streptokinase	7929111	surgery	y
Percut translum inject therap subst to coronary artery NEC	7929200	surgery	y
Rotary blade coronary angioplasty	7929300	surgery	y
Insertion of coronary artery stent	7929400	surgery	y
Insertion of drug-eluting coronary artery stent	7929500	surgery	y
Percutaneous transluminal atherectomy of coronary artery	7929600	surgery	y
Other therapeutic transluminal op on coronary artery OS	7929y00	surgery	y
Other therapeutic transluminal op on coronary artery NOS	7929z00	surgery	y
Diagnostic transluminal operations on coronary artery	792A.00	surgery	y
Diagnostic transluminal operation on coronary artery OS	792Ay00	surgery	y
Diagnostic transluminal operation on coronary artery NOS	792Az00	surgery	y
Repair of coronary artery NEC	792B.00	surgery	y
Endarterectomy of coronary artery NEC	792B000	surgery	y
Other specified repair of coronary artery	792By00	surgery	y
Repair of coronary artery NOS	792Bz00	surgery	y
Other replacement of coronary artery	792C.00	surgery	y
Replacement of coronary arteries using multiple methods	792C000	surgery	y
Other specified replacement of coronary artery	792Cy00	surgery	y
Replacement of coronary artery NOS	792Cz00	surgery	y
Other bypass of coronary artery	792D.00	surgery	y
Other specified other bypass of coronary artery	792Dy00	surgery	y
Other bypass of coronary artery NOS	792Dz00	surgery	y
Other specified operations on coronary artery	792y.00	surgery	y
Coronary artery operations NOS	792z.00	surgery	y
Perc translumin balloon angioplasty stenting coronary artery	793G.00	surgery	y
Perc translum ball angio insert 1-2 drug elut stents cor art	793G000	surgery	y
Perc tran ball angio ins 3 or more drug elut stents cor art	793G100	surgery	y
Perc translum balloon angioplasty insert 1-2 stents cor art	793G200	surgery	y
Percutaneous cor balloon angiop 3 more stents cor art NEC	793G300	surgery	y
OS perc translumina balloon angioplast stenting coronary art	793Gy00	surgery	y
Perc translum balloon angioplasty stenting coronary art NOS	793Gz00	surgery	y
Transluminal operations on cardiac conduit	793H.00	surgery	y
Percutaneous transluminal balloon dilation cardiac conduit	793H000	surgery	y
Rotary blade angioplasty	7A54500	surgery	y
Peroperative angioplasty	7A6G100	surgery	y
Prosthetic graft patch angioplasty	7A6H300	surgery	y

description (CVD)	MedCode	CVDType	Incident
Percutaneous transluminal angioplasty of vascular graft	7A6H400	surgery	y
Delivery of rehabilitation for acute cardiac disorders	7P24000	CVD unspecified	n
Delivery of rehabilitation for stroke	7P24200	ischaemic/unspecified stroke	n
Transient ischaemic attack clinical management plan	8CRB.00	TIA	y
Admit ischaemic heart disease emergency	8H2V.00	CHD unspecified	y
Stroke / transient ischaemic attack referral	8HBJ.00	ischaemic/unspecified stroke	y
Ref to multidisciplinary stroke function improvement service	8HHM.00	ischaemic/unspecified stroke	n
Referral to stroke clinic	8HTQ.00	ischaemic/unspecified stroke	n
Seen in stroke clinic	9N0p.00	ischaemic/unspecified stroke	n
DNA - Did not attend stroke clinic	9N4X.00	ischaemic/unspecified stroke	n
Amaurosis fugax	F423600	ischaemic/unspecified stroke	y
Ischaemic heart disease	G3...00	CHD unspecified	y
Arteriosclerotic heart disease	G3...11	CHD unspecified	y
Atherosclerotic heart disease	G3...12	CHD unspecified	y
IHD - Ischaemic heart disease	G3...13	CHD unspecified	y
Acute myocardial infarction	G30..00	MI	y
Attack - heart	G30..11	MI	y
Coronary thrombosis	G30..12	MI	y
Cardiac rupture following myocardial infarction (MI)	G30..13	MI	y
Heart attack	G30..14	MI	y
MI - acute myocardial infarction	G30..15	MI	y
Thrombosis - coronary	G30..16	MI	y
Silent myocardial infarction	G30..17	MI	y
Acute anterolateral infarction	G300.00	MI	y
Other specified anterior myocardial infarction	G301.00	MI	y
Acute anteroapical infarction	G301000	MI	y
Acute anteroseptal infarction	G301100	MI	y
Anterior myocardial infarction NOS	G301z00	MI	y
Acute inferolateral infarction	G302.00	MI	y
Acute inferoposterior infarction	G303.00	MI	y
Posterior myocardial infarction NOS	G304.00	MI	y
Lateral myocardial infarction NOS	G305.00	MI	y
True posterior myocardial infarction	G306.00	MI	y
Acute subendocardial infarction	G307.00	MI	y
Acute non-Q wave infarction	G307000	MI	y
Acute non-ST segment elevation myocardial infarction	G307100	MI	y
Inferior myocardial infarction NOS	G308.00	MI	y
Acute Q-wave infarct	G309.00	MI	y
Mural thrombosis	G30A.00	MI	y
Acute posterolateral myocardial infarction	G30B.00	MI	y
Acute transmural myocardial infarction of unspecif site	G30X.00	MI	y
Acute ST segment elevation myocardial infarction	G30X000	MI	y
Other acute myocardial infarction	G30y.00	MI	y
Acute atrial infarction	G30y000	MI	y
Acute papillary muscle infarction	G30y100	MI	y

description (CVD)	MedCode	CVD Type	Incident
Acute septal infarction	G30y200	MI	y
Other acute myocardial infarction NOS	G30yz00	MI	y
Acute myocardial infarction NOS	G30z.00	MI	y
Other acute and subacute ischaemic heart disease	G31..00	MI	y
Postmyocardial infarction syndrome	G310.00	MI	y
Dressler's syndrome	G310.11	MI	y
Preinfarction syndrome	G311.00	unstable angina/ACS	y
Crescendo angina	G311.11	unstable angina/ACS	y
Impending infarction	G311.12	unstable angina/ACS	y
Unstable angina	G311.13	unstable angina/ACS	y
Angina at rest	G311.14	unstable angina/ACS	y
Myocardial infarction aborted	G311000	CHD unspecified	y
MI - myocardial infarction aborted	G311011	CHD unspecified	y
Unstable angina	G311100	unstable angina/ACS	y
Angina at rest	G311200	unstable angina/ACS	y
Refractory angina	G311300	unstable angina/ACS	y
Worsening angina	G311400	unstable angina/ACS	y
Acute coronary syndrome	G311500	unstable angina/ACS	y
Preinfarction syndrome NOS	G311z00	unstable angina/ACS	y
Coronary thrombosis not resulting in myocardial infarction	G312.00	unstable angina/ACS	y
Other acute and subacute ischaemic heart disease	G31y.00	unstable angina/ACS	y
Acute coronary insufficiency	G31y000	unstable angina/ACS	y
Microinfarction of heart	G31y100	unstable angina/ACS	y
Subendocardial ischaemia	G31y200	unstable angina/ACS	y
Transient myocardial ischaemia	G31y300	unstable angina/ACS	y
Other acute and subacute ischaemic heart disease NOS	G31yz00	unstable angina/ACS	y
Old myocardial infarction	G32..00	MI	n
Healed myocardial infarction	G32..11	MI	n
Personal history of myocardial infarction	G32..12	MI	n
Angina pectoris	G33..00	angina	y
Angina decubitus	G330.00	angina	y
Nocturnal angina	G330000	angina	y
Angina decubitus NOS	G330z00	angina	y
Prinzmetal's angina	G331.00	angina	y
Variant angina pectoris	G331.11	angina	y
Coronary artery spasm	G332.00	unstable angina/ACS	y
Angina pectoris NOS	G33z.00	angina	y
Status anginosus	G33z000	angina	y
Stenocardia	G33z100	unstable angina/ACS	y
Syncope anginosa	G33z200	angina	y
Angina on effort	G33z300	angina	y
Ischaemic chest pain	G33z400	CHD unspecified	y
Post infarct angina	G33z500	angina	y
New onset angina	G33z600	angina	y
Stable angina	G33z700	angina	y
Angina pectoris NOS	G33zz00	angina	y
Other chronic ischaemic heart disease	G34..00	CHD unspecified	y
Coronary atherosclerosis	G340.00	CHD unspecified	y
Triple vessel disease of the heart	G340.11	CHD unspecified	y

description (CVD)	MedCode	CVDType	Incident
Coronary artery disease	G340.12	CHD unspecified	y
Single coronary vessel disease	G340000	CHD unspecified	y
Double coronary vessel disease	G340100	CHD unspecified	y
Atherosclerotic cardiovascular disease	G342.00	CHD unspecified	y
Ischaemic cardiomyopathy	G343.00	CHD unspecified	y
Silent myocardial ischaemia	G344.00	MI	y
Other specified chronic ischaemic heart disease	G34y.00	angina	y
Chronic coronary insufficiency	G34y000	angina	y
Chronic myocardial ischaemia	G34y100	angina	y
Other specified chronic ischaemic heart disease NOS	G34yz00	angina	y
Other chronic ischaemic heart disease NOS	G34z.00	angina	y
Asymptomatic coronary heart disease	G34z000	CHD unspecified	y
Subsequent myocardial infarction	G35..00	MI	y
Subsequent myocardial infarction of anterior wall	G350.00	MI	y
Subsequent myocardial infarction of inferior wall	G351.00	MI	y
Subsequent myocardial infarction of other sites	G353.00	MI	y
Subsequent myocardial infarction of unspecified site	G35X.00	MI	y
Certain current complication follow acute myocardial infarct	G36..00	MI	y
Haemopericardium/current comp folow acut myocard infarct	G360.00	MI	y
Atrial septal defect/curr comp folow acut myocardal infarct	G361.00	MI	y
Ventric septal defect/curr comp fol acut myocardal infarctn	G362.00	MI	y
Ruptur cardiac wall w'out haemopericard/cur comp fol ac MI	G363.00	MI	y
Ruptur chordae tendinae/curr comp fol acute myocard infarct	G364.00	MI	y
Rupture papillary muscle/curr comp fol acute myocard infarct	G365.00	MI	y
Thrombosis atrium,auric append&vent/curr comp foll acute MI	G366.00	MI	y
Postoperative myocardial infarction	G38..00	MI	y
Postoperative transmural myocardial infarction anterior wall	G380.00	MI	y
Postoperative transmural myocardial infarction inferior wall	G381.00	MI	y
Postoperative transmural myocardial infarction other sites	G382.00	MI	y
Postoperative transmural myocardial infarction unspec site	G383.00	MI	y
Postoperative subendocardial myocardial infarction	G384.00	MI	y
Postoperative myocardial infarction, unspecified	G38z.00	MI	y
Other specified ischaemic heart disease	G3y..00	CHD unspecified	y
Ischaemic heart disease NOS	G3z..00	CHD unspecified	y
Post infarction pericarditis	G501.00	MI	y
Cerebrovascular disease	G6...00	ischaemic/unspecified stroke	y
Intracerebral haemorrhage	G61..00	haemorrhagic stroke	y
CVA - cerebrovascular accid due to intracerebral haemorrhage	G61..11	haemorrhagic stroke	y
Stroke due to intracerebral haemorrhage	G61..12	haemorrhagic stroke	y
Cortical haemorrhage	G610.00	haemorrhagic stroke	y
Internal capsule haemorrhage	G611.00	haemorrhagic stroke	y
Basal nucleus haemorrhage	G612.00	haemorrhagic stroke	y
Cerebellar haemorrhage	G613.00	haemorrhagic stroke	y

description (CVD)	MedCode	CVDType	Incident
Pontine haemorrhage	G614.00	haemorrhagic stroke	y
Bulbar haemorrhage	G615.00	haemorrhagic stroke	y
External capsule haemorrhage	G616.00	haemorrhagic stroke	y
Intracerebral haemorrhage, intraventricular	G617.00	haemorrhagic stroke	y
Intracerebral haemorrhage, multiple localized	G618.00	haemorrhagic stroke	y
Intracerebral haemorrhage in hemisphere, unspecified	G61X.00	haemorrhagic stroke	y
Left sided intracerebral haemorrhage, unspecified	G61X000	haemorrhagic stroke	y
Right sided intracerebral haemorrhage, unspecified	G61X100	haemorrhagic stroke	y
Intracerebral haemorrhage NOS	G61z.00	haemorrhagic stroke	y
Precerebral arterial occlusion	G63..00	ischaemic/unspecified stroke	y
Infarction - precerebral	G63..11	ischaemic/unspecified stroke	y
Stenosis of precerebral arteries	G63..12	CVD unspecified	y
Basilar artery occlusion	G630.00	ischaemic/unspecified stroke	y
Carotid artery occlusion	G631.00	ischaemic/unspecified stroke	y
Stenosis, carotid artery	G631.11	CVD unspecified	y
Thrombosis, carotid artery	G631.12	ischaemic/unspecified stroke	y
Vertebral artery occlusion	G632.00	ischaemic/unspecified stroke	y
Multiple and bilateral precerebral arterial occlusion	G633.00	ischaemic/unspecified stroke	y
Other precerebral artery occlusion	G63y.00	ischaemic/unspecified stroke	y
Cerebral infarct due to thrombosis of precerebral arteries	G63y000	ischaemic/unspecified stroke	y
Cerebral infarction due to embolism of precerebral arteries	G63y100	ischaemic/unspecified stroke	y
Precerebral artery occlusion NOS	G63z.00	ischaemic/unspecified stroke	y
Cerebral arterial occlusion	G64..00	ischaemic/unspecified stroke	y
CVA - cerebral artery occlusion	G64..11	ischaemic/unspecified stroke	y
Infarction - cerebral	G64..12	ischaemic/unspecified stroke	y
Stroke due to cerebral arterial occlusion	G64..13	ischaemic/unspecified stroke	y
Cerebral thrombosis	G640.00	ischaemic/unspecified stroke	y
Cerebral infarction due to thrombosis of cerebral arteries	G640000	ischaemic/unspecified stroke	y
Cerebral embolism	G641.00	ischaemic/unspecified stroke	y
Cerebral embolus	G641.11	ischaemic/unspecified stroke	y
Cerebral infarction due to embolism of cerebral arteries	G641000	ischaemic/unspecified stroke	y
Cerebral infarction NOS	G64z.00	ischaemic/unspecified stroke	y
Brainstem infarction NOS	G64z.11	ischaemic/unspecified stroke	y
Cerebellar infarction	G64z.12	ischaemic/unspecified stroke	y
Brainstem infarction	G64z000	ischaemic/unspecified stroke	y
Wallenberg syndrome	G64z100	ischaemic/unspecified stroke	y
Lateral medullary syndrome	G64z111	ischaemic/unspecified stroke	y
Left sided cerebral infarction	G64z200	ischaemic/unspecified stroke	y
Right sided cerebral infarction	G64z300	ischaemic/unspecified	y

description (CVD)	MedCode	CVDType	Incident
		stroke	
Infarction of basal ganglia	G64z400	ischaemic/unspecified stroke	y
Transient cerebral ischaemia	G65..00	TIA	y
Transient ischaemic attack	G65..12	TIA	y
Vertebro-basilar insufficiency	G65..13	CVD unspecified	y
Basilar artery syndrome	G650.00	CVD unspecified	y
Insufficiency - basilar artery	G650.11	CVD unspecified	y
Vertebral artery syndrome	G651.00	ischaemic/unspecified stroke	y
Vertebro-basilar artery syndrome	G651000	CVD unspecified	y
Subclavian steal syndrome	G652.00	ischaemic/unspecified stroke	y
Carotid artery syndrome hemispheric	G653.00	ischaemic/unspecified stroke	y
Multiple and bilateral precerebral artery syndromes	G654.00	ischaemic/unspecified stroke	y
Vertebrobasilar insufficiency	G656.00	CVD unspecified	y
Other transient cerebral ischaemia	G65y.00	TIA	y
Transient cerebral ischaemia NOS	G65z.00	TIA	y
Impending cerebral ischaemia	G65z000	CVD unspecified	y
Intermittent cerebral ischaemia	G65z100	TIA	y
Transient cerebral ischaemia NOS	G65zz00	TIA	y
Stroke and cerebrovascular accident unspecified	G66..00	ischaemic/unspecified stroke	y
CVA unspecified	G66..11	ischaemic/unspecified stroke	y
Stroke unspecified	G66..12	ischaemic/unspecified stroke	y
CVA - Cerebrovascular accident unspecified	G66..13	ischaemic/unspecified stroke	y
Middle cerebral artery syndrome	G660.00	ischaemic/unspecified stroke	y
Anterior cerebral artery syndrome	G661.00	CVD unspecified	y
Posterior cerebral artery syndrome	G662.00	CVD unspecified	y
Brain stem stroke syndrome	G663.00	ischaemic/unspecified stroke	y
Cerebellar stroke syndrome	G664.00	ischaemic/unspecified stroke	y
Pure motor lacunar syndrome	G665.00	ischaemic/unspecified stroke	y
Pure sensory lacunar syndrome	G666.00	ischaemic/unspecified stroke	y
Left sided CVA	G667.00	ischaemic/unspecified stroke	y
Right sided CVA	G668.00	ischaemic/unspecified stroke	y
Other cerebrovascular disease	G67..00	CVD unspecified	y
Cerebral atherosclerosis	G670.00	CVD unspecified	y
Precerebral atherosclerosis	G670.11	CVD unspecified	y
Generalised ischaemic cerebrovascular disease NOS	G671.00	CVD unspecified	y
Acute cerebrovascular insufficiency NOS	G671000	CVD unspecified	y
Chronic cerebral ischaemia	G671100	CVD unspecified	y
Generalised ischaemic cerebrovascular disease NOS	G671z00	CVD unspecified	y
Cereb infarct due cerebral venous thrombosis, nonpyogenic	G676000	ischaemic/unspecified stroke	y
Occlusion/stenosis cerebral arts not result cerebral infarct	G677.00	CVD unspecified	y
Occlusion and stenosis of middle cerebral artery	G677000	ischaemic/unspecified stroke	y
Occlusion and stenosis of anterior cerebral artery	G677100	ischaemic/unspecified stroke	y

description (CVD)	MedCode	CVDType	Incident
Occlusion and stenosis of posterior cerebral artery	G677200	ischaemic/unspecified stroke	y
Occlusion and stenosis of cerebellar arteries	G677300	ischaemic/unspecified stroke	y
Occlusion+stenosis of multiple and bilat cerebral arteries	G677400	ischaemic/unspecified stroke	y
Small vessel cerebrovascular disease	G679.00	CVD unspecified	y
Other cerebrovascular disease OS	G67y.00	CVD unspecified	y
Other cerebrovascular disease NOS	G67z.00	CVD unspecified	y
Late effects of cerebrovascular disease	G68..00	CVD unspecified	y
Sequelae of intracerebral haemorrhage	G681.00	haemorrhagic stroke	n
Sequelae of other nontraumatic intracranial haemorrhage	G682.00	ischaemic/unspecified stroke	n
Sequelae of cerebral infarction	G683.00	ischaemic/unspecified stroke	n
Sequelae/other + unspecified cerebrovascular diseases	G68W.00	ischaemic/unspecified stroke	n
Sequelae of stroke,not specfd as h'morrhage or infarction	G68X.00	CVD unspecified	n
Cereb infarct due unsp occlus/stenos precerebr arteries	G6W..00	ischaemic/unspecified stroke	y
Cerebrl infarctn due/unspcf occlusn or sten/cerebrl artrs	G6X..00	CVD unspecified	y
Other specified cerebrovascular disease	G6y..00	CVD unspecified	y
Cerebrovascular disease NOS	G6z..00	CVD unspecified	y
[X]Ischaemic heart diseases	Gyu3.00	CHD unspecified	y
[X]Other forms of angina pectoris	Gyu3000	angina	y
[X]Other current complicatns following acute myocard infarct	Gyu3100	MI	y
[X]Other forms of acute ischaemic heart disease	Gyu3200	CHD unspecified	y
[X]Other forms of chronic ischaemic heart disease	Gyu3300	angina	y
[X]Acute transmural myocardial infarction of unspecif site	Gyu3400	MI	y
[X]Subsequent myocardial infarction of other sites	Gyu3500	MI	y
[X]Subsequent myocardial infarction of unspecified site	Gyu3600	MI	y
[X]Cerebrovascular diseases	Gyu6.00	CVD unspecified	y
[X]Other intracerebral haemorrhage	Gyu6200	haemorrhagic stroke	y
[X]Cerebrl infarctn due/unspcf occlusn or sten/cerebrl artrs	Gyu6300	ischaemic/unspecified stroke	y
[X]Other cerebral infarction	Gyu6400	ischaemic/unspecified stroke	y
[X]Occlusion and stenosis of other precerebral arteries	Gyu6500	ischaemic/unspecified stroke	y
[X]Occlusion and stenosis of other cerebral arteries	Gyu6600	ischaemic/unspecified stroke	y
[X]Other specified cerebrovascular diseases	Gyu6700	CVD unspecified	y
[X]Other cerebrovascular disorders in diseases CE	Gyu6A00	CVD unspecified	y
[X]Sequelae of other nontraumatic intracranial haemorrhage	Gyu6B00	haemorrhagic stroke	n
[X]Sequelae of stroke,not specfd as h'morrhage or infarction	Gyu6C00	ischaemic/unspecified stroke	n
[X]Sequelae/other + unspecified cerebrovascular diseases	Gyu6D00	ischaemic/unspecified stroke	n
[X]Intracerebral haemorrhage in hemisphere, unspecified	Gyu6F00	haemorrhagic stroke	y
[X]Cereb infarct due unsp occlus/stenos precerebr arteries	Gyu6G00	ischaemic/unspecified stroke	y
Coronary artery bypass graft occlusion	SP07600	surgery	y
Discharge from stroke serv	ZLEP.00	ischaemic/unspecified stroke	n
[V]Personal history of stroke	ZV12511	ischaemic/unspecified stroke	n

description (CVD)	MedCode	CVDType	Incident
[V]Presence of aortocoronary bypass graft	ZV45700	surgery	n
[V]Presence of coronary angioplasty implant and graft	ZV45800	surgery	n
[V]Presence of coronary artery bypass graft	ZV45K00	surgery	n
[V]Presence of coronary artery bypass graft - CABG	ZV45K11	surgery	n
[V]Status following coronary angioplasty NOS	ZV45L00	surgery	n

20.3 Statins

Statin generic name	Drug Code
FLUVASTATIN 24 hr mr tabs 80mg	82002998
FLUVASTATIN 24 hr mr tabs 80mg	82073998
FLUVASTATIN 24 hr mr tabs 80mg	82907998
SIMVASTATIN tabs 80mg	83030998
SIMVASTATIN sf oral susp 40mg/5ml	83099998
PRAVASTATIN oral liq	83899998
SIMVASTATIN (IPU) tabs 5mg	85181998
SIMVASTATIN oral liq	85440998
SIMVASTATIN sf oral susp 20mg/5ml	86020998
ROSUVASTATIN tabs 5mg	86467998
ROSUVASTATIN tabs 5mg	86468998
SIMVASTATIN + EZETIMIBE tabs 80mg + 10mg	86787998
SIMVASTATIN + EZETIMIBE tabs 40mg + 10mg	86788998
SIMVASTATIN + EZETIMIBE tabs 20mg + 10mg	86789998
EZETIMIBE + SIMVASTATIN tabs 10mg + 80mg	86791998
EZETIMIBE + SIMVASTATIN tabs 10mg + 80mg	86794998
EZETIMIBE + SIMVASTATIN tabs 10mg + 40mg	86795998
EZETIMIBE + SIMVASTATIN tabs 10mg + 40mg	86796998
EZETIMIBE + SIMVASTATIN tabs 10mg + 20mg	86797998
EZETIMIBE + SIMVASTATIN tabs 10mg + 20mg	86798998
SIMVASTATIN tabs 10mg	87373998
SIMVASTATIN tabs 40mg	87416998
SIMVASTATIN tabs 20mg	87417998
SIMVASTATIN tabs 10mg	87418998
SIMVASTATIN tabs 40mg	87916998
SIMVASTATIN tabs 20mg	87917998
SIMVASTATIN tabs 10mg	87918998
ROSUVASTATIN tabs 10mg	88534998
CERIVASTATIN tabs 300micrograms	89153996
CERIVASTATIN tabs 200micrograms	89153997
CERIVASTATIN tabs 100micrograms	89153998
CERIVASTATIN tabs 300micrograms	89154996
CERIVASTATIN tabs 200micrograms	89154997
CERIVASTATIN tabs 100micrograms	89154998
ATORVASTATIN tabs 40mg	89306996
ATORVASTATIN tabs 20mg	89306997
ATORVASTATIN tabs 10mg	89306998
ATORVASTATIN tabs 40mg	89311996
ATORVASTATIN tabs 20mg	89311997
ATORVASTATIN tabs 10mg	89311998

Statin generic name	Drug Code
ATORVASTATIN tabs 80mg	90309998
ATORVASTATIN tabs 80mg	90310998
ROSUVASTATIN tabs 20mg	90973998
FLUVASTATIN 24 hr mr tabs 80mg	91194998
SIMVASTATIN sf oral susp 40mg/5ml	92110990
SIMVASTATIN sf oral susp 20mg/5ml	92154990
FLUVASTATIN caps 40mg	92206990
FLUVASTATIN caps 20mg	92207990
SIMVASTATIN tabs 80mg	92220998
FLUVASTATIN caps 40mg	92274990
FLUVASTATIN caps 20mg	92275990
SIMVASTATIN tabs 80mg	92278990
ROSUVASTATIN tabs 20mg	92408998
ROSUVASTATIN tabs 10mg	92409998
ROSUVASTATIN tabs 40mg	92410998
CERIVASTATIN tabs 800micrograms	92447997
CERIVASTATIN tabs 400micrograms	92447998
CERIVASTATIN tabs 800micrograms	92448997
CERIVASTATIN tabs 400micrograms	92448998
SIMVASTATIN tabs 80mg	92471998
SIMVASTATIN tabs 80mg	92504990
ROSUVASTATIN tabs 40mg	92539998
FLUVASTATIN 24 hr mr tabs 80mg	92650990
FLUVASTATIN caps 40mg	92651990
FLUVASTATIN caps 20mg	92652990
FLUVASTATIN caps 40mg	92659990
FLUVASTATIN caps 20mg	92660990
FLUVASTATIN caps 40mg	92664990
FLUVASTATIN caps 20mg	92665990
FLUVASTATIN 24 hr mr tabs 80mg	92804996
FLUVASTATIN caps 40mg	92804997
FLUVASTATIN caps 20mg	92804998
FLUVASTATIN caps 40mg	92805997
FLUVASTATIN caps 20mg	92805998
SIMVASTATIN tabs 40mg	93230990
SIMVASTATIN tabs 20mg	93231990
SIMVASTATIN tabs 10mg	93232990
PRAVASTATIN tabs 40mg	93243996
PRAVASTATIN tabs 20mg	93243997
PRAVASTATIN tabs 10mg	93243998
PRAVASTATIN tabs 40mg	93244996
PRAVASTATIN tabs 20mg	93244997
PRAVASTATIN tabs 10mg	93244998
SIMVASTATIN sf oral susp 20mg/5ml	93504990
SIMVASTATIN tabs 40mg	93619996
SIMVASTATIN tabs 20mg	93619997
SIMVASTATIN tabs 10mg	93619998
SIMVASTATIN tabs 40mg	93620996
SIMVASTATIN tabs 20mg	93620997
SIMVASTATIN tabs 10mg	93620998
SIMVASTATIN tabs 80mg	93870990

Statin generic name	Drug Code
SIMVASTATIN tabs 40mg	93871990
SIMVASTATIN tabs 20mg	93872990
SIMVASTATIN tabs 10mg	93873990
SIMVASTATIN tabs 80mg	94196990
SIMVASTATIN tabs 40mg	94197990
SIMVASTATIN tabs 20mg	94198990
SIMVASTATIN tabs 10mg	94199990
PRAVASTATIN tabs 40mg	94321990
PRAVASTATIN tabs 20mg	94322990
PRAVASTATIN tabs 10mg	94323990
PRAVASTATIN tabs 40mg	94324990
PRAVASTATIN tabs 20mg	94325990
PRAVASTATIN tabs 10mg	94326990
PRAVASTATIN tabs 40mg	94327990
PRAVASTATIN tabs 20mg	94328990
PRAVASTATIN tabs 10mg	94329990
PRAVASTATIN tabs 40mg	94363990
PRAVASTATIN tabs 20mg	94364990
PRAVASTATIN tabs 10mg	94365990
PRAVASTATIN tabs 40mg	94392990
PRAVASTATIN tabs 20mg	94393990
PRAVASTATIN tabs 10mg	94394990
SIMVASTATIN tabs 40mg	94406990
SIMVASTATIN tabs 20mg	94407990
SIMVASTATIN tabs 10mg	94408990
PRAVASTATIN tabs 40mg	94702990
PRAVASTATIN tabs 20mg	94703990
PRAVASTATIN tabs 10mg	94704990
PRAVASTATIN tabs 40mg	94777990
PRAVASTATIN tabs 20mg	94778990
PRAVASTATIN tabs 10mg	94779990
PRAVASTATIN tabs 40mg	94781990
PRAVASTATIN tabs 20mg	94782990
PRAVASTATIN tabs 10mg	94783990
PRAVASTATIN tabs 40mg	94787990
PRAVASTATIN tabs 20mg	94788990
PRAVASTATIN tabs 10mg	94789990
PRAVASTATIN tabs 40mg	94794990
PRAVASTATIN tabs 20mg	94795990
PRAVASTATIN tabs 10mg	94796990
PRAVASTATIN tabs 40mg	94802990
PRAVASTATIN tabs 20mg	94803990
PRAVASTATIN tabs 10mg	94804990
PRAVASTATIN tabs 40mg	94805990
PRAVASTATIN tabs 20mg	94806990
PRAVASTATIN tabs 10mg	94807990
PRAVASTATIN tabs 40mg	94811990
PRAVASTATIN tabs 20mg	94812990
PRAVASTATIN tabs 10mg	94813990
PRAVASTATIN tabs 40mg	94829990
PRAVASTATIN tabs 20mg	94830990

Statin generic name	Drug Code
PRAVASTATIN tabs 10mg	94831990
PRAVASTATIN tabs 40mg	94849990
PRAVASTATIN tabs 20mg	94850990
PRAVASTATIN tabs 10mg	94851990
SIMVASTATIN tabs 40mg	94919990
SIMVASTATIN tabs 20mg	94920990
SIMVASTATIN tabs 10mg	94921990
SIMVASTATIN tabs 80mg	94927990
SIMVASTATIN tabs 80mg	95185990
SIMVASTATIN tabs 40mg	95277990
SIMVASTATIN tabs 20mg	95278990
SIMVASTATIN tabs 10mg	95279990
SIMVASTATIN tabs 40mg	95372990
SIMVASTATIN tabs 20mg	95373990
SIMVASTATIN tabs 10mg	95374990
SIMVASTATIN tabs 40mg	95405990
SIMVASTATIN tabs 20mg	95406990
SIMVASTATIN tabs 10mg	95408990
SIMVASTATIN tabs 40mg	95414990
SIMVASTATIN tabs 20mg	95415990
SIMVASTATIN tabs 10mg	95416990
SIMVASTATIN tabs 80mg	95442990
SIMVASTATIN tabs 40mg	95443990
SIMVASTATIN tabs 20mg	95444990
SIMVASTATIN tabs 10mg	95445990
SIMVASTATIN tabs 80mg	95448990
SIMVASTATIN tabs 40mg	95449990
SIMVASTATIN tabs 20mg	95450990
SIMVASTATIN tabs 10mg	95451990
SIMVASTATIN tabs 40mg	95471990
SIMVASTATIN tabs 20mg	95472990
SIMVASTATIN tabs 10mg	95473990
SIMVASTATIN tabs 40mg	95474990
SIMVASTATIN tabs 20mg	95475990
SIMVASTATIN tabs 10mg	95476990
SIMVASTATIN tabs 40mg	95478990
SIMVASTATIN tabs 20mg	95479990
SIMVASTATIN tabs 10mg	95480990
SIMVASTATIN tabs 40mg	95481990
SIMVASTATIN tabs 20mg	95482990
SIMVASTATIN tabs 10mg	95483990
SIMVASTATIN tabs 40mg	95486990
SIMVASTATIN tabs 20mg	95487990
SIMVASTATIN tabs 10mg	95488990
SIMVASTATIN tabs 40mg	95493990
SIMVASTATIN tabs 20mg	95494990
SIMVASTATIN tabs 10mg	95495990
SIMVASTATIN tabs 80mg	95500990
SIMVASTATIN tabs 40mg	95501990
SIMVASTATIN tabs 20mg	95502990
SIMVASTATIN tabs 10mg	95508990

Statin generic name	Drug Code
SIMVASTATIN tabs 40mg	95549990
SIMVASTATIN tabs 20mg	95550990
SIMVASTATIN tabs 10mg	95551990

20.4 Non-statin lipid modifying drugs

Non-statin lipid modifying drug generic name	Drug Code
NICOTINIC ACID 1000mg m/r tab	87850998
Nicotinic acid 1g modified-release tablets	87853998
Ciprofibrate 100mg tablets	97723998
GEMFIBROZIL 600mg tablets	97247997
Colestyramine sugar free pdr	91316998
CLOFIBRATE 500mg capsules	98455998
Fenofibrate 200mg capsules	94188997
ISPAG HSK 3.5g ornge s/f gran	89617998
Colestyramine 4g oral powder sachets sugar free	96134990
FENOFIBRATE 200mg capsules	90649998
Colestipol with aspartame granules	94605998
Nicotinic acid 375mg + 500mg + 750mg Modified-release tablet	87849998
CIPROFIBRATE 100mg tablets	97433979
FENOFIBRATE 200mg capsules	94189997
FISH OIL(CONC) 1g capsules	97078998
Gemfibrozil 300mg capsules	96295998
Gemfibrozil 600mg tablets	97808989
BEZAFIBRATE 400mg m/r tablets	83187998
FENOFIBRATE 267mg capsules	88297996
Colestyramine with aspartame 4g sugar free powder	90653998
Bezafibrate 200mg tablets	96656990
Fenofibrate 100mg Capsule	94188998
Colestyramine 4g oral powder sachets	96678998
Probucol 250mg tablet	95401998
Colesevelam 625mg tablets	84268998
Bezafibrate 200mg tablets	96685989
BEZAFIBRATE 400mg m/r tablets	89401998
Clofibrate 500mg capsules	96642998
FENOFIBRATE 200mg capsules	88297997
Acipimox 250mg capsules	94883998
BEZAFIBRATE 400mg m/r tablets	89089998
CHOLESTYRAMINE POW	94827992
NICOFURANOSE 250mg e/c tabs	98108998
Colestyramine 4g oral powder sachets sugar free	93541998
NICOTINIC ACID 500 MG TAB	97800992
ACIPIMOX 250mg capsules	94882998
COLESTY+ASPART 4g/sach s/f pdr	93542998
Colestyramine 4g oral powder sachets sugar free	95847990
Nicotinic acid 50mg tablets	99725990
Ezetimibe 10mg tablets	92292998
Eicosapentaenoic acid 460mg / Docosahexaenoic acid 380mg capsules	89800998
FISH OIL(CONC) oral liquid	97078997
Fenofibrate micronised 200mg capsules	96021990

Non-statin lipid modifying drug generic name	Drug Code
BEZAFIBRATE 400mg m/r tablets	97895997
COLESEVELAM 625mg tablets	84267998
BEZAFIBRATE 400mg m/r tablets	95805998
COLESTIPOL HCl GRA	93851992
Fenofibrate micronised 160mg tablets	92460998
COLESTIPOL orang 5g/sach grans	87760998
Bezafibrate 200mg tablets	95952998
Nicotinic acid 50mg tablets	98066997
BEZAFIBRATE 400mg m/r tablets	99014998
NICOTINIC ACID starter pack	87848998
Fenofibrate micronised 200mg capsules	92549990
Eicosapentaenoic acid 170mg/g / Docosahexaenoic acid 115mg/g oral liquid	94925997
Gemfibrozil 600mg tablets	96295997
Bezafibrate 400mg modified-release tablets	95952997
Nicotinic acid 100mg Tablet	98066996
BEZAFIBRATE 400mg m/r tablets	87025998
Fenofibrate micronised 267mg capsules	88298997
Colestyramine 4g oral powder sachets sugar free	97655990
GEMFIBROZIL 300mg capsules	97247998
FISH OIL(CONC) oral emulsion	97078996
BEZAFIBRATE 200mg tablets	83188998
COLESTIPOL granules 5g sachet	94661998
Bezafibrate 400mg modified-release tablets	96685990
Nicotinic acid 750mg modified-release tablets	87854998
CHOLESTYRAMINE 325 MG CAP	94112992
Fenofibrate micronised 200mg capsules	88298996
NICOTINIC ACID 750mg m/r tabs	87851998
Colestipol 5g granules sachets sugar free	94662998
CIPROFIBRATE 100mg tablets	97751998
NICOTINIC ACID 500mg m/r tabs	87852998
EZETIMIBE 10mg tablets	92293998
COLESTYRAMINE powder 4g/sachet	99197998
NICOTINC/LAROP 1g/20mg m/r tab	82655998
Bezafibrate 200mg tablets	93838990
Eicosapentaenoic acid 170mg / Docosahexaenoic acid 115mg capsules	94925998
Fenofibrate micronised 67mg capsules	88298998
FENOFIBRATE 160mg m/r tablets	94799998
Nicofuranose 250mg Tablet	95728998
HEXOPAL 200 MG TAB	95098992
Nicotinic acid 25mg Tablet	98066998
FENOFIBRATE 67mg capsules	88297998
Nicotinic acid 500mg modified-release tablets	87855998
FENOFIBRATE 100mg capsules	94189998
COLESTIPOL orang 5g/sach grans	94661997
Bezafibrate 400mg modified-release tablets	97595979
Nicotinic acid 1g / Laropiprant 20mg modified-release tablets	83594998
BEZAFIBRATE 200mg tablets	97895998
PROBUCOL 250mg tablets	99456998
Eicosapentaenoic acid 460mg / Docosahexaenoic acid 380mg capsules	92329998

20.5 Diabetes

Diabetes description	Med Code	Incident
Diabetic lipid lowering diet	13AB.00	0
Diabetic weight reducing diet	13AC.00	0
Diabetic diet	13B1.00	0
Diabetic association member	13Y1.00	0
H/O: diabetes mellitus	1434.00	0
H/O: Admission in last year for diabetes foot problem	14F4.00	0
Retinal abnormality - diabetes related	2BBF.00	0
O/E - diabetic maculopathy present both eyes	2BBL.00	0
O/E - diabetic maculopathy absent both eyes	2BBM.00	0
O/E - right eye background diabetic retinopathy	2BBP.00	0
O/E - left eye background diabetic retinopathy	2BBQ.00	0
O/E - right eye preproliferative diabetic retinopathy	2BBR.00	0
O/E - left eye preproliferative diabetic retinopathy	2BBS.00	0
O/E - right eye proliferative diabetic retinopathy	2BBT.00	0
O/E - left eye proliferative diabetic retinopathy	2BBV.00	0
O/E - right eye diabetic maculopathy	2BBW.00	0
O/E - left eye diabetic maculopathy	2BBX.00	0
O/E - right eye stable treated prolif diabetic retinopathy	2BBk.00	0
O/E - left eye stable treated prolif diabetic retinopathy	2BBl.00	0
O/E - sight threatening diabetic retinopathy	2BBo.00	0
Foot abnormality - diabetes related	2G51000	0
O/E - Right diabetic foot at risk	2G5A.00	0
O/E - Left diabetic foot at risk	2G5B.00	0
Foot abnormality - diabetes related	2G5C.00	0
O/E - Right diabetic foot at low risk	2G5E.00	0
O/E - Right diabetic foot at moderate risk	2G5F.00	0
O/E - Right diabetic foot at high risk	2G5G.00	0
O/E - Right diabetic foot - ulcerated	2G5H.00	0
O/E - Left diabetic foot at low risk	2G5I.00	0
O/E - Left diabetic foot at moderate risk	2G5J.00	0
O/E - Left diabetic foot at high risk	2G5K.00	0
O/E - Left diabetic foot - ulcerated	2G5L.00	0
O/E - right chronic diabetic foot ulcer	2G5V.00	0
O/E - left chronic diabetic foot ulcer	2G5W.00	0
Education score - diabetes	3881.00	0
Diabetes well being questionnaire	3882.00	0
Diabetes treatment satisfaction questionnaire	3883.00	0
Insulin tolerance test	4545.00	0
Diabetic monitoring	66A..00	0
Follow-up diabetic assessment	66A2.00	0
Has seen dietician - diabetes	66A8.00	0
Understands diet - diabetes	66A9.00	0
Injection sites - diabetic	66AA.11	0
Diabetic drug side effects	66AG.00	0
Diabetic treatment changed	66AH.00	0
Conversion to insulin	66AH000	0
Diabetic - good control	66AI.00	0
Diabetic - poor control	66AJ.00	0

Diabetes description	Med Code	Incident
Brittle diabetes	66AJ100	0
Diabetic - poor control NOS	66AJz00	0
Diabetic - cooperative patient	66AK.00	0
Diabetic-uncooperative patient	66AL.00	0
Diabetic - follow-up default	66AM.00	0
Date diabetic treatment start	66AN.00	0
Date diabetic treatment stopp.	66AO.00	0
Diabetes: practice programme	66AP.00	0
Diabetes management plan given	66AR.00	0
Diabetic annual review	66AS.00	0
Annual diabetic blood test	66AT.00	0
Diabetes care by hospital only	66AU.00	0
Diabetic foot risk assessment	66AW.00	0
Diabetes: shared care in pregnancy - diabetol and obstet	66AX.00	0
Diabetic diet - good compliance	66AY.00	0
Diabetic monitoring NOS	66AZ.00	0
Diabetic diet - poor compliance	66Aa.00	0
Diabetic foot examination	66Ab.00	0
Diabetic peripheral neuropathy screening	66Ac.00	0
Patient diabetes education review	66Af.00	0
Insulin needles changed daily	66Ag.00	0
Insulin needles changed for each injection	66Ah.00	0
Diabetic 6 month review	66Ai.00	0
Insulin needles changed less than once a day	66Aj.00	0
Diabetic monitoring - lower risk albumin excretion	66Ak.00	0
Diabetic monitoring - higher risk albumin excretion	66Al.00	0
Insulin dose changed	66Am.00	0
Diabetes type 1 review	66An.00	0
Diabetes type 2 review	66Ao.00	0
Diabetic pre-pregnancy counselling	6761.00	0
Health education - diabetes	679L.00	0
Patient offered diabetes structured education programme	679R.00	0
Diab mellit insulin-glucose infus acute myocardial infarct	889A.00	0
Diabetic crisis monitoring	8A12.00	0
Diabetic stabilisation	8A13.00	0
Diabetes medication review	8B3l.00	0
Patient on maximal tolerated therapy for diabetes	8BL2.00	0
Pt advised re diabetic diet	8CA4100	0
Diabetic leaflet given	8CE0.00	0
Transition of diabetes care options discussed	8CP2.00	0
Diabetes clinical management plan	8CR2.00	0
Diabetes care plan agreed	8CS0.00	0
Admit diabetic emergency	8H2J.00	0
Non-urgent diabetic admission	8H3O.00	0
Referral to diabetologist	8H4F.00	0
Refer, diabetic liaison nurse	8H7C.00	0
Referral to diabetes nurse	8H7f.00	0
Refer to diabetic foot screener	8H7r.00	0
Diabetic retinopathy 12 month review	8HBG.00	0
Diabetic retinopathy 6 month review	8HBH.00	0
Referral to diabetic register	8HHy.00	0

Diabetes description	Med Code	Incident
Diabetology D.V. requested	8HKE.00	0
Diabetology D.V. done	8HLE.00	0
Listed for Diabetology admissn	8HME.00	0
Referral to diabetes preconception counselling clinic	8HTe.00	0
Referral to multidisciplinary diabetic clinic	8HTi.00	0
Referral to diabetic eye clinic	8HTk.00	0
Private referral to diabetologist	8HVU.00	0
Discharged from care of diabetes specialist nurse	8Hg4.00	0
Referral to diabetes structured education programme	8Hj0.00	0
Family/carer referral to diabetes structured education prog	8Hj1.00	0
Referral for diabetic retinopathy screening	8Hl1.00	0
Referral to community diabetes specialist nurse	8Hl4.00	0
Diabetic foot examination declined	8I3W.00	0
Diabetic retinopathy screening refused	8I3X.00	0
Patient held diabetic record declined	8I57.00	0
Diabetic retinopathy screening not indicated	8I6F.00	0
Diabetic foot examination not indicated	8I6G.00	0
Patient held diabetic record issued	9360.00	0
Patient consent given for addition to diabetic register	93C4.00	0
Informed consent for diabetes national audit	9M00.00	0
Informed dissent for diabetes national audit	9M10.00	0
Seen in diabetic nurse consultant clinic	9N0m.00	0
Seen in community diabetes specialist clinic	9N0n.00	0
Seen in community diabetic specialist nurse clinic	9N0o.00	0
Seen in diabetic clinic	9N1Q.00	0
Seen in diabetic foot clinic	9N1i.00	0
Seen in multidisciplinary diabetic clinic	9N1o.00	0
Seen in diabetic eye clinic	9N1v.00	0
Seen by diabetologist	9N2d.00	0
Seen by diabetic liaison nurse	9N2i.00	0
DNA - Did not attend diabetic clinic	9N4I.00	0
Did not attend diabetic retinopathy clinic	9N4p.00	0
Attending diabetes clinic	9NM0.00	0
Under care of diabetologist	9NN8.00	0
Under care of diabetes specialist nurse	9NN9.00	0
Under care of diabetic foot screener	9NND.00	0
Diabetes monitoring admin.	9OL..00	0
Diabetes clinic administration	9OL..11	0
Attends diabetes monitoring	9OL1.00	0
Refuses diabetes monitoring	9OL2.00	0
Diabetes monitoring default	9OL3.00	0
Diabetes monitoring 1st letter	9OL4.00	0
Diabetes monitoring 2nd letter	9OL5.00	0
Diabetes monitoring 3rd letter	9OL6.00	0
Diabetes monitor.verbal invite	9OL7.00	0
Diabetes monitor.phone invite	9OL8.00	0
Diabetes monitor. check done	9OLA.00	0
Diabetes monitored	9OLA.11	0
Attended diabetes structured education programme	9OLB.00	0
Family/carer attended diabetes structured education prog	9OLC.00	0
Diabetic patient unsuitable for digital retinal photography	9OLD.00	0

Diabetes description	Med Code	Incident
Diabetes monitoring admin.NOS	9OLZ.00	0
Exception reporting: diabetes quality indicators	9h4..00	0
Excepted from diabetes qual indicators: Patient unsuitable	9h41.00	0
Excepted from diabetes quality indicators: Informed dissent	9h42.00	0
Diabetes mellitus with ketoacidosis	C101.00	0
Diabetes mellitus, juvenile type, with ketoacidosis	C101000	0
Diabetes mellitus, adult onset, with ketoacidosis	C101100	0
Other specified diabetes mellitus with ketoacidosis	C101y00	0
Diabetes mellitus NOS with ketoacidosis	C101z00	0
Diabetes mellitus with hyperosmolar coma	C102.00	0
Diabetes mellitus, juvenile type, with hyperosmolar coma	C102000	0
Diabetes mellitus, adult onset, with hyperosmolar coma	C102100	0
Diabetes mellitus NOS with hyperosmolar coma	C102z00	0
Diabetes mellitus with ketoacidotic coma	C103.00	0
Diabetes mellitus, juvenile type, with ketoacidotic coma	C103000	0
Diabetes mellitus, adult onset, with ketoacidotic coma	C103100	0
Other specified diabetes mellitus with coma	C103y00	0
Diabetes mellitus NOS with ketoacidotic coma	C103z00	0
Diabetes mellitus with renal manifestation	C104.00	0
Diabetic nephropathy	C104.11	0
Diabetes mellitus, juvenile type, with renal manifestation	C104000	0
Diabetes mellitus, adult onset, with renal manifestation	C104100	0
Other specified diabetes mellitus with renal complications	C104y00	0
Diabetes mellitis with nephropathy NOS	C104z00	0
Diabetes mellitus with ophthalmic manifestation	C105.00	0
Diabetes mellitus, juvenile type, + ophthalmic manifestation	C105000	0
Diabetes mellitus, adult onset, + ophthalmic manifestation	C105100	0
Other specified diabetes mellitus with ophthalmic complicatn	C105y00	0
Diabetes mellitus NOS with ophthalmic manifestation	C105z00	0
Diabetes mellitus with neurological manifestation	C106.00	0
Diabetic amyotrophy	C106.11	0
Diabetes mellitus with neuropathy	C106.12	0
Diabetes mellitus with polyneuropathy	C106.13	0
Diabetes mellitus, juvenile, + neurological manifestation	C106000	0
Diabetes mellitus, adult onset, + neurological manifestation	C106100	0
Other specified diabetes mellitus with neurological comps	C106y00	0
Diabetes mellitus NOS with neurological manifestation	C106z00	0
Diabetes mellitus with peripheral circulatory disorder	C107.00	0
Diabetes mellitus with gangrene	C107.11	0
Diabetes with gangrene	C107.12	0
Diabetes mellitus, juvenile +peripheral circulatory disorder	C107000	0
Diabetes mellitus, adult, + peripheral circulatory disorder	C107100	0
Diabetes mellitus, adult with gangrene	C107200	0
IDDM with peripheral circulatory disorder	C107300	0
NIDDM with peripheral circulatory disorder	C107400	0
Other specified diabetes mellitus with periph circ comps	C107y00	0
Diabetes mellitus NOS with peripheral circulatory disorder	C107z00	0
Insulin-dependent diabetes mellitus with renal complications	C108000	0
Type I diabetes mellitus with renal complications	C108011	0
Type 1 diabetes mellitus with renal complications	C108012	0
Insulin-dependent diabetes mellitus with ophthalmic comps	C108100	0

Diabetes description	Med Code	Incident
Type I diabetes mellitus with ophthalmic complications	C108111	0
Type 1 diabetes mellitus with ophthalmic complications	C108112	0
Insulin-dependent diabetes mellitus with neurological comps	C108200	0
Type I diabetes mellitus with neurological complications	C108211	0
Type 1 diabetes mellitus with neurological complications	C108212	0
Insulin dependent diabetes mellitus with multiple complicatn	C108300	0
Type I diabetes mellitus with multiple complications	C108311	0
Type 1 diabetes mellitus with multiple complications	C108312	0
Unstable insulin dependent diabetes mellitus	C108400	0
Unstable type I diabetes mellitus	C108411	0
Unstable type 1 diabetes mellitus	C108412	0
Insulin dependent diabetes mellitus with ulcer	C108500	0
Type I diabetes mellitus with ulcer	C108511	0
Type 1 diabetes mellitus with ulcer	C108512	0
Insulin dependent diabetes mellitus with gangrene	C108600	0
Type I diabetes mellitus with gangrene	C108611	0
Type 1 diabetes mellitus with gangrene	C108612	0
Insulin dependent diabetes mellitus with retinopathy	C108700	0
Type I diabetes mellitus with retinopathy	C108711	0
Type 1 diabetes mellitus with retinopathy	C108712	0
Insulin dependent diabetes mellitus with mononeuropathy	C108B00	0
Type I diabetes mellitus with mononeuropathy	C108B11	0
Type 1 diabetes mellitus with mononeuropathy	C108B12	0
Insulin dependent diabetes mellitus with polyneuropathy	C108C00	0
Type I diabetes mellitus with polyneuropathy	C108C11	0
Type 1 diabetes mellitus with polyneuropathy	C108C12	0
Insulin dependent diabetes mellitus with nephropathy	C108D00	0
Type I diabetes mellitus with nephropathy	C108D11	0
Type 1 diabetes mellitus with nephropathy	C108D12	0
Insulin dependent diabetes mellitus with hypoglycaemic coma	C108E00	0
Type I diabetes mellitus with hypoglycaemic coma	C108E11	0
Type 1 diabetes mellitus with hypoglycaemic coma	C108E12	0
Insulin dependent diabetes mellitus with diabetic cataract	C108F00	0
Type I diabetes mellitus with diabetic cataract	C108F11	0
Type 1 diabetes mellitus with diabetic cataract	C108F12	0
Insulin dependent diab mell with peripheral angiopathy	C108G00	0
Type I diabetes mellitus with peripheral angiopathy	C108G11	0
Type 1 diabetes mellitus with peripheral angiopathy	C108G12	0
Insulin dependent diabetes mellitus with arthropathy	C108H00	0
Type I diabetes mellitus with arthropathy	C108H11	0
Type 1 diabetes mellitus with arthropathy	C108H12	0
Insulin dependent diab mell with neuropathic arthropathy	C108J00	0
Type I diabetes mellitus with neuropathic arthropathy	C108J11	0
Type 1 diabetes mellitus with neuropathic arthropathy	C108J12	0
Other specified diabetes mellitus with multiple comps	C108y00	0
Unspecified diabetes mellitus with multiple complications	C108z00	0
Non-insulin-dependent diabetes mellitus with renal comps	C109000	0
Type II diabetes mellitus with renal complications	C109011	0
Type 2 diabetes mellitus with renal complications	C109012	0
Non-insulin-dependent diabetes mellitus with ophthalm comps	C109100	0
Type II diabetes mellitus with ophthalmic complications	C109111	0

Diabetes description	Med Code	Incident
Type 2 diabetes mellitus with ophthalmic complications	C109112	0
Non-insulin-dependent diabetes mellitus with neuro comps	C109200	0
Type II diabetes mellitus with neurological complications	C109211	0
Type 2 diabetes mellitus with neurological complications	C109212	0
Non-insulin-dependent diabetes mellitus with multiple comps	C109300	0
Type II diabetes mellitus with multiple complications	C109311	0
Type 2 diabetes mellitus with multiple complications	C109312	0
Non-insulin dependent diabetes mellitus with ulcer	C109400	0
Type II diabetes mellitus with ulcer	C109411	0
Type 2 diabetes mellitus with ulcer	C109412	0
Non-insulin dependent diabetes mellitus with gangrene	C109500	0
Type II diabetes mellitus with gangrene	C109511	0
Type 2 diabetes mellitus with gangrene	C109512	0
Non-insulin-dependent diabetes mellitus with retinopathy	C109600	0
Type II diabetes mellitus with retinopathy	C109611	0
Type 2 diabetes mellitus with retinopathy	C109612	0
Non-insulin dependent diabetes mellitus with mononeuropathy	C109A00	0
Type II diabetes mellitus with mononeuropathy	C109A11	0
Type 2 diabetes mellitus with mononeuropathy	C109A12	0
Non-insulin dependent diabetes mellitus with polyneuropathy	C109B00	0
Type II diabetes mellitus with polyneuropathy	C109B11	0
Type 2 diabetes mellitus with polyneuropathy	C109B12	0
Non-insulin dependent diabetes mellitus with nephropathy	C109C00	0
Type II diabetes mellitus with nephropathy	C109C11	0
Type 2 diabetes mellitus with nephropathy	C109C12	0
Non-insulin dependent diabetes mellitus with hypoglyca coma	C109D00	0
Type II diabetes mellitus with hypoglycaemic coma	C109D11	0
Type 2 diabetes mellitus with hypoglycaemic coma	C109D12	0
Non-insulin depend diabetes mellitus with diabetic cataract	C109E00	0
Type II diabetes mellitus with diabetic cataract	C109E11	0
Type 2 diabetes mellitus with diabetic cataract	C109E12	0
Non-insulin-dependent d m with peripheral angiopath	C109F00	0
Type II diabetes mellitus with peripheral angiopathy	C109F11	0
Type 2 diabetes mellitus with peripheral angiopathy	C109F12	0
Non-insulin dependent diabetes mellitus with arthropathy	C109G00	0
Type II diabetes mellitus with arthropathy	C109G11	0
Type 2 diabetes mellitus with arthropathy	C109G12	0
Non-insulin dependent d m with neuropathic arthropathy	C109H00	0
Type II diabetes mellitus with neuropathic arthropathy	C109H11	0
Type 2 diabetes mellitus with neuropathic arthropathy	C109H12	0
Hyperosmolar non-ketotic state in type 2 diabetes mellitus	C109K00	0
Malnutrition-related diabetes mellitus	C10A.00	0
Malnutrition-related diabetes mellitus with coma	C10A000	0
Malnutrition-related diabetes mellitus with ketoacidosis	C10A100	0
Malnutrition-related diabetes mellitus with renal complicatn	C10A200	0
Malnutrit-related diabetes mellitus wth ophthalmic complicat	C10A300	0
Malnutrition-related diabetes mellitus wth neuro complicatns	C10A400	0
Malnutritn-relat diabetes melitus wth periph circul complctn	C10A500	0
Malnutrition-related diabetes mellitus with multiple comps	C10A600	0
Malnutrition-related diabetes mellitus without complications	C10A700	0
Malnutrit-related diabetes mellitus with unspec complics	C10AW00	0

Diabetes description	Med Code	Incident
Malnutrit-relat diabetes mellitus with other spec comps	C10AX00	0
Diabetes mellitus induced by steroids	C10B.00	0
Steroid induced diabetes mellitus without complication	C10B000	0
Type 1 diabetes mellitus with renal complications	C10E000	0
Type I diabetes mellitus with renal complications	C10E011	0
Insulin-dependent diabetes mellitus with renal complications	C10E012	0
Type 1 diabetes mellitus with ophthalmic complications	C10E100	0
Type I diabetes mellitus with ophthalmic complications	C10E111	0
Insulin-dependent diabetes mellitus with ophthalmic comps	C10E112	0
Type 1 diabetes mellitus with neurological complications	C10E200	0
Type I diabetes mellitus with neurological complications	C10E211	0
Insulin-dependent diabetes mellitus with neurological comps	C10E212	0
Type 1 diabetes mellitus with multiple complications	C10E300	0
Type I diabetes mellitus with multiple complications	C10E311	0
Insulin dependent diabetes mellitus with multiple complicat	C10E312	0
Type 1 diabetes mellitus with ulcer	C10E500	0
Type I diabetes mellitus with ulcer	C10E511	0
Insulin dependent diabetes mellitus with ulcer	C10E512	0
Type 1 diabetes mellitus with gangrene	C10E600	0
Type I diabetes mellitus with gangrene	C10E611	0
Insulin dependent diabetes mellitus with gangrene	C10E612	0
Type 1 diabetes mellitus with retinopathy	C10E700	0
Type I diabetes mellitus with retinopathy	C10E711	0
Insulin dependent diabetes mellitus with retinopathy	C10E712	0
Type 1 diabetes mellitus with mononeuropathy	C10EB00	0
Type I diabetes mellitus with mononeuropathy	C10EB11	0
Insulin dependent diabetes mellitus with mononeuropathy	C10EB12	0
Type 1 diabetes mellitus with polyneuropathy	C10EC00	0
Type I diabetes mellitus with polyneuropathy	C10EC11	0
Insulin dependent diabetes mellitus with polyneuropathy	C10EC12	0
Type 1 diabetes mellitus with nephropathy	C10ED00	0
Type I diabetes mellitus with nephropathy	C10ED11	0
Insulin dependent diabetes mellitus with nephropathy	C10ED12	0
Type 1 diabetes mellitus with hypoglycaemic coma	C10EE00	0
Type I diabetes mellitus with hypoglycaemic coma	C10EE11	0
Insulin dependent diabetes mellitus with hypoglycaemic coma	C10EE12	0
Type 1 diabetes mellitus with diabetic cataract	C10EF00	0
Type I diabetes mellitus with diabetic cataract	C10EF11	0
Insulin dependent diabetes mellitus with diabetic cataract	C10EF12	0
Type 1 diabetes mellitus with peripheral angiopathy	C10EG00	0
Type I diabetes mellitus with peripheral angiopathy	C10EG11	0
Insulin dependent diab mell with peripheral angiopathy	C10EG12	0
Type 1 diabetes mellitus with arthropathy	C10EH00	0
Type I diabetes mellitus with arthropathy	C10EH11	0
Insulin dependent diabetes mellitus with arthropathy	C10EH12	0
Type 1 diabetes mellitus with neuropathic arthropathy	C10EJ00	0
Type I diabetes mellitus with neuropathic arthropathy	C10EJ11	0
Insulin dependent diab mell with neuropathic arthropathy	C10EJ12	0
Type 1 diabetes mellitus with persistent proteinuria	C10EK00	0
Type I diabetes mellitus with persistent proteinuria	C10EK11	0
Type 1 diabetes mellitus with persistent microalbuminuria	C10EL00	0

Diabetes description	Med Code	Incident
Type I diabetes mellitus with persistent microalbuminuria	C10EL11	0
Type 1 diabetes mellitus with ketoacidosis	C10EM00	0
Type I diabetes mellitus with ketoacidosis	C10EM11	0
Type 1 diabetes mellitus with ketoacidotic coma	C10EN00	0
Type I diabetes mellitus with ketoacidotic coma	C10EN11	0
Type 1 diabetes mellitus with exudative maculopathy	C10EP00	0
Type I diabetes mellitus with exudative maculopathy	C10EP11	0
Type 1 diabetes mellitus with gastroparesis	C10EQ00	0
Type 2 diabetes mellitus with renal complications	C10F000	0
Type II diabetes mellitus with renal complications	C10F011	0
Type 2 diabetes mellitus with ophthalmic complications	C10F100	0
Type II diabetes mellitus with ophthalmic complications	C10F111	0
Type 2 diabetes mellitus with neurological complications	C10F200	0
Type II diabetes mellitus with neurological complications	C10F211	0
Type 2 diabetes mellitus with multiple complications	C10F300	0
Type II diabetes mellitus with multiple complications	C10F311	0
Type 2 diabetes mellitus with ulcer	C10F400	0
Type II diabetes mellitus with ulcer	C10F411	0
Type 2 diabetes mellitus with gangrene	C10F500	0
Type II diabetes mellitus with gangrene	C10F511	0
Type 2 diabetes mellitus with retinopathy	C10F600	0
Type II diabetes mellitus with retinopathy	C10F611	0
Type 2 diabetes mellitus with mononeuropathy	C10FA00	0
Type II diabetes mellitus with mononeuropathy	C10FA11	0
Type 2 diabetes mellitus with polyneuropathy	C10FB00	0
Type II diabetes mellitus with polyneuropathy	C10FB11	0
Type 2 diabetes mellitus with nephropathy	C10FC00	0
Type II diabetes mellitus with nephropathy	C10FC11	0
Type 2 diabetes mellitus with hypoglycaemic coma	C10FD00	0
Type II diabetes mellitus with hypoglycaemic coma	C10FD11	0
Type 2 diabetes mellitus with diabetic cataract	C10FE00	0
Type II diabetes mellitus with diabetic cataract	C10FE11	0
Type 2 diabetes mellitus with peripheral angiopathy	C10FF00	0
Type II diabetes mellitus with peripheral angiopathy	C10FF11	0
Type 2 diabetes mellitus with arthropathy	C10FG00	0
Type II diabetes mellitus with arthropathy	C10FG11	0
Type 2 diabetes mellitus with neuropathic arthropathy	C10FH00	0
Type II diabetes mellitus with neuropathic arthropathy	C10FH11	0
Hyperosmolar non-ketotic state in type 2 diabetes mellitus	C10FK00	0
Type 2 diabetes mellitus with persistent proteinuria	C10FL00	0
Type II diabetes mellitus with persistent proteinuria	C10FL11	0
Type 2 diabetes mellitus with persistent microalbuminuria	C10FM00	0
Type II diabetes mellitus with persistent microalbuminuria	C10FM11	0
Type 2 diabetes mellitus with ketoacidosis	C10FN00	0
Type II diabetes mellitus with ketoacidosis	C10FN11	0
Type 2 diabetes mellitus with ketoacidotic coma	C10FP00	0
Type II diabetes mellitus with ketoacidotic coma	C10FP11	0
Type 2 diabetes mellitus with exudative maculopathy	C10FQ00	0
Type II diabetes mellitus with exudative maculopathy	C10FQ11	0
Type 2 diabetes mellitus with gastroparesis	C10FR00	0
Secondary pancreatic diabetes mellitus	C10G.00	0

Diabetes description	Med Code	Incident
Secondary pancreatic diabetes mellitus without complication	C10G000	0
Diabetes mellitus induced by non-steroid drugs	C10H.00	0
DM induced by non-steroid drugs without complication	C10H000	0
Insulin autoimmune syndrome	C10J.00	0
Insulin autoimmune syndrome without complication	C10J000	0
Type A insulin resistance	C10K.00	0
Type A insulin resistance without complication	C10K000	0
Fibrocalculous pancreatopathy	C10L.00	0
Fibrocalculous pancreatopathy without complication	C10L000	0
Lipoatrophic diabetes mellitus	C10M.00	0
Lipoatrophic diabetes mellitus without complication	C10M000	0
Secondary diabetes mellitus	C10N.00	0
Secondary diabetes mellitus without complication	C10N000	0
Cystic fibrosis related diabetes mellitus	C10N100	0
Diabetes mellitus with other specified manifestation	C10y.00	0
Diabetes mellitus, juvenile, + other specified manifestation	C10y000	0
Diabetes mellitus, adult, + other specified manifestation	C10y100	0
Other specified diabetes mellitus with other spec comps	C10yy00	0
Diabetes mellitus NOS with other specified manifestation	C10yz00	0
Diabetes mellitus with unspecified complication	C10z.00	0
Diabetes mellitus, juvenile type, + unspecified complication	C10z000	0
Diabetes mellitus, adult onset, + unspecified complication	C10z100	0
Other specified diabetes mellitus with unspecified comps	C10zy00	0
Diabetes mellitus NOS with unspecified complication	C10zz00	0
[X]Malnutrit-relat diabetes mellitus with other spec comps	Cyu2100	0
[X]Malnutrit-related diabetes mellitus with unspec complics	Cyu2200	0
[X]Unspecified diabetes mellitus with renal complications	Cyu2300	0
Autonomic neuropathy due to diabetes	F171100	0
Diabetic mononeuritis multiplex	F345000	0
Diabetic mononeuritis NOS	F35z000	0
Polyneuropathy in diabetes	F372.00	0
Diabetic polyneuropathy	F372.11	0
Diabetic neuropathy	F372.12	0
Acute painful diabetic neuropathy	F372000	0
Chronic painful diabetic neuropathy	F372100	0
Asymptomatic diabetic neuropathy	F372200	0
Myasthenic syndrome due to diabetic amyotrophy	F381300	0
Diabetic amyotrophy	F381311	0
Diabetic mononeuropathy	F3y0.00	0
Diabetic retinopathy	F420.00	0
Background diabetic retinopathy	F420000	0
Proliferative diabetic retinopathy	F420100	0
Preproliferative diabetic retinopathy	F420200	0
Advanced diabetic maculopathy	F420300	0
Diabetic maculopathy	F420400	0
Advanced diabetic retinal disease	F420500	0
Non proliferative diabetic retinopathy	F420600	0
High risk proliferative diabetic retinopathy	F420700	0
High risk non proliferative diabetic retinopathy	F420800	0
Diabetic retinopathy NOS	F420z00	0
Diabetic iritis	F440700	0

Diabetes description	Med Code	Incident
Diabetic cataract	F464000	0
Diabetic peripheral angiopathy	G73y000	0
Nephrotic syndrome in diabetes mellitus	K01x100	0
[X]Glomerular disorders in diabetes mellitus	Kyu0300	0
Diabetes mellitus during pregnancy/childbirth/puerperium	L180.00	0
Diabetes mellitus - unspec whether in pregnancy/puerperium	L180000	0
Diabetes mellitus during pregnancy - baby delivered	L180100	0
Diabetes mellitus in puerperium - baby delivered	L180200	0
Diabetes mellitus during pregnancy - baby not yet delivered	L180300	0
Diabetes mellitus in pueperium - baby previously delivered	L180400	0
Pre-existing diabetes mellitus, insulin-dependent	L180500	0
Pre-existing diabetes mellitus, non-insulin-dependent	L180600	0
Pre-existing malnutrition-related diabetes mellitus	L180700	0
Diabetes mellitus arising in pregnancy	L180800	0
Gestational diabetes mellitus	L180811	0
Gestational diabetes mellitus	L180900	0
Pre-existing diabetes mellitus, unspecified	L180X00	0
Diabetes mellitus in pregnancy/childbirth/puerperium NOS	L180z00	0
[X]Pre-existing diabetes mellitus, unspecified	Lyu2900	0
Cellulitis in diabetic foot	M037200	0
Ischaemic ulcer diabetic foot	M271000	0
Neuropathic diabetic ulcer - foot	M271100	0
Mixed diabetic ulcer - foot	M271200	0
Diabetic cheiroarthropathy	N030000	0
Diabetic cheiropathy	N030011	0
Diabetic Charcot arthropathy	N030100	0
[D]Gangrene of toe in diabetic	R054200	0
[D]Widespread diabetic foot gangrene	R054300	0
Dietary advice for diabetes mellitus	ZC2C800	0
Dietary advice for type I diabetes	ZC2C900	0
Diet advice for insulin-dependent diabetes	ZC2C911	0
Dietary advice for type II diabetes	ZC2CA00	0
Dietary advice non-insulin-dependent diabetes	ZC2CA11	0
Dietary advice for gestational diabetes	ZC2CB00	0
Under care of diabetic liaison nurse	ZL22500	0
Referral to diabetes nurse	ZL62500	0
Referral to diabetic liaison nurse	ZL62600	0
Seen by diabetic liaison nurse	ZLA2500	0
Discharge by diabetic liaison nurse	ZLD7500	0
Diabetes clinic satisfaction questionnaire	ZRB4.00	0
CSQ - Diabetes clinic satisfaction questionnaire	ZRB4.11	0
Diabetes treatment satisfaction questionnaire	ZRB5.00	0
DTSQ - Diabetes treatment satisfaction questionnaire	ZRB5.11	0
Diabetes wellbeing questionnaire	ZRB6.00	0
DWBQ - Diabetes wellbeing questionnaire	ZRB6.11	0
Education score - diabetes	ZRBa.00	0
Perceived control of insulin-dependent diabetes	ZRbH.00	0
[V]Dietary counselling in diabetes mellitus	ZV65312	0

20.6 Smoking status

Smoking description	Med Code	Smoker type
Tobacco consumption	137..00	Current smoker
Smoker - amount smoked	137..11	Current smoker
Never smoked tobacco	1371.00	Never smoker
Non-smoker	1371.11	Never smoker
Trivial smoker - < 1 cig/day	1372.00	Current smoker
Occasional smoker	1372.11	Current smoker
Light smoker - 1-9 cigs/day	1373.00	Current smoker
Moderate smoker - 10-19 cigs/d	1374.00	Current smoker
Heavy smoker - 20-39 cigs/day	1375.00	Current smoker
Very heavy smoker - 40+cigs/d	1376.00	Current smoker
Ex-trivial smoker (<1/day)	1377.00	Ex smoker
Ex-light smoker (1-9/day)	1378.00	Ex smoker
Ex-moderate smoker (10-19/day)	1379.00	Ex smoker
Ex-heavy smoker (20-39/day)	137A.00	Ex smoker
Ex-very heavy smoker (40+/day)	137B.00	Ex smoker
Keeps trying to stop smoking	137C.00	Current smoker
Admitted tobacco cons untrue ?	137D.00	Current smoker
Ex-smoker - amount unknown	137F.00	Ex smoker
Trying to give up smoking	137G.00	Current smoker
Pipe smoker	137H.00	Current smoker
Cigar smoker	137J.00	Current smoker
Stopped smoking	137K.00	Ex smoker
Recently stopped smoking	137K000	Ex smoker
Current non-smoker	137L.00	Ex smoker
Rolls own cigarettes	137M.00	Current smoker
Ex pipe smoker	137N.00	Ex smoker
Ex cigar smoker	137O.00	Ex smoker
Cigarette smoker	137P.00	Current smoker
Smoker	137P.11	Current smoker
Smoking started	137Q.00	Current smoker
Smoking restarted	137Q.11	Current smoker
Current smoker	137R.00	Current smoker
Ex smoker	137S.00	Ex smoker
Date ceased smoking	137T.00	Ex smoker
Smoking reduced	137V.00	Current smoker
Cigarette consumption	137X.00	Current smoker
Cigar consumption	137Y.00	Current smoker
Tobacco consumption NOS	137Z.00	Current smoker
Pipe tobacco consumption	137a.00	Current smoker
Ready to stop smoking	137b.00	Current smoker
Thinking about stopping smoking	137c.00	Current smoker
Not interested in stopping smoking	137d.00	Current smoker
Smoking restarted	137e.00	Current smoker
Reason for restarting smoking	137f.00	Current smoker
Cigarette pack-years	137g.00	Current smoker
Minutes from waking to first tobacco consumption	137h.00	Current smoker
Ex-cigarette smoker	137j.00	Ex smoker
Ex roll-up cigarette smoker	137l.00	Ex smoker

Smoking description	Med Code	Smoker type
No smokers in the household	13WK.00	Never smoker
Smoking cessation milestones	13p..00	Current smoker
Negotiated date for cessation of smoking	13p0.00	Current smoker
Smoking status at 4 weeks	13p1.00	Current smoker
Smoking free weeks	13p4.00	Ex smoker
Smoking cessation programme start date	13p5.00	Current smoker
Fagerstr test for nicotine dep	38DH.00	Current smoker
Health ed. - smoking	6791.00	Current smoker
Pregnancy smoking advice	67A3.00	Current smoker
Lifestyle advice regarding smoking	67H1.00	Current smoker
Brief intervention for smoking cessation	67H6.00	Current smoker
Smoking cessation therapy	745H.00	Current smoker
Nicotine replacement therapy using nicotine patches	745H000	Current smoker
Nicotine replacement therapy using nicotine gum	745H100	Current smoker
Nicotine replacement therapy using nicotine inhalator	745H200	Current smoker
Nicotine replacement therapy using nicotine lozenges	745H300	Current smoker
Smoking cessation drug therapy	745H400	Current smoker
Other specified smoking cessation therapy	745Hy00	Current smoker
Smoking cessation therapy NOS	745Hz00	Current smoker
Nicotine replacement therapy	8B2B.00	Current smoker
Over the counter nicotine replacement therapy	8B3Y.00	Current smoker
Nicotine replacement therapy provided free	8B3f.00	Current smoker
Nicotine replacement therapy provided by community pharmacis	8BP3.00	Current smoker
Smoking cessation advice	8CAL.00	Current smoker
Smoking cessation advice provided by community pharmacist	8CAg.00	Current smoker
Referral to smoking cessation advisor	8H7i.00	Current smoker
Stop smoking face to face follow-up	8HBM.00	Current smoker
Referral to stop-smoking clinic	8HTK.00	Current smoker
Referral to NHS stop smoking service	8HkQ.00	Current smoker
Nicotine replacement therapy contraindicated	8I2I.00	Current smoker
Nicotine replacement therapy refused	8I39.00	Current smoker
Smoking cessation advice declined	8IAj.00	Current smoker
Seen by smoking cessation advisor	9N2k.00	Current smoker
DNA - Did not attend smoking cessation clinic	9N4M.00	Current smoker
Ex-smoker annual review	9km..11	Ex smoker
Non-smoker annual review	9kn..11	Never smoker
Current smoker annual review	9ko..11	Current smoker
Nicotine withdrawal	E023.00	Current smoker
Tobacco dependence	E251.00	Current smoker
Tobacco dependence, unspecified	E251000	Current smoker
Tobacco dependence, continuous	E251100	Current smoker
Tobacco dependence, episodic	E251200	Current smoker
Tobacco dependence in remission	E251300	Ex smoker
Tobacco dependence NOS	E251z00	Current smoker
[X]Mental and behavioural disorder due to use of tobacco	Eu17.00	Current smoker
[X]Mental and behav dis due to use of tobacco: harmful use	Eu17100	Current smoker
[X]Mental and behav dis due to use tobacco: dependence syndr	Eu17200	Current smoker
[X]Mental and behav dis due to use tobacco: withdrawal state	Eu17300	Current smoker
[X]Men & behav dis due tobacco: withdrawl state wth delirium	Eu17400	Current smoker
[X]Mental & behav dis due to use tobacco: psychotic disorder	Eu17500	Current smoker
[X]Mental and behav dis due to use tobacco: amnesic syndrome	Eu17600	Current smoker

Smoking description	Med Code	Smoker type
[X]Men & beh dis due tobacco: resid & late-onset psychot dis	Eu17700	Current smoker
[X]Men & behav dis due to use tobacco: oth men & behav dis	Eu17y00	Current smoker
[X]Ment & behav dis due use tobacco: unsp ment & behav dis	Eu17z00	Current smoker
Advice on smoking	ZG23300	Current smoker
Fagerstrom test for nicotine dependence	ZRBm200	Current smoker
FTND - Fagerstrom test for nicotine dependence	ZRBm211	Current smoker
Motives for smoking scale	ZRaM.00	Current smoker
MFS - Motives for smoking scale	ZRaM.11	Current smoker
Occasions for smoking scale	ZRao.00	Current smoker
OFS - Occasions for smoking scale	ZRao.11	Current smoker
Reasons for smoking scale	ZRh4.00	Current smoker
RFS - Reasons for smoking scale	ZRh4.11	Current smoker
[V]Tobacco use	ZV4K000	Current smoker
[V]Tobacco abuse counselling	ZV6D800	Current smoker

20.7 Smoking cessation drugs

Smoking cessation drug generic name	Drug Code
NICOTINE	84442998
NICOTINE	84443998
NICOTINE PATCHES	84466998
NICOTINE PATCHES	84468998
NICOTINE PATCHES	84469998
VARENICLINE	85397998
VARENICLINE	85398998
VARENICLINE	85399998
VARENICLINE	85400998
VARENICLINE	85401998
VARENICLINE	85403998
NICOTINE	87919998
NICOTINE	87920998
NICOTINE	87922998
NICOTINE	88005996
NICOTINE	88005997
NICOTINE	88005998
NICOTINE	88288998
NICOTINE	88291998
NICOTINE	89110998
NICOTINE	89112998
NICOTINE	89863998
MENTHYL VALERATE+QUININE&AROMATICS	90293998
MENTHYL VALERATE+QUININE&AROMATICS	90295998
NICOTINE	91162998
NICOTINE	91248996
NICOTINE	91248997
NICOTINE	91248998
NICOTINE	91384998
NICOTINE	91848998
BUPROPION	92309998
BUPROPION	92311998

Smoking cessation drug generic name	Drug Code
NICOTINE	92657998
NICOTINE	92836998
NICOTINE	92840996
NICOTINE	92840997
NICOTINE	92840998
NICOTINE	92841997
NICOTINE	92841998
NICOTINE	92888990
NICOTINE	92889990
NICOTINE	92892997
NICOTINE	92892998
NICOTINE TRANSDERMAL PATCH	93447992
NICOTINE	95727996
NICOTINE	95727997
NICOTINE	95727998
NICOTINE TRANSDERMAL PATCH 30CM	96844992
NICOTINE TRANSDERMAL PATCH 20CM	96845992
NICOTINE TRANSDERMAL PATCH	96868992
NICOTINE TRANSDERMAL PATCH	96869992
NICOTINE TRANSDERMAL PATCH	96924992
NICOTINE TRANSDERMAL PATCH	96930992
NICOTINE	97673996
NICOTINE	97673997
NICOTINE	97673998
NICOTINE	97737996
NICOTINE	97737997
NICOTINE	97737998
NICOTINE	97739996
NICOTINE	97739997
NICOTINE	97739998
NICOTINE	97740996
NICOTINE	97740997
NICOTINE	97740998
NICOTINE	97763996
NICOTINE	97763997
NICOTINE	97763998
NICOTINE	98082998
NICOTINE	98430998
NICOTINE	98581997
NICOTINE	98581998
NICOTINE	98904996
NICOTINE	98904997
NICOTINE	98904998

20.8 Heavy drinking

Alcohol use description	Med Code	Alcohol use type
Moderate drinker - 3-6u/day	1364.00	Moderate/Heavy
Heavy drinker - 7-9u/day	1365.00	Heavy
Very heavy drinker - >9u/day	1366.00	Heavy

Alcohol use description	Med Code	Alcohol use type
Alcohol intake above recommended sensible limits	136K.00	Moderate/Heavy
Moderate drinker	136O.00	Moderate/Heavy
Heavy drinker	136P.00	Heavy
Very heavy drinker	136Q.00	Heavy
Binge drinker	136R.00	Moderate/Heavy
Harmful alcohol use	136T.00	Heavy
Alcoholics anonymous	13Y8.00	Heavy
H/O: liver disease	14C5.00	Heavy
Compensation for liver failure	7L1f.00	Heavy
Other specified compensation for liver failure	7L1fy00	Heavy
Compensation for liver failure NOS	7L1fz00	Heavy
Hepatitis status 6 months post treatment - enhanced serv adm	9kX..00	Heavy
Hepatitis status 6 months post treatment	9kX..11	Heavy
Wernicke's encephalopathy	C251.11	Heavy
Wernicke's encephalopathy	C253.00	Heavy
Deficiency of coagulation factor due to liver disease	D307000	Heavy
Alcoholic psychoses	E01..00	Heavy
Alcohol amnestic syndrome	E011.00	Heavy
Korsakov's alcoholic psychosis	E011000	Heavy
Korsakov's alcoholic psychosis with peripheral neuritis	E011100	Heavy
Wernicke-Korsakov syndrome	E011200	Heavy
Alcohol amnestic syndrome NOS	E011z00	Heavy
Other alcoholic dementia	E012.00	Heavy
Alcoholic dementia NOS	E012.11	Heavy
Chronic alcoholic brain syndrome	E012000	Heavy
Alcohol withdrawal hallucinosis	E013.00	Heavy
Other alcoholic psychosis	E01y.00	Heavy
Alcohol withdrawal syndrome	E01y000	Heavy
Other alcoholic psychosis NOS	E01yz00	Heavy
Alcoholic psychosis NOS	E01z.00	Heavy
Alcohol dependence syndrome	E23..00	Heavy
Alcoholism	E23..11	Heavy
Alcohol problem drinking	E23..12	Heavy
Chronic alcoholism in remission	E231300	Heavy
Nondependent alcohol abuse	E250.00	Moderate/Heavy
Nondependent alcohol abuse, unspecified	E250000	Heavy
Nondependent alcohol abuse, episodic	E250200	Heavy
[X]Acute alcoholic drunkenness	Eu10011	Heavy
[X]Chronic alcoholism	Eu10212	Heavy
[X]Mental and behav dis due to use alcohol: withdrawal state	Eu10300	Heavy
[X]Men & behav dis due alcohl: withdrawl state with delirium	Eu10400	Heavy
[X]Delirium tremens, alcohol induced	Eu10411	Heavy
[X]Mental & behav dis due to use alcohol: psychotic disorder	Eu10500	Heavy
[X]Alcoholic hallucinosis	Eu10511	Heavy
[X]Alcoholic jealousy	Eu10512	Heavy
[X]Alcoholic psychosis NOS	Eu10514	Heavy
[X]Korsakov's psychosis, alcohol induced	Eu10611	Heavy
[X]Men & behav dis due alcoh: resid & late-onset psychot dis	Eu10700	Heavy
[X]Alcoholic dementia NOS	Eu10711	Heavy

Alcohol use description	Med Code	Alcohol use type
[X]Chronic alcoholic brain syndrome	Eu10712	Heavy
[X]Alcohol withdrawal-induced seizure	Eu10800	Heavy
Cerebral degeneration due to alcoholism	F11x000	Heavy
Alcoholic encephalopathy	F11x011	Heavy
Oesophageal varices in cirrhosis of the liver	G852200	Heavy
Oesophageal varices in alcoholic cirrhosis of the liver	G852300	Heavy
Acute hepatic failure	J600000	Heavy
Acute liver failure	J600011	Heavy
Subacute hepatic failure	J601000	Heavy
Cirrhosis and chronic liver disease	J61..00	Heavy
Acute alcoholic hepatitis	J611.00	Heavy
Alcoholic cirrhosis of liver	J612.00	Heavy
Florid cirrhosis	J612.11	Heavy
Laennec's cirrhosis	J612.12	Heavy
Alcoholic fibrosis and sclerosis of liver	J612000	Heavy
Alcoholic liver damage unspecified	J613.00	Heavy
Alcoholic hepatic failure	J613000	Heavy
Chronic hepatitis	J614.00	Heavy
Chronic persistent hepatitis	J614000	Heavy
Chronic active hepatitis	J614100	Heavy
Chronic aggressive hepatitis	J614200	Heavy
Recurrent hepatitis	J614300	Heavy
Chronic lobular hepatitis	J614400	Heavy
Chronic hepatitis unspecified	J614y00	Heavy
Chronic hepatitis NOS	J614z00	Heavy
Portal cirrhosis	J615.11	Heavy
Unilobular portal cirrhosis	J615000	Heavy
Multilobular portal cirrhosis	J615100	Heavy
Postnecrotic cirrhosis of liver	J615111	Heavy
Mixed portal cirrhosis	J615200	Heavy
Diffuse nodular cirrhosis	J615300	Heavy
Fatty portal cirrhosis	J615400	Heavy
Hypertrophic portal cirrhosis	J615500	Heavy
Capsular portal cirrhosis	J615600	Heavy
Cardiac portal cirrhosis	J615700	Heavy
Congestive cirrhosis	J615711	Heavy
Pipe-stem portal cirrhosis	J615A00	Heavy
Toxic portal cirrhosis	J615B00	Heavy
Xanthomatous portal cirrhosis	J615C00	Heavy
Portal cirrhosis unspecified	J615y00	Heavy
Macronodular cirrhosis of liver	J615z11	Heavy
Cirrhosis of liver NOS	J615z13	Heavy
Laennec's cirrhosis, non-alcoholic	J615z14	Heavy
Hepatic fibrosis	J615z15	Heavy
Alcoholic hepatitis	J617.00	Heavy
Chronic alcoholic hepatitis	J617000	Heavy
Portal fibrosis without cirrhosis	J61y300	Heavy
Hepatic fibrosis	J61y400	Heavy
Hepatic fibrosis with hepatic sclerosis	J61y600	Heavy
Chronic liver disease NOS	J61z.00	Heavy
[X] Hepatic failure	J625.00	Heavy

Alcohol use description	Med Code	Alcohol use type
[X] Liver failure	J625.11	Heavy
Other sequelae of chronic liver disease	J62y.00	Heavy
Hepatic failure NOS	J62y.11	Heavy
Liver failure NOS	J62y.12	Heavy
Hepatic failure	J62y.13	Heavy
Hepatitis unspecified	J633.00	Heavy
Toxic hepatitis	J633000	Heavy
Hepatitis unspecified NOS	J633z00	Heavy
Toxic liver disease	J635.00	Heavy
Toxic liver disease with cholestasis	J635000	Heavy
Toxic liver disease with hepatic necrosis	J635100	Heavy
Toxic liver disease with acute hepatitis	J635200	Heavy
Toxic liver disease with chronic persistent hepatitis	J635300	Heavy
Toxic liver disease with chronic lobular hepatitis	J635400	Heavy
Toxic liver disease with chronic active hepatitis	J635500	Heavy
Toxic liver disease with fibrosis and cirrhosis of liver	J635600	Heavy
Toxic liver disease, unspecified	J635X00	Heavy
Autoimmune hepatitis	J63B.00	Heavy
Granulomatous hepatitis, not elsewhere classified	J63X.00	Heavy
Nonspecific reactive hepatitis	J63y100	Heavy
Alcohol-induced chronic pancreatitis	J671000	Heavy
[X]Toxic liver disease with other disorders of liver	Jyu7000	Heavy
[X]Other and unspecified cirrhosis of liver	Jyu7100	Heavy
[X]Other specified inflammatory liver diseases	Jyu7200	Heavy
[X]Toxic liver disease, unspecified	Jyu7600	Heavy
[X]Granulomatous hepatitis, not elsewhere classified	Jyu7700	Heavy
Dietary advice for liver disease	ZC2CH11	Heavy

20.9 Antipsychotics

Antipsychotic generic drug name	Drug Code	Generation
amisulpride	94546990	2
amisulpride	88387998	2
amisulpride	94846990	2
amisulpride	94545990	2
amisulpride	94544990	2
amisulpride	90209998	2
amisulpride	88383997	2
amisulpride	91785990	2
amisulpride	86433998	2
amisulpride	88383998	2
amisulpride	88387996	2
amisulpride	88387997	2
amisulpride	91425998	2
amisulpride	94845990	2
amisulpride	91083998	2
amisulpride	94844990	2
amisulpride	88383996	2
amisulpride	91077998	2
aripiprazole	87450998	2

Antipsychotic generic drug name	Drug Code	Generation
aripiprazole	87452998	2
aripiprazole	87448998	2
aripiprazole	87449998	2
aripiprazole	85835998	2
aripiprazole	87089998	2
aripiprazole	87090998	2
aripiprazole	87453998	2
aripiprazole	85832998	2
aripiprazole	85836998	2
aripiprazole	87451998	2
aripiprazole	85834998	2
aripiprazole	83903998	2
aripiprazole	85833998	2
aripiprazole	85837998	2
asenapine	81172998	2
asenapine	81170998	2
benperidol	95980998	1
benperidol	82225998	1
benperidol	95979998	1
benperidol	88885998	1
chlorpromazine	94821992	1
chlorpromazine	96691998	1
chlorpromazine	97134992	1
chlorpromazine	98062989	1
chlorpromazine	96102992	1
chlorpromazine	96689996	1
chlorpromazine	97236990	1
chlorpromazine	95200992	1
chlorpromazine	97877998	1
chlorpromazine	82892998	1
chlorpromazine	96614992	1
chlorpromazine	97880996	1
chlorpromazine	95687990	1
chlorpromazine	96689998	1
chlorpromazine	98186990	1
chlorpromazine	97871998	1
chlorpromazine	93593998	1
chlorpromazine	99010990	1
chlorpromazine	97236988	1
chlorpromazine	96674979	1
chlorpromazine	97880997	1
chlorpromazine	96691996	1
chlorpromazine	97879998	1
chlorpromazine	93587998	1
chlorpromazine	95365990	1
chlorpromazine	94107992	1
chlorpromazine	98192988	1
chlorpromazine	94761998	1
chlorpromazine	97129992	1
chlorpromazine	96690998	1
chlorpromazine	94761997	1

Antipsychotic generic drug name	Drug Code	Generation
chlorpromazine	94111992	1
chlorpromazine	98192990	1
chlorpromazine	93242998	1
chlorpromazine	97236989	1
chlorpromazine	97880998	1
chlorpromazine	98062990	1
chlorpromazine	98189990	1
chlorpromazine	96689997	1
chlorpromazine	98192989	1
chlorpromazine	96690996	1
chlorpromazine	96919990	1
chlorpromazine	95364990	1
chlorpromazine	99007990	1
chlorpromazine	96691997	1
chlorpromazine	97132992	1
chlorpromazine	96919989	1
chlorpromazine	93593997	1
chlorprothixene	96686997	1
clozapine	82802998	2
clozapine	82800998	2
clozapine	93595997	2
clozapine	82803998	2
clozapine	93596997	2
clozapine	93596998	2
clozapine	87020998	2
clozapine	87341998	2
clozapine	82801998	2
clozapine	87340998	2
clozapine	93595998	2
clozapine	87019998	2
clozapine	82799998	2
thiopropazate	94891992	1
droperidol	97343998	1
droperidol	97343997	1
droperidol	93675998	1
droperidol	96303997	1
droperidol	93674998	1
droperidol	96303998	1
droperidol	97334992	1
flupentixol	98766997	1
flupentixol	98766998	1
flupentixol	97516998	1
flupentixol	86421998	1
flupentixol	94879998	1
flupentixol	86422998	1
flupentixol	86420998	1
flupentixol	99775998	1
flupentixol	96502996	1
flupentixol	85614998	1
flupentixol	99776998	1
flupentixol	96503998	1

Antipsychotic generic drug name	Drug Code	Generation
flupentixol	96502998	1
flupentixol	85613998	1
flupentixol	86423998	1
flupentixol	96502997	1
fluphenazine	99414998	1
fluphenazine	96342992	1
fluphenazine	85300998	1
fluphenazine	85298998	1
fluphenazine	96500998	1
fluphenazine	85299998	1
fluphenazine	98759998	1
fluphenazine	99408998	1
fluphenazine	96742990	1
fluphenazine	93032992	1
fluphenazine	96498997	1
fluphenazine	99411998	1
fluphenazine	85296998	1
fluphenazine	85301998	1
fluphenazine	97466992	1
fluphenazine	96501996	1
fluphenazine	96498998	1
fluphenazine	96501998	1
fluphenazine	99411996	1
fluphenazine	96286990	1
fluphenazine	85303998	1
fluphenazine	85295998	1
fluphenazine	85297998	1
fluphenazine	99411997	1
fluphenazine	85302998	1
fluphenazine	85294998	1
fluphenazine	96501997	1
fluspirilene	96494998	1
fluspirilene	99189998	1
haloperidol	96265992	1
haloperidol	95086992	1
haloperidol	98544988	1
haloperidol	97346998	1
haloperidol	79934979	1
haloperidol	97345997	1
haloperidol	95242990	1
haloperidol	96248998	1
haloperidol	98625989	1
haloperidol	97344997	1
haloperidol	96245997	1
haloperidol	91932990	1
haloperidol	87190998	1
haloperidol	92815998	1
haloperidol	93695997	1
haloperidol	96248997	1
haloperidol	96249998	1
haloperidol	81468998	1

Antipsychotic generic drug name	Drug Code	Generation
haloperidol	96244998	1
haloperidol	96247996	1
haloperidol	81081998	1
haloperidol	96249997	1
haloperidol	96245998	1
haloperidol	97346996	1
haloperidol	98155990	1
haloperidol	98360988	1
haloperidol	96115990	1
haloperidol	98625990	1
haloperidol	97945997	1
haloperidol	97946997	1
haloperidol	97944997	1
haloperidol	97945998	1
haloperidol	97946996	1
haloperidol	97944998	1
haloperidol	97344998	1
haloperidol	97568992	1
haloperidol	98131989	1
haloperidol	98154990	1
haloperidol	96247998	1
haloperidol	92815996	1
haloperidol	98544990	1
haloperidol	98625988	1
haloperidol	96242997	1
haloperidol	96247997	1
haloperidol	83786998	1
haloperidol	97135990	1
haloperidol	83787998	1
haloperidol	96889990	1
haloperidol	96248996	1
haloperidol	97346997	1
haloperidol	93695998	1
haloperidol	96249996	1
haloperidol	96307992	1
haloperidol	67935979	1
haloperidol	96242998	1
haloperidol	96246998	1
haloperidol	98080990	1
haloperidol	96758992	1
haloperidol	91921998	1
haloperidol	97135989	1
haloperidol	98131990	1
haloperidol	96889988	1
haloperidol	92815997	1
haloperidol	97946998	1
haloperidol	81467998	1
haloperidol	97945996	1
levomepromazine	95919997	1
levomepromazine	95918998	1
levomepromazine	95919998	1

Antipsychotic generic drug name	Drug Code	Generation
levomepromazine	98853998	1
levomepromazine	96634979	1
levomepromazine	98853997	1
loxapine	94006996	1
loxapine	94007996	1
loxapine	94006997	1
loxapine	94007998	1
loxapine	94006998	1
loxapine	94007997	1
olanzapine	97433998	2
olanzapine	86325998	2
olanzapine	91618998	2
olanzapine	89567998	2
olanzapine	97995998	2
olanzapine	89567996	2
olanzapine	97111998	2
olanzapine	90659997	2
olanzapine	90659996	2
olanzapine	87647998	2
olanzapine	89567997	2
olanzapine	91618997	2
olanzapine	96421979	2
olanzapine	91364998	2
olanzapine	86324998	2
olanzapine	80976998	2
olanzapine	80981998	2
olanzapine	80980998	2
olanzapine	80970998	2
olanzapine	81041998	2
olanzapine	89569997	2
olanzapine	82201998	2
olanzapine	80971998	2
olanzapine	80977998	2
olanzapine	89569998	2
olanzapine	80978998	2
olanzapine	80969998	2
olanzapine	80974998	2
olanzapine	89569996	2
olanzapine	90664998	2
olanzapine	80979998	2
olanzapine	80972998	2
olanzapine	80973998	2
olanzapine	85376998	2
olanzapine	61579979	2
olanzapine	90659998	2
olanzapine	87646998	2
olanzapine	85377998	2
oxypertine	93699998	2
oxypertine	95649998	2
oxypertine	99530998	2
oxypertine	95650998	2

Antipsychotic generic drug name	Drug Code	Generation
paliperidone	81419998	2
paliperidone	81418998	2
paliperidone	84526998	2
paliperidone	81424998	2
paliperidone	84527998	2
paliperidone	81421998	2
paliperidone	84524998	2
paliperidone	81422998	2
paliperidone	81425998	2
paliperidone	81420998	2
paliperidone	84525998	2
paliperidone	81423998	2
paliperidone	84523998	2
pericyazine	99362997	1
pericyazine	95577996	1
pericyazine	83020998	1
pericyazine	97878992	1
pericyazine	83019998	1
pericyazine	99362996	1
pericyazine	95577997	1
pericyazine	95576998	1
pericyazine	98865998	1
pericyazine	95577998	1
pericyazine	99362998	1
perphenazine	99651998	1
perphenazine	97786997	1
perphenazine	97786998	1
perphenazine	95575998	1
perphenazine	95575997	1
perphenazine	99651997	1
perphenazine	95575996	1
perphenazine	94164992	1
perphenazine	98587998	1
perphenazine	97877992	1
pimozide	97342997	1
pimozide	97342998	1
pimozide	95516997	1
pimozide	95516996	1
pimozide	97342996	1
pimozide	95516998	1
pipotiazine	85410998	1
pipotiazine	85411998	1
pipotiazine	85413998	1
pipotiazine	85409998	1
pipotiazine	98622998	1
pipotiazine	95503998	1
promazine	98063990	1
promazine	98063989	1
promazine	95386996	1
promazine	95386997	1
promazine	95386998	1

Antipsychotic generic drug name	Drug Code	Generation
promazine	98783998	1
promazine	98786996	1
promazine	97406989	1
promazine	93708997	1
promazine	93477997	1
promazine	99093990	1
promazine	95385997	1
promazine	93708998	1
promazine	99093988	1
promazine	95385998	1
promazine	96750992	1
promazine	98786997	1
promazine	93476998	1
promazine	99117998	1
promazine	93477998	1
promazine	98786998	1
quetiapine	81923998	2
quetiapine	81924998	2
quetiapine	83996998	2
quetiapine	83492998	2
quetiapine	88734996	2
quetiapine	59469979	2
quetiapine	83995998	2
quetiapine	87907998	2
quetiapine	59468979	2
quetiapine	83994998	2
quetiapine	83493998	2
quetiapine	83993998	2
quetiapine	88736998	2
quetiapine	88938979	2
quetiapine	88737996	2
quetiapine	88737998	2
quetiapine	83490998	2
quetiapine	83491998	2
quetiapine	88734997	2
quetiapine	88733997	2
quetiapine	88734998	2
quetiapine	88733998	2
quetiapine	87908998	2
quetiapine	88736997	2
quetiapine	59467979	2
quetiapine	58638979	2
quetiapine	88737997	2
remoxipride	93344997	2
remoxipride	93344998	2
remoxipride	93335998	2
remoxipride	93335997	2
risperidone	88163998	2
risperidone	98585996	2
risperidone	96914992	2
risperidone	92957990	2

Antipsychotic generic drug name	Drug Code	Generation
risperidone	93240998	2
risperidone	99649998	2
risperidone	90395998	2
risperidone	99637998	2
risperidone	99649996	2
risperidone	98585998	2
risperidone	91676998	2
risperidone	88164998	2
risperidone	92107998	2
risperidone	99649997	2
risperidone	86984998	2
risperidone	85042998	2
risperidone	85039998	2
risperidone	99637996	2
risperidone	86983998	2
risperidone	95519998	2
risperidone	98585997	2
risperidone	85040998	2
risperidone	92089998	2
risperidone	93240997	2
risperidone	85038998	2
risperidone	99637997	2
risperidone	91374998	2
risperidone	92023998	2
risperidone	89908998	2
risperidone	92953990	2
risperidone	91968998	2
risperidone	93240996	2
risperidone	92491990	2
risperidone	90396998	2
sertindole	89812998	2
sertindole	89812996	2
sertindole	89811998	2
sertindole	89812997	2
sertindole	89809996	2
sertindole	89809997	2
sertindole	89809998	2
sulpiride	90158998	2
sulpiride	97966990	2
sulpiride	97163989	2
sulpiride	95226996	2
sulpiride	95226997	2
sulpiride	90805998	2
sulpiride	97176998	2
sulpiride	97163990	2
sulpiride	98796998	2
sulpiride	98796997	2
sulpiride	97858990	2
sulpiride	98149992	2
sulpiride	95226998	2
thiopropazate	98174992	1

Antipsychotic generic drug name	Drug Code	Generation
thioproperazine	98173992	1
thioproperazine	96492992	1
thioridazine	99437997	1
thioridazine	95173996	1
thioridazine	95175996	1
thioridazine	99437996	1
thioridazine	95174997	1
thioridazine	95174998	1
thioridazine	99437998	1
thioridazine	97715989	1
thioridazine	97715990	1
thioridazine	98899997	1
thioridazine	95173997	1
thioridazine	98404990	1
thioridazine	98899998	1
thioridazine	95174996	1
thioridazine	98003988	1
thioridazine	95175998	1
thioridazine	92821997	1
thioridazine	99436998	1
thioridazine	96570992	1
thioridazine	98403989	1
thioridazine	95175997	1
thioridazine	92821998	1
thioridazine	95173998	1
thioridazine	98403990	1
thioridazine	98404988	1
thioridazine	98899996	1
thioridazine	98404989	1
thioridazine	98003989	1
thioridazine	98003990	1
trifluoperazine	92623998	1
trifluoperazine	99107997	1
trifluoperazine	99109998	1
trifluoperazine	95119996	1
trifluoperazine	92623997	1
trifluoperazine	95118997	1
trifluoperazine	99108998	1
trifluoperazine	95607992	1
trifluoperazine	95119997	1
trifluoperazine	95119998	1
trifluoperazine	99109997	1
trifluoperazine	99109996	1
trifluoperazine	95118998	1
trifluoperazine	98052990	1
trifluoperazine	92623996	1
trifluoperazine	98203992	1
trifluoperazine	98052989	1
trifluoperazine	95118996	1
trifluoperazine	99108997	1
trifluoperazine	99107998	1

Antipsychotic generic drug name	Drug Code	Generation
trifluoperazine	98400990	1
trifluoperazine	98206992	1
trifluoperazine	99108996	1
trifluoperazine	87435998	1
trifluperidol	98204992	1
trifluperidol	95116997	1
trifluperidol	95117998	1
trifluperidol	95117997	1
trifluperidol	95116998	1
zotepine	98190997	2
zotepine	98190996	2
zotepine	99337998	2
zotepine	99337996	2
zotepine	99337997	2
zotepine	98190998	2
zuclopenthixol	85607998	1
zuclopenthixol	95071998	1
zuclopenthixol	96629997	1
zuclopenthixol	86333998	1
zuclopenthixol	86335998	1
zuclopenthixol	93520998	1
zuclopenthixol	99821997	1
zuclopenthixol	85609998	1
zuclopenthixol	96629998	1
zuclopenthixol	86334998	1
zuclopenthixol	96629996	1
zuclopenthixol	96628997	1
zuclopenthixol	86332998	1
zuclopenthixol	96628998	1
zuclopenthixol	99821998	1
zuclopenthixol	93519998	1
zuclopenthixol	98767998	1
zuclopenthixol	99821996	1

20.10 Antidepressants

Antidepressant generic drug name	Drug code	Antidepressant type
Mirtazapine 45mg orodispersible tablets sugar free	58745979	Other
Mirtazapine 15mg orodispersible tablets sugar free	58747979	Other
Dosulepin 25mg/5ml oral solution	80274979	Tricyclic antidepressant
Amitriptyline 10mg/5ml oral suspension	81084998	Tricyclic antidepressant
Amitriptyline 10mg/5ml oral solution	81085998	Tricyclic antidepressant
VENLAFAXINE 37.5mg m/r tablets	81505998	Other
Venlafaxine 37.5mg modified-release tablets	81506998	Other
Venlafaxine 150mg modified-release capsules	81749998	Other
Venlafaxine 75mg modified-release capsules	81750998	Other
Venlafaxine 150mg modified-release capsules	81929998	Other
Venlafaxine 75mg modified-release capsules	81930998	Other
VENLAFAXINE 75mg m/r capsules	82191998	Other
Imipramine 25mg/5ml oral solution sugar free	82432998	Tricyclic antidepressant

Venlafaxine 75mg modified-release capsules	82540998	Other
ESCITALOPRAM 20mg/mL oral dps	82790998	SSRI
Escitalopram 20mg/ml oral drops sugar free	82791998	SSRI
AGOMELATINE 25mg tablets	82861998	Other
Agomelatine 25mg tablets	82862998	Other
VENLAFAXINE 150mg m/r capsules	82874998	Other
VENLAFAXINE 75mg m/r capsules	82875998	Other
VENLAFAXINE 225mg m/r tablets	82959998	Other
Venlafaxine 225mg modified-release tablets	82961998	Other
VENLAFAXINE 150mg m/r tablets	82962998	Other
VENLAFAXINE 75mg m/r tablets	82963998	Other
VENLAFAXINE 150mg m/r capsules	83074998	Other
Venlafaxine 75mg modified-release capsules	83075998	Other
VENLAFAXINE 150mg m/r capsules	83114998	Other
VENLAFAXINE 75mg m/r capsules	83115998	Other
Venlafaxine 150mg modified-release capsules	83145998	Other
Venlafaxine 75mg modified-release capsules	83146998	Other
VENLAFAXINE 150mg m/r capsules	83149998	Other
VENLAFAXINE 75mg m/r capsules	83150998	Other
VENLAFAXINE 150mg m/r tablets	83157998	Other
VENLAFAXINE 75mg m/r tablets	83158998	Other
Venlafaxine 150mg modified-release tablets	83159998	Other
Venlafaxine 75mg modified-release tablets	83160998	Other
VENLAFAXINE 75mg m/r tablets	83162998	Other
VENLAFAXINE 37.5mg tablets	83163998	Other
VENLAFAXINE 150mg m/r capsules	83204998	Other
VENLAFAXINE 75mg m/r capsules	83205998	Other
VENLAFAXINE 150mg m/r capsules	83217998	Other
VENLAFAXINE 75mg m/r capsules	83218998	Other
VENLAFAXINE 150mg m/r capsules	83264998	Other
VENLAFAXINE 75mg m/r capsules	83265998	Other
Amitrip+perphen 10/2mg tablet	83620998	Tricyclic antidepressant
Clomipramine 50mg/5ml oral suspension	83878998	Tricyclic antidepressant
Fluoxetine 20mg/5ml oral solution sugar free	84403998	SSRI
Fluoxetine 20mg/5ml oral solution sugar free	84436998	SSRI
PAROXETINE 10mg tablets	84807998	SSRI
DOXEPIN 50mg capsules	85171998	Tricyclic antidepressant
DOXEPIN 25mg capsules	85172998	Tricyclic antidepressant
Paroxetine 10mg tablets	85382998	SSRI
ESCITALOPRAM 10mg/mL oral dps	85970998	SSRI
Escitalopram 10mg/ml oral drops sugar free	85971998	SSRI
Sertraline 50mg/5ml oral suspension	86159998	SSRI
Venlafaxine 37.5mg/5ml oral suspension	86431998	Other
Mirtazapine 45mg tablets	86981998	Other
Mirtazapine 15mg tablets	86982998	Other
DULOXETINE 60mg g/r capsules	86996998	Other
DULOXETINE 30mg g/r capsules	86997998	Other
Duloxetine 60mg gastro-resistant capsules	86998998	Other
Duloxetine 30mg gastro-resistant capsules	86999998	Other
CITALOPRAM 10mg tablets	87251998	SSRI
Mirtazapine 15mg/ml oral solution sugar free	87430998	Other
ESCITALOPRAM 5mg tablets	87662998	SSRI

Escitalopram 5mg tablets	87663998	SSRI
MIRTAZAPINE 45mg disp tabs	87684998	Other
MIRTAZAPINE 15mg disp tabs	87685998	Other
Mirtazapine 45mg orodispersible tablets	87686998	Other
Mirtazapine 15mg orodispersible tablets	87687998	Other
MIRTAZAPINE 30mg disp tabs	87945998	Other
Mirtazapine 30mg orodispersible tablets	87946998	Other
ESCITALOPRAM 10mg tablets	88285998	SSRI
MIRTAZAPINE 30mg tablets	88715998	Other
Mirtazapine 30mg tablets	88717998	Other
VENLAFAXINE 150mg m/r capsules	88755997	Other
VENLAFAXINE 75mg m/r capsules	88755998	Other
Venlafaxine 150mg modified-release capsules	88776997	Other
Venlafaxine 75mg modified-release capsules	88776998	Other
REBOXETINE 4mg tablets	88836998	Other
Reboxetine 4mg tablets	88838998	Other
DOSULEPIN HCL 75mg tablets	88906997	Tricyclic antidepressant
DOSULEPIN HCL 25mg capsules	88906998	Tricyclic antidepressant
LOFEPRAMINE 70mg/5mL s/f susp	89205998	Tricyclic antidepressant
MIRTAZAPINE 30mg disp tabs	90094979	Other
Mirtazapine 15mg tablets	90125979	Other
FLUOXETINE 20mg capsules	90159998	SSRI
FLUOXETINE 20mg/5mL oral liq	90766998	SSRI
FLUOXETINE 20mg capsules	90814998	SSRI
Nefazodone Starter pack	91361996	Other
Nefazodone 200mg tablets	91361997	Other
Nefazodone 100mg tablets	91361998	Other
NEFAZODONE initiation tabs pk	91362996	Other
NEFAZODONE HCL 200mg tabs	91362997	Other
NEFAZODONE HCL 100mg tabs	91362998	Other
Citalopram 40mg tablets	91380996	SSRI
Citalopram 10mg tablets	91380997	SSRI
Citalopram 20mg tablets	91380998	SSRI
CITALOPRAM 40mg tablets	91395996	SSRI
CITALOPRAM 10mg tablets	91395997	SSRI
CITALOPRAM 20mg tablets	91395998	SSRI
Escitalopram 10mg tablets	91671998	SSRI
CITALOPRAM 40mg/mL oral drops	92172998	SSRI
Citalopram 40mg/ml oral drops sugar free	92174998	SSRI
Mirtazapine 15mg orodispersible tablets	92454990	Other
Sertraline 50mg tablets	92728990	SSRI
Sertraline 100mg tablets	92729990	SSRI
Amitriptyline 10mg/5ml sugar free oral solution	92808996	Tricyclic antidepressant
Amitriptyline 25mg/5ml oral solution sugar free	92808997	Tricyclic antidepressant
Amitriptyline 50mg/5ml oral solution sugar free	92808998	Tricyclic antidepressant
Mirtazapine 45mg tablets	92813990	Other
Mirtazapine 15mg tablets	92814990	Other
Mirtazapine 45mg orodispersible tablets	92903990	Other
Mirtazapine 15mg orodispersible tablets	92906990	Other
Mirtazapine 45mg orodispersible tablets	92979990	Other
Mirtazapine 30mg orodispersible tablets	92980990	Other
Mirtazapine 15mg orodispersible tablets	92981990	Other

Mirtazapine 45mg orodispersible tablets	92986990	Other
Mirtazapine 15mg orodispersible tablets	92988990	Other
Mirtazapine 45mg orodispersible tablets	92992990	Other
Fluoxetine 20mg capsules	93066990	SSRI
Sertraline 100mg tablets	93173997	SSRI
Sertraline 50mg tablets	93173998	SSRI
SERTRALINE 100mg tablets	93174997	SSRI
SERTRALINE 50mg tablets	93174998	SSRI
Mirtazapine 45mg orodispersible tablets	93178990	Other
Mirtazapine 15mg orodispersible tablets	93180990	Other
CLOMIPRAMINE HCL 50mg capsules	93358992	Tricyclic antidepressant
CLOMIPRAMINE HCL 10mg capsules	93360992	Tricyclic antidepressant
Paroxetine 30mg tablets	93487990	SSRI
PAROXETINE 10mg/5mLs/f liq	93489996	SSRI
PAROXETINE 30mg tablets	93489997	SSRI
PAROXETINE 20mg tablets	93489998	SSRI
Paroxetine 10mg/5ml oral suspension sugar free	93490996	SSRI
Paroxetine 30mg tablets	93490997	SSRI
Paroxetine 20mg tablets	93490998	SSRI
Sertraline 100mg tablets	93732990	SSRI
Sertraline 50mg tablets	93749990	SSRI
Moclobemide 300mg tablets	93749997	Monoamine-oxidase inhibitor
Moclobemide 150mg tablets	93749998	Monoamine-oxidase inhibitor
MOCLOBEMIDE 300mg tablets	93759997	Monoamine-oxidase inhibitor
MOCLOBEMIDE 150mg tablets	93759998	Monoamine-oxidase inhibitor
Trimipramine 50mg capsules	93839990	Tricyclic antidepressant
Trimipramine 25mg tablets	93840990	Tricyclic antidepressant
Trimipramine 10mg tablets	93841990	Tricyclic antidepressant
Sertraline 100mg tablets	93842990	SSRI
Citalopram 10mg tablets	93948990	SSRI
Citalopram 10mg tablets	93994990	SSRI
Citalopram 20mg tablets	93996990	SSRI
Amoxapine 150mg tablets	94004998	Tricyclic antidepressant
Amoxapine 100mg tablets	94005996	Tricyclic antidepressant
Amoxapine 50mg tablets	94005997	Tricyclic antidepressant
Amoxapine 25mg tablets	94005998	Tricyclic antidepressant
AMOXAPINE 150mg tablets	94008998	Tricyclic antidepressant
AMOXAPINE 100mg tablets	94009996	Tricyclic antidepressant
AMOXAPINE 50mg tablets	94009997	Tricyclic antidepressant
AMOXAPINE 25mg tablets	94009998	Tricyclic antidepressant
Mirtazapine 45mg tablets	94035990	Other
Mirtazapine 15mg tablets	94037990	Other
AMITRIPTYLINE 75 MG TAB	94067992	Tricyclic antidepressant
Amitriptyline 25mg tablets	94076990	Tricyclic antidepressant
Mirtazapine 30mg tablets	94126990	Other
DOTHIEPIN HCl 75 MG SYR	94145992	Tricyclic antidepressant
DOTHIEPIN HCl 100 MG SYR	94146992	Tricyclic antidepressant
MERITAL 50 50 MG CAP	94234992	Tricyclic antidepressant
NORTRIPTYLINE 10 MG ELI	94249992	Tricyclic antidepressant
Mirtazapine 15mg tablets	94250990	Other

Mirtazapine 45mg tablets	94400990	Other
Mirtazapine 15mg tablets	94401990	Other
Fluoxetine 60mg capsules	94447996	SSRI
Fluoxetine 20mg/5ml oral solution	94447997	SSRI
Fluoxetine 20mg capsules	94447998	SSRI
DOTHIEPIN HCl 75 MG MIX	94452992	Tricyclic antidepressant
FLUOXETINE 60mg capsules	94490996	SSRI
FLUOXETINE 20mg/5mL oral liq	94490997	SSRI
FLUOXETINE 20mg capsules	94490998	SSRI
MERITAL 25 25 MG CAP	94498992	Tricyclic antidepressant
TRYPTOPHAN 1g/6g powder	94512992	Other
Trifluoperazine with tranylcypromine 1mg + 10mg Tablet	94626998	Monoamine-oxidase inhibitor
Nortriptyline 30mg / Fluphenazine 1.5mg tablets	94630997	Tricyclic antidepressant
Nortriptyline 10mg / Fluphenazine 500microgram tablets	94630998	Tricyclic antidepressant
ASCORBIC ACID/PYRIDOXINE HCL/L-TRYPTOPHA 20 MG POW	94663992	Other
Butriptyline 25mg tablets	94688998	Tricyclic antidepressant
Amitriptyline 25mg / Perphenazine 2mg tablets	94703997	Tricyclic antidepressant
Amitriptyline 10mg / Perphenazine 2mg tablets	94703998	Tricyclic antidepressant
Amitriptyline 25mg / Chlordiazepoxide 10mg capsules	94704997	Tricyclic antidepressant
Amitriptyline 12.5mg / Chlordiazepoxide 5mg capsules	94704998	Tricyclic antidepressant
Amitriptyline 25mg tablets	94771990	Tricyclic antidepressant
Mirtazapine 30mg tablets	94773990	Other
Mirtazapine 30mg tablets	94797990	Other
Dosulepin 75mg tablets	94800990	Tricyclic antidepressant
Dosulepin 25mg capsules	94801990	Tricyclic antidepressant
Mirtazapine 30mg tablets	94847990	Other
Citalopram 40mg tablets	94880990	SSRI
Citalopram 40mg tablets	94893990	SSRI
Citalopram 20mg tablets	94894990	SSRI
Citalopram 10mg tablets	94895990	SSRI
Citalopram 40mg tablets	94936990	SSRI
Citalopram 20mg tablets	94937990	SSRI
DOTHIEPIN 100 MG SYR	94940992	Tricyclic antidepressant
DOTHIEPIN 25 MG SYR	94941992	Tricyclic antidepressant
DOTHIEPIN HCl 50 MG ELI	94942992	Tricyclic antidepressant
DOTHIEPIN HCl 25 MG SYR	94943992	Tricyclic antidepressant
DOTHIEPIN HCl 25 MG MIX	94944992	Tricyclic antidepressant
Paroxetine 30mg tablets	95007990	SSRI
Paroxetine 30mg tablets	95028990	SSRI
Paroxetine 20mg tablets	95051990	SSRI
Tryptophan with ascorbic acid and pyridoxine powder	95098997	Other
Tryptophan 500mg tablets	95099998	Other
Trimipramine 50mg capsules	95107996	Tricyclic antidepressant
Trimipramine 25mg tablets	95107997	Tricyclic antidepressant
Trimipramine 10mg tablets	95107998	Tricyclic antidepressant
Trazodone 150mg modified-release tablets	95141997	Tricyclic antidepressant
Trazodone 50mg/5ml oral solution sugar free	95141998	Tricyclic antidepressant
Trazodone 150mg tablets	95142996	Tricyclic antidepressant
Trazodone 100mg capsules	95142997	Tricyclic antidepressant
Trazodone 50mg capsules	95142998	Tricyclic antidepressant
Tranylcypromine with trifluoperazine Tablet	95143998	Monoamine-oxidase inhibitor

Tranylcypromine 10mg tablets	95144998	Monoamine-oxidase inhibitor
IMIPRAMINE 75 MG TAB	95154992	Tricyclic antidepressant
IMIPRAMINE 25 MG CAP	95155992	Tricyclic antidepressant
IMIPRAMINE 50 MG TAB	95156992	Tricyclic antidepressant
MERITAL AM 100 MG TAB	95262992	Tricyclic antidepressant
Citalopram 40mg tablets	95269990	SSRI
Citalopram 20mg tablets	95270990	SSRI
Citalopram 10mg tablets	95271990	SSRI
Paroxetine 20mg tablets	95332990	SSRI
Citalopram 40mg tablets	95333990	SSRI
Citalopram 20mg tablets	95334990	SSRI
Citalopram 10mg tablets	95335990	SSRI
Paroxetine 20mg tablets	95350990	SSRI
TRYPTOPHAN 500mg tablets	95352992	Other
Protriptyline 10mg tablet	95372997	Tricyclic antidepressant
Protriptyline 5mg tablet	95372998	Tricyclic antidepressant
Fluoxetine 20mg capsules	95388990	SSRI
Citalopram 40mg tablets	95418990	SSRI
Citalopram 20mg tablets	95420990	SSRI
Citalopram 10mg tablets	95421990	SSRI
Fluoxetine 20mg/5ml oral solution	95426990	SSRI
Trazodone 150mg tablets	95527990	Tricyclic antidepressant
Phenelzine 15mg tablets	95560998	Monoamine-oxidase inhibitor
Perphenazine 2mg with Amitriptyline 25mg tablet	95574997	Tricyclic antidepressant
Perphenazine 2mg with Amitriptyline 10mg tablet	95574998	Tricyclic antidepressant
Paroxetine 20mg tablets	95578990	SSRI
Fluoxetine 60mg capsules	95610990	SSRI
Viloxazine hcl 50mg tablets	95624998	Tricyclic antidepressant
Citalopram 40mg tablets	95631990	SSRI
Citalopram 20mg tablets	95632990	SSRI
Citalopram 10mg tablets	95633990	SSRI
Tranylcypromine 10mg tablets	95665990	Monoamine-oxidase inhibitor
Citalopram 40mg tablets	95666990	SSRI
Citalopram 20mg tablets	95667990	SSRI
Citalopram 10mg tablets	95668990	SSRI
Nortriptyline 10mg/5ml Liquid	95695996	Tricyclic antidepressant
Nortriptyline 25mg Capsule	95695997	Tricyclic antidepressant
Nortriptyline 10mg Capsule	95695998	Tricyclic antidepressant
Nortriptyline 25mg tablets	95696997	Tricyclic antidepressant
Nortriptyline 10mg tablets	95696998	Tricyclic antidepressant
Citalopram 40mg tablets	95703990	SSRI
Citalopram 20mg tablets	95704990	SSRI
Citalopram 10mg tablets	95705990	SSRI
Mianserin 30mg tablets	95809996	Tricyclic antidepressant
Mianserin 20mg tablets	95809997	Tricyclic antidepressant
Mianserin 10mg tablets	95809998	Tricyclic antidepressant
Fluoxetine 20mg/5ml oral solution	95813990	SSRI
Fluoxetine 20mg/5ml oral solution	95820990	SSRI
Maprotiline 75mg tablets	95927998	Tricyclic antidepressant
Maprotiline 50mg tablets	95928996	Tricyclic antidepressant
Maprotiline 25mg tablets	95928997	Tricyclic antidepressant

Maprotiline 10mg tablets	95928998	Tricyclic antidepressant
Lofepramine 70mg/5ml oral suspension sugar free	95999997	Tricyclic antidepressant
Lofepramine 70mg tablets	95999998	Tricyclic antidepressant
VENLAFAXINE 150mg m/r capsules	96022979	Other
VENLAFAXINE 150mg m/r capsules	96029979	Other
VENLAFAXINE 75mg m/r capsules	96033979	Other
Venlafaxine 75mg modified-release capsules	96034979	Other
Moclobemide 150mg tablets	96061990	Monoamine-oxidase inhibitor
Paroxetine 20mg tablets	96087990	SSRI
Isocarboxazid 10mg tablets	96105998	Monoamine-oxidase inhibitor
Iproniazid 25mg	96107998	Monoamine-oxidase inhibitor
IPRINDOLE 15mg tablets	96108998	Tricyclic antidepressant
Iprindole hc 30mg	96109997	Tricyclic antidepressant
Iprindole hc 15mg	96109998	Tricyclic antidepressant
Imipramine 25mg/5ml oral solution	96130998	Tricyclic antidepressant
Dosulepin 25mg capsules	96158990	Tricyclic antidepressant
Fluoxetine 20mg capsules	96272990	SSRI
Fluoxetine 20mg capsules	96281990	SSRI
Trazodone 150mg tablets	96295988	Tricyclic antidepressant
Trazodone 100mg capsules	96295989	Tricyclic antidepressant
Trazodone 50mg capsules	96295990	Tricyclic antidepressant
Doxepin 75mg capsules	96307998	Tricyclic antidepressant
Doxepin 50mg capsules	96308996	Tricyclic antidepressant
Doxepin 25mg capsules	96308997	Tricyclic antidepressant
Doxepin 10mg capsules	96308998	Tricyclic antidepressant
Dosulepin 25mg/5ml oral solution sugar free	96311996	Tricyclic antidepressant
Dosulepin 75mg tablets	96311997	Tricyclic antidepressant
Dosulepin 25mg capsules	96311998	Tricyclic antidepressant
Fluvoxamine 100mg tablets	96345989	SSRI
NOMIFENSINE HYDROGEN MALEATE50 MG CAP	96365992	Tricyclic antidepressant
PROTRIPTYLINE HCl 10 MG TAB	96416992	Tricyclic antidepressant
Trazodone 150mg tablets	96422988	Tricyclic antidepressant
Trazodone 100mg capsules	96422989	Tricyclic antidepressant
Trazodone 50mg capsules	96422990	Tricyclic antidepressant
Desipramine 25mg tablets	96442998	Tricyclic antidepressant
Trazodone 150mg tablets	96443988	Tricyclic antidepressant
Trazodone 100mg capsules	96443989	Tricyclic antidepressant
Trazodone 50mg capsules	96443990	Tricyclic antidepressant
Dosulepin 25mg capsules	96467990	Tricyclic antidepressant
FLUVOXAMINE MALEATE100mg tabs	96492997	SSRI
FLUVOXAMINE MALEATE50mg tabs	96492998	SSRI
Fluvoxamine 100mg tablets	96493997	SSRI
Fluvoxamine 50mg tablets	96493998	SSRI
Fluphen+nortri 500mcg/10mg ta	96499998	Tricyclic antidepressant
Flupentixol 1mg tablets	96504997	Other
Flupentixol 500microgram tablets	96504998	Other
Fluoxetine 20mg capsules	96606990	SSRI
CLOMIPRAMINE HCL 25mg/2mL inj	96637998	Tricyclic antidepressant
Clomipramine 75mg modified-release tablets	96638998	Tricyclic antidepressant
Clomipramine 25mg/5ml oral solution	96639998	Tricyclic antidepressant
Clomipramine 50mg capsules	96640996	Tricyclic antidepressant

Clomipramine 25mg capsules	96640997	Tricyclic antidepressant
Clomipramine 10mg capsules	96640998	Tricyclic antidepressant
Fluoxetine 20mg capsules	96644990	SSRI
Fluoxetine 20mg capsules	96647990	SSRI
Fluoxetine 20mg capsules	96651990	SSRI
Fluoxetine 20mg capsules	96654990	SSRI
Fluoxetine 20mg capsules	96659990	SSRI
Fluoxetine 20mg capsules	96674990	SSRI
IMIPRAMINE 100 MG TAB	96687992	Tricyclic antidepressant
Fluoxetine 20mg capsules	96709990	SSRI
Trazodone 100mg capsules	96726989	Tricyclic antidepressant
Trazodone 50mg capsules	96726990	Tricyclic antidepressant
Fluoxetine 20mg capsules	96729990	SSRI
Lofepramine 70mg tablets	96793990	Tricyclic antidepressant
Fluvoxamine 100mg tablets	96810989	SSRI
Dosulepin 75mg tablets	96868989	Tricyclic antidepressant
Dosulepin 25mg capsules	96868990	Tricyclic antidepressant
AMITRIPTYLINE S/F 25 MG/5ML SYR	96891992	Tricyclic antidepressant
Clomipramine 50mg capsules	96901988	Tricyclic antidepressant
Clomipramine 25mg capsules	96901989	Tricyclic antidepressant
Amitriptyline 10mg/ml injection	96924998	Tricyclic antidepressant
Amitriptyline 75mg modified-release capsules	96925996	Tricyclic antidepressant
Amitriptyline 50mg modified-release capsules	96925997	Tricyclic antidepressant
Amitriptyline 25mg modified-release capsules	96925998	Tricyclic antidepressant
Lofepramine 70mg tablets	96963990	Tricyclic antidepressant
Dosulepin 25mg capsules	96964990	Tricyclic antidepressant
BOLVIDON 60 MG TAB	96987992	Tricyclic antidepressant
IMIPRAMINE HCL 10mg tablets	97091998	Tricyclic antidepressant
Imipramine 25mg tablets	97112997	Tricyclic antidepressant
Imipramine 10mg tablets	97112998	Tricyclic antidepressant
Lofepramine 70mg tablets	97142990	Tricyclic antidepressant
CLOMIPRAMINE 25 MG TAB	97167992	Tricyclic antidepressant
Isocarboxazid 10mg tablets	97169990	Monoamine-oxidase inhibitor
Lofepramine 70mg tablets	97192990	Tricyclic antidepressant
Amitriptyline 50mg tablets	97223996	Tricyclic antidepressant
Amitriptyline 25mg tablets	97223997	Tricyclic antidepressant
Amitriptyline 10mg tablets	97223998	Tricyclic antidepressant
PROTRIPTYLINE HCL 10mg tabs	97505998	Tricyclic antidepressant
PROTRIPTYLINE HCL 5mg tablets	97507998	Tricyclic antidepressant
Clomipramine 50mg capsules	97548988	Tricyclic antidepressant
Clomipramine 25mg capsules	97548989	Tricyclic antidepressant
Clomipramine 10mg capsules	97548990	Tricyclic antidepressant
IMIPRAMINE HCl 12.5 MG INJ	97593992	Tricyclic antidepressant
Fluphen+nortrip 1.5/30mg tab	97632998	Tricyclic antidepressant
Fluphen+nortri 500mcg/10mg ta	97634998	Tricyclic antidepressant
MAPROTILINE HCl 75 MG TAB	97704992	Tricyclic antidepressant
DOSULEPIN HCL 75mg tablets	97722997	Tricyclic antidepressant
DOSULEPIN HCL 25mg capsules	97722998	Tricyclic antidepressant
Lofepramine 70mg tablets	97743990	Tricyclic antidepressant
Dosulepin 75mg tablets	97762989	Tricyclic antidepressant
Dosulepin 25mg capsules	97762990	Tricyclic antidepressant

Clomipramine 25mg capsules	97773989	Tricyclic antidepressant
NOMIFENSINE HYDROGEN MALEATE25 MG CAP	97807992	Tricyclic antidepressant
DOSULEPIN HCL 75mg tablets	97818997	Tricyclic antidepressant
DOSULEPIN HCL 25mg capsules	97818998	Tricyclic antidepressant
Lofepramine 70mg tablets	97861990	Tricyclic antidepressant
SINEQUAN 15 MG TAB	98027992	Tricyclic antidepressant
Amitriptyline 10mg/5ml sugar free oral solution	98067988	Tricyclic antidepressant
Amitriptyline 50mg/5ml oral solution sugar free	98067989	Tricyclic antidepressant
Amitriptyline 25mg/5ml oral solution sugar free	98067990	Tricyclic antidepressant
Lofepramine 70mg/5ml oral suspension sugar free	98077990	Tricyclic antidepressant
Dosulepin 75mg/5ml oral solution sugar free	98078989	Tricyclic antidepressant
Dosulepin 25mg/5ml oral solution sugar free	98078990	Tricyclic antidepressant
ESCITALOPRAM 20mg tablets	98088998	SSRI
DOXEPIN 75mg capsules	98123998	Tricyclic antidepressant
DOXEPIN 50mg capsules	98124996	Tricyclic antidepressant
DOXEPIN 25mg capsules	98124997	Tricyclic antidepressant
DOXEPIN 10mg capsules	98124998	Tricyclic antidepressant
DOSULEPIN HCL 75mg tablets	98126997	Tricyclic antidepressant
DOSULEPIN HCL 25mg capsules	98126998	Tricyclic antidepressant
Amitriptyline 10mg/5ml sugar free oral solution	98128998	Tricyclic antidepressant
AMITRIPTYLINE 75mg m/r caps	98129997	Tricyclic antidepressant
AMITRIPTYLINE 100mg/10mL inj	98129998	Tricyclic antidepressant
AMITRIPTYLINE 50mg tablets	98130996	Tricyclic antidepressant
AMITRIPTYLINE 25mg tablets	98130997	Tricyclic antidepressant
AMITRIPTYLINE 10mg tablets	98130998	Tricyclic antidepressant
LOFEPRAMINE 70mg tablets	98132998	Tricyclic antidepressant
BUTRIPTYLINE 25mg tablets	98134998	Tricyclic antidepressant
TRIMIPRAMINE 50mg capsules	98136996	Tricyclic antidepressant
TRIMIPRAMINE 25mg tablets	98136997	Tricyclic antidepressant
TRIMIPRAMINE 10mg tablets	98136998	Tricyclic antidepressant
AMITRIPTYLINE 50mg m/r caps	98138997	Tricyclic antidepressant
AMITRIPTYLINE 25mg m/r caps	98138998	Tricyclic antidepressant
IMIPRAMINE HCL 25mg/5mL syrup	98140996	Tricyclic antidepressant
IMIPRAMINE 25mg tablets	98140997	Tricyclic antidepressant
IMIPRAMINE HCL 10mg tablets	98140998	Tricyclic antidepressant
CLOMIPRAMINE HCL 75mg m/r tabs	98142998	Tricyclic antidepressant
CLOMIPRAMINE HCL 25mg/5mL syr	98143998	Tricyclic antidepressant
CLOMIPRAMINE HCL 50mg capsules	98144996	Tricyclic antidepressant
CLOMIPRAMINE HCL 25mg capsules	98144997	Tricyclic antidepressant
CLOMIPRAMINE HCL 10mg capsules	98144998	Tricyclic antidepressant
DESIPRAMINE HCL 25mg tablets	98146998	Tricyclic antidepressant
MAPROTILINE HCL 75mg tablets	98147998	Tricyclic antidepressant
MAPROTILINE HCL 50mg tabs	98148996	Tricyclic antidepressant
MAPROTILINE HCL 25mg tablets	98148997	Tricyclic antidepressant
MAPROTILINE HCL 10mg tabs	98148998	Tricyclic antidepressant
Imipramine 25mg tablets	98149990	Tricyclic antidepressant
AMITRIPTYLINE 50mg tablets	98150996	Tricyclic antidepressant
AMITRIPTYLINE 25mg tablets	98150997	Tricyclic antidepressant
AMITRIPTYLINE 10mg tablets	98150998	Tricyclic antidepressant
NORTRIPTYLINE 25mg tablets	98152997	Tricyclic antidepressant
NORTRIPTYLINE 10mg tablets	98152998	Tricyclic antidepressant
NORTRIPTYLINE 10mg/5mL liquid	98154996	Tricyclic antidepressant

NORTRIPTYLINE 25mg capsules	98154997	Tricyclic antidepressant
NORTRIPTYLINE 10mg capsules	98154998	Tricyclic antidepressant
TOFRANIL 50 MG TAB	98183992	Tricyclic antidepressant
TRIMIPRAMINE 50 MG TAB	98212992	Tricyclic antidepressant
TRYPTOPHAN 500mg tablets	98257998	Other
TRAZODONE HCL 150mg m/r tabs	98312997	Tricyclic antidepressant
TRAZODONE HCL 50mg/5mL liquid	98312998	Tricyclic antidepressant
ZIMELIDINE HCl 100 MG TAB	98327992	Tricyclic antidepressant
Dosulepin 25mg/5ml mixture	98327997	Tricyclic antidepressant
Dosulepin 75mg/5ml oral solution sugar free	98327998	Tricyclic antidepressant
Venlafaxine 50mg tablets	98336996	Other
Venlafaxine 75mg tablets	98336997	Other
Venlafaxine 37.5mg tablets	98336998	Other
Clomipramine 50mg capsules	98340988	Tricyclic antidepressant
Clomipramine 25mg capsules	98340989	Tricyclic antidepressant
Clomipramine 10mg capsules	98340990	Tricyclic antidepressant
Amitriptyline 25mg / Chlordiazepoxide 10mg capsules	98343998	Tricyclic antidepressant
Dosulepin 25mg capsules	98351989	Tricyclic antidepressant
Dosulepin 75mg tablets	98351990	Tricyclic antidepressant
TRAZODONE HCL 150mg tablets	98486996	Tricyclic antidepressant
TRAZODONE HCL 100mg capsules	98486997	Tricyclic antidepressant
TRAZODONE HCL 50mg capsules	98486998	Tricyclic antidepressant
Escitalopram 20mg tablets	98561998	SSRI
Dosulepin 25mg capsules	98563989	Tricyclic antidepressant
Dosulepin 75mg tablets	98563990	Tricyclic antidepressant
Dosulepin 25mg capsules	98783990	Tricyclic antidepressant
VILOXAZINE 50mg tablets	98959998	Tricyclic antidepressant
Amitrip+perphen 10/2mg tablet	99017997	Tricyclic antidepressant
Amitrip+perphen 25/2mg tablet	99017998	Tricyclic antidepressant
Tranylcyp+trifluop 10/1mg tab	99280998	Monoamine-oxidase inhibitor
TRANYLCYPROMINE 10mg tablets	99281998	Monoamine-oxidase inhibitor
TRYPTOPHAN 500mg tablets	99294998	Other
Clomipramine 50mg capsules	99297988	Tricyclic antidepressant
Clomipramine 25mg capsules	99297989	Tricyclic antidepressant
Clomipramine 10mg capsules	99297990	Tricyclic antidepressant
TRYPTOPHAN 500mg tablets	99316998	Other
MIANSERIN 30mg tablets	99338996	Tricyclic antidepressant
MIANSERIN 20mg tablets	99338997	Tricyclic antidepressant
MIANSERIN 10mg tablets	99338998	Tricyclic antidepressant
PHENELZINE 15mg tablets	99377998	Monoamine-oxidase inhibitor
IPRONIAZID 25mg tablets	99448998	Monoamine-oxidase inhibitor
ISOCARBOXAZID 10mg tablets	99450998	Monoamine-oxidase inhibitor
Amitrip+chlordiaz 12.5/5mg ca	99472998	Tricyclic antidepressant
Mianserin 20mg tablets	99494989	Tricyclic antidepressant
Imipramine 25mg tablets	99554989	Tricyclic antidepressant
Imipramine 10mg tablets	99554990	Tricyclic antidepressant
Imipramine 25mg tablets	99555989	Tricyclic antidepressant
Imipramine 10mg tablets	99555990	Tricyclic antidepressant
Imipramine 25mg tablets	99556989	Tricyclic antidepressant
FLUOXETINE 20mg capsules	99592998	SSRI

Dosulepin 75mg tablets	99614989	Tricyclic antidepressant
Dosulepin 25mg capsules	99614990	Tricyclic antidepressant
FLUPENTIXOL 1mg tablets	99634997	Other
FLUPENTIXOL 500mcg tablets	99634998	Other
AMOXAPINE 25 MG TAB	99791992	Tricyclic antidepressant
CLOMIPRAMINE HCL 25mg/2mL inj	99794992	Tricyclic antidepressant
AMITRIPTYLINE 100 MG TAB	99824992	Tricyclic antidepressant
AMITRIPTYLINE 300 MG TAB	99825992	Tricyclic antidepressant
AMITRIPTYLINE 200 MG TAB	99826992	Tricyclic antidepressant
Amitriptyline 25mg tablets	99861989	Tricyclic antidepressant
Amitriptyline 10mg tablets	99861990	Tricyclic antidepressant
Amitriptyline 25mg tablets	99862990	Tricyclic antidepressant
Amitriptyline 50mg tablets	99863988	Tricyclic antidepressant
Amitriptyline 25mg tablets	99863989	Tricyclic antidepressant
Amitriptyline 10mg tablets	99863990	Tricyclic antidepressant
Amitriptyline 50mg tablets	99864988	Tricyclic antidepressant
Amitriptyline 25mg tablets	99864989	Tricyclic antidepressant
Amitriptyline 10mg tablets	99864990	Tricyclic antidepressant
Amitriptyline 25mg tablets	99865990	Tricyclic antidepressant
Amitriptyline 50mg tablets	99866988	Tricyclic antidepressant
Amitriptyline 25mg tablets	99866989	Tricyclic antidepressant
Amitriptyline 10mg tablets	99866990	Tricyclic antidepressant
Amitriptyline 25mg tablets	99867989	Tricyclic antidepressant
Amitriptyline 50mg tablets	99868988	Tricyclic antidepressant
Amitriptyline 25mg tablets	99868989	Tricyclic antidepressant
Amitriptyline 10mg tablets	99868990	Tricyclic antidepressant
Amitriptyline 25mg tablets	99869988	Tricyclic antidepressant
Amitriptyline 50mg tablets	99869989	Tricyclic antidepressant
Amitriptyline 10mg tablets	99869990	Tricyclic antidepressant
Amitriptyline 50mg tablets	99870988	Tricyclic antidepressant
Amitriptyline 25mg tablets	99870989	Tricyclic antidepressant
Amitriptyline 10mg tablets	99870990	Tricyclic antidepressant
Amitriptyline 50mg tablets	99871988	Tricyclic antidepressant
Amitriptyline 25mg tablets	99871989	Tricyclic antidepressant
Amitriptyline 10mg tablets	99871990	Tricyclic antidepressant
MIANSERIN 30mg tablets	99882996	Tricyclic antidepressant
MIANSERIN 20mg tablets	99882997	Tricyclic antidepressant
MIANSERIN 10mg tablets	99882998	Tricyclic antidepressant
VENLAFAXINE 50mg tablets	99896996	Other
VENLAFAXINE 75mg tablets	99896997	Other
VENLAFAXINE 37.5mg tablets	99896998	Other
L-TRYPTOPHAN 500 MG CAP	99937992	Other

20.11 Mood stabilising drugs

Mood stabilising drug generic name	Drug Code	Drug Type
CARBAMAZEPINE 100mg chew tabs	93531998	carbamazepine
Carbamazepine 100mg chewable tablets sugar free	93530998	carbamazepine
Carbamazepine 100mg tablets	99751990	carbamazepine
Carbamazepine 100mg tablets	98338990	carbamazepi

Mood stabilising drug generic name	Drug Code	Drug Type
		ne
Carbamazepine 100mg tablets	99752990	carbamazepine
CARBAMAZEPINE 100mg tablets	92837998	carbamazepine
Carbamazepine 100mg tablets	96697989	carbamazepine
Carbamazepine 100mg tablets	97033998	carbamazepine
CARBAMAZEPINE 100mg tablets	98361998	carbamazepine
Carbamazepine 100mg tablets	97779990	carbamazepine
Carbamazepine 100mg/5ml oral suspension sugar free	96885998	carbamazepine
CARBAMAZEPINE 100mg/5mL sf liq	96479992	carbamazepine
CARBAMAZEPINE 100mg/5mL sf liq	98360998	carbamazepine
Carbamazepine 125mg suppositories	92734998	carbamazepine
CARBAMAZEPINE 125mg supps	92735998	carbamazepine
CARBAMAZEPINE 200mg chew tabs	93531997	carbamazepine
Carbamazepine 200mg chewable tablets sugar free	93530997	carbamazepine
CARBAMAZEPINE 200mg m/r tabs	81480998	carbamazepine
CARBAMAZEPINE 200mg m/r tabs	93532998	carbamazepine
CARBAMAZEPINE 200mg m/r tabs	89384998	carbamazepine
CARBAMAZEPINE 200mg m/r tabs	92131998	carbamazepine
Carbamazepine 200mg modified-release tablets	96446990	carbamazepine
Carbamazepine 200mg modified-release tablets	96536990	carbamazepine
Carbamazepine 200mg modified-release tablets	93579998	carbamazepine
Carbamazepine 200mg modified-release tablets	97128990	carbamazepine
Carbamazepine 200mg modified-release tablets	96128990	carbamazepine
Carbamazepine 200mg tablets	97779989	carbamazepine
Carbamazepine 200mg tablets	99751989	carbamazepine
CARBAMAZEPINE 200mg tablets	97086998	carbamazepine
Carbamazepine 200mg tablets	96916989	carbamazepine
Carbamazepine 200mg tablets	98338989	carbamazepine
Carbamazepine 200mg tablets	99752989	carbamazepine
Carbamazepine 200mg tablets	96697988	carbamazepine
CARBAMAZEPINE 200mg tablets	92837997	carbamazepine
CARBAMAZEPINE 200mg tablets	98361997	carbamazepine
Carbamazepine 200mg tablets	97033997	carbamazepine
Carbamazepine 250mg suppositories	92734997	carbamazepine
CARBAMAZEPINE 250mg supps	92735997	carbamazepine
CARBAMAZEPINE 400mg m/r tabs	95266979	carbamazepine

Mood stabilising drug generic name	Drug Code	Drug Type
CARBAMAZEPINE 400mg m/r tabs	88217997	carbamazepine
CARBAMAZEPINE 400mg m/r tabs	89384997	carbamazepine
CARBAMAZEPINE 400mg m/r tabs	81479998	carbamazepine
CARBAMAZEPINE 400mg m/r tabs	93532997	carbamazepine
Carbamazepine 400mg modified-release tablets	96536989	carbamazepine
Carbamazepine 400mg modified-release tablets	93579997	carbamazepine
Carbamazepine 400mg modified-release tablets	96446989	carbamazepine
Carbamazepine 400mg modified-release tablets	92131997	carbamazepine
Carbamazepine 400mg modified-release tablets	97128989	carbamazepine
Carbamazepine 400mg modified-release tablets	96127990	carbamazepine
CARBAMAZEPINE 400mg tablets	98361996	carbamazepine
Carbamazepine 400mg tablets	99751988	carbamazepine
Carbamazepine 400mg tablets	98338988	carbamazepine
CARBAMAZEPINE 400mg tablets	92837996	carbamazepine
Carbamazepine 400mg tablets	97033996	carbamazepine
Carbamazepine 400mg tablets	96916988	carbamazepine
Carbamazepine 400mg tablets	97779988	carbamazepine
Carbamazepine 500mg/5ml oral suspension	84311998	carbamazepine
LAMOTRIGINE 100mg disp tablets	92709996	lamotrigine
Lamotrigine 100mg dispersible tablets sugar free	92700996	lamotrigine
LAMOTRIGINE 100mg tablets	95404997	lamotrigine
Lamotrigine 100mg tablets	94118990	lamotrigine
Lamotrigine 100mg tablets	95444997	lamotrigine
Lamotrigine 100mg tablets	94011990	lamotrigine
Lamotrigine 200mg tablets	94010990	lamotrigine
Lamotrigine 200mg tablets	91465998	lamotrigine
LAMOTRIGINE 200mg tablets	91596998	lamotrigine
LAMOTRIGINE 25mg disp tablets	92709997	lamotrigine
Lamotrigine 25mg dispersible tablets sugar free	92700997	lamotrigine
LAMOTRIGINE 25mg tablets	95112979	lamotrigine
Lamotrigine 25mg tablets	94120990	lamotrigine
LAMOTRIGINE 25mg tablets	95404996	lamotrigine
Lamotrigine 25mg tablets	95444996	lamotrigine
Lamotrigine 25mg tablets	94013990	lamotrigine
LAMOTRIGINE 2mg disp tablets	91596997	lamotrigine
Lamotrigine 2mg dispersible tablets sugar free	91465997	lamotrigine
Lamotrigine 50mg dispersible tablets sugar free	86019998	lamotrigine
Lamotrigine 50mg Suppository	81677998	lamotrigine
LAMOTRIGINE 50mg tablets	95404998	lamotrigine
LAMOTRIGINE 50mg tablets	93460992	lamotrigine
Lamotrigine 50mg tablets	94012990	lamotrigine
Lamotrigine 50mg tablets	95444998	lamotrigine
LAMOTRIGINE 5mg disp tablets	92709998	lamotrigine

Mood stabilising drug generic name	Drug Code	Drug Type
Lamotrigine 5mg dispersible tablets sugar free	92700998	lamotrigine
LITH CITRATE 564mg m/r tabs	97534998	lithium
LITHIUM 10.8 MMOLS/5MLS LIQ	96865992	lithium
LITHIUM 250 MG CAP	97674992	lithium
LITHIUM CAR 520mg/5mL s/f liq	93412998	lithium
LITHIUM CARB 200mg m/r tabs	99217998	lithium
LITHIUM CARB 300mg m/r tabs	96001998	lithium
LITHIUM CARB 400mg m/r tabs	92542998	lithium
LITHIUM CARB 400mg m/r tabs	99217997	lithium
LITHIUM CARB 400mg m/r tabs	98814998	lithium
LITHIUM CARB 450mg m/r tabs	99465998	lithium
Lithium carbonate 200mg modified-release tablets	96004998	lithium
Lithium carbonate 200mg/5ml oral suspension	84977998	lithium
Lithium carbonate 250mg tablets	96004997	lithium
LITHIUM CARBONATE 250mg tabs	99858998	lithium
Lithium carbonate 300mg Modified-release tablet	96004996	lithium
Lithium carbonate 400mg modified-release tablets	97979990	lithium
Lithium carbonate 400mg modified-release tablets	96003998	lithium
Lithium carbonate 450mg modified-release tablets	96002998	lithium
LITHIUM CITR 10.8mmol/5mL liq	97705997	lithium
LITHIUM CITR 5.4mmol/5mL liq	97705998	lithium
Lithium citrate 1.018g/5ml oral solution	97716998	lithium
Lithium citrate 509mg/5ml oral solution	96000996	lithium
Lithium citrate 520mg/5ml oral solution sugar free	96000997	lithium
Lithium citrate 564mg modified-release tablets	96000998	lithium
PRIADEL 800 MG TAB	97951992	lithium
SOD VALPROATE 100mg crush tabs	94409996	valproate
SOD VALPROATE 100mg m/r grans	83707998	valproate
SOD VALPROATE 200mg m/r tabs	92918998	valproate
SOD VALPROATE 200mg m/r tabs	95186979	valproate
SOD VALPROATE 200mg m/r tabs	95184979	valproate
SOD VALPROATE 250mg m/r grans	83706998	valproate
SOD VALPROATE 300mg m/r tabs	92918997	valproate
SOD VALPROATE 300mg m/r tabs	95177979	valproate
SOD VALPROATE 300mg m/r tabs	88177998	valproate
SOD VALPROATE 500mg m/r grans	84665998	valproate
SOD VALPROATE 500mg m/r tabs	95172979	valproate
SOD VALPROATE 500mg m/r tabs	92918996	valproate
SOD VALPROATE 500mg m/r tabs	88178998	valproate
SOD VALPROATE 50mg m/r grans	83708998	valproate
SOD VALPROATE 750mg m/r grans	83704998	valproate
SOD VALPROATE C/R 200 MG TAB	96463992	valproate
SOD VALPROTE 1g/sach m/r grans	84664998	valproate
SOD. VALPROATE 200mg e/c tabs	92802998	valproate
SOD. VALPROATE 200mg e/c tabs	83480998	valproate
SOD. VALPROATE 200mg e/c tabs	94409998	valproate
SOD. VALPROATE 200mg/5mL sfliq	94408997	valproate
SOD. VALPROATE 200mg/5mL sfliq	92802996	valproate
SOD. VALPROATE 500mg e/c tabs	94409997	valproate
SOD. VALPROATE 500mg e/c tabs	83479998	valproate

Mood stabilising drug generic name	Drug Code	Drug Type
Sodium valproate 100mg modified-release granules sachets sugar free	81956998	valproate
Sodium valproate 100mg tablets	97910990	valproate
Sodium valproate 100mg tablets	94568998	valproate
Sodium valproate 150mg modified-release capsules	84671998	valproate
Sodium valproate 1g modified-release granules sachets sugar free	82857998	valproate
Sodium valproate 1g modified-release granules sachets sugar free	84668998	valproate
Sodium valproate 1g/10ml solution for injection ampoules	84089998	valproate
Sodium valproate 200mg gastro-resistant tablets	98929990	valproate
Sodium valproate 200mg gastro-resistant tablets	97721990	valproate
Sodium valproate 200mg gastro-resistant tablets	96986990	valproate
Sodium valproate 200mg gastro-resistant tablets	97911989	valproate
Sodium valproate 200mg gastro-resistant tablets	93444990	valproate
Sodium valproate 200mg gastro-resistant tablets	96977989	valproate
Sodium valproate 200mg gastro-resistant tablets	91690990	valproate
Sodium valproate 200mg gastro-resistant tablets	94606998	valproate
Sodium valproate 200mg gastro-resistant tablets	97910989	valproate
Sodium valproate 200mg gastro-resistant tablets	98385990	valproate
Sodium valproate 200mg modified-release tablets	83321998	valproate
Sodium valproate 200mg/5ml oral solution	94568996	valproate
Sodium valproate 200mg/5ml oral solution	95810990	valproate
Sodium valproate 200mg/5ml oral solution sugar free	94568997	valproate
Sodium valproate 200mg/5ml oral solution sugar free	96159990	valproate
Sodium valproate 200mg/5ml oral solution sugar free	97911990	valproate
Sodium valproate 200mg/5ml oral solution sugar free	98929988	valproate
SODIUM VALPROATE 200mg/5mL syr	95160979	valproate
SODIUM VALPROATE 200mg/5mL syr	94408998	valproate
Sodium valproate 250mg modified-release granules sachets sugar free	81955998	valproate
Sodium valproate 300mg modified-release capsules	84670998	valproate
Sodium valproate 300mg modified-release tablets	95180979	valproate
Sodium valproate 300mg modified-release tablets	92345998	valproate
Sodium valproate 300mg suppositories	84720998	valproate
Sodium valproate 300mg/3ml solution for injection ampoules	85030998	valproate
Sodium valproate 400mg powder and solvent for solution for injection vials	93148998	valproate
SODIUM VALPROATE 400mg/4mL inj	94408996	valproate
Sodium valproate 500mg gastro-resistant tablets	98084990	valproate
Sodium valproate 500mg gastro-resistant tablets	98385989	valproate
Sodium valproate 500mg gastro-resistant tablets	96977990	valproate
Sodium valproate 500mg gastro-resistant tablets	92802997	valproate
Sodium valproate 500mg gastro-resistant tablets	98929989	valproate
Sodium valproate 500mg gastro-resistant tablets	94606997	valproate
Sodium valproate 500mg gastro-resistant tablets	93443990	valproate
Sodium valproate 500mg modified-release granules sachets sugar free	84669998	valproate
Sodium valproate 500mg modified-release granules sachets sugar free	83705998	valproate
Sodium valproate 500mg modified-release tablets	90505998	valproate
Sodium valproate 50mg modified-release granules sachets sugar free	81957998	valproate
Sodium valproate 600mg/5ml oral solution	65489979	valproate
Sodium valproate 750mg modified-release granules sachets sugar free	81954998	valproate
Sodium valproate oral solution	83766998	valproate

Mood stabilising drug generic name	Drug Code	Drug Type
Sodium valproate with valproic acid 1000mg modified release granules	83790998	valproate
Sodium valproate with valproic acid 100mg modified release granules	83794998	valproate
Sodium valproate with valproic acid 200mg modified release tablets	92917998	valproate
Sodium valproate with valproic acid 250mg modified release granules	83793998	valproate
Sodium valproate with valproic acid 300mg modified release tablets	95217990	valproate
Sodium valproate with valproic acid 300mg modified release tablets	92917997	valproate
Sodium valproate with valproic acid 500mg modified release granules	83792998	valproate
Sodium valproate with valproic acid 500mg modified release tablets	95216990	valproate
Sodium valproate with valproic acid 500mg modified release tablets	92917996	valproate
Sodium valproate with valproic acid 50mg modified release granules	83709998	valproate
Sodium valproate with valproic acid 750mg modified release granules	83791998	valproate
SODUM VALPROATE150mg m/r caps	84667998	valproate
SODUM VALPROATE300mg m/r caps	84666998	valproate
VALPROIC ACID 150mg e/c caps	93016998	valproate
Valproic acid 150mg gastro-resistant capsules	93015998	valproate
VALPROIC ACID 250mg e/c tabs	94068998	valproate
Valproic acid 250mg gastro-resistant tablets	97628998	valproate
VALPROIC ACID 300mg e/c caps	93016997	valproate
Valproic acid 300mg gastro-resistant capsules	93015997	valproate
VALPROIC ACID 500mg e/c caps	93016996	valproate
VALPROIC ACID 500mg e/c tabs	94068997	valproate
Valproic acid 500mg gastro-resistant capsules	93015996	valproate
Valproic acid 500mg gastro-resistant tablets	97628997	valproate

20.12 Asthma

Asthma code description	Med Code
Acute exacerbation of asthma	H333.00
Allergic asthma	H330.11
Allergic asthma NEC	H33zz12
Allergic bronchitis NEC	H33zz13
Asthma	H33..00
Asthma attack	H33z100
Asthma attack NOS	H33z111
Asthma NOS	H33zz00
Asthma unspecified	H33z.00
Brittle asthma	H334.00
Bronchial asthma	H33..11
Childhood asthma	H330.12
Exercise induced asthma	H33zz11
Extrinsic (atopic) asthma	H330.00
Extrinsic asthma NOS	H330z00
Extrinsic asthma with asthma attack	H330111
Extrinsic asthma with status asthmaticus	H330100
Extrinsic asthma without status asthmaticus	H330000
Hay fever with asthma	H330.13
Hay fever with asthma	H330011

Asthma code description	Med Code
Hyperreactive airways disease	H33z.11
Intrinsic asthma	H331.00
Intrinsic asthma NOS	H331z00
Intrinsic asthma with asthma attack	H331111
Intrinsic asthma with status asthmaticus	H331100
Intrinsic asthma without status asthmaticus	H331000
Late onset asthma	H331.11
Late-onset asthma	H33z200
Mixed asthma	H332.00
Pollen asthma	H330.14
Severe asthma attack	H33z011
Status asthmaticus NOS	H33z000

20.13 CKD

CKD description	Med Code
Chronic kidney disease stage 3	1Z12.00
Chronic kidney disease stage 4	1Z13.00
Chronic kidney disease stage 5	1Z14.00
Chronic kidney disease stage 3A	1Z15.00
Chronic kidney disease stage 3B	1Z16.00
Chronic kidney disease stage 3 with proteinuria	1Z1B.00
CKD stage 3 with proteinuria	1Z1B.11
Chronic kidney disease stage 3 without proteinuria	1Z1C.00
CKD stage 3 without proteinuria	1Z1C.11
Chronic kidney disease stage 3A with proteinuria	1Z1D.00
CKD stage 3A with proteinuria	1Z1D.11
Chronic kidney disease stage 3A without proteinuria	1Z1E.00
CKD stage 3A without proteinuria	1Z1E.11
Chronic kidney disease stage 3B with proteinuria	1Z1F.00
CKD stage 3B with proteinuria	1Z1F.11
Chronic kidney disease stage 3B without proteinuria	1Z1G.00
CKD stage 3B without proteinuria	1Z1G.11
Chronic kidney disease stage 4 with proteinuria	1Z1H.00
CKD stage 4 with proteinuria	1Z1H.11
Chronic kidney disease stage 4 without proteinuria	1Z1J.00
CKD stage 4 without proteinuria	1Z1J.11
Chronic kidney disease stage 5 with proteinuria	1Z1K.00
CKD stage 5 with proteinuria	1Z1K.11
Chronic kidney disease stage 5 without proteinuria	1Z1L.00
CKD stage 5 without proteinuria	1Z1L.11

20.14 COPD

COPD description	Med Code
Acute interstitial emphysema	H32y111
Acute vesicular emphysema	H32y000
Atrophic (senile) emphysema	H32y100
Bronchiolitis obliterans	H312300
Bullous emphysema with collapse	H320300

COPD description	Med Code
Centrilobular emphysema	H322.00
Chron obstruct pulmonary dis wth acute exacerbation, unspec	H3y1.00
Chronic asthmatic bronchitis	H312000
Chronic bronchitis	H31..00
Chronic bronchitis NOS	H31z.00
Chronic bullous emphysema	H320.00
Chronic bullous emphysema NOS	H320z00
Chronic catarrhal bronchitis	H310000
Chronic obstruct pulmonary dis with acute lower resp infectn	H3y0.00
Chronic obstructive airways disease	H3...11
Chronic obstructive airways disease NOS	H3z..00
Chronic obstructive pulmonary disease	H3...00
Chronic obstructive pulmonary disease NOS	H3z..11
Chronic tracheobronchitis	H31y100
Chronic wheezy bronchitis	H312011
Emphysema	H32..00
Emphysema NOS	H32z.00
Emphysematous bronchitis	H312100
Fetid chronic bronchitis	H311100
Giant bullous emphysema	H320200
MacLeod's unilateral emphysema	H32y200
Mild chronic obstructive pulmonary disease	H36..00
Mixed simple and mucopurulent chronic bronchitis	H313.00
Moderate chronic obstructive pulmonary disease	H37..00
Mucopurulent chronic bronchitis	H311.00
Mucopurulent chronic bronchitis NOS	H311z00
Obstructive chronic bronchitis	H312.00
Obstructive chronic bronchitis NOS	H312z00
Other chronic bronchitis	H31y.00
Other chronic bronchitis NOS	H31yz00
Other emphysema	H32y.00
Other emphysema NOS	H32yz00
Other specified chronic obstructive airways disease	H3y..00
Other specified chronic obstructive pulmonary disease	H3y..11
Panlobular emphysema	H321.00
Purulent chronic bronchitis	H311000
Sawyer - Jones syndrome	H32yz11
Segmental bullous emphysema	H320000
Severe chronic obstructive pulmonary disease	H38..00
Simple chronic bronchitis	H310.00
Simple chronic bronchitis NOS	H310z00
Tension pneumatocoele	H320311
Very severe chronic obstructive pulmonary disease	H39..00
Zonal bullous emphysema	H320100

20.15 Familial hypercholesterolaemia

Familial hypercholesterolaemia description	Med Code
Pure hypercholesterolaemia	C320.00
Familial hypercholesterolaemia	C320.11

Familial hypercholesterolaemia description	Med Code
Familial hypercholesterolaemia	C320000
Polygenic hypercholesterolaemia	C320600
Other specified pure hypercholesterolaemia	C320y00
Pure hypercholesterolaemia NOS	C320z00
[V]Dietary surveillance in hypercholesterolaemia	ZV65317

20.16 Hypothyroidism

Hypothyroidism	Med Code
Acquired atrophy of thyroid	C045.00
Acquired hypothyroidism	C04..00
Autoimmune myxoedema	C046.00
Congenital hypothyroidism	C03..00
Congenital hypothyroidism NOS	C03z.00
Congenital hypothyroidism with diffuse goitre	C03y000
Congenital hypothyroidism without goitre	C03y100
Congenital thyroid insufficiency	C03z.11
Cretinism	C03..11
Cretinism	C03z.12
Goitrous cretin	C031.00
Hypothyroid goitre, acquired	C04z.13
Hypothyroidism	C04..13
Hypothyroidism NOS	C04z.00
Hypothyroidism resulting from para-aminosalicylic acid	C043000
Hypothyroidism resulting from phenylbutazone	C043100
Hypothyroidism resulting from resorcinol	C043200
Iatrogenic hypothyroidism NOS	C043z00
Iodine hypothyroidism	C042.00
Irradiation hypothyroidism	C041000
Myxoedema	C04..11
Myxoedema coma	C04z100
Other acquired hypothyroidism	C04y.00
Other iatrogenic hypothyroidism	C043.00
Other postablative hypothyroidism	C041.00
Other specified congenital hypothyroidism	C03y.00
Pendred's syndrome	C030.00
Post ablative hypothyroidism	C040.11
Postablative hypothyroidism NOS	C041z00
Postinfectious hypothyroidism	C044.00
Postsurgical hypothyroidism	C040.00
Premature puberty due to hypothyroidism	C04z000
Pretibial myxoedema - hypothyroid	C04z.11
Subclinical hypothyroidism	C047.00
Thyroid deficiency	C04..12
Thyroid insufficiency	C04z.12

20.17 Cancer

Cancer description	Med Code	Cancer type

Cancer description	Med Code	Cancer type
[M]Acute leukaemia NOS	BBr0100	HEMA--Leukemia
[M]Acute lymphoid leukaemia	BBr2100	HEMA--Leukemia
[M]Acute megakaryoblastic leukaemia	BBrA500	HEMA--Leukemia
[M]Acute myelofibrosis	BBrA700	HEMA--Leukemia
[M]Acute myeloid leukaemia	BBr6100	HEMA--Leukemia
[M]Acute myelomonocytic leukaemia	BBr6700	HEMA--Leukemia
[M]Acute promyelocytic leukaemia	BBr6600	HEMA--Leukemia
[M]Adult T-cell leukaemia/lymphoma	BBr2700	HEMA--Leukemia
[M]Blast cell leukaemia	BBr0111	HEMA--Leukemia
[M]Burkitt's cell leukaemia	BBr2600	HEMA--Leukemia
[M]Chronic leukaemia NOS	BBr0300	HEMA--Leukemia
[M]Chronic lymphoid leukaemia	BBr2300	HEMA--Leukemia
[M]Chronic myeloid leukaemia	BBr6300	HEMA--Leukemia
[M]Chronic myelomonocytic leukaemia	BBr6800	HEMA--Leukemia
[M]Eosinophilic leukaemia	BBr8000	HEMA--Leukemia
[M]Eosinophilic leukaemias	BBr8.00	HEMA--Leukemia
[M]Erythroleukaemias	BBr4.00	HEMA--Leukemia
[M]Granulocytic leukaemia NOS	BBr6011	HEMA--Leukemia
[M]Hairy cell leukaemia	BBrA400	HEMA--Leukemia
[M]Leukaemia NOS	BBr0000	HEMA--Leukemia
[M]Leukaemia NOS	BBrz.00	HEMA--Leukemia
[M]Leukaemia unspecified, NOS	BBr0z00	HEMA--Leukemia
[M]Leukaemias	BBr..00	HEMA--Leukemia
[M]Leukaemias unspecified	BBr0.00	HEMA--Leukemia
[M]Lymphatic leukaemia	BBr2011	HEMA--Leukemia
[M]Lymphoid leukaemia NOS	BBr2000	HEMA--Leukemia
[M]Lymphoid leukaemias	BBr2.00	HEMA--Leukemia
[M]Myeloid leukaemia NOS	BBr6000	HEMA--Leukemia
[M]Myeloid leukaemias	BBr6.00	HEMA--Leukemia
[M]Myelosis NOS	BBr6012	HEMA--Leukemia
[M]Other lymphoid leukaemia NOS	BBr2z00	HEMA--Leukemia
[M]Other myeloid leukaemia NOS	BBr6z00	HEMA--Leukemia
[M]Plasma cell leukaemias	BBr3.00	HEMA--Leukemia
[M]Prolymphocytic leukaemia	BBr2500	HEMA--Leukemia
[M]Stem cell leukaemia	BBr0113	HEMA--Leukemia
[M]Thrombocytic leukaemia	BBrA111	HEMA--Leukemia
[X]Other lymphoid leukaemia	ByuD500	HEMA--Leukemia
Acute erythraemia and erythroleukaemia	B670.00	HEMA--Leukemia
Acute leukaemia NOS	B680.00	HEMA--Leukemia
Acute lymphoid leukaemia	B640.00	HEMA--Leukemia
Acute monocytic leukaemia	B660.00	HEMA--Leukemia
Acute myelofibrosis	B675.00	HEMA--Leukemia
Acute myeloid leukaemia	B650.00	HEMA--Leukemia
Acute myelomonocytic leukaemia	B690.00	HEMA--Leukemia
Acute promyelocytic leukaemia	B65y100	HEMA--Leukemia
Adult T-cell leukaemia	B64y200	HEMA--Leukemia
Aleukaemic myeloid leukaemia	B65y000	HEMA--Leukemia
Chloroma	B653000	HEMA--Leukemia
Chronic eosinophilic leukaemia	B651000	HEMA--Leukemia
Chronic erythraemia	B671.00	HEMA--Leukemia

Cancer description	Med Code	Cancer type
Chronic granulocytic leukaemia	B651.11	HEMA--Leukemia
Chronic leukaemia NOS	B681.00	HEMA--Leukemia
Chronic lymphatic leukaemia	B641.11	HEMA--Leukemia
Chronic lymphoid leukaemia	B641.00	HEMA--Leukemia
Chronic monocytic leukaemia	B661.00	HEMA--Leukemia
Chronic myeloid leukaemia	B651.00	HEMA--Leukemia
Chronic myeloid leukaemia NOS	B651z00	HEMA--Leukemia
Chronic myelomonocytic leukaemia	B691.00	HEMA--Leukemia
Di Guglielmo's disease	B670.11	HEMA--Leukemia
Hairy cell leukaemia	B624.12	HEMA--Leukemia
Heilmeyer - Schoner disease	B671.11	HEMA--Leukemia
Histiocytic leukaemia	B66..11	HEMA--Leukemia
Leukaemia NOS	B68z.00	HEMA--Leukemia
Leukaemia of unspecified cell type	B68..00	HEMA--Leukemia
Leukaemic reticuloend of intra-abdominal lymph nodes	B624300	HEMA--Leukemia
Leukaemic reticuloendotheliosis	B624.00	HEMA--Leukemia
Leukaemic reticuloendotheliosis	B624.11	HEMA--Leukemia
Leukaemic reticuloendotheliosis of unspecified sites	B624000	HEMA--Leukemia
Lymphatic leukaemia	B64..11	HEMA--Leukemia
Lymphoid leukaemia	B64..00	HEMA--Leukemia
Lymphoid leukaemia NOS	B64z.00	HEMA--Leukemia
Malignant neoplasm lymphatic or haematopoietic tissue OS	B6y..00	HEMA--Leukemia
Mast cell leukaemia	B673.00	HEMA--Leukemia
Monoblastic leukaemia	B66..12	HEMA--Leukemia
Monocytic leukaemia	B66..00	HEMA--Leukemia
Monocytic leukaemia NOS	B66z.00	HEMA--Leukemia
Myeloid leukaemia	B65..00	HEMA--Leukemia
Myeloid leukaemia NOS	B65z.00	HEMA--Leukemia
Myeloid sarcoma	B653.00	HEMA--Leukemia
Myelomonocytic leukaemia	B69..00	HEMA--Leukemia
Myeloproliferative disease	B6y0.11	HEMA--Leukemia
Myeloproliferative disorder	B6y0.00	HEMA--Leukemia
Myelosclerosis with myeloid metaplasia	B6y1.00	HEMA--Leukemia
Other and unspecified leukaemia	B67y.00	HEMA--Leukemia
Other leukaemia of unspecified cell type	B68y.00	HEMA--Leukemia
Other lymphoid leukaemia	B64y.00	HEMA--Leukemia
Other lymphoid leukaemia NOS	B64yz00	HEMA--Leukemia
Other myeloid leukaemia NOS	B65yz00	HEMA--Leukemia
Other specified leukaemia	B67..00	HEMA--Leukemia
Other specified leukaemia NOS	B67z.00	HEMA--Leukemia
Prolymphocytic leukaemia	B64y100	HEMA--Leukemia
Subacute lymphoid leukaemia	B642.00	HEMA--Leukemia
Subacute myeloid leukaemia	B652.00	HEMA--Leukemia
Thrombocytic leukaemia	B672.11	HEMA--Leukemia
[X]Additional neoplasm classification terms	Byu..00	HEMA--Myeloma
Immunoproliferative neoplasm or myeloma NOS	B63z.00	HEMA--Myeloma
Kahler's disease	B630.11	HEMA--Myeloma
Lambda light chain myeloma	B630300	HEMA--Myeloma
Malignant plasma cell neoplasm, extramedullary plasmacytoma	B630000	HEMA--Myeloma
Multiple myeloma	B630.00	HEMA--Myeloma

Cancer description	Med Code	Cancer type
Multiple myeloma and immunoproliferative neoplasms	B63..00	HEMA--Myeloma
Myelomatosis	B630.12	HEMA--Myeloma
Other immunoproliferative neoplasms	B63y.00	HEMA--Myeloma
Plasma cell leukaemia	B631.00	HEMA--Myeloma
Plasmacytoma NOS	B630200	HEMA--Myeloma
Solitary myeloma	B630100	HEMA--Myeloma
[M]Adenoma of the nipple	BB9A.11	Breast
[M]Comedocarcinoma NOS	BB93.00	Breast
[M]Cystosarcoma phyllodes NOS	BBM8.00	Breast
[M]Cystosarcoma phyllodes, malignant	BBM9.00	Breast
[M]Duct adenoma NOS	BB95.11	Breast
[M]Duct carcinoma NOS	BB91.11	Breast
[M]Ductal papilloma	BB95.12	Breast
[M]Ductal, lobular and medullary neoplasms	BB9..00	Breast
[M]Ductal, lobular or medullary neoplasm NOS	BB9z.00	Breast
[M]Erosive nipple adenomatosis	BB9A.12	Breast
[M]Infiltrating duct and lobular carcinoma	BB91100	Breast
[M]Infiltrating duct carcinoma	BB91.00	Breast
[M]Intracystic carcinoma NOS	BB9M.00	Breast
[M]Intracystic papillary adenoma	BB97.00	Breast
[M]Intraductal carcinoma, noninfiltrating NOS	BB90.00	Breast
[M]Intraductal papillary adenocarcinoma with invasion	BB91000	Breast
[M]Intraductal papilloma	BB95.00	Breast
[M]Intraductal papillomatosis NOS	BB99.00	Breast
[M]Juvenile breast carcinoma	BB94.00	Breast
[M]Secretory breast carcinoma	BB94.11	Breast
[M]Subareolar duct papillomatosis	BB9A.00	Breast
[X]Malignant neoplasm of breast	Byu6.00	Breast
Ca female breast	B34..11	Breast
Cystosarcoma phyllodes	B933.11	Breast
Malignant neoplasm of areola of female breast	B340100	Breast
Malignant neoplasm of areola of male breast	B350100	Breast
Malignant neoplasm of axillary tail of female breast	B346.00	Breast
Malignant neoplasm of central part of female breast	B341.00	Breast
Malignant neoplasm of female breast	B34..00	Breast
Malignant neoplasm of female breast NOS	B34z.00	Breast
Malignant neoplasm of lower-inner quadrant of female breast	B343.00	Breast
Malignant neoplasm of lower-outer quadrant of female breast	B345.00	Breast
Malignant neoplasm of male breast	B35..00	Breast
Malignant neoplasm of male breast NOS	B35zz00	Breast
Malignant neoplasm of nipple and areola of female breast	B340.00	Breast
Malignant neoplasm of nipple and areola of male breast	B350.00	Breast
Malignant neoplasm of nipple of female breast	B340000	Breast
Malignant neoplasm of nipple of male breast	B350000	Breast
Malignant neoplasm of nipple or areola of female breast NOS	B340z00	Breast
Malignant neoplasm of other site of female breast	B34y.00	Breast
Malignant neoplasm of other site of female breast NOS	B34yz00	Breast
Malignant neoplasm of upper-inner quadrant of female breast	B342.00	Breast
Malignant neoplasm of upper-outer quadrant of female breast	B344.00	Breast
Malignant neoplasm, overlapping lesion of breast	B347.00	Breast

Cancer description	Med Code	Cancer type
Neoplasm of uncertain behaviour of breast	B933.00	Breast
Neoplasm of unspecified nature of breast	BA03.00	Breast
[X]Malignant melanoma of other+unspecified parts of face	Byu4000	DERM--Melanoma
[X]Malignant melanoma of skin, unspecified	Byu4100	DERM--Melanoma
H/O Malignant melanoma	1425000	DERM--Melanoma
Malignant melanoma of ankle	B327500	DERM--Melanoma
Malignant melanoma of auricle (ear)	B322000	DERM--Melanoma
Malignant melanoma of axilla	B325000	DERM--Melanoma
Malignant melanoma of back	B325700	DERM--Melanoma
Malignant melanoma of breast	B325100	DERM--Melanoma
Malignant melanoma of buttock	B325200	DERM--Melanoma
Malignant melanoma of chest wall	B325800	DERM--Melanoma
Malignant melanoma of chin	B323100	DERM--Melanoma
Malignant melanoma of ear and external auricular canal	B322.00	DERM--Melanoma
Malignant melanoma of external surface of cheek	B323000	DERM--Melanoma
Malignant melanoma of external surface of nose	B323400	DERM--Melanoma
Malignant melanoma of eyebrow	B323200	DERM--Melanoma
Malignant melanoma of eyelid including canthus	B321.00	DERM--Melanoma
Malignant melanoma of face NOS	B323z00	DERM--Melanoma
Malignant melanoma of finger	B326400	DERM--Melanoma
Malignant melanoma of foot	B327700	DERM--Melanoma
Malignant melanoma of fore-arm	B326200	DERM--Melanoma
Malignant melanoma of forehead	B323300	DERM--Melanoma
Malignant melanoma of great toe	B327900	DERM--Melanoma
Malignant melanoma of groin	B325300	DERM--Melanoma
Malignant melanoma of hand	B326300	DERM--Melanoma
Malignant melanoma of heel	B327600	DERM--Melanoma
Malignant melanoma of knee	B327200	DERM--Melanoma
Malignant melanoma of lip	B320.00	DERM--Melanoma
Malignant melanoma of lower leg	B327400	DERM--Melanoma
Malignant melanoma of lower limb and hip	B327.00	DERM--Melanoma
Malignant melanoma of lower limb or hip NOS	B327z00	DERM--Melanoma
Malignant melanoma of neck	B324100	DERM--Melanoma
Malignant melanoma of other and unspecified parts of face	B323.00	DERM--Melanoma
Malignant melanoma of other specified skin site	B32y.00	DERM--Melanoma
Malignant melanoma of perianal skin	B325400	DERM--Melanoma
Malignant melanoma of perineum	B325500	DERM--Melanoma
Malignant melanoma of popliteal fossa area	B327300	DERM--Melanoma
Malignant melanoma of scalp	B324000	DERM--Melanoma
Malignant melanoma of scalp and neck	B324.00	DERM--Melanoma
Malignant melanoma of shoulder	B326000	DERM--Melanoma
Malignant melanoma of skin	B32..00	DERM--Melanoma
Malignant melanoma of skin NOS	B32z.00	DERM--Melanoma
Malignant melanoma of temple	B323500	DERM--Melanoma
Malignant melanoma of thigh	B327100	DERM--Melanoma
Malignant melanoma of thumb	B326500	DERM--Melanoma
Malignant melanoma of toe	B327800	DERM--Melanoma
Malignant melanoma of trunk (excluding scrotum)	B325.00	DERM--Melanoma
Malignant melanoma of trunk, excluding scrotum, NOS	B325z00	DERM--Melanoma
Malignant melanoma of umbilicus	B325600	DERM--Melanoma

Cancer description	Med Code	Cancer type
Malignant melanoma of upper arm	B326100	DERM--Melanoma
Malignant melanoma of upper limb and shoulder	B326.00	DERM--Melanoma
Malignant melanoma of upper limb or shoulder NOS	B326z00	DERM--Melanoma
[M]Adnexal and skin appendage neoplasms	BB6..00	DERM--Basal
[M]Basal cell adenoma	BB5A.00	DERM--Basal
[M]Basal cell carcinoma NOS	BB31.00	DERM--Basal
[M]Basal cell carcinoma, fibroepithelial type	BB34.00	DERM--Basal
[M]Basal cell carcinoma, morphoea type	BB33.00	DERM--Basal
[M]Basal cell neoplasm NOS	BB3z.00	DERM--Basal
[M]Basal cell neoplasms	BB3..00	DERM--Basal
[M]Basal cell tumour	BB30.00	DERM--Basal
[M]Basosquamous carcinoma	BB35.00	DERM--Basal
[M]Granular cell carcinoma	BB5b.00	DERM--Basal
[M]Metatypical carcinoma	BB36.00	DERM--Basal
[M]Multicentric basal cell carcinoma	BB32.00	DERM--Basal
[M]Skin appendage carcinoma	BB60100	DERM--Basal
Basal cell carcinoma	B33..11	DERM--Basal
Epithelioma basal cell	B33..16	DERM--Basal
Cervical carcinoma (uterus)	B41..11	GU--Cervix
Malignant neoplasm of cervical stump	B41y000	GU--Cervix
Malignant neoplasm of cervix uteri	B41..00	GU--Cervix
Malignant neoplasm of cervix uteri NOS	B41z.00	GU--Cervix
Malignant neoplasm of endocervical canal	B410000	GU--Cervix
Malignant neoplasm of endocervical gland	B410100	GU--Cervix
Malignant neoplasm of endocervix	B410.00	GU--Cervix
Malignant neoplasm of endocervix NOS	B410z00	GU--Cervix
Malignant neoplasm of exocervix	B411.00	GU--Cervix
Malignant neoplasm of other site of cervix	B41y.00	GU--Cervix
Malignant neoplasm of other site of cervix NOS	B41yz00	GU--Cervix
Malignant neoplasm of squamocolumnar junction of cervix	B41y100	GU--Cervix
Malignant neoplasm, overlapping lesion of cervix uteri	B412.00	GU--Cervix
[M]Dysgerminoma	BBQ0.00	GU--Testis
[M]Leydig cell tumour	BBCC.00	GU--Testis
[M]Pick's tubular adenoma	BBC9.11	GU--Testis
[M]Seminoma NOS	BBQ1z00	GU--Testis
[M]Seminoma, anaplastic type	BBQ1000	GU--Testis
[M]Seminomas	BBQ1.00	GU--Testis
[M]Sertoli cell carcinoma	BBCA.00	GU--Testis
[M]Sertoli cell tumour	BBC9.13	GU--Testis
[M]Spermatocytic seminoma	BBQ1100	GU--Testis
[M]Testicular adenoma	BBC9.14	GU--Testis
[M]Testicular stromal tumour	BBC0.13	GU--Testis
Malignant neoplasm of descended testis	B471.00	GU--Testis
Malignant neoplasm of descended testis NOS	B471z00	GU--Testis
Malignant neoplasm of testis	B47..00	GU--Testis
Malignant neoplasm of testis NOS	B47z.00	GU--Testis
Malignant neoplasm of undescended testis	B470.00	GU--Testis
Neoplasm of uncertain behaviour of testis	B914.00	GU--Testis
Seminoma of descended testis	B471000	GU--Testis
Seminoma of testis	B47z.11	GU--Testis

Cancer description	Med Code	Cancer type
Seminoma of undescended testis	B470200	GU--Testis
Teratoma of descended testis	B471100	GU--Testis
Teratoma of testis	B47z.12	GU--Testis
Teratoma of undescended testis	B470300	GU--Testis
[M]Borderline mucinous cystadenoma of the ovary	BB80200	GU--Ovary
[M]Brenner tumour NOS	BBM0z00	GU--Ovary
[M]Brenner tumour, borderline malignancy	BBM0000	GU--Ovary
[M]Brenner tumour, malignant	BBM0100	GU--Ovary
[M]Brenner tumours	BBM0.00	GU--Ovary
[M]Hilar cell tumour	BBCD.00	GU--Ovary
[M]Lipid cell tumour of ovary	BBCE.00	GU--Ovary
[M]Ovarian cystadenoma or carcinoma	BB81.11	GU--Ovary
[M]Ovarian cystic, mucinous and serous neoplasms	BB81.00	GU--Ovary
[M]Ovarian cystic, mucinous or serous neoplasm NOS	BB81z00	GU--Ovary
[M]Ovarian mucinous tumour	BB81.12	GU--Ovary
[M]Ovarian papillary tumour	BB81.13	GU--Ovary
[M]Ovarian serous tumour	BB81.14	GU--Ovary
[M]Ovarian stromal tumour	BBC0.12	GU--Ovary
[M]Papillary cystadenocarcinoma, NOS	BB81500	GU--Ovary
[M]Papillary cystadenoma NOS	BB81300	GU--Ovary
[M]Papillary cystadenoma, borderline malignancy	BB81400	GU--Ovary
[M]Papillary serous cystadenocarcinoma	BB81800	GU--Ovary
[M]Papillary serous cystadenoma NOS	BB81600	GU--Ovary
[M]Papillary serous cystadenoma, borderline malignancy	BB81700	GU--Ovary
[M]Serous cystadenocarcinoma, NOS	BB81200	GU--Ovary
[M]Serous cystadenoma NOS	BB81000	GU--Ovary
[M]Serous cystadenoma, borderline malignancy	BB81100	GU--Ovary
[M]Struma ovarii NOS	BBQA000	GU--Ovary
[M]Struma ovarii, malignant	BBQA100	GU--Ovary
[M]Strumal carcinoid	BBQA200	GU--Ovary
Cancer of ovary	B440.11	GU--Ovary
Malignant neoplasm of ovary	B440.00	GU--Ovary
Malignant neoplasm of ovary and other uterine adnexa	B44..00	GU--Ovary
Neoplasm of uncertain behaviour of ovary	B912.00	GU--Ovary
Malignant neoplasm of prostate	B46..00	GU--Prostate
Neoplasm of uncertain behaviour of prostate	B915.00	GU--Prostate
[M]Adenofibroma NOS	BBM4.00	GU--Uterus
[M]Cellular intracanalicular fibroadenoma	BBM7.00	GU--Uterus
[M]Cystadenofibroma NOS	BBM4.11	GU--Uterus
[M]Endometrial stromal sarcoma	BBL0.00	GU--Uterus
[M]Endometrioid adenoma NOS	BB5j000	GU--Uterus
[M]Endometrioid adenoma or carcinoma NOS	BB5jz00	GU--Uterus
[M]Endometrioid adenoma, borderline malignancy	BB5j100	GU--Uterus
[M]Endometrioid adenomas and carcinomas	BB5j.00	GU--Uterus
[M]Endometrioid carcinoma	BB5j200	GU--Uterus
[M]Endometrioid cystadenoma NOS	BB5j011	GU--Uterus
[M]Fibroadenoma phyllodes	BBM7.12	GU--Uterus
[M]Giant fibroadenoma NOS	BBM7.13	GU--Uterus
[M]Intracanalicular fibroadenoma NOS	BBM2.00	GU--Uterus
[M]Mucinous adenofibroma	BBM6.00	GU--Uterus

Cancer description	Med Code	Cancer type
[M]Serous adenofibroma	BBM5.00	GU--Uterus
[M]Tubular adenocarcinoma	BB5M100	GU--Uterus
[M]Tubular adenoma NOS	BB5M000	GU--Uterus
[M]Tubular adenoma or adenocarcinoma NOS	BB5Mz00	GU--Uterus
[M]Tubular adenomas and adenocarcinomas	BB5M.00	GU--Uterus
Malignant neoplasm of body of uterus	B43..00	GU--Uterus
Malignant neoplasm of body of uterus NOS	B43z.00	GU--Uterus
Malignant neoplasm of cornu of corpus uteri	B430000	GU--Uterus
Malignant neoplasm of corpus uteri NOS	B430z00	GU--Uterus
Malignant neoplasm of corpus uteri, excluding isthmus	B430.00	GU--Uterus
Malignant neoplasm of endometrium	B430211	GU--Uterus
Malignant neoplasm of endometrium of corpus uteri	B430200	GU--Uterus
Malignant neoplasm of fundus of corpus uteri	B430100	GU--Uterus
Malignant neoplasm of isthmus of uterine body	B431.00	GU--Uterus
Malignant neoplasm of isthmus of uterine body NOS	B431z00	GU--Uterus
Malignant neoplasm of lower uterine segment	B431000	GU--Uterus
Malignant neoplasm of myometrium of corpus uteri	B430300	GU--Uterus
Malignant neoplasm of other site of uterine body	B43y.00	GU--Uterus
Malignant neoplasm of overlapping lesion of corpus uteri	B432.00	GU--Uterus
Malignant neoplasm of uterine adnexa NOS	B44z.00	GU--Uterus
Malignant neoplasm of uterus, part unspecified	B40..00	GU--Uterus
Neoplasm of uncertain behaviour of uterus	B910.00	GU--Uterus
[M]Glucagonoma NOS	BB5B400	GI--Pancreas
[M]Glucagonoma, malignant	BB5B500	GI--Pancreas
[M]Insulinoma NOS	BB5B200	GI--Pancreas
[M]Islet cell adenoma	BB5B000	GI--Pancreas
[M]Islet cell carcinoma	BB5B100	GI--Pancreas
[M]Nesidioblastoma	BB5B011	GI--Pancreas
[M]Pancreatic adenoma or carcinoma NOS	BB5Bz00	GI--Pancreas
[M]Pancreatic adenomas and carcinomas	BB5B.00	GI--Pancreas
Malignant neoplasm of body of pancreas	B171.00	GI--Pancreas
Malignant neoplasm of ectopic pancreatic tissue	B17y000	GI--Pancreas
Malignant neoplasm of head of pancreas	B170.00	GI--Pancreas
Malignant neoplasm of Islets of Langerhans	B174.00	GI--Pancreas
Malignant neoplasm of other specified sites of pancreas	B17y.00	GI--Pancreas
Malignant neoplasm of pancreas	B17..00	GI--Pancreas
Malignant neoplasm of pancreas NOS	B17z.00	GI--Pancreas
Malignant neoplasm of pancreatic duct	B173.00	GI--Pancreas
Malignant neoplasm of tail of pancreas	B172.00	GI--Pancreas
Malignant neoplasm, overlapping lesion of pancreas	B175.00	GI--Pancreas
Neoplasm of uncertain behaviour of pancreas	B905100	GI--Pancreas
Gastric neoplasm	B11..11	GI--Upper
Malignant neoplasm of abdominal oesophagus	B102.00	GI--Upper
Malignant neoplasm of body of stomach	B114.00	GI--Upper
Malignant neoplasm of cardia of stomach	B110.00	GI--Upper
Malignant neoplasm of cardia of stomach NOS	B110z00	GI--Upper
Malignant neoplasm of cardiac orifice of stomach	B110000	GI--Upper
Malignant neoplasm of cardio-oesophageal junction of stomach	B110100	GI--Upper
Malignant neoplasm of cervical oesophagus	B100.00	GI--Upper
Malignant neoplasm of fundus of stomach	B113.00	GI--Upper

Cancer description	Med Code	Cancer type
Malignant neoplasm of greater curve of stomach unspecified	B116.00	GI--Upper
Malignant neoplasm of lesser curve of stomach unspecified	B115.00	GI--Upper
Malignant neoplasm of lower third of oesophagus	B105.00	GI--Upper
Malignant neoplasm of middle third of oesophagus	B104.00	GI--Upper
Malignant neoplasm of oesophagus	B10..00	GI--Upper
Malignant neoplasm of oesophagus NOS	B10z.00	GI--Upper
Malignant neoplasm of other specified part of oesophagus	B10y.00	GI--Upper
Malignant neoplasm of other specified site of stomach	B11y.00	GI--Upper
Malignant neoplasm of other specified site of stomach NOS	B11yz00	GI--Upper
Malignant neoplasm of prepylorus of stomach	B111000	GI--Upper
Malignant neoplasm of pyloric antrum of stomach	B112.00	GI--Upper
Malignant neoplasm of pyloric canal of stomach	B111100	GI--Upper
Malignant neoplasm of pylorus of stomach	B111.00	GI--Upper
Malignant neoplasm of pylorus of stomach NOS	B111z00	GI--Upper
Malignant neoplasm of stomach	B11..00	GI--Upper
Malignant neoplasm of stomach NOS	B11z.00	GI--Upper
Malignant neoplasm of thoracic oesophagus	B101.00	GI--Upper
Malignant neoplasm of upper third of oesophagus	B103.00	GI--Upper
Malignant neoplasm, overlapping lesion of oesophagus	B106.00	GI--Upper
Malignant neoplasm, overlapping lesion of stomach	B117.00	GI--Upper
Neoplasm of uncertain behaviour of duodenum	B902100	GI--Upper
Neoplasm of uncertain behaviour of oesophagus	B905000	GI--Upper
Neoplasm of uncertain behaviour of stomach	B902000	GI--Upper
Oesophageal cancer	B10z.11	GI--Upper
[M]Adenocarcinoma in adenomatous polyp	BB5L100	GI--Lower
[M]Adenocarcinoma in multiple adenomatous polyps	BB5L300	GI--Lower
[M]Adenoma or or adenocarcinoma in polyposis coli	BB5N.11	GI--Lower
[M]Adenomatosis NOS	BB5N011	GI--Lower
[M]Adenomatous and adenocarcinomatous polyps	BB5L.00	GI--Lower
[M]Adenomatous and adenocarcinomatous polyps of colon	BB5N.00	GI--Lower
[M]Adenomatous or adenocarcinomatous polyp NOS	BB5Lz00	GI--Lower
[M]Adenomatous or adenocarcinomatous polyps of the colon NOS	BB5Nz00	GI--Lower
[M]Adenomatous polyp NOS	BB5L000	GI--Lower
[M]Adenomatous polyposis coli	BB5N000	GI--Lower
[M]Familial polyposis coli	BB5N012	GI--Lower
[M]Multiple adenomatous polyps	BB5N200	GI--Lower
[M]Multiple polyposis	BB5N211	GI--Lower
[M]Polypoid adenoma	BB5L011	GI--Lower
Anal carcinoma	B142.11	GI--Lower
Cancer of bowel	B1z0.11	GI--Lower
Carcinoma of caecum	B134.11	GI--Lower
Carcinoma of rectum	B141.11	GI--Lower
Colonic cancer	B13z.11	GI--Lower
Malig neop other site rectum, rectosigmoid junction and anus	B14y.00	GI--Lower
Malignant neoplasm of anal canal	B142.00	GI--Lower
Malignant neoplasm of anus unspecified	B143.00	GI--Lower
Malignant neoplasm of appendix	B135.00	GI--Lower
Malignant neoplasm of ascending colon	B136.00	GI--Lower
Malignant neoplasm of caecum	B134.00	GI--Lower
Malignant neoplasm of cloacogenic zone	B142000	GI--Lower

Cancer description	Med Code	Cancer type
Malignant neoplasm of colon	B13..00	GI--Lower
Malignant neoplasm of colon NOS	B13z.00	GI--Lower
Malignant neoplasm of descending colon	B132.00	GI--Lower
Malignant neoplasm of duodenum	B120.00	GI--Lower
Malignant neoplasm of hepatic flexure of colon	B130.00	GI--Lower
Malignant neoplasm of ileum	B122.00	GI--Lower
Malignant neoplasm of jejunum	B121.00	GI--Lower
Malignant neoplasm of Meckel's diverticulum	B123.00	GI--Lower
Malignant neoplasm of other specified site small intestine	B12y.00	GI--Lower
Malignant neoplasm of other specified sites of colon	B13y.00	GI--Lower
Malignant neoplasm of rectosigmoid junction	B140.00	GI--Lower
Malignant neoplasm of rectum	B141.00	GI--Lower
Malignant neoplasm of rectum, rectosigmoid junction and anus	B14..00	GI--Lower
Malignant neoplasm of sigmoid colon	B133.00	GI--Lower
Malignant neoplasm of small intestine and duodenum	B12..00	GI--Lower
Malignant neoplasm of small intestine NOS	B12z.00	GI--Lower
Malignant neoplasm of splenic flexure of colon	B137.00	GI--Lower
Malignant neoplasm of transverse colon	B131.00	GI--Lower
Malignant neoplasm rectum,rectosigmoid junction and anus NOS	B14z.00	GI--Lower
Malignant neoplasm, overlapping lesion of colon	B138.00	GI--Lower
Malignant neoplasm, overlapping lesion of small intestine	B124.00	GI--Lower
Neoplasm of uncertain behaviour of anal canal and sphincter	B905200	GI--Lower
Neoplasm of uncertain behaviour of colon	B902400	GI--Lower
Neoplasm of uncertain behaviour of rectum	B902500	GI--Lower
Neoplasm of uncertain or unknown behaviour of appendix	B902600	GI--Lower
Rectal carcinoma	B141.12	GI--Lower
[M]Basaloid carcinoma	BB48.00	GU--Bladder
[M]Cloacogenic carcinoma	BB49.00	GU--Bladder
[M]Papillary transitional cell carcinoma	BB4A.00	GU--Bladder
[M]Schneiderian papilloma	BB44.00	GU--Bladder
[M]Transitional cell carcinoma NOS	BB43.00	GU--Bladder
[M]Transitional cell carcinoma, spindle cell type	BB47.00	GU--Bladder
[M]Transitional cell papilloma or carcinoma NOS	BB4z.00	GU--Bladder
[M]Transitional cell papilloma, inverted type	BB45.00	GU--Bladder
[M]Urinary bladder papilloma	BB41.11	GU--Bladder
[M]Urothelial carcinoma	BB43.11	GU--Bladder
[M]Urothelial papilloma	BB41.00	GU--Bladder
Malignant neoplasm of anterior wall of urinary bladder	B493.00	GU--Bladder
Malignant neoplasm of bladder neck	B495.00	GU--Bladder
Malignant neoplasm of dome of urinary bladder	B491.00	GU--Bladder
Malignant neoplasm of lateral wall of urinary bladder	B492.00	GU--Bladder
Malignant neoplasm of other site of urinary bladder	B49y.00	GU--Bladder
Malignant neoplasm of posterior wall of urinary bladder	B494.00	GU--Bladder
Malignant neoplasm of trigone of urinary bladder	B490.00	GU--Bladder
Malignant neoplasm of urachus	B497.00	GU--Bladder
Malignant neoplasm of ureteric orifice	B496.00	GU--Bladder
Malignant neoplasm of urinary bladder	B49..00	GU--Bladder
Malignant neoplasm of urinary bladder NOS	B49z.00	GU--Bladder
Malignant neoplasm, overlapping lesion of bladder	B49y000	GU--Bladder
Neoplasm of uncertain behaviour of bladder	B917.00	GU--Bladder

Cancer description	Med Code	Cancer type
Neoplasm of unspecified nature of bladder	BA04.00	GU--Bladder
Transitional cell papilloma of bladder	B917.12	GU--Bladder
[M]Adenosarcoma	BBL7111	GU--Kidney
[M]Adrenal cortical adenoma NOS	BB5h000	GU--Kidney
[M]Adrenal cortical carcinoma	BB5h100	GU--Kidney
[M]Adrenal cortical tumours	BB5h.00	GU--Kidney
[M]Adrenal cortical tumours NOS	BB5hz00	GU--Kidney
[M]Grawitz tumour	BB5a011	GU--Kidney
[M]Hypernephroma	BB5a012	GU--Kidney
[M]Mesoblastic nephroma	BBL7000	GU--Kidney
[M]Mesonephroma, malignant	BBS2.00	GU--Kidney
[M]Mesonephromas	BBS..00	GU--Kidney
[M]Mixed and stromal renal neoplasms	BBL7.00	GU--Kidney
[M]Nephroblastoma NOS	BBL7100	GU--Kidney
[M]Nephromas and nephroblastomas	BBL7.11	GU--Kidney
[M]Renal adenoma and carcinoma	BB5a.00	GU--Kidney
[M]Renal adenoma or carcinoma NOS	BB5az00	GU--Kidney
[M]Renal cell carcinoma	BB5a000	GU--Kidney
[M]Wilms' tumour	BBL7112	GU--Kidney
Hypernephroma	B4A0000	GU--Kidney
Malig neop of kidney and other unspecified urinary organs	B4A..00	GU--Kidney
Malignant neoplasm of kidney or urinary organs NOS	B4Az.00	GU--Kidney
Malignant neoplasm of kidney parenchyma	B4A0.00	GU--Kidney
Malignant neoplasm of other urinary organs	B4Ay.00	GU--Kidney
Malignant neoplasm of renal calyces	B4A1000	GU--Kidney
Malignant neoplasm of renal pelvis	B4A1.00	GU--Kidney
Malignant neoplasm of renal pelvis NOS	B4A1z00	GU--Kidney
Malignant neoplasm of ureter	B4A2.00	GU--Kidney
Malignant neoplasm of urethra	B4A3.00	GU--Kidney
Neoplasm of uncertain behaviour of kidney	B91z100	GU--Kidney
Neoplasm of uncertain or unknown behaviour of renal pelvis	B91z300	GU--Kidney
Renal malignant neoplasm	B4A..11	GU--Kidney
Renal neoplasm of uncertain behaviour	B91z111	GU--Kidney
Uncertain neoplasm ureter	B91z200	GU--Kidney
[M]Cribriform carcinoma	BB5K.00	Head and Neck
[X]Malignant neoplasm of lip, oral cavity and pharynx	Byu0.00	Head and Neck
Malig neop auditory tube, middle ear and mastoid air cells	B201.00	Head and Neck
Malig neop nasal cavities, middle ear and accessory sinuses	B20..00	Head and Neck
Malig neop other site nasal cavity, middle ear and sinuses	B20y.00	Head and Neck
Malig neop other/ill-defined sites lip, oral cavity, pharynx	B0z..00	Head and Neck
Malignant neoplasm aryepiglottic fold, hypopharyngeal aspect	B082.00	Head and Neck
Malignant neoplasm of accessory sinus NOS	B20z.00	Head and Neck
Malignant neoplasm of adenoid	B071000	Head and Neck
Malignant neoplasm of anterior 2/3 of tongue unspecified	B014.00	Head and Neck
Malignant neoplasm of anterior epiglottis	B064.00	Head and Neck
Malignant neoplasm of anterior epiglottis NOS	B064z00	Head and Neck
Malignant neoplasm of anterior portion of floor of mouth	B040.00	Head and Neck
Malignant neoplasm of anterior wall of nasopharynx	B073.00	Head and Neck
Malignant neoplasm of arytenoid cartilage	B213000	Head and Neck
Malignant neoplasm of base of tongue	B010.00	Head and Neck

Cancer description	Med Code	Cancer type
Malignant neoplasm of base of tongue dorsal surface	B010000	Head and Neck
Malignant neoplasm of buccal mucosa	B050.11	Head and Neck
Malignant neoplasm of cheek mucosa	B050.00	Head and Neck
Malignant neoplasm of cheek NOS	B550100	Head and Neck
Malignant neoplasm of cricoid cartilage	B213100	Head and Neck
Malignant neoplasm of dorsal surface of tongue	B011.00	Head and Neck
Malignant neoplasm of dorsum of tongue NOS	B011z00	Head and Neck
Malignant neoplasm of epiglottis NOS	B215.00	Head and Neck
Malignant neoplasm of epiglottis, free border	B064000	Head and Neck
Malignant neoplasm of ethmoid sinus	B203.00	Head and Neck
Malignant neoplasm of faucial pillar	B062000	Head and Neck
Malignant neoplasm of faucial tonsil	B060000	Head and Neck
Malignant neoplasm of floor of mouth	B04..00	Head and Neck
Malignant neoplasm of floor of mouth NOS	B04z.00	Head and Neck
Malignant neoplasm of frenulum linguae	B013100	Head and Neck
Malignant neoplasm of frontal sinus	B204.00	Head and Neck
Malignant neoplasm of glossoepiglottic fold	B064100	Head and Neck
Malignant neoplasm of glottis	B210.00	Head and Neck
Malignant neoplasm of gum	B03..00	Head and Neck
Malignant neoplasm of gum NOS	B03z.00	Head and Neck
Malignant neoplasm of hard palate	B052.00	Head and Neck
Malignant neoplasm of head NOS	B550000	Head and Neck
Malignant neoplasm of head, neck and face	B550.00	Head and Neck
Malignant neoplasm of head, neck and face NOS	B550z00	Head and Neck
Malignant neoplasm of hypopharynx	B08..00	Head and Neck
Malignant neoplasm of hypopharynx NOS	B08z.00	Head and Neck
Malignant neoplasm of jaw NOS	B550300	Head and Neck
Malignant neoplasm of junctional region of epiglottis	B065.00	Head and Neck
Malignant neoplasm of laryngeal cartilage	B213.00	Head and Neck
Malignant neoplasm of laryngopharynx	B0z2.00	Head and Neck
Malignant neoplasm of larynx	B21..00	Head and Neck
Malignant neoplasm of larynx NOS	B21z.00	Head and Neck
Malignant neoplasm of larynx, other specified site	B21y.00	Head and Neck
Malignant neoplasm of lateral portion of floor of mouth	B041.00	Head and Neck
Malignant neoplasm of lateral wall of nasopharynx NOS	B072z00	Head and Neck
Malignant neoplasm of lateral wall of oropharynx	B066.00	Head and Neck
Malignant neoplasm of lingual tonsil	B016.00	Head and Neck
Malignant neoplasm of lip, oral cavity and pharynx NOS	B0zz.00	Head and Neck
Malignant neoplasm of lower buccal sulcus	B051100	Head and Neck
Malignant neoplasm of lower gum	B031.00	Head and Neck
Malignant neoplasm of major salivary gland NOS	B02z.00	Head and Neck
Malignant neoplasm of major salivary glands	B02..00	Head and Neck
Malignant neoplasm of mastoid air cells	B201300	Head and Neck
Malignant neoplasm of maxillary sinus	B202.00	Head and Neck
Malignant neoplasm of mouth NOS	B05z.00	Head and Neck
Malignant neoplasm of nasal cavities	B200.00	Head and Neck
Malignant neoplasm of nasal cavities NOS	B200z00	Head and Neck
Malignant neoplasm of nasopharynx	B07..00	Head and Neck
Malignant neoplasm of nasopharynx NOS	B07z.00	Head and Neck
Malignant neoplasm of neck NOS	B550400	Head and Neck

Cancer description	Med Code	Cancer type
Malignant neoplasm of nose NOS	B550200	Head and Neck
Malignant neoplasm of oropharynx	B06..00	Head and Neck
Malignant neoplasm of oropharynx NOS	B06z.00	Head and Neck
Malignant neoplasm of oropharynx, other specified sites	B06y.00	Head and Neck
Malignant neoplasm of other and unspecified parts of mouth	B05..00	Head and Neck
Malignant neoplasm of other major salivary glands	B02y.00	Head and Neck
Malignant neoplasm of other sites lip, oral cavity, pharynx	B0zy.00	Head and Neck
Malignant neoplasm of other sites of floor of mouth	B04y.00	Head and Neck
Malignant neoplasm of other specified hypopharyngeal site	B08y.00	Head and Neck
Malignant neoplasm of other specified mouth parts	B05y.00	Head and Neck
Malignant neoplasm of other specified site of oropharynx NOS	B06yz00	Head and Neck
Malignant neoplasm of overlapping lesion of tonsil	B060200	Head and Neck
Malignant neoplasm of palate NOS	B055z00	Head and Neck
Malignant neoplasm of palate unspecified	B055.00	Head and Neck
Malignant neoplasm of palatine tonsil	B060100	Head and Neck
Malignant neoplasm of palatoglossal arch	B062200	Head and Neck
Malignant neoplasm of parotid gland	B020.00	Head and Neck
Malignant neoplasm of pharyngeal recess	B072000	Head and Neck
Malignant neoplasm of pharyngeal tonsil	B071100	Head and Neck
Malignant neoplasm of pharynx unspecified	B0z0.00	Head and Neck
Malignant neoplasm of postcricoid region	B080.00	Head and Neck
Malignant neoplasm of posterior pharynx	B083.00	Head and Neck
Malignant neoplasm of posterior wall of nasopharynx	B071.00	Head and Neck
Malignant neoplasm of posterior wall of nasopharynx NOS	B071z00	Head and Neck
Malignant neoplasm of pyriform sinus	B081.00	Head and Neck
Malignant neoplasm of retromolar area	B056.00	Head and Neck
Malignant neoplasm of roof of mouth	B055100	Head and Neck
Malignant neoplasm of roof of nasopharynx	B070.00	Head and Neck
Malignant neoplasm of septum of nose	B200200	Head and Neck
Malignant neoplasm of soft palate	B053.00	Head and Neck
Malignant neoplasm of sphenoidal sinus	B205.00	Head and Neck
Malignant neoplasm of subglottis	B212.00	Head and Neck
Malignant neoplasm of sublingual gland	B022.00	Head and Neck
Malignant neoplasm of submandibular gland	B021.00	Head and Neck
Malignant neoplasm of supraclavicular fossa NOS	B550500	Head and Neck
Malignant neoplasm of supraglottis	B211.00	Head and Neck
Malignant neoplasm of thyroid cartilage	B213300	Head and Neck
Malignant neoplasm of tongue	B01..00	Head and Neck
Malignant neoplasm of tongue NOS	B01z.00	Head and Neck
Malignant neoplasm of tongue, junctional zone	B015.00	Head and Neck
Malignant neoplasm of tongue, tip and lateral border	B012.00	Head and Neck
Malignant neoplasm of tonsil	B060.00	Head and Neck
Malignant neoplasm of tonsillar fossa	B061.00	Head and Neck
Malignant neoplasm of tonsillar fossa NOS	B062z00	Head and Neck
Malignant neoplasm of tonsillar pillar	B062.00	Head and Neck
Malignant neoplasm of tympanic cavity	B201100	Head and Neck
Malignant neoplasm of upper gum	B030.00	Head and Neck
Malignant neoplasm of uvula	B054.00	Head and Neck
Malignant neoplasm of vallecula	B063.00	Head and Neck
Malignant neoplasm of ventral surface of tongue	B013.00	Head and Neck

Cancer description	Med Code	Cancer type
Malignant neoplasm of ventral tongue surface NOS	B013z00	Head and Neck
Malignant neoplasm of vestibule of nose	B200300	Head and Neck
Malignant neoplasm tonsil NOS	B060z00	Head and Neck
Malignant neoplasm, overlapping lesion of accessory sinuses	B206.00	Head and Neck
Malignant neoplasm, overlapping lesion of floor of mouth	B042.00	Head and Neck
Malignant neoplasm, overlapping lesion of larynx	B214.00	Head and Neck
Malignant neoplasm, overlapping lesion of nasopharynx	B074.00	Head and Neck
Malignant overlapping lesion of tongue	B017.00	Head and Neck
Mixed parotid tumour	B900011	Head and Neck
Neoplasm of uncertain behaviour of aryepiglottic fold	B906600	Head and Neck
Neoplasm of uncertain behaviour of cheek	B901500	Head and Neck
Neoplasm of uncertain behaviour of epiglottis	B906200	Head and Neck
Neoplasm of uncertain behaviour of ethmoidal sinus	B90z600	Head and Neck
Neoplasm of uncertain behaviour of floor of mouth	B901400	Head and Neck
Neoplasm of uncertain behaviour of gums	B901300	Head and Neck
Neoplasm of uncertain behaviour of hypopharynx	B901900	Head and Neck
Neoplasm of uncertain behaviour of larynx	B906.00	Head and Neck
Neoplasm of uncertain behaviour of major salivary glands	B900.00	Head and Neck
Neoplasm of uncertain behaviour of mastoid air cells	B90z400	Head and Neck
Neoplasm of uncertain behaviour of maxillary sinus	B90z500	Head and Neck
Neoplasm of uncertain behaviour of nasopharynx	B901700	Head and Neck
Neoplasm of uncertain behaviour of oral cavity	B901.11	Head and Neck
Neoplasm of uncertain behaviour of oropharynx	B901800	Head and Neck
Neoplasm of uncertain behaviour of palate	B901600	Head and Neck
Neoplasm of uncertain behaviour of parotid gland	B900000	Head and Neck
Neoplasm of uncertain behaviour of pharynx	B901.12	Head and Neck
Neoplasm of uncertain behaviour of submandibular gland	B900200	Head and Neck
Neoplasm of uncertain behaviour of thyroid cartilage	B906000	Head and Neck
Neoplasm of uncertain behaviour of tongue	B901100	Head and Neck
Neoplasm of uncertain behaviour of trachea	B907000	Head and Neck
Neoplasm of uncertain behaviour of tympanic cavity	B90z100	Head and Neck
Neoplasm of uncertain behaviour of vocal cord	B906800	Head and Neck
Overlapping lesion of other and unspecified parts of mouth	B057.00	Head and Neck
[M] Epithelioid cell naevus	BBEb.00	DERM--NOS
[M] Spitz naevus	BBEN.13	DERM--NOS
[M]Abdominal desmoid	BBGB.11	DERM--NOS
[M]Abdominal fibromatosis	BBGB.00	DERM--NOS
[M]Achromic naevus	BBE9.11	DERM--NOS
[M]Acral lentiginous melanoma, malignant	BBEG000	DERM--NOS
[M]Adenoid squamous cell carcinoma	BB2G.00	DERM--NOS
[M]Aggressive fibromatosis	BBGA.00	DERM--NOS
[M]Amelanotic melanoma	BBEA.00	DERM--NOS
[M]Angioblastoma	BBTF.11	DERM--NOS
[M]Angioendothelioma	BBT7z11	DERM--NOS
[M]Angiofibroma NOS	BBTE.00	DERM--NOS
[M]Angiokeratoma	BBTB.00	DERM--NOS
[M]Angioma NOS	BBT0.11	DERM--NOS
[M]Angiosarcoma	BBT1.11	DERM--NOS
[M]Arteriovenous haemangioma	BBT4.11	DERM--NOS
[M]Atypical fibrous histiocytoma	BBGE.00	DERM--NOS

Cancer description	Med Code	Cancer type
[M]Atypical fibroxanthoma	BBGH.00	DERM--NOS
[M]Basal cell adenocarcinoma	BB5y000	DERM--NOS
[M]Blood vessel tumours	BBT..00	DERM--NOS
[M]Blue naevus NOS	BBEU.00	DERM--NOS
[M]Blue naevus, malignant	BBEV.00	DERM--NOS
[M]Capillary haemangioma	BBT8.00	DERM--NOS
[M]Cavernous haemangioma	BBT2.00	DERM--NOS
[M]Cellular blue naevus	BBEW.00	DERM--NOS
[M]Chorioangioma	BBT0.12	DERM--NOS
[M]Compound naevus	BBEK.00	DERM--NOS
[M]Dermal naevus	BBEJ.11	DERM--NOS
[M]Dermatofibroma lenticulare	BBGK.11	DERM--NOS
[M]Dermatofibroma NOS	BBGK.00	DERM--NOS
[M]Dermatofibroma protuberans	BBGL.00	DERM--NOS
[M]Dermatofibrosarcoma NOS	BBGM.00	DERM--NOS
[M]Desmoid NOS	BBGA.11	DERM--NOS
[M]Desmoplastic fibroma	BBGC.00	DERM--NOS
[M]Desmoplastic melanoma, malignant	BBE1100	DERM--NOS
[M]Dyskeratotic papilloma	BB25.11	DERM--NOS
[M]Dysplastic naevus	BBEY.00	DERM--NOS
[M]Eccrine dermal cylindroma	BB5H.00	DERM--NOS
[M]Elastofibroma	BBG9.00	DERM--NOS
[M]Epidermoid carcinoma NOS	BB2A.11	DERM--NOS
[M]Epidermoid carcinoma, keratinising type	BB2C.11	DERM--NOS
[M]Epithelial neoplasms NOS	BB1..00	DERM--NOS
[M]Epithelioid and spindle cell naevus	BBEN.00	DERM--NOS
[M]Epithelioid haemangioendothelioma NOS	BBTJ.00	DERM--NOS
[M]Epithelioid haemangioendothelioma, malignant	BBTK.00	DERM--NOS
[M]Epithelioid haemangioma	BBTG.00	DERM--NOS
[M]Epitheliomaadenoides cyst	BB38.12	DERM--NOS
[M]Extra-abdominal desmoid	BBGA.12	DERM--NOS
[M]Fascial fibroma	BBG6.00	DERM--NOS
[M]Fibroma durum	BBG0.11	DERM--NOS
[M]Fibroma NOS	BBG0.00	DERM--NOS
[M]Fibromatous neoplasm NOS	BBGz.00	DERM--NOS
[M]Fibromatous neoplasms	BBG..00	DERM--NOS
[M]Fibromyxoma	BBG2.00	DERM--NOS
[M]Fibromyxosarcoma	BBG3.00	DERM--NOS
[M]Fibrosarcoma NOS	BBG1.00	DERM--NOS
[M]Fibrous histiocytoma NOS	BBGD.00	DERM--NOS
[M]Fibrous histiocytoma, malignant	BBGF.00	DERM--NOS
[M]Fibrous papule of nose	BBE6.00	DERM--NOS
[M]Fibroxanthoma NOS	BBGG.00	DERM--NOS
[M]Fibroxanthoma, malignant	BBGJ.00	DERM--NOS
[M]Fibroxanthosarcoma	BBGJ.11	DERM--NOS
[M]Giant pigmented naevus	BBEL.00	DERM--NOS
[M]Haemangioblastoma	BBTF.00	DERM--NOS
[M]Haemangioendothelioma, malignant	BBT7100	DERM--NOS
[M]Haemangioma NOS	BBT0.00	DERM--NOS
[M]Haemangiomatous tumours	BBT..11	DERM--NOS

Cancer description	Med Code	Cancer type
[M]Haemangiopericytoma NOS	BBTD100	DERM--NOS
[M]Haemangiosarcoma	BBT1.00	DERM--NOS
[M]Hairy naevus NOS	BBE0.11	DERM--NOS
[M]Halo naevus	BBE5.00	DERM--NOS
[M]Histiocytoid haemangioma	BBTH.00	DERM--NOS
[M]Histiocytoma NOS	BBGK.12	DERM--NOS
[M]Hutchinson's melanotic freckle	BBEF.00	DERM--NOS
[M]Hyperkeratotic papilloma	BB25.12	DERM--NOS
[M]Infantile fibrosarcoma	BBG8.00	DERM--NOS
[M]Infantile haemangioma	BBT8.12	DERM--NOS
[M]Intradermal naevus	BBEJ.00	DERM--NOS
[M]Intraepidermal carcinoma NOS	BB29.12	DERM--NOS
[M]Intraepidermal epithelioma of Jadassohn	BB37.00	DERM--NOS
[M]Intraepidermal naevus	BBEB.11	DERM--NOS
[M]Intraepithelial squamous cell carcinoma	BB29.13	DERM--NOS
[M]Intramuscular haemangioma	BBT9.00	DERM--NOS
[M]Intravascular bronchial alveolar tumour	BBTL.00	DERM--NOS
[M]Invasive fibroma	BBGA.13	DERM--NOS
[M]Inverted papilloma	BB27.00	DERM--NOS
[M]Involuting naevus	BBE6.11	DERM--NOS
[M]Jadassohn's blue naevus	BBEU.11	DERM--NOS
[M]Junctional naevus	BBEB.00	DERM--NOS
[M]Juvenila melanoma	BBEN.11	DERM--NOS
[M]Juvenila naevus	BBEN.12	DERM--NOS
[M]Juvenile angiofibroma	BBTE.11	DERM--NOS
[M]Juvenile haemangioma	BBT8.13	DERM--NOS
[M]Kaposi's sarcoma	BBTA.00	DERM--NOS
[M]Keratotic papilloma	BB25.13	DERM--NOS
[M]Lentigo maligna	BBEF.11	DERM--NOS
[M]Lentigo maligna melanoma	BBEG.11	DERM--NOS
[M]Lymphoepithelial carcinoma	BB2M.00	DERM--NOS
[M]Magnocellular naevus	BBE8.00	DERM--NOS
[M]Malherbe's calcified epithelioma	BB3B.11	DERM--NOS
[M]Malignant melanoma in Hutchinson's melanotic freckle	BBEG.00	DERM--NOS
[M]Malignant melanoma in junctional naevus	BBEC.00	DERM--NOS
[M]Malignant melanoma NOS	BBE1.00	DERM--NOS
[M]Malignant melanoma, regressing	BBE1000	DERM--NOS
[M]Melanocarcinoma	BBE1.11	DERM--NOS
[M]Melanocytoma of eyeball	BBE8.11	DERM--NOS
[M]Melanoma in situ	BBEX.00	DERM--NOS
[M]Melanoma NOS	BBE1.12	DERM--NOS
[M]Melanosarcoma NOS	BBE1.13	DERM--NOS
[M]Mixed epithelioid and spindle melanoma	BBET.00	DERM--NOS
[M]Myofibromatosis	BBGN.00	DERM--NOS
[M]Myxofibroma NOS	BBG2.11	DERM--NOS
[M]Naevi and melanomas	BBE..00	DERM--NOS
[M]Naevi or melanoma NOS	BBEz.00	DERM--NOS
[M]Naevocarcinoma	BBE1.14	DERM--NOS
[M]Naevus NOS	BBE0.12	DERM--NOS
[M]Neuronaevus	BBE7.00	DERM--NOS

Cancer description	Med Code	Cancer type
[M]Nodular melanoma	BBE2.00	DERM--NOS
[M]Nonpigmented naevus	BBE9.00	DERM--NOS
[M]Papillary and squamous cell neoplasms	BB2..00	DERM--NOS
[M]Papillary carcinoma NOS	BB22.00	DERM--NOS
[M]Papillary epidermoid carcinoma	BB26.11	DERM--NOS
[M]Papillary neoplasms	BB2..11	DERM--NOS
[M]Papillary or squamous cell neoplasm NOS	BB2z.00	DERM--NOS
[M]Papillary squamous cell carcinoma	BB26.00	DERM--NOS
[M]Papilloma NOS (excluding papilloma of urinary bladder)	BB20.00	DERM--NOS
[M]Papillomatosis NOS	BB28.00	DERM--NOS
[M]Parakeratotic papilloma	BB25.14	DERM--NOS
[M]Periosteal fibroma	BBG4.00	DERM--NOS
[M]Pigmented dermatofibrosarcoma protuberans	BBGP.00	DERM--NOS
[M]Pigmented naevus NOS	BBE0.00	DERM--NOS
[M]Pilomatrixoma	BB3B.00	DERM--NOS
[M]Plexiform haemangioma	BBT8.14	DERM--NOS
[M]Precancerous melanosis NOS	BBED.00	DERM--NOS
[M]Racemose haemangioma	BBT4.00	DERM--NOS
[M]Sclerosing haemangioma	BBGK.13	DERM--NOS
[M]Spindle cell melanoma NOS	BBEQ.00	DERM--NOS
[M]Spindle cell naevus	BBEa.00	DERM--NOS
[M]Squamous cell carcinoma NOS	BB2A.00	DERM--NOS
[M]Squamous cell carcinoma of skin NOS	BB2A.13	DERM--NOS
[M]Squamous cell carcinoma, keratinising type NOS	BB2C.00	DERM--NOS
[M]Squamous cell carcinoma, microinvasive	BB2J.00	DERM--NOS
[M]Squamous cell carcinoma, spindle cell type	BB2F.00	DERM--NOS
[M]Squamous cell neoplasms	BB2..12	DERM--NOS
[M]Squamous cell papilloma	BB25.00	DERM--NOS
[M]Subepidermal nodular fibrosis	BBGK.14	DERM--NOS
[M]Superficial spreading melanoma	BBEH.00	DERM--NOS
[M]Transitional cell papilloma NOS	BB40.00	DERM--NOS
[M]Transitional cell papillomas and carcinomas	BB4..00	DERM--NOS
[M]Trichoepithelioma	BB38.00	DERM--NOS
[M]Trichofolliculoma	BB39.00	DERM--NOS
[M]Tricholemmoma	BB3A.00	DERM--NOS
[M]Turban tumour	BB5H.11	DERM--NOS
[M]Venous haemangioma	BBT3.00	DERM--NOS
[M]Verrucous keratotic haemangioma	BBTC.00	DERM--NOS
[M]Verrucous papilloma	BB23.00	DERM--NOS
[M]Xanthofibroma	BBGG.11	DERM--NOS
[X]Malignant neoplasm of skin, unspecified	Byu4300	DERM--NOS
[X]Malignant neoplasm overlapping lesion of skin	Byu5A00	DERM--NOS
[X]Melanoma and other malignant neoplasms of skin	Byu4.00	DERM--NOS
[X]Oth malignant neoplasm/skin of oth+unspecfd parts of face	Byu4200	DERM--NOS
Basal cell naevus syndrome	B33z111	DERM--NOS
Carcinoma of lip	B00..11	DERM--NOS
Carcinoma of lip, oral cavity and pharynx	B0...11	DERM--NOS
Dermatofibrosarcoma protuberans	B339.00	DERM--NOS
Epithelioma	B33..12	DERM--NOS
Kaposi's sarcoma of skin	B33z000	DERM--NOS

Cancer description	Med Code	Cancer type
Kaposi's sarcoma, unspecified	B59zX00	DERM--NOS
Malig neop skin of ear and external auricular canal NOS	B332z00	DERM--NOS
Malignant neoplasm of canthus	B331000	DERM--NOS
Malignant neoplasm of commissure of lip	B005.00	DERM--NOS
Malignant neoplasm of eyelid including canthus	B331.00	DERM--NOS
Malignant neoplasm of lip	B00..00	DERM--NOS
Malignant neoplasm of lip, oral cavity and pharynx	B0...00	DERM--NOS
Malignant neoplasm of lip, unspecified	B007.00	DERM--NOS
Malignant neoplasm of lip, vermilion border NOS	B00zz00	DERM--NOS
Malignant neoplasm of lower eyelid	B331200	DERM--NOS
Malignant neoplasm of lower lip, buccal aspect	B003000	DERM--NOS
Malignant neoplasm of lower lip, external	B001000	DERM--NOS
Malignant neoplasm of lower lip, inner aspect	B003.00	DERM--NOS
Malignant neoplasm of lower lip, mucosa	B003200	DERM--NOS
Malignant neoplasm of lower lip, vermilion border	B001.00	DERM--NOS
Malignant neoplasm of lower lip, vermilion border NOS	B001z00	DERM--NOS
Malignant neoplasm of other specified skin sites	B33y.00	DERM--NOS
Malignant neoplasm of overlapping lesion of lip	B006.00	DERM--NOS
Malignant neoplasm of perianal skin	B335900	DERM--NOS
Malignant neoplasm of pinna NEC	B332200	DERM--NOS
Malignant neoplasm of scalp	B334000	DERM--NOS
Malignant neoplasm of scalp and skin of neck	B334.00	DERM--NOS
Malignant neoplasm of scalp or skin of neck NOS	B334z00	DERM--NOS
Malignant neoplasm of sebaceous gland	B33..14	DERM--NOS
Malignant neoplasm of skin NOS	B33z.00	DERM--NOS
Malignant neoplasm of skin of abdominal wall	B335300	DERM--NOS
Malignant neoplasm of skin of ankle	B337500	DERM--NOS
Malignant neoplasm of skin of auricle (ear)	B332000	DERM--NOS
Malignant neoplasm of skin of axillary fold	B335000	DERM--NOS
Malignant neoplasm of skin of back	B335700	DERM--NOS
Malignant neoplasm of skin of breast	B335200	DERM--NOS
Malignant neoplasm of skin of buttock	B335800	DERM--NOS
Malignant neoplasm of skin of cheek, external	B333000	DERM--NOS
Malignant neoplasm of skin of chest, excluding breast	B335100	DERM--NOS
Malignant neoplasm of skin of chin	B333100	DERM--NOS
Malignant neoplasm of skin of external auditory meatus	B332100	DERM--NOS
Malignant neoplasm of skin of eyebrow	B333200	DERM--NOS
Malignant neoplasm of skin of finger	B336400	DERM--NOS
Malignant neoplasm of skin of foot	B337700	DERM--NOS
Malignant neoplasm of skin of fore-arm	B336200	DERM--NOS
Malignant neoplasm of skin of forehead	B333300	DERM--NOS
Malignant neoplasm of skin of great toe	B337900	DERM--NOS
Malignant neoplasm of skin of groin	B335500	DERM--NOS
Malignant neoplasm of skin of hand	B336300	DERM--NOS
Malignant neoplasm of skin of hip	B337000	DERM--NOS
Malignant neoplasm of skin of knee	B337200	DERM--NOS
Malignant neoplasm of skin of lip	B330.00	DERM--NOS
Malignant neoplasm of skin of lower leg	B337400	DERM--NOS
Malignant neoplasm of skin of lower limb and hip	B337.00	DERM--NOS
Malignant neoplasm of skin of lower limb or hip NOS	B337z00	DERM--NOS

Cancer description	Med Code	Cancer type
Malignant neoplasm of skin of neck	B334100	DERM--NOS
Malignant neoplasm of skin of nose (external)	B333400	DERM--NOS
Malignant neoplasm of skin of perineum	B335600	DERM--NOS
Malignant neoplasm of skin of popliteal fossa area	B337300	DERM--NOS
Malignant neoplasm of skin of scapular region	B335A00	DERM--NOS
Malignant neoplasm of skin of shoulder	B336000	DERM--NOS
Malignant neoplasm of skin of temple	B333500	DERM--NOS
Malignant neoplasm of skin of thigh	B337100	DERM--NOS
Malignant neoplasm of skin of thumb	B336500	DERM--NOS
Malignant neoplasm of skin of toe	B337800	DERM--NOS
Malignant neoplasm of skin of trunk, excluding scrotum	B335.00	DERM--NOS
Malignant neoplasm of skin of trunk, excluding scrotum, NOS	B335z00	DERM--NOS
Malignant neoplasm of skin of upper arm	B336100	DERM--NOS
Malignant neoplasm of skin of upper limb and shoulder	B336.00	DERM--NOS
Malignant neoplasm of skin of upper limb or shoulder NOS	B336z00	DERM--NOS
Malignant neoplasm of sweat gland	B33..15	DERM--NOS
Malignant neoplasm of upper eyelid	B331100	DERM--NOS
Malignant neoplasm of upper lip, buccal aspect	B002000	DERM--NOS
Malignant neoplasm of upper lip, external	B000000	DERM--NOS
Malignant neoplasm of upper lip, lipstick area	B000100	DERM--NOS
Malignant neoplasm of upper lip, mucosa	B002200	DERM--NOS
Malignant neoplasm of upper lip, oral aspect	B002300	DERM--NOS
Malignant neoplasm of upper lip, vermilion border	B000.00	DERM--NOS
Malignant neoplasm overlapping lesion of skin	B33X.00	DERM--NOS
Malignant neoplasm skin of ear and external auricular canal	B332.00	DERM--NOS
Malignant neoplasm skin of other and unspecified parts face	B333.00	DERM--NOS
Malignant neoplasm skin other and unspec part of face NOS	B333z00	DERM--NOS
Naevoid basal cell carcinoma syndrome	B33z100	DERM--NOS
Neoplasm of uncertain behaviour of lip	B901000	DERM--NOS
Neoplasm of uncertain behaviour of skin	B932.00	DERM--NOS
Neoplasm of unspecified nature of skin	BA02200	DERM--NOS
Other malignant neoplasm of skin	B33..00	DERM--NOS
Rodent ulcer	B33..13	DERM--NOS
Squamous cell carcinoma of skin	B338.00	DERM--NOS
Squamous cell carcinoma of skin NOS	B33z.11	DERM--NOS
[M] Alpha heavy chain disease	BBm6.00	HEMA--NOS
[M] Monoclonal gammopathy	BBm7.00	HEMA--NOS
[M]Acute panmyelosis	BBs1.00	HEMA--NOS
[M]Acute progressive histiocytosis X	BBm3.12	HEMA--NOS
[M]Chronic lymphoproliferative disease	BBs5.00	HEMA--NOS
[M]Chronic myeloproliferative disease	BBs2.00	HEMA--NOS
[M]Idiopathic thrombocythaemia	BBs4.00	HEMA--NOS
[M]Letterer - Siwe disease	BBm3.00	HEMA--NOS
[M]Malignant histiocytosis	BBm1.00	HEMA--NOS
[M]Malignant reticulosis	BBm1.11	HEMA--NOS
[M]Misc myeloproliferative and lymphoproliferative disorders	BBs..00	HEMA--NOS
[M]Misc myeloproliferative or lymphoproliferative dis NOS	BBsz.00	HEMA--NOS
[M]Monostotic myeloma	BBn2.11	HEMA--NOS
[M]Multiple myeloma	BBn0.11	HEMA--NOS
[M]Mycosis fungoides	BBl..00	HEMA--NOS

Cancer description	Med Code	Cancer type
[M]Mycosis fungoides	BBl0.00	HEMA--NOS
[M]Mycosis fungoides NOS	BBlz.00	HEMA--NOS
[M]Myeloma NOS	BBn0.12	HEMA--NOS
[M]Myelomatosis	BBn0.13	HEMA--NOS
[M]Myelosclerosis with myeloid metaplasia	BBs3.00	HEMA--NOS
[M]Plasma cell myeloma	BBn0.00	HEMA--NOS
[M]Plasma cell tumour NOS	BBnz.00	HEMA--NOS
[M]Plasma cell tumours	BBn..00	HEMA--NOS
[M]Plasmacytic myeloma	BBn0.14	HEMA--NOS
[M]Plasmacytoma NOS	BBn2.00	HEMA--NOS
[M]Polycythaemia rubra vera	BBs0.11	HEMA--NOS
[M]Polycythaemia vera	BBs0.00	HEMA--NOS
[M]Waldenstrom's macroglobulinaemia	BBmK.00	HEMA--NOS
Histiocytic tumour NOS	B935.11	HEMA--NOS
Idiopathic thrombocythaemia	B937.12	HEMA--NOS
Malignant histiocytosis	B623.00	HEMA--NOS
Malignant histiocytosis NOS	B623z00	HEMA--NOS
Malignant histiocytosis of intra-abdominal lymph nodes	B623300	HEMA--NOS
Malignant histiocytosis of unspecified site	B623000	HEMA--NOS
Malignant neoplasm of histiocytic tissue	B6...11	HEMA--NOS
Malignant neoplasm of spleen NEC	B1z1.00	HEMA--NOS
Malignant neoplasm of spleen NOS	B1z1z00	HEMA--NOS
Mastocytoma NOS	B935.12	HEMA--NOS
Myelodysplasia	B937.14	HEMA--NOS
Myeloma - solitary	B936.11	HEMA--NOS
Neo/uncertn+unknwn behav/lymph,h'matopetc+rel tiss,unspcf	B93X.00	HEMA--NOS
Neop uncertain behaviour other lymphatic/haematopoietic tiss	B937.00	HEMA--NOS
Neoplasm of uncertain behaviour of histiocytic and mast cell	B935.00	HEMA--NOS
Neoplasm of uncertain behaviour of plasma cells	B936.00	HEMA--NOS
Neoplasm of uncertain behaviour of spleen	B905300	HEMA--NOS
Plasmacytoma NOS	B936.12	HEMA--NOS
Polycythaemia rubra vera	B934.11	HEMA--NOS
Polycythaemia vera	B934.00	HEMA--NOS
Primary polycythaemia	B934.12	HEMA--NOS
[M]Adenocarcinoid tumour	BB5R800	GI--NOS
[M]Chief cell adenoma	BB5c000	GI--NOS
[M]G cell tumour NOS	BB5C011	GI--NOS
[M]Gastrinoma and carcinomas	BB5C.00	GI--NOS
[M]Gastrinoma NOS	BB5C000	GI--NOS
[M]Gastrinoma or carcinoma NOS	BB5Cz00	GI--NOS
[M]Gastrinoma, malignant	BB5C100	GI--NOS
[M]Goblet cell tumour	BB5R611	GI--NOS
[M]Merkel cell carcinoma	BB5RA00	GI--NOS
[X]Malignant neoplasm of digestive organs	Byu1.00	GI--NOS
[X]Malignant neoplasm of intestinal tract, part unspecified	Byu1200	GI--NOS
[X]Malignant neoplsm/ill-defin sites within digestive system	Byu1300	GI--NOS
Carcinoma of digestive organs and peritoneum	B1...11	GI--NOS
Malig neop oth/ill-defined sites digestive tract/peritoneum	B1z..00	GI--NOS
Malignant neoplasm of digestive organs and peritoneum	B1...00	GI--NOS
Malignant neoplasm of digestive tract and peritoneum NOS	B1zz.00	GI--NOS

Cancer description	Med Code	Cancer type
Malignant neoplasm of intestinal tract, part unspecified	B1z0.00	GI--NOS
Malignant neoplasm of mesentery	B18y700	GI--NOS
Malignant neoplasm of omentum	B18y300	GI--NOS
Malignant neoplasm of parietal peritoneum	B18y400	GI--NOS
Malignant neoplasm of pelvic peritoneum	B18y500	GI--NOS
Malignant neoplasm of perinephric tissue	B180100	GI--NOS
Malignant neoplasm of retrocaecal tissue	B180200	GI--NOS
Malignant neoplasm of retroperitoneum	B180.00	GI--NOS
Malignant neoplasm of retroperitoneum and peritoneum	B18..00	GI--NOS
Malignant neoplasm of retroperitoneum and peritoneum NOS	B18z.00	GI--NOS
Malignant neoplasm of retroperitoneum NOS	B180z00	GI--NOS
Malignant neoplasm of specified parts of peritoneum	B18y.00	GI--NOS
Malignant neoplasm of specified parts of peritoneum NOS	B18yz00	GI--NOS
Malignant neoplasm of the pouch of Douglas	B18y600	GI--NOS
Malignant neoplasm other spec digestive tract and peritoneum	B1zy.00	GI--NOS
Malignant neoplasm, overlapping lesion of digestive system	B1z2.00	GI--NOS
Mesothelioma of peritoneum	B181.00	GI--NOS
Neoplasm of uncertain behaviour of peritoneum	B904100	GI--NOS
Neoplasm of uncertain behaviour of retroperitoneum	B904000	GI--NOS
Neoplasm of unspecified nature of digestive system	BA00.00	GI--NOS
Overlapping malign lesion of retroperitoneum and peritoneum	B182.00	GI--NOS
[M]Acidophil adenoma	BB5V200	Endocrinologic
[M]Adrenal rest tumour	BBCF.00	Endocrinologic
[M]Basophil adenoma	BB5V600	Endocrinologic
[M]C cell carcinoma	BB9B.11	Endocrinologic
[M]Carcinoid tumours NOS	BB5Rz00	Endocrinologic
[M]Chromophobe adenoma	BB5V000	Endocrinologic
[M]Chromophobe carcinoma	BB5V100	Endocrinologic
[M]Colloid adenoma	BB5f511	Endocrinologic
[M]Cylindroid adenocarcinoma	BB5J.11	Endocrinologic
[M]Extra-adrenal paraganglioma, NOS	BBD7.00	Endocrinologic
[M]Follicular adenocarcinoma NOS	BB5f100	Endocrinologic
[M]Follicular adenocarcinoma, well differentiated type	BB5f200	Endocrinologic
[M]Follicular adenoma	BB5f000	Endocrinologic
[M]Follicular carcinoma	BB5f111	Endocrinologic
[M]Hurthle cell adenocarcinoma	BB5W111	Endocrinologic
[M]Hurthle cell adenoma	BB5W011	Endocrinologic
[M]Macrofollicular adenoma	BB5f500	Endocrinologic
[M]Medullary carcinoma NOS	BB9B.00	Endocrinologic
[M]Medullary carcinoma with amyloid stroma	BB9C.00	Endocrinologic
[M]Microfollicular adenoma	BB5f400	Endocrinologic
[M]Mucoid cell adenoma	BB5V611	Endocrinologic
[M]Mucoid cell carcinoma	BB5V711	Endocrinologic
[M]Multiple endocrine adenomas	BB5g.00	Endocrinologic
[M]Neuroendocrine carcinoma	BB5R900	Endocrinologic
[M]Oxyphilic adenoma	BB5W000	Endocrinologic
[M]Oxyphilic adenomas and adenocarcinomas	BB5W.00	Endocrinologic
[M]Papillary and follicular adenocarcinoma	BB5f600	Endocrinologic
[M]Parathyroid adenoma or adenocarcinoma NOS	BB5cz00	Endocrinologic

Cancer description	Med Code	Cancer type
[M]Parathyroid adenomas and adenocarcinomas	BB5c.00	Endocrinologic
[M]Phaeochromocytoma NOS	BBD9.00	Endocrinologic
[M]Phaeochromocytoma, malignant	BBDA.00	Endocrinologic
[M]Pituitary adenoma or carcinoma NOS	BB5Vz00	Endocrinologic
[M]Pituitary adenomas and carcinomas	BB5V.00	Endocrinologic
[M]Prolactinoma	BB5y400	Endocrinologic
[M]Thyroid adenoma and adenocarcinoma	BB5f.00	Endocrinologic
[M]Thyroid adenoma or adenocarcinoma NOS	BB5fz00	Endocrinologic
[X]Malignant neoplasm of thyroid and other endocrine glands	ByuB.00	Endocrinologic
Malig neop of endocrine gland or related structure NOS	B54z.00	Endocrinologic
Malig neop of other endocrine glands and related structures	B54..00	Endocrinologic
Malig neop pituitary gland or craniopharyngeal duct NOS	B542z00	Endocrinologic
Malignant neoplasm of adrenal cortex	B540000	Endocrinologic
Malignant neoplasm of adrenal gland	B540.00	Endocrinologic
Malignant neoplasm of adrenal gland NOS	B540z00	Endocrinologic
Malignant neoplasm of aortic body	B545100	Endocrinologic
Malignant neoplasm of aortic body and other paraganglia	B545.00	Endocrinologic
Malignant neoplasm of carotid body	B544.00	Endocrinologic
Malignant neoplasm of coccygeal body	B545200	Endocrinologic
Malignant neoplasm of craniopharyngeal duct	B542100	Endocrinologic
Malignant neoplasm of glomus jugulare	B545000	Endocrinologic
Malignant neoplasm of other specified endocrine gland	B54y.00	Endocrinologic
Malignant neoplasm of parathyroid gland	B541.00	Endocrinologic
Malignant neoplasm of pineal gland	B543.00	Endocrinologic
Malignant neoplasm of pituitary gland	B542000	Endocrinologic
Malignant neoplasm of thyroid gland	B53..00	Endocrinologic
Malignant neoplasm pituitary gland and craniopharyngeal duct	B542.00	Endocrinologic
Neop of uncertain behaviour of endocrine and nervous system	B92..00	Endocrinologic
Neop uncertain behaviour pituitary and craniopharyngeal duct	B920.00	Endocrinologic
Neop uncertain behaviour pituitary and craniopharyngeal NOS	B920z00	Endocrinologic
Neoplasm of uncertain behaviour of craniopharyngeal duct	B920100	Endocrinologic
Neoplasm of uncertain behaviour of endocrine gland NOS	B924z00	Endocrinologic
Neoplasm of uncertain behaviour of parathyroid gland	B924100	Endocrinologic
Neoplasm of uncertain behaviour of pituitary gland	B920000	Endocrinologic
Neoplasm of uncertain behaviour of thyroid gland	B924000	Endocrinologic
Phaeochromocytoma	B540.11	Endocrinologic
[M]Angiomyxoma	BBHZ.00	Chest--(not lung)
[M]Aortic body tumour	BBD5.00	Chest--(not lung)
[M]Carotid body tumour	BBD6.00	Chest--(not lung)
[M]Myxoma NOS	BBH0.00	Chest--(not lung)
[M]Myxomatous neoplasm NOS	BBHz.00	Chest--(not lung)
[M]Myxomatous neoplasms	BBH..00	Chest--(not lung)
[M]Myxosarcoma	BBH1.00	Chest--(not lung)
[M]Thymoma	BBB6.00	Chest--(not lung)
[M]Thymoma NOS	BBB6z00	Chest--(not lung)
[X]Malignant neoplasm/overlap lesion/heart,mediastinm+pleura	Byu2100	Chest--(not lung)
Carcinoma of respiratory tract and intrathoracic organs	B2...11	Chest--(not lung)
Malig neo, overlapping lesion of heart, mediastinum & pleura	B25..00	Chest--(not lung)
Malig neop of respiratory tract and intrathoracic organs	B2...00	Chest--(not lung)
Malig neop of upper respiratory tract, part unspecified	B2z0.00	Chest--(not lung)

Cancer description	Med Code	Cancer type
Malig neop other/ill-defined sites resp/intrathoracic organs	B2z..00	Chest--(not lung)
Malignant neoplasm of anterior mediastinum	B242.00	Chest--(not lung)
Malignant neoplasm of axilla NOS	B551000	Chest--(not lung)
Malignant neoplasm of chest wall NOS	B551100	Chest--(not lung)
Malignant neoplasm of endocardium	B241000	Chest--(not lung)
Malignant neoplasm of heart, thymus and mediastinum NOS	B24z.00	Chest--(not lung)
Malignant neoplasm of mediastinum, part unspecified	B24X.00	Chest--(not lung)
Malignant neoplasm of myocardium	B241200	Chest--(not lung)
Malignant neoplasm of posterior mediastinum	B243.00	Chest--(not lung)
Malignant neoplasm of respiratory tract NOS	B2zz.00	Chest--(not lung)
Malignant neoplasm of thorax	B551.00	Chest--(not lung)
Malignant neoplasm of thorax NOS	B551z00	Chest--(not lung)
Malignant neoplasm of thymus	B240.00	Chest--(not lung)
Malignant neoplasm of thymus, heart and mediastinum	B24..00	Chest--(not lung)
Malignant neoplasm, overlap lesion of resp & intrathor orgs	B26..00	Chest--(not lung)
Mesothelioma of pericardium	B241400	Chest--(not lung)
Neoplasm of uncertain behaviour of heart	B93y100	Chest--(not lung)
Neoplasm of uncertain behaviour of mediastinum	B908200	Chest--(not lung)
Neoplasm of uncertain behaviour of thymus	B908100	Chest--(not lung)
Malignant neoplasm of clitoris	B453.00	GU--External
Malignant neoplasm of female genital organ NOS	B45z.00	GU--External
Malignant neoplasm of greater vestibular (Bartholin's) gland	B451000	GU--External
Malignant neoplasm of labia majora	B451.00	GU--External
Malignant neoplasm of labia majora NOS	B451z00	GU--External
Malignant neoplasm of labia minora	B452.00	GU--External
Malignant neoplasm of overlapping lesion of vulva	B45y000	GU--External
Malignant neoplasm of vagina	B450.00	GU--External
Malignant neoplasm of vagina NOS	B450z00	GU--External
Malignant neoplasm of vaginal vault	B450100	GU--External
Malignant neoplasm of vulva unspecified	B454.00	GU--External
Malignant neoplasm/overlapping lesion/feml genital organs	B45X.00	GU--External
Neoplasm of uncertain behaviour of penis	B916000	GU--External
Neoplasm of uncertain behaviour of vagina	B913000	GU--External
Neoplasm of uncertain behaviour of vulva	B913100	GU--External
Primary vulval cancer	B454.11	GU--External
[M] Angioimmunoblastic lymphadenopathy	BBm8.00	HEMA--Lymph
[M] Cutaneous lymphoma	BBmD.00	HEMA--Lymph
[M] Large cell lymphoma	BBmH.00	HEMA--Lymph
[M] Monocytoid B-cell lymphoma	BBm9.00	HEMA--Lymph
[M] Peripheral T-cell lymphoma NOS	BBm5.00	HEMA--Lymph
[M] T-gamma lymphoproliferative disease	BBmC.00	HEMA--Lymph
[M]Angiocentric T-cell lymphoma	BBv2.00	HEMA--Lymph
[M]Brill - Symmers' disease	BBk0.11	HEMA--Lymph
[M]Capillary lymphangioma	BBU2.00	HEMA--Lymph
[M]Cavernous lymphangioma	BBU3.00	HEMA--Lymph
[M]Cystic hygroma	BBU4.11	HEMA--Lymph
[M]Cystic lymphangioma	BBU4.00	HEMA--Lymph
[M]Follicular lymphosarcoma NOS	BBk0.12	HEMA--Lymph
[M]Giant follicular lymphoma	BBk0.13	HEMA--Lymph
[M]Haemolymphangioma	BBU7.00	HEMA--Lymph

Cancer description	Med Code	Cancer type
[M]Hodgkin,s disease, lymphocytic predominance, diffuse	BBj1000	HEMA--Lymph
[M]Hodgkin,s disease, lymphocytic predominance, nodular	BBj1100	HEMA--Lymph
[M]Hodgkin,s disease, nodular sclerosis, lymphocytic deplet	BBj6200	HEMA--Lymph
[M]Hodgkin,s disease, nodular sclerosis, lymphocytic predom	BBj6000	HEMA--Lymph
[M]Hodgkin,s disease, nodular sclerosis, mixed cellularity	BBj6100	HEMA--Lymph
[M]Hodgkin's disease	BBj..00	HEMA--Lymph
[M]Hodgkin's disease NOS	BBj0.00	HEMA--Lymph
[M]Hodgkin's disease NOS	BBjz.00	HEMA--Lymph
[M]Hodgkin's disease, lymphocytic predominance	BBj1.00	HEMA--Lymph
[M]Hodgkin's disease, mixed cellularity	BBj2.00	HEMA--Lymph
[M]Hodgkin's disease, nodular sclerosis NOS	BBj6.00	HEMA--Lymph
[M]Hodgkin's disease, nodular sclerosis, cellular phase	BBj7.00	HEMA--Lymph
[M]Hodgkin's sarcoma	BBjA.00	HEMA--Lymph
[M]Hygroma	BBU4.12	HEMA--Lymph
[M]Lymphangioma NOS	BBU0.00	HEMA--Lymph
[M]Lymphangiomatous tumours	BBU..11	HEMA--Lymph
[M]Lymphangiomyoma	BBU5.00	HEMA--Lymph
[M]Lymphangiomyomatosis	BBU6.00	HEMA--Lymph
[M]Lymphangiosarcoma	BBU1.00	HEMA--Lymph
[M]Lymphatic vessel tumours	BBU..00	HEMA--Lymph
[M]Lymphoblastic lymphoma NOS	BBgG.12	HEMA--Lymph
[M]Lymphoblastic lymphosarcoma NOS	BBgG.11	HEMA--Lymph
[M]Lymphoblastoma NOS	BBgG.13	HEMA--Lymph
[M]Lymphocytic lymphoma NOS	BBgC.11	HEMA--Lymph
[M]Lymphocytic lymphosarcoma NOS	BBgC.12	HEMA--Lymph
[M]Lymphoma NOS	BBg1.11	HEMA--Lymph
[M]Lymphoma, diffuse or NOS	BBgz.00	HEMA--Lymph
[M]Lymphoma, nodular or follicular NOS	BBkz.00	HEMA--Lymph
[M]Lymphomas, nodular or follicular	BBk..00	HEMA--Lymph
[M]Lymphomas, NOS or diffuse	BBg..00	HEMA--Lymph
[M]Malig lymp, follicular centre cell, cleaved, follicular	BBk5.00	HEMA--Lymph
[M]Malig lymphoma, follicular centre cell, non-cleaved NOS	BBgK.00	HEMA--Lymph
[M]Malig lymphoma, lymphocytic, intermediate different NOS	BBgD.00	HEMA--Lymph
[M]Malign lymphoma,lymphocytic,intermediate differn, diffuse	BBgN.00	HEMA--Lymph
[M]Malignant lymphoma NOS	BBg1.00	HEMA--Lymph
[M]Malignant lymphoma, centroblastic type NOS	BBgJ.00	HEMA--Lymph
[M]Malignant lymphoma, centroblastic type, follicular	BBk7.00	HEMA--Lymph
[M]Malignant lymphoma, centroblastic-centrocytic, diffuse	BBgA.00	HEMA--Lymph
[M]Malignant lymphoma, centrocytic	BBgE.00	HEMA--Lymph
[M]Malignant lymphoma, convoluted cell type NOS	BBg5.00	HEMA--Lymph
[M]Malignant lymphoma, diffuse NOS	BBg1000	HEMA--Lymph
[M]Malignant lymphoma, follicular centre cell NOS	BBgB.00	HEMA--Lymph
[M]Malignant lymphoma, immunoblastic type	BBg8.00	HEMA--Lymph
[M]Malignant lymphoma, large cell, cleaved, diffuse	BBgS.00	HEMA--Lymph
[M]Malignant lymphoma, large cell, diffuse NOS	BBgR.00	HEMA--Lymph
[M]Malignant lymphoma, large cell, noncleaved, diffuse	BBgT.00	HEMA--Lymph
[M]Malignant lymphoma, lymphocytic, poorly different NOS	BBgG.00	HEMA--Lymph
[M]Malignant lymphoma, lymphocytic, well differentiated NOS	BBgC.00	HEMA--Lymph
[M]Malignant lymphoma, lymphoplasmacytoid type	BBg7.00	HEMA--Lymph
[M]Malignant lymphoma, mixed small and large cell, diffuse	BBgP.00	HEMA--Lymph

Cancer description	Med Code	Cancer type
[M]Malignant lymphoma, nodular NOS	BBk0.00	HEMA--Lymph
[M]Malignant lymphoma, non Hodgkin's type	BBg2.00	HEMA--Lymph
[M]Malignant lymphoma, small cell, noncleaved, diffuse	BBgV.00	HEMA--Lymph
[M]Malignant lymphoma, small cleaved cell, diffuse	BBgM.00	HEMA--Lymph
[M]Malignant lymphoma, small lymphocytic NOS	BBgL.00	HEMA--Lymph
[M]Malignant lymphoma, stem cell type	BBg4.00	HEMA--Lymph
[M]Malignant lymphoma, undifferentiated cell type NOS	BBg3.00	HEMA--Lymph
[M]Malignant lymphomatous polyposis	BBgQ.00	HEMA--Lymph
[M]Monocytoid B-cell lymphoma	BBv0.00	HEMA--Lymph
[M]Myelodysplastic syndrome	BBv..00	HEMA--Lymph
[M]Non Hodgkins lymphoma	BBg2.11	HEMA--Lymph
[M]True histiocytic lymphoma	BBm4.00	HEMA--Lymph
[X]2ndry+unspcf malignant neoplasm lymph nodes/multi regions	ByuC200	HEMA--Lymph
[X]Diffuse non-Hodgkin's lymphoma, unspecified	ByuDC00	HEMA--Lymph
[X]Malignant neoplasms of lymphoid, haematopoietic and rela	ByuD.00	HEMA--Lymph
[X]Non-Hodgkin's lymphoma NOS	ByuDF11	HEMA--Lymph
[X]Non-Hodgkin's lymphoma, unspecified type	ByuDF00	HEMA--Lymph
[X]Oth and unspecif peripheral & cutaneous T-cell lymphomas	ByuDD00	HEMA--Lymph
[X]Other Hodgkin's disease	ByuD000	HEMA--Lymph
[X]Other specified types of non-Hodgkin's lymphoma	ByuD300	HEMA--Lymph
[X]Other types of diffuse non-Hodgkin's lymphoma	ByuD200	HEMA--Lymph
[X]Other types of follicular non-Hodgkin's lymphoma	ByuD100	HEMA--Lymph
[X]Unspecified B-cell non-Hodgkin's lymphoma	ByuDE00	HEMA--Lymph
Burkitt's lymphoma	B602.00	HEMA--Lymph
Burkitt's lymphoma NOS	B602z00	HEMA--Lymph
Burkitt's lymphoma of lymph nodes of head, face and neck	B602100	HEMA--Lymph
Diffuse non-Hodgkin mixed sml & lge cell (diffuse) lymphoma	B627500	HEMA--Lymph
Diffuse non-Hodgkin's centroblastic lymphoma	B627D00	HEMA--Lymph
Diffuse non-Hodgkin's immunoblastic (diffuse) lymphoma	B627600	HEMA--Lymph
Diffuse non-Hodgkin's lymphoblastic (diffuse) lymphoma	B627700	HEMA--Lymph
Diffuse non-Hodgkin's lymphoma undifferentiated (diffuse)	B627800	HEMA--Lymph
Diffuse non-Hodgkin's lymphoma, unspecified	B627X00	HEMA--Lymph
Diffuse non-Hodgkin's small cell (diffuse) lymphoma	B627300	HEMA--Lymph
Follicular lymphoma NOS	B627C11	HEMA--Lymph
Follicular non-Hodg mixed sml cleavd & lge cell lymphoma	B627100	HEMA--Lymph
Follicular non-Hodgkin's large cell lymphoma	B627200	HEMA--Lymph
Follicular non-Hodgkin's lymphoma	B627C00	HEMA--Lymph
Follicular non-Hodgkin's small cleaved cell lymphoma	B627000	HEMA--Lymph
Histiocytosis X (acute, progressive)	B625.11	HEMA--Lymph
Hodgkin's disease	B61..00	HEMA--Lymph
Hodgkin's disease NOS	B61z.00	HEMA--Lymph
Hodgkin's disease NOS	B61zz00	HEMA--Lymph
Hodgkin's disease NOS of intrathoracic lymph nodes	B61z200	HEMA--Lymph
Hodgkin's disease NOS of lymph nodes of axilla and arm	B61z400	HEMA--Lymph
Hodgkin's disease NOS of lymph nodes of head, face and neck	B61z100	HEMA--Lymph
Hodgkin's disease NOS of lymph nodes of multiple sites	B61z800	HEMA--Lymph
Hodgkin's disease NOS, unspecified site	B61z000	HEMA--Lymph
Hodgkin's disease, lymphocytic depletion	B616.00	HEMA--Lymph
Hodgkin's disease, lymphocytic depletion NOS	B616z00	HEMA--Lymph
Hodgkin's disease, lymphocytic-histiocytic predominance	B613.00	HEMA--Lymph

Cancer description	Med Code	Cancer type
Hodgkin's disease, mixed cellularity	B615.00	HEMA--Lymph
Hodgkin's disease, mixed cellularity NOS	B615z00	HEMA--Lymph
Hodgkin's disease, nodular sclerosis	B614.00	HEMA--Lymph
Hodgkin's disease, nodular sclerosis NOS	B614z00	HEMA--Lymph
Hodgkin's disease, nodular sclerosis of unspecified site	B614000	HEMA--Lymph
Hodgkin's granuloma	B611.00	HEMA--Lymph
Hodgkin's lymphocytic depletion lymph nodes axilla and arm	B616400	HEMA--Lymph
Hodgkin's nodular sclerosis of head, face and neck	B614100	HEMA--Lymph
Hodgkin's nodular sclerosis of intra-abdominal lymph nodes	B614300	HEMA--Lymph
Hodgkin's nodular sclerosis of intrathoracic lymph nodes	B614200	HEMA--Lymph
Hodgkin's nodular sclerosis of lymph nodes of multiple sites	B614800	HEMA--Lymph
Hodgkin's paragranuloma	B610.00	HEMA--Lymph
Hodgkin's sarcoma	B612.00	HEMA--Lymph
Hodgkin's, lymphocytic-histiocytic pred intrathoracic nodes	B613200	HEMA--Lymph
Hodgkin's, lymphocytic-histiocytic pred of head, face, neck	B613100	HEMA--Lymph
Hodgkin's, lymphocytic-histiocytic predominance unspec site	B613000	HEMA--Lymph
Immunoproliferative neoplasm	B62zz11	HEMA--Lymph
Kaposi's sarcoma of lymph nodes	B6z0.00	HEMA--Lymph
Letterer-Siwe disease	B625.00	HEMA--Lymph
Letterer-Siwe disease NOS	B625z00	HEMA--Lymph
Letterer-Siwe disease of intrathoracic lymph nodes	B625200	HEMA--Lymph
Letterer-Siwe disease of lymph nodes of multiple sites	B625800	HEMA--Lymph
Lymphoepithelioid lymphoma	B62x100	HEMA--Lymph
Lymphosarcoma	B601.00	HEMA--Lymph
Lymphosarcoma and reticulosarcoma	B60..00	HEMA--Lymph
Lymphosarcoma NOS	B601z00	HEMA--Lymph
Lymphosarcoma of intra-abdominal lymph nodes	B601300	HEMA--Lymph
Lymphosarcoma of intrathoracic lymph nodes	B601200	HEMA--Lymph
Lymphosarcoma of lymph nodes of head, face and neck	B601100	HEMA--Lymph
Lymphosarcoma of lymph nodes of inguinal region and leg	B601500	HEMA--Lymph
Lymphosarcoma of unspecified site	B601000	HEMA--Lymph
Malignant immunoproliferative small intestinal disease	B62x500	HEMA--Lymph
Malignant lymphoma NOS	B62y.00	HEMA--Lymph
Malignant lymphoma NOS	B62yz00	HEMA--Lymph
Malignant lymphoma NOS of intra-abdominal lymph nodes	B62y300	HEMA--Lymph
Malignant lymphoma NOS of intrapelvic lymph nodes	B62y600	HEMA--Lymph
Malignant lymphoma NOS of intrathoracic lymph nodes	B62y200	HEMA--Lymph
Malignant lymphoma NOS of lymph node inguinal region and leg	B62y500	HEMA--Lymph
Malignant lymphoma NOS of lymph nodes of axilla and arm	B62y400	HEMA--Lymph
Malignant lymphoma NOS of lymph nodes of head, face and neck	B62y100	HEMA--Lymph
Malignant lymphoma NOS of lymph nodes of multiple sites	B62y800	HEMA--Lymph
Malignant lymphoma NOS of spleen	B62y700	HEMA--Lymph
Malignant lymphoma NOS of unspecified site	B62y000	HEMA--Lymph
Malignant lymphoma otherwise specified	B62x.00	HEMA--Lymph
Malignant mast cell tumour NOS	B626z00	HEMA--Lymph
Malignant mast cell tumours	B626.00	HEMA--Lymph
Malignant neoplasm lymphatic or haematopoietic tissue NOS	B6z..00	HEMA--Lymph
Malignant neoplasm of lymphatic and haemopoietic tissue	B6...00	HEMA--Lymph
Malignant neoplasms of lymphoid and histiocytic tissue NOS	B62z.00	HEMA--Lymph
Malignant reticulosis	B62x400	HEMA--Lymph

Cancer description	Med Code	Cancer type
Mast cell malignancy of lymph nodes of multiple sites	B626800	HEMA--Lymph
Mycosis fungoides	B621.00	HEMA--Lymph
Mycosis fungoides NOS	B621z00	HEMA--Lymph
Mycosis fungoides of intra-abdominal lymph nodes	B621300	HEMA--Lymph
Mycosis fungoides of lymph nodes of inguinal region and leg	B621500	HEMA--Lymph
Mycosis fungoides of unspecified site	B621000	HEMA--Lymph
Nodular lymphoma (Brill - Symmers disease)	B620.00	HEMA--Lymph
Nodular lymphoma NOS	B620z00	HEMA--Lymph
Nodular lymphoma of intra-abdominal lymph nodes	B620300	HEMA--Lymph
Nodular lymphoma of lymph nodes of head, face and neck	B620100	HEMA--Lymph
Nodular lymphoma of lymph nodes of inguinal region and leg	B620500	HEMA--Lymph
Nodular lymphoma of lymph nodes of multiple sites	B620800	HEMA--Lymph
Nodular lymphoma of unspecified site	B620000	HEMA--Lymph
Non - Hodgkin's lymphoma	B627.00	HEMA--Lymph
Oth and unspecif peripheral & cutaneous T-cell lymphomas	B62xX00	HEMA--Lymph
Other malignant neoplasm of lymphoid and histiocytic tissue	B62..00	HEMA--Lymph
Other types of follicular non-Hodgkin's lymphoma	B627B00	HEMA--Lymph
Peripheral T-cell lymphoma	B62x200	HEMA--Lymph
Reticulosarcoma	B600.00	HEMA--Lymph
Reticulosarcoma of intra-abdominal lymph nodes	B600300	HEMA--Lymph
Reticulosarcoma of lymph nodes of head, face and neck	B600100	HEMA--Lymph
Reticulosarcoma of unspecified site	B600000	HEMA--Lymph
Sezary's disease	B622.00	HEMA--Lymph
Unspec malig neop lymphoid/histiocytic lymph node head/neck	B62z100	HEMA--Lymph
Unspec malig neop lymphoid/histiocytic nodes inguinal/leg	B62z500	HEMA--Lymph
Unspec malig neop lymphoid/histiocytic of intrathoracic node	B62z200	HEMA--Lymph
Unspecified B-cell non-Hodgkin's lymphoma	B627W00	HEMA--Lymph
[M]Bile duct carcinoma	BB5D111	GI--Liver Gallbladder
[M]Bile duct cystadenocarcinoma	BB5D300	GI--Liver Gallbladder
[M]Bile duct cystadenoma	BB5D200	GI--Liver Gallbladder
[M]Biliary tract adenomas and adenocarcinomas	BB5D.11	GI--Liver Gallbladder
[M]Cholangiocarcinoma	BB5D100	GI--Liver Gallbladder
[M]Cholangioma	BB5D011	GI--Liver Gallbladder
[M]Hepatobiliary adenoma or carcinoma NOS	BB5Dz00	GI--Liver Gallbladder
[M]Hepatobiliary tract adenomas and carcinomas	BB5D.00	GI--Liver Gallbladder
[M]Hepatoblastoma	BBL8.00	GI--Liver Gallbladder
[M]Hepatocellular adenoma	BB5D411	GI--Liver Gallbladder
[M]Hepatocellular carcinoma NOS	BB5D500	GI--Liver Gallbladder
[M]Hepatocellular carcinoma, fibrolamellar	BB5D800	GI--Liver Gallbladder
[M]Hepatoma NOS	BB5D511	GI--Liver Gallbladder
[M]Hepatoma, malignant	BB5D512	GI--Liver Gallbladder
[M]Infiltrating ductular carcinoma	BB9G.00	GI--Liver Gallbladder
[M]Liver cell adenoma	BB5D400	GI--Liver Gallbladder

Cancer description	Med Code	Cancer type
[M]Liver cell carcinoma	BB5D513	GI--Liver Gallbladder
[X]Malignant neoplasm of respiratory and intrathoracic orga	Byu2.00	GI--Liver Gallbladder
[X]Other specified carcinomas of liver	Byu1100	GI--Liver Gallbladder
Carcinoma common bile duct	B161211	GI--Liver Gallbladder
Carcinoma gallbladder	B160.11	GI--Liver Gallbladder
Hepatoblastoma of liver	B150100	GI--Liver Gallbladder
Hepatocellular carcinoma	B150300	GI--Liver Gallbladder
Malignant neoplasm gallbladder and extrahepatic bile ducts	B16..00	GI--Liver Gallbladder
Malignant neoplasm gallbladder/extrahepatic bile ducts NOS	B16z.00	GI--Liver Gallbladder
Malignant neoplasm of ampulla of Vater	B162.00	GI--Liver Gallbladder
Malignant neoplasm of common bile duct	B161200	GI--Liver Gallbladder
Malignant neoplasm of extrahepatic bile ducts	B161.00	GI--Liver Gallbladder
Malignant neoplasm of extrahepatic bile ducts NOS	B161z00	GI--Liver Gallbladder
Malignant neoplasm of gallbladder	B160.00	GI--Liver Gallbladder
Malignant neoplasm of hepatic duct	B161100	GI--Liver Gallbladder
Malignant neoplasm of interlobular bile ducts	B151000	GI--Liver Gallbladder
Malignant neoplasm of intrahepatic bile ducts	B151.00	GI--Liver Gallbladder
Malignant neoplasm of intrahepatic biliary passages	B151200	GI--Liver Gallbladder
Malignant neoplasm of intrahepatic gall duct	B151400	GI--Liver Gallbladder
Malignant neoplasm of liver and intrahepatic bile ducts	B15..00	GI--Liver Gallbladder
Malignant neoplasm of liver and intrahepatic bile ducts NOS	B15z.00	GI--Liver Gallbladder
Malignant neoplasm of liver unspecified	B152.00	GI--Liver Gallbladder
Malignant neoplasm other gallbladder/extrahepatic bile duct	B16y.00	GI--Liver Gallbladder
Malignant neoplasm, overlapping lesion of biliary tract	B163.00	GI--Liver Gallbladder
Neoplasm of uncertain behaviour of biliary system	B903.11	GI--Liver Gallbladder
Neoplasm of uncertain behaviour of gall bladder	B903300	GI--Liver Gallbladder
Neoplasm of uncertain behaviour of liver	B903000	GI--Liver Gallbladder
Neoplasm of uncertain behaviour of liver and biliary passage	B903.00	GI--Liver Gallbladder
Neoplasm of uncertain behaviour of sphincter of Oddi	B903700	GI--Liver Gallbladder
Primary angiosarcoma of liver	B150200	GI--Liver Gallbladder
Primary carcinoma of liver	B150000	GI--Liver Gallbladder
Primary malignant neoplasm of liver	B150.00	GI--Liver Gallbladder
Primary malignant neoplasm of liver NOS	B150z00	GI--Liver Gallbladder
[M]Androblastoma	BBC6.00	GU--NOS
[M]Arrhenoblastoma NOS	BBC6z11	GU--NOS
[M]Chorioadenoma	BBR1.11	GU--NOS
[M]Choriocarcinoma	BBR2.00	GU--NOS

Cancer description	Med Code	Cancer type
[M]Choriocarcinoma combined with teratoma	BBR3.00	GU--NOS
[M]Classical hydatidiform mole	BBR7.00	GU--NOS
[M]Complete hydatidiform mole	BBR8.00	GU--NOS
[M]Cystadenocarcinoma NOS	BB80100	GU--NOS
[M]Cystadenoma and carcinoma	BB80.00	GU--NOS
[M]Cystadenoma NOS	BB80000	GU--NOS
[M]Cystoma NOS	BB80011	GU--NOS
[M]Embryonal carcinoma NOS	BBQ3.00	GU--NOS
[M]Endodermal sinus tumour	BBQ4.00	GU--NOS
[M]Germinoma	BBQ2.00	GU--NOS
[M]Gonadal stromal tumour	BBC0.11	GU--NOS
[M]Gonadoblastoma	BBQ6.00	GU--NOS
[M]Granulosa cell tumour NOS	BBC3.00	GU--NOS
[M]Granulosa cell tumour, malignant	BBC4.00	GU--NOS
[M]Granulosa cell-theca cell tumour	BBC5.00	GU--NOS
[M]Hydatid mole	BBR0.11	GU--NOS
[M]Hydatidiform mole NOS	BBR0.00	GU--NOS
[M]Invasive hydatidiform mole	BBR1.00	GU--NOS
[M]Invasive mole NOS	BBR1.13	GU--NOS
[M]Juvenile granulosa cell tumour	BBC3000	GU--NOS
[M]Krukenberg tumour	BB85111	GU--NOS
[M]Malignant teratoma, trophoblastic	BBR4.00	GU--NOS
[M]Mucinous adenocarcinoma	BB82100	GU--NOS
[M]Mucinous adenoma	BB82000	GU--NOS
[M]Mucinous adenoma and adenocarcinoma	BB82.00	GU--NOS
[M]Mucinous adenoma or adenocarcinoma NOS	BB82z00	GU--NOS
[M]Mucinous cystadenocarcinoma NOS	BB81E00	GU--NOS
[M]Mucinous cystadenoma NOS	BB81C00	GU--NOS
[M]Mucinous cystadenoma, borderline malignancy	BB81D00	GU--NOS
[M]Mucin-producing adenocarcinoma	BB84.00	GU--NOS
[M]Mucoid adenocarcionoma	BB82113	GU--NOS
[M]Mucous adenocarcinoma	BB82114	GU--NOS
[M]Orchioblastoma	BBQ4.12	GU--NOS
[M]Papillary cystadenoma, borderline malignancy	BB81K00	GU--NOS
[M]Papillary cystic tumour	BB81L00	GU--NOS
[M]Papillary mucinous cystadenocarcinoma	BB81H00	GU--NOS
[M]Papillary mucinous cystadenoma NOS	BB81F00	GU--NOS
[M]Papillary serous cystadenoma, borderline malignancy	BB81M00	GU--NOS
[M]Partial hydatidiform mole	BBR5.00	GU--NOS
[M]Placental site trophoblastic tumour	BBR6.00	GU--NOS
[M]Pseudomucinous adenocarcinoma	BB81E11	GU--NOS
[M]Pseudomucinous cystadenoma NOS	BB81C11	GU--NOS
[M]Pseudomyxoma peritonei	BB83.00	GU--NOS
[M]Serous cystadenoma, borderline malignancy	BB81J00	GU--NOS
[M]Serous surface papillary carcinoma	BB81B00	GU--NOS
[M]Serous surface papilloma NOS	BB81900	GU--NOS
[M]Sertoli-Leydig cell tumour	BBC7.00	GU--NOS
[M]Sex cord tumour with annular tubules	BBC0000	GU--NOS
[M]Sex cord-stromal tumour	BBC0.00	GU--NOS
[M]Signet ring carcinoma	BB85.00	GU--NOS

Cancer description	Med Code	Cancer type
[M]Signet ring cell carcinoma	BB85000	GU--NOS
[M]Specialised gonadal neoplasms	BBC..00	GU--NOS
[M]Thecal cell neoplasm NOS	BBC1z00	GU--NOS
[M]Thecal cell neoplasms	BBC1.00	GU--NOS
[M]Thecoma NOS	BBC1000	GU--NOS
[M]Thecoma, luteinized	BBC1200	GU--NOS
[M]Trophoblastic neoplasm NOS	BBRz.00	GU--NOS
[M]Trophoblastic neoplasms	BBR..00	GU--NOS
[M]Yolk sac tumour	BBQ4.14	GU--NOS
[X]Malignant neoplasm of female genital organ, unspecified	Byu7300	GU--NOS
[X]Malignant neoplasm of female genital organs	Byu7.00	GU--NOS
[X]Malignant neoplasm of male genital organ, unspecified	Byu8200	GU--NOS
[X]Malignant neoplasm of male genital organs	Byu8.00	GU--NOS
[X]Malignant neoplasm of urinary tract	Byu9.00	GU--NOS
[X]Malignant neoplasm of uterine adnexa, unspecified	Byu7000	GU--NOS
[X]Malignant neoplasm/other specified female genital organs	Byu7100	GU--NOS
[X]Malignant neoplasm/other specified male genital organs	Byu8000	GU--NOS
Carcinoma of genitourinary organ	B4...11	GU--NOS
Choriocarcinoma	B420.00	GU--NOS
Choriocarcinoma	B911013	GU--NOS
Malig neop of other and unspecified female genital organs	B45..00	GU--NOS
Malignant hydatidiform mole	B911000	GU--NOS
Malignant neoplasm of body of penis	B482.00	GU--NOS
Malignant neoplasm of epididymis	B484.00	GU--NOS
Malignant neoplasm of fallopian tube	B441.00	GU--NOS
Malignant neoplasm of genitourinary organ	B4...00	GU--NOS
Malignant neoplasm of genitourinary organ NOS	B4z..00	GU--NOS
Malignant neoplasm of genitourinary organ OS	B4y..00	GU--NOS
Malignant neoplasm of glans penis	B481.00	GU--NOS
Malignant neoplasm of other male genital organ	B48y.00	GU--NOS
Malignant neoplasm of other male genital organ NOS	B48yz00	GU--NOS
Malignant neoplasm of other site of uterine adnexa	B44y.00	GU--NOS
Malignant neoplasm of parametrium	B443.00	GU--NOS
Malignant neoplasm of penis and other male genital organ NOS	B48z.00	GU--NOS
Malignant neoplasm of penis and other male genital organs	B48..00	GU--NOS
Malignant neoplasm of penis, part unspecified	B483.00	GU--NOS
Malignant neoplasm of placenta	B42..00	GU--NOS
Malignant neoplasm of prepuce (foreskin)	B480.00	GU--NOS
Malignant neoplasm of round ligament	B444.00	GU--NOS
Malignant neoplasm of scrotum	B486.00	GU--NOS
Malignant neoplasm of seminal vesicle	B48y000	GU--NOS
Malignant neoplasm of spermatic cord	B485.00	GU--NOS
Malignant neoplasm of tunica vaginalis	B48y100	GU--NOS
Malignant neoplasm, overlapping lesion male genital orgs	B48y200	GU--NOS
Malignant neoplasm, overlapping lesion of penis	B487.00	GU--NOS
Neoplasm of uncertain behaviour of epididymis	B916100	GU--NOS
Neoplasm of uncertain behaviour of genitourinary organs	B91..00	GU--NOS
Neoplasm of uncertain behaviour of scrotum	B916200	GU--NOS
Neoplasm of uncertain behaviour of urinary organ NOS	B91z.11	GU--NOS
Neoplasm of uncertain behaviour other female genital organs	B913.00	GU--NOS

Cancer description	Med Code	Cancer type
Neoplasm of unspecified nature of other genitourinary organs	BA05.00	GU--NOS
[M]Adenocarcinoma in villous adenoma	BB5U100	RESP--Lung Cancer
[M]Alveolar adenocarcinoma	BB5S400	RESP--Lung Cancer
[M]Alveolar cell carcinoma	BB5S211	RESP--Lung Cancer
[M]Bronchial adenoma NOS	BB5S100	RESP--Lung Cancer
[M]Bronchiolar carcinoma	BB5S212	RESP--Lung Cancer
[M]Bronchiolo-alveolar adenocarcinoma	BB5S200	RESP--Lung Cancer
[M]Cylindroid bronchial adenoma	BB5J.12	RESP--Lung Cancer
[M]Cystic mesothelioma	BBP9.00	RESP--Lung Cancer
[M]Epithelioid mesothelioma, malignant	BBP5.00	RESP--Lung Cancer
[M]Lobular carcinoma NOS	BB9F.00	RESP--Lung Cancer
[M]Mesothelial neoplasm NOS	BBPz.00	RESP--Lung Cancer
[M]Mesothelial neoplasms	BBP..00	RESP--Lung Cancer
[M]Mesothelioma, malignant	BBP1.00	RESP--Lung Cancer
[M]Mesothelioma, unspecified	BBPX.00	RESP--Lung Cancer
[M]Oat cell carcinoma	BB1K.00	RESP--Lung Cancer
[M]Papillary adenocarcinoma NOS	BB5T100	RESP--Lung Cancer
[M]Papillary adenoma NOS	BB5T000	RESP--Lung Cancer
[M]Papillary adenoma or adenocarcinoma NOS	BB5Tz00	RESP--Lung Cancer
[M]Papillary adenomas and adenocarcinomas	BB5T.00	RESP--Lung Cancer
[M]Papillotubular adenoma	BB5U311	RESP--Lung Cancer
[M]Pulmonary adenomatosis	BB5S000	RESP--Lung Cancer
[M]Respiratory tract adenoma or adenocarcinoma NOS	BB5Sz00	RESP--Lung Cancer
[M]Respiratory tract adenomas and adenocarcinomas	BB5S.00	RESP--Lung Cancer
[M]Round cell carcinoma	BB1J.12	RESP--Lung Cancer
[M]Small cell carcinoma NOS	BB1J.00	RESP--Lung Cancer
[M]Small cell carcinoma, fusiform cell type	BB1L.00	RESP--Lung Cancer
[M]Small cell carcinoma, intermediate cell	BB1M.00	RESP--Lung Cancer
[M]Small cell-large cell carcinoma	BB1N.00	RESP--Lung Cancer
[M]Tubulovillous adenoma	BB5U300	RESP--Lung Cancer
[M]Villoglandular adenoma	BB5U312	RESP--Lung Cancer
[M]Villous adenocarcinoma	BB5U200	RESP--Lung Cancer
[M]Villous adenoma NOS	BB5U000	RESP--Lung Cancer
[M]Villous adenoma or adenocarcinoma NOS	BB5Uz00	RESP--Lung Cancer
[M]Villous adenomas and adenocarcinomas	BB5U.00	RESP--Lung Cancer
[M]Villous papilloma	BB5U011	RESP--Lung Cancer

Cancer description	Med Code	Cancer type
[X]Malignant neoplasm of bronchus or lung, unspecified	Byu2000	RESP--Lung Cancer
[X]Malignant neoplasm/ill-defined sites within resp system	Byu2400	RESP--Lung Cancer
[X]Mesothelioma of lung	Byu5011	RESP--Lung Cancer
[X]Mesothelioma of other sites	Byu5000	RESP--Lung Cancer
Lung cancer	B22z.11	RESP--Lung Cancer
Malignant neoplasm of bronchus or lung NOS	B22z.00	RESP--Lung Cancer
Malignant neoplasm of carina of bronchus	B221000	RESP--Lung Cancer
Malignant neoplasm of hilus of lung	B221100	RESP--Lung Cancer
Malignant neoplasm of lower lobe bronchus	B224000	RESP--Lung Cancer
Malignant neoplasm of lower lobe of lung	B224100	RESP--Lung Cancer
Malignant neoplasm of lower lobe, bronchus or lung	B224.00	RESP--Lung Cancer
Malignant neoplasm of lower lobe, bronchus or lung NOS	B224z00	RESP--Lung Cancer
Malignant neoplasm of main bronchus	B221.00	RESP--Lung Cancer
Malignant neoplasm of main bronchus NOS	B221z00	RESP--Lung Cancer
Malignant neoplasm of middle lobe bronchus	B223000	RESP--Lung Cancer
Malignant neoplasm of middle lobe of lung	B223100	RESP--Lung Cancer
Malignant neoplasm of middle lobe, bronchus or lung	B223.00	RESP--Lung Cancer
Malignant neoplasm of middle lobe, bronchus or lung NOS	B223z00	RESP--Lung Cancer
Malignant neoplasm of other sites of bronchus or lung	B22y.00	RESP--Lung Cancer
Malignant neoplasm of overlapping lesion of bronchus & lung	B225.00	RESP--Lung Cancer
Malignant neoplasm of parietal pleura	B230.00	RESP--Lung Cancer
Malignant neoplasm of pleura	B23..00	RESP--Lung Cancer
Malignant neoplasm of pleura NOS	B23z.00	RESP--Lung Cancer
Malignant neoplasm of trachea	B220.00	RESP--Lung Cancer
Malignant neoplasm of trachea NOS	B220z00	RESP--Lung Cancer
Malignant neoplasm of trachea, bronchus and lung	B22..00	RESP--Lung Cancer
Malignant neoplasm of upper lobe bronchus	B222000	RESP--Lung Cancer
Malignant neoplasm of upper lobe of lung	B222100	RESP--Lung Cancer
Malignant neoplasm of upper lobe, bronchus or lung	B222.00	RESP--Lung Cancer
Malignant neoplasm of upper lobe, bronchus or lung NOS	B222z00	RESP--Lung Cancer
Malignant neoplasm of visceral pleura	B231.00	RESP--Lung Cancer
Mesothelioma	B226.00	RESP--Lung Cancer
Mesothelioma of pleura	B232.00	RESP--Lung Cancer
Neoplasm of uncertain behaviour of bronchus	B907100	RESP--Lung Cancer
Neoplasm of uncertain behaviour of lung	B907200	RESP--Lung Cancer
Neoplasm of uncertain behaviour of pleura	B908000	RESP--Lung Cancer

Cancer description	Med Code	Cancer type
Neoplasm of uncertain behaviour trachea, bronchus and lung	B907.00	RESP--Lung Cancer
Neoplasm of unspecified nature of respiratory system	BA01.00	RESP--Lung Cancer
Pancoast's syndrome	B222.11	RESP--Lung Cancer
[M]Adenoacanthoma	BBB2.11	CNS--Brain
[M]Adenocarcinoma with cartilaginous and osseous metaplasia	BBB3.00	CNS--Brain
[M]Adenocarcinoma with squamous metaplasia	BBB2.00	CNS--Brain
[M]Adenolymphoma	BBB1.00	CNS--Brain
[M]Adenosquamous carcinoma	BBB0.00	CNS--Brain
[M]Aesthesioneuroblastoma	BBcC.00	CNS--Brain
[M]Astroblastoma	BBbK.00	CNS--Brain
[M]Astrocytic glioma	BBbB.11	CNS--Brain
[M]Astrocytoma NOS	BBbB.00	CNS--Brain
[M]Astrocytoma, anaplastic type	BBbC.00	CNS--Brain
[M]Cerebellar sarcoma NOS	BBbW.00	CNS--Brain
[M]Chordoma	BBa5.00	CNS--Brain
[M]Choroid plexus papilloma NOS	BBb5.00	CNS--Brain
[M]Complex epithelial neoplasm NOS	BBBz.00	CNS--Brain
[M]Complex epithelial neoplasms	BBB..00	CNS--Brain
[M]Craniopharyngioma	BBa0.00	CNS--Brain
[M]Desmoplastic medulloblastoma	BBbU.00	CNS--Brain
[M]Ependymoblastoma	BBb8.11	CNS--Brain
[M]Ependymoma NOS	BBb7.00	CNS--Brain
[M]Ependymoma, anaplastic type	BBb8.00	CNS--Brain
[M]Fibrillary astrocytoma	BBbF.00	CNS--Brain
[M]Gangliocytoma	BBc0011	CNS--Brain
[M]Ganglioglioma	BBc6.00	CNS--Brain
[M]Ganglioneuroblastoma	BBc0100	CNS--Brain
[M]Ganglioneuroma	BBc0000	CNS--Brain
[M]Ganglioneuromatosis	BBc0200	CNS--Brain
[M]Ganglioneuromatous neoplasms	BBc0.00	CNS--Brain
[M]Gemistocytic astrocytoma	BBbE.00	CNS--Brain
[M]Giant cell glioblastoma	BBbM.00	CNS--Brain
[M]Glioblastoma multiforme	BBbL.11	CNS--Brain
[M]Glioblastoma NOS	BBbL.00	CNS--Brain
[M]Glioma NOS	BBb0.11	CNS--Brain
[M]Glioma NOS	BBbz.00	CNS--Brain
[M]Glioma, malignant	BBb0.00	CNS--Brain
[M]Gliomas	BBb..00	CNS--Brain
[M]Gliomatosis cerebri	BBb1.00	CNS--Brain
[M]Gliosarcoma	BBb0.12	CNS--Brain
[M]Juvenile astrocytoma	BBbG.11	CNS--Brain
[M]Medulloblastoma NOS	BBbT.00	CNS--Brain
[M]Medulloepithelioma NOS	BBc2.00	CNS--Brain
[M]Medullomyoblastoma	BBbV.00	CNS--Brain
[M]Melanoameloblastoma	BBa4.11	CNS--Brain
[M]Melanotic neuroectodermal tumour	BBa4.00	CNS--Brain
[M]Melanotic progonoma	BBa4.12	CNS--Brain
[M]Mixed glioma	BBb2.00	CNS--Brain
[M]Mixed glioma	BBb2.11	CNS--Brain

Cancer description	Med Code	Cancer type
[M]Myxopapillary ependymoma	BBbA.00	CNS--Brain
[M]Neuroastrocytoma	BBc7.11	CNS--Brain
[M]Neuroblastoma NOS	BBc1.00	CNS--Brain
[M]Neurocytoma	BBc7.00	CNS--Brain
[M]Neuroepithelioma NOS	BBc4.00	CNS--Brain
[M]Neuroepitheliomatous neoplasms	BBc..00	CNS--Brain
[M]Olfactory neuroblastoma	BBcC.11	CNS--Brain
[M]Olfactory neurogenic tumour	BBcA.00	CNS--Brain
[M]Oligodendroblastoma	BBbS.00	CNS--Brain
[M]Oligodendroglioma NOS	BBbQ.00	CNS--Brain
[M]Oligodendroglioma, anaplastic type	BBbR.00	CNS--Brain
[M]Papillary ependymoma	BBb9.00	CNS--Brain
[M]Pilocytic astrocytoma	BBbG.00	CNS--Brain
[M]Piloid astrocytoma	BBbG.12	CNS--Brain
[M]Pinealoma	BBa1.00	CNS--Brain
[M]Pineoblastoma	BBa3.00	CNS--Brain
[M]Pineocytoma	BBa2.00	CNS--Brain
[M]Pleomorphic xanthoastrocytoma	BBbZ.00	CNS--Brain
[M]Primitive neuroectodermal tumour	BBba.00	CNS--Brain
[M]Retinoblastoma NOS	BBc9z00	CNS--Brain
[M]Retinoblastomas	BBc9.00	CNS--Brain
[M]Spongioblastoma polare	BBbJ.00	CNS--Brain
[M]Subependymal astrocytoma NOS	BBb3.11	CNS--Brain
[M]Subependymal astrocytoma NOS	BBb3.12	CNS--Brain
[M]Subependymal giant cell astrocytoma	BBb4.00	CNS--Brain
[M]Subependymal glioma	BBb3.00	CNS--Brain
[M]Subependymoma	BBb3.13	CNS--Brain
[M]Warthin's tumour	BBB1.11	CNS--Brain
Cerebral tumour - malignant	B51..11	CNS--Brain
Malignant neoplasm cerebrum (excluding lobes and ventricles)	B510.00	CNS--Brain
Malignant neoplasm of basal ganglia	B510000	CNS--Brain
Malignant neoplasm of brain	B51..00	CNS--Brain
Malignant neoplasm of brain NOS	B51z.00	CNS--Brain
Malignant neoplasm of brain stem	B517.00	CNS--Brain
Malignant neoplasm of brain stem NOS	B517z00	CNS--Brain
Malignant neoplasm of cerebellum	B516.00	CNS--Brain
Malignant neoplasm of cerebral cortex	B510100	CNS--Brain
Malignant neoplasm of cerebral peduncle	B517000	CNS--Brain
Malignant neoplasm of cerebral ventricles	B515.00	CNS--Brain
Malignant neoplasm of cerebrum NOS	B510z00	CNS--Brain
Malignant neoplasm of choroid plexus	B515000	CNS--Brain
Malignant neoplasm of corpus callosum	B51y000	CNS--Brain
Malignant neoplasm of frontal lobe	B511.00	CNS--Brain
Malignant neoplasm of hippocampus	B512000	CNS--Brain
Malignant neoplasm of hypothalamus	B510400	CNS--Brain
Malignant neoplasm of medulla oblongata	B517100	CNS--Brain
Malignant neoplasm of occipital lobe	B514.00	CNS--Brain
Malignant neoplasm of other parts of brain	B51y.00	CNS--Brain
Malignant neoplasm of parietal lobe	B513.00	CNS--Brain
Malignant neoplasm of pons	B517300	CNS--Brain

Cancer description	Med Code	Cancer type
Malignant neoplasm of temporal lobe	B512.00	CNS--Brain
Malignant neoplasm of temporal lobe NOS	B512z00	CNS--Brain
Malignant neoplasm of thalamus	B510500	CNS--Brain
Neoplasm of uncertain behaviour of adrenal gland	B922.00	CNS--Brain
Neoplasm of uncertain behaviour of brain	B925000	CNS--Brain
Neoplasm of uncertain behaviour of carotid body	B923000	CNS--Brain
Neoplasm of uncertain behaviour of meninges	B926.00	CNS--Brain
Neoplasm of uncertain behaviour of pineal gland	B921.00	CNS--Brain
Neoplasm of uncertain or unknown behav brain, supratentorial	B925200	CNS--Brain
Neoplasm of unspecified nature of brain	BA06.00	CNS--Brain
[M]Acoustic neuroma	BBe5.11	CNS--NOS
[M]Angioblastic meningioma	BBd7.11	CNS--NOS
[M]Angiomatous meningioma	BBd6.00	CNS--NOS
[M]Chemodectoma	BBD7.11	CNS--NOS
[M]Fibrous meningioma	BBd4.00	CNS--NOS
[M]Glomus jugulare tumour	BBD4.00	CNS--NOS
[M]Gynandroblastoma	BBC8.00	CNS--NOS
[M]Haemangioblastic meningioma	BBd7.00	CNS--NOS
[M]Haemangiopericytic meningioma	BBd8.00	CNS--NOS
[M]Jugular paraganglioma	BBD4.11	CNS--NOS
[M]Leptomeningeal sarcoma	BBd2.11	CNS--NOS
[M]Melanotic neurofibroma	BBe3.00	CNS--NOS
[M]Meningioma NOS	BBd0.00	CNS--NOS
[M]Meningioma NOS	BBdz.00	CNS--NOS
[M]Meningioma, malignant	BBd2.00	CNS--NOS
[M]Meningiomas	BBd..00	CNS--NOS
[M]Meningotheliomatous meningioma	BBd3.00	CNS--NOS
[M]Multiple meningiomatosis	BBd1.12	CNS--NOS
[M]Multiple neurofibromatosis	BBe1.11	CNS--NOS
[M]Nerve sheath tumour	BBe..00	CNS--NOS
[M]Nerve sheath tumour NOS	BBez.00	CNS--NOS
[M]Neurilemmoma NOS	BBe5.00	CNS--NOS
[M]Neurilemmoma, malignant	BBe7.00	CNS--NOS
[M]Neurinoma	BBe5.12	CNS--NOS
[M]Neurinomatosis	BBe6.00	CNS--NOS
[M]Neuroepitheliomatous neoplasm NOS	BBcz.00	CNS--NOS
[M]Neurofibroma NOS	BBe0.00	CNS--NOS
[M]Neurofibromas	BBe..11	CNS--NOS
[M]Neurofibromatosis NOS	BBe1.00	CNS--NOS
[M]Neurofibrosarcoma	BBe2.00	CNS--NOS
[M]Neuroma NOS	BBe8.00	CNS--NOS
[M]Neurothekeoma	BBeA.00	CNS--NOS
[M]Paraganglioma NOS	BBD0.00	CNS--NOS
[M]Paragangliomas and glomus tumours	BBD..00	CNS--NOS
[M]Plexiform neurofibroma	BBe4.00	CNS--NOS
[M]Psammomatous meningioma	BBd5.00	CNS--NOS
[M]Schwannoma NOS	BBe5.13	CNS--NOS
[M]Schwannoma, malignant	BBe7.11	CNS--NOS
[M]Transitional meningioma	BBd9.00	CNS--NOS
[M]Triton tumour, malignant	BBe9.00	CNS--NOS

Cancer description	Med Code	Cancer type
[M]Von Recklinghausen's disease	BBe1.12	CNS--NOS
[X]Malig neopl, overlap lesion brain & other part of CNS	ByuA300	CNS--NOS
[X]Malignant neoplasm of eye, brain and other parts of cent	ByuA.00	CNS--NOS
[X]Malignant neoplasm of meninges, unspecified	ByuA200	CNS--NOS
[X]Malignant neoplasm/central nervous system, unspecified	ByuA100	CNS--NOS
[X]Malignant neoplasm/other and unspecified cranial nerves	ByuA000	CNS--NOS
[X]Malignant neoplasm/peripheral nerves of trunk,unspecified	Byu5400	CNS--NOS
Malig neop of other and unspecified parts of nervous system	B52..00	CNS--NOS
Malig neopl peripheral nerves and autonomic nervous system	B524.00	CNS--NOS
Malig neopl, overlap lesion brain & other part of CNS	B52W.00	CNS--NOS
Malignant neoplasm of acoustic nerve	B520200	CNS--NOS
Malignant neoplasm of cauda equina	B525.00	CNS--NOS
Malignant neoplasm of cerebral meninges	B521.00	CNS--NOS
Malignant neoplasm of choroid	B506.00	CNS--NOS
Malignant neoplasm of ciliary body	B500000	CNS--NOS
Malignant neoplasm of conjunctiva	B503.00	CNS--NOS
Malignant neoplasm of cornea	B504.00	CNS--NOS
Malignant neoplasm of cranial nerves	B520.00	CNS--NOS
Malignant neoplasm of cranial nerves NOS	B520z00	CNS--NOS
Malignant neoplasm of eye	B50..00	CNS--NOS
Malignant neoplasm of eye NOS	B50z.00	CNS--NOS
Malignant neoplasm of eyeball NOS	B500z00	CNS--NOS
Malignant neoplasm of iris	B500100	CNS--NOS
Malignant neoplasm of lacrimal duct	B507.00	CNS--NOS
Malignant neoplasm of lacrimal gland	B502.00	CNS--NOS
Malignant neoplasm of meninges, unspecified	B52X.00	CNS--NOS
Malignant neoplasm of nasolacrimal duct	B507100	CNS--NOS
Malignant neoplasm of nervous system NOS	B52z.00	CNS--NOS
Malignant neoplasm of optic nerve	B520100	CNS--NOS
Malignant neoplasm of orbit	B501.00	CNS--NOS
Malignant neoplasm of orbit NOS	B501z00	CNS--NOS
Malignant neoplasm of other specified part of nervous system	B52y.00	CNS--NOS
Malignant neoplasm of other specified site of eye	B50y.00	CNS--NOS
Malignant neoplasm of peripheral nerve of low limb, incl hip	B524200	CNS--NOS
Malignant neoplasm of peripheral nerve of pelvis	B524500	CNS--NOS
Malignant neoplasm of peripheral nerve,upp limb,incl should	B524100	CNS--NOS
Malignant neoplasm of peripheral nerves of head, face & neck	B524000	CNS--NOS
Malignant neoplasm of retina	B505.00	CNS--NOS
Malignant neoplasm of spinal cord	B522.00	CNS--NOS
Malignant neoplasm of spinal meninges	B523.00	CNS--NOS
Malignant neoplasm of spinal meninges NOS	B523z00	CNS--NOS
Malignant neoplasm, overlapping lesion of eye and adnexa	B508.00	CNS--NOS
Neop unspec nature of endocrine glands, other nervous system	BA07.00	CNS--NOS
Neopl uncert/unkn behav of periph nerves & autonom nerv sys	B928.00	CNS--NOS
Neoplasm of uncertain behaviour of eye	B93y000	CNS--NOS
Neoplasm of uncertain behaviour of nervous system OS/NOS	B92z.00	CNS--NOS
Neoplasm of uncertain behaviour of spinal cord	B925100	CNS--NOS
Neurofibromatosis - Von Recklinghausen's disease	B927.00	CNS--NOS
Von Recklinghausen's disease	B927.11	CNS--NOS
[M]Adult rhabdomyoma	BBK3500	CONN--NOS

Cancer description	Med Code	Cancer type
[M]Alveolar rhabdomyosarcoma	BBK3700	CONN--NOS
[M]Angioleiomyoma	BBK1011	CONN--NOS
[M]Angiomyoma	BBK1000	CONN--NOS
[M]Angiomyomatous neoplasm NOS	BBK1z00	CONN--NOS
[M]Angiomyomatous neoplasms	BBK1.00	CONN--NOS
[M]Angiomyosarcoma	BBK1100	CONN--NOS
[M]Cellular leiomyoma	BBK0500	CONN--NOS
[M]Clear cell sarcoma of tendons and aponeuroses	BBN5.00	CONN--NOS
[M]Embryonal rhabdomyosarcoma	BBK3600	CONN--NOS
[M]Epithelioid cell sarcoma	BBF6.00	CONN--NOS
[M]Epithelioid leiomyoma	BBK0300	CONN--NOS
[M]Epithelioid leiomyosarcoma	BBK0400	CONN--NOS
[M]Fibroepithelial neoplasm NOS	BBMz.00	CONN--NOS
[M]Fibroepithelial neoplasms	BBM..00	CONN--NOS
[M]Fibroid uterus	BBK0011	CONN--NOS
[M]Fibromyoma	BBK0012	CONN--NOS
[M]Giant fibroadenoma	BBMB.00	CONN--NOS
[M]Granular cell tumour NOS	BBf0.00	CONN--NOS
[M]Granular cell tumours and alveolar soft part sarcoma	BBf..00	CONN--NOS
[M]Intravascular leiomyomatosis	BBK0100	CONN--NOS
[M]Juvenile fibroadenoma	BBMA.00	CONN--NOS
[M]Leiomyoblastoma	BBK0311	CONN--NOS
[M]Leiomyofibroma	BBK0013	CONN--NOS
[M]Leiomyoma NOS	BBK0000	CONN--NOS
[M]Leiomyomatous neoplasm NOS	BBK0z00	CONN--NOS
[M]Leiomyomatous neoplasms	BBK0.00	CONN--NOS
[M]Leiomyosarcoma NOS	BBK0200	CONN--NOS
[M]Miscellaneous reticuloendothelial neoplasm NOS	BBmz.00	CONN--NOS
[M]Miscellaneous reticuloendothelial neoplasms	BBm..00	CONN--NOS
[M]Myofibroma	BBK0014	CONN--NOS
[M]Myoma	BBK2000	CONN--NOS
[M]Myoma and myosarcoma	BBK2.00	CONN--NOS
[M]Myoma or myosarcoma NOS	BBK2z00	CONN--NOS
[M]Myomatous neoplasm NOS	BBKz.00	CONN--NOS
[M]Myomatous neoplasms	BBK..00	CONN--NOS
[M]Myosarcoma	BBK2100	CONN--NOS
[M]Myxoid leiomyosarcoma	BBK0700	CONN--NOS
[M]Pleomorphic cell sarcoma	BBF4.11	CONN--NOS
[M]Pleomorphic rhabdomyosarcoma	BBK3200	CONN--NOS
[M]Reticulum cell sarcoma NOS	BBh0.11	CONN--NOS
[M]Rhabdomyoma NOS	BBK3000	CONN--NOS
[M]Rhabdomyomatous neoplasms	BBK3.00	CONN--NOS
[M]Rhabdomyosarcoma NOS	BBK3100	CONN--NOS
[M]Round cell sarcoma	BBF5.11	CONN--NOS
[M]Sarcoma botryoides	BBK3611	CONN--NOS
[M]Sarcoma NOS	BBF1.00	CONN--NOS
[M]Sarcomatosis NOS	BBF2.00	CONN--NOS
[M]Small cell sarcoma	BBF5.00	CONN--NOS
[M]Smooth muscle tumour NOS	BBK3800	CONN--NOS
[M]Soft tissue tumour or sarcoma NOS	BBFz.00	CONN--NOS

Cancer description	Med Code	Cancer type
[M]Soft tissue tumours and sarcomas NOS	BBF..00	CONN--NOS
[M]Spindle cell sarcoma	BBF3.00	CONN--NOS
[M]Synovial neoplasm NOS	BBNz.00	CONN--NOS
[M]Synovial neoplasms	BBN..00	CONN--NOS
[M]Synovial sarcoma NOS	BBN1.00	CONN--NOS
[M]Synovial sarcoma, biphasic type	BBN4.00	CONN--NOS
[M]Synovioma NOS	BBN1.11	CONN--NOS
[M]Vascular leiomyoma	BBK1012	CONN--NOS
[X]Malignant neoplasm/bone+articular cartilage, unspecified	Byu3300	CONN--NOS
Carcinoma of bone, connective tissue, skin and breast	B3...11	CONN--NOS
Malig neop connective and soft tissue head, face, neck NOS	B310z00	CONN--NOS
Malig neop connective and soft tissue hip and leg NOS	B312z00	CONN--NOS
Malig neop connective and soft tissue of popliteal space	B312200	CONN--NOS
Malig neop connective and soft tissue upper limb/shoulder	B311.00	CONN--NOS
Malig neop of bone, connective tissue, skin and breast	B3...00	CONN--NOS
Malig neop of bone, connective tissue, skin and breast NOS	B3z..00	CONN--NOS
Malig neop of bone, connective tissue, skin and breast OS	B3y..00	CONN--NOS
Malig neop of connective and soft tissue head, face and neck	B310.00	CONN--NOS
Malig neop of connective and soft tissue of abdomen NOS	B314z00	CONN--NOS
Malig neop of connective and soft tissue of abdominal wall	B314000	CONN--NOS
Malig neop of connective and soft tissue of hip and leg	B312.00	CONN--NOS
Malig neop of connective and soft tissue of inguinal region	B315100	CONN--NOS
Malig neop of connective and soft tissue of lower leg	B312300	CONN--NOS
Malig neop of connective and soft tissue of pelvis NOS	B315z00	CONN--NOS
Malig neop of connective and soft tissue of thorax NOS	B313z00	CONN--NOS
Malig neop of connective and soft tissue thigh and upper leg	B312100	CONN--NOS
Malig neop of connective and soft tissue trunk unspecified	B316.00	CONN--NOS
Malignant neoplasm of cartilage of ear	B310300	CONN--NOS
Malignant neoplasm of connective and other soft tissue	B31..00	CONN--NOS
Malignant neoplasm of connective and soft tissue of abdomen	B314.00	CONN--NOS
Malignant neoplasm of connective and soft tissue of axilla	B313000	CONN--NOS
Malignant neoplasm of connective and soft tissue of buttock	B315000	CONN--NOS
Malignant neoplasm of connective and soft tissue of finger	B311400	CONN--NOS
Malignant neoplasm of connective and soft tissue of foot	B312400	CONN--NOS
Malignant neoplasm of connective and soft tissue of fore-arm	B311200	CONN--NOS
Malignant neoplasm of connective and soft tissue of hand	B311300	CONN--NOS
Malignant neoplasm of connective and soft tissue of pelvis	B315.00	CONN--NOS
Malignant neoplasm of connective and soft tissue of perineum	B315200	CONN--NOS
Malignant neoplasm of connective and soft tissue of shoulder	B311000	CONN--NOS
Malignant neoplasm of connective and soft tissue of thorax	B313.00	CONN--NOS
Malignant neoplasm of connective and soft tissue of thumb	B311500	CONN--NOS
Malignant neoplasm of connective and soft tissue, site NOS	B31z.00	CONN--NOS
Malignant neoplasm of connective and soft tissue, upper arm	B311100	CONN--NOS
Malignant neoplasm of great vessels	B313200	CONN--NOS
Malignant neoplasm of soft tissue of face	B310100	CONN--NOS
Malignant neoplasm of soft tissue of head	B310000	CONN--NOS
Malignant neoplasm of soft tissue of neck	B310200	CONN--NOS
Malignant neoplasm of tarsus of eyelid	B310400	CONN--NOS
Neoplasm of unspec nature of bone, skin or soft tissue NOS	BA02z00	CONN--NOS
Neoplasm of unspecified nature of bone, skin and soft tissue	BA02.00	CONN--NOS

Cancer description	Med Code	Cancer type
Sarcoma of bone and connective tissue	B3...12	CONN--NOS
[M] Small cell osteosarcoma	BBVA.00	CONN--Bone
[M]Adamantinoma NOS	BBZF.11	CONN--Bone
[M]Adamantinoma of long bones	BBY1.00	CONN--Bone
[M]Adenomatoid odontogenic tumour	BBZD.00	CONN--Bone
[M]Ameloblastic fibroma	BBZM.00	CONN--Bone
[M]Ameloblastic fibro-odontoma	BBZB.00	CONN--Bone
[M]Ameloblastic fibrosarcoma	BBZN.00	CONN--Bone
[M]Ameloblastic odontosarcoma	BBZC.00	CONN--Bone
[M]Ameloblastoma NOS	BBZF.00	CONN--Bone
[M]Ameloblastoma, malignant	BBZG.00	CONN--Bone
[M]Calcifying epithelial odontogenic tumour	BBZP.00	CONN--Bone
[M]Calcifying odontogenic cyst	BBZE.00	CONN--Bone
[M]Cartilaginous exostosis	BBW0.11	CONN--Bone
[M]Cementifying fibroma	BBZ6.00	CONN--Bone
[M]Cementoma NOS	BBZ4.00	CONN--Bone
[M]Chondroblastic osteosarcoma	BBV2.00	CONN--Bone
[M]Chondroblastoma NOS	BBW7.00	CONN--Bone
[M]Chondroma NOS	BBW2.00	CONN--Bone
[M]Chondromatosis NOS	BBW3.00	CONN--Bone
[M]Chondromatous giant cell tumour	BBW7.11	CONN--Bone
[M]Chondromatous neoplasm NOS	BBWz.00	CONN--Bone
[M]Chondromatous neoplasms	BBW..00	CONN--Bone
[M]Chondromyxoid fibroma	BBWA.00	CONN--Bone
[M]Chondrosarcoma NOS	BBW4.00	CONN--Bone
[M]Dentinoma	BBZ3.00	CONN--Bone
[M]Ecchondroma	BBW0.12	CONN--Bone
[M]Ecchondrosis	BBW1.11	CONN--Bone
[M]Enchondroma	BBW2.11	CONN--Bone
[M]Endothelial bone sarcoma	BBY0.11	CONN--Bone
[M]Ewing's sarcoma	BBY0.00	CONN--Bone
[M]Fibroblastic osteosarcoma	BBV3.00	CONN--Bone
[M]Fibrochondrosarcoma	BBW4.11	CONN--Bone
[M]Giant cell bone sarcoma	BBX1.11	CONN--Bone
[M]Giant cell tumour of bone NOS	BBX0.00	CONN--Bone
[M]Giant osteoid osteoma	BBV8.11	CONN--Bone
[M]Gigantiform cementoma	BBZ7.00	CONN--Bone
[M]Juxtacortical chondrosarcoma	BBW6.00	CONN--Bone
[M]Mesenchymal chondrosarcoma	BBW9.00	CONN--Bone
[M]Miscellaneous bone tumour NOS	BBYz.00	CONN--Bone
[M]Miscellaneous bone tumours	BBY..00	CONN--Bone
[M]Myxoid chondrosarcoma	BBV9.00	CONN--Bone
[M]Odontogenic fibroma NOS	BBZL.00	CONN--Bone
[M]Odontogenic myxoma	BBZK.00	CONN--Bone
[M]Odontogenic tumour NOS	BBZ1.00	CONN--Bone
[M]Odontogenic tumours	BBZ..00	CONN--Bone
[M]Odontoma NOS	BBZ8.00	CONN--Bone
[M]Ossifying fibroma	BBY2.00	CONN--Bone
[M]Ossifying fibroma	BBY2.11	CONN--Bone
[M]Osteoblastic sarcoma	BBV1.11	CONN--Bone

Cancer description	Med Code	Cancer type
[M]Osteoblastoma	BBV8.00	CONN--Bone
[M]Osteocartilaginous exostosis	BBW0.13	CONN--Bone
[M]Osteochondroma	BBW0.00	CONN--Bone
[M]Osteochondromatosis NOS	BBW1.00	CONN--Bone
[M]Osteochondrosarcoma	BBV1.12	CONN--Bone
[M]Osteoclastoma	BBX0.11	CONN--Bone
[M]Osteoclastoma, malignant	BBX1.12	CONN--Bone
[M]Osteofibroma	BBY2.12	CONN--Bone
[M]Osteogenic sarcoma NOS	BBV1.13	CONN--Bone
[M]Osteoid osteoma NOS	BBV7.00	CONN--Bone
[M]Osteoma NOS	BBV0.00	CONN--Bone
[M]Osteoma or osteosarcoma NOS	BBVz.00	CONN--Bone
[M]Osteomas and osteosarcomas	BBV..00	CONN--Bone
[M]Osteosarcoma in Paget's disease of bone	BBV5.00	CONN--Bone
[M]Osteosarcoma NOS	BBV1.00	CONN--Bone
[M]Paget's disease and infiltrating breast duct carcinoma	BB9K.00	CONN--Bone
[M]Paget's disease and intraductal carcinoma of breast	BB9K000	CONN--Bone
[M]Paget's disease, breast	BB9J.11	CONN--Bone
[M]Paget's disease, extramammary, exc Paget's disease bone	BB9L.00	CONN--Bone
[M]Paget's disease, mammary	BB9J.00	CONN--Bone
[M]Parosteal osteosarcoma	BBV..12	CONN--Bone
[M]Periosteal chondroma	BBW5.11	CONN--Bone
[M]Squamous odontogenic tumour	BBZJ.00	CONN--Bone
[M]Telangiectatic osteosarcoma	BBV4.00	CONN--Bone
[M]Tibial adamantinoma	BBY1.11	CONN--Bone
[X]Malignant neoplasm of bone and articular cartilage	Byu3.00	CONN--Bone
[X]Malignant neoplasm/overlap lesion/bone+articulr cartilage	Byu3200	CONN--Bone
Chondroma	B30..11	CONN--Bone
Malignant neoplasm of bone and articular cartilage	B30..00	CONN--Bone
Malignant neoplasm of bone and articular cartilage NOS	B30z.00	CONN--Bone
Malignant neoplasm of bones of skull and face	B300.00	CONN--Bone
Malignant neoplasm of bones of skull and face NOS	B300z00	CONN--Bone
Malignant neoplasm of carpal bone - lunate	B305100	CONN--Bone
Malignant neoplasm of carpal bone - scaphoid	B305000	CONN--Bone
Malignant neoplasm of cervical vertebra	B302000	CONN--Bone
Malignant neoplasm of clavicle	B303200	CONN--Bone
Malignant neoplasm of coccygeal vertebra	B306400	CONN--Bone
Malignant neoplasm of costal cartilage	B303300	CONN--Bone
Malignant neoplasm of costo-vertebral joint	B303400	CONN--Bone
Malignant neoplasm of femur	B307000	CONN--Bone
Malignant neoplasm of fibula	B307100	CONN--Bone
Malignant neoplasm of humerus	B304200	CONN--Bone
Malignant neoplasm of ilium	B306000	CONN--Bone
Malignant neoplasm of ischium	B306100	CONN--Bone
Malignant neoplasm of long bones of leg	B307.00	CONN--Bone
Malignant neoplasm of long bones of leg NOS	B307z00	CONN--Bone
Malignant neoplasm of lumbar vertebra	B302200	CONN--Bone
Malignant neoplasm of malar bone	B300200	CONN--Bone
Malignant neoplasm of mandible	B301.00	CONN--Bone
Malignant neoplasm of maxilla	B300A00	CONN--Bone

Cancer description	Med Code	Cancer type
Malignant neoplasm of metacarpal bones	B305.12	CONN--Bone
Malignant neoplasm of occipital bone	B300400	CONN--Bone
Malignant neoplasm of orbital bone	B300500	CONN--Bone
Malignant neoplasm of parietal bone	B300600	CONN--Bone
Malignant neoplasm of pelvic bones, sacrum and coccyx	B306.00	CONN--Bone
Malignant neoplasm of pelvis, sacrum or coccyx NOS	B306z00	CONN--Bone
Malignant neoplasm of phalanges of foot	B308D00	CONN--Bone
Malignant neoplasm of phalanges of hand	B305D00	CONN--Bone
Malignant neoplasm of rib	B303000	CONN--Bone
Malignant neoplasm of rib, sternum and clavicle NOS	B303z00	CONN--Bone
Malignant neoplasm of ribs, sternum and clavicle	B303.00	CONN--Bone
Malignant neoplasm of sacral vertebra	B306300	CONN--Bone
Malignant neoplasm of scapula	B304000	CONN--Bone
Malignant neoplasm of scapula and long bones of upper arm	B304.00	CONN--Bone
Malignant neoplasm of sphenoid bone	B300700	CONN--Bone
Malignant neoplasm of sternum	B303100	CONN--Bone
Malignant neoplasm of temporal bone	B300800	CONN--Bone
Malignant neoplasm of thoracic vertebra	B302100	CONN--Bone
Malignant neoplasm of tibia	B307200	CONN--Bone
Malignant neoplasm of vertebral column	B302.00	CONN--Bone
Malignant neoplasm of vertebral column NOS	B302z00	CONN--Bone
Malignant neoplasm of vomer	B300C00	CONN--Bone
Malignant neoplasm of xiphoid process	B303500	CONN--Bone
Malignant neoplasm of zygomatic bone	B300900	CONN--Bone
Malignant neoplasm/bones+articular cartilage/limb,unspfd	B30X.00	CONN--Bone
Malignant neoplasm/overlap lesion/bone+articulr cartilage	B30W.00	CONN--Bone
Malignant sacral teratoma	B306500	CONN--Bone
Neoplasm of unspecified nature of bone	BA02000	CONN--Bone
Osteoma	B30..12	CONN--Bone
Osteosarcoma	B30z000	CONN--Bone
[M]Acinar cell carcinoma	BBA2.00	Neoplasm--NOS
[M]Acinar cell neoplasms	BBA..00	Neoplasm--NOS
[M]Acinar cell tumour	BBA1.00	Neoplasm--NOS
[M]Adenocarcinoma in tubulovillous adenoma	BB52000	Neoplasm--NOS
[M]Adenocarcinoma NOS	BB52.00	Neoplasm--NOS
[M]Adenocarcinoma, intestinal type	BB57.00	Neoplasm--NOS
[M]Adenocarcinomas	BB5..11	Neoplasm--NOS
[M]Adenoid cystic carcinoma	BB5J.00	Neoplasm--NOS
[M]Adenoma and adenocarcinoms OS	BB5y.00	Neoplasm--NOS
[M]Adenoma NOS	BB50.00	Neoplasm--NOS
[M]Adenoma or adenocarcinoma NOS	BB5z.00	Neoplasm--NOS
[M]Adenomas	BB5..12	Neoplasm--NOS
[M]Adenomas and adenocarcinomas	BB5..00	Neoplasm--NOS
[M]Adenomatoid tumour NOS	BBP8.00	Neoplasm--NOS
[M]Adenosarcoma	BBLE.00	Neoplasm--NOS
[M]Adnexal and skin appendage neoplasm NOS	BB6z.00	Neoplasm--NOS
[M]Adult cystic teratoma	BBQ7011	Neoplasm--NOS
[M]Angiolipoma NOS	BBJB200	Neoplasm--NOS
[M]Angiolipomatous neoplasms	BBJB.00	Neoplasm--NOS
[M]Angiomyolipoma	BBJB000	Neoplasm--NOS

Cancer description	Med Code	Cancer type
[M]Apocrine adenoma	BB62000	Neoplasm--NOS
[M]Apocrine adenoma and adenocarcinomas	BB62.00	Neoplasm--NOS
[M]Apudoma	BB5y300	Neoplasm--NOS
[M]Argentaffinoma NOS	BB5R211	Neoplasm--NOS
[M]Brown fat tumour	BBJD.11	Neoplasm--NOS
[M]Carcinoid bronchial adenoma	BB5R111	Neoplasm--NOS
[M]Carcinoid tumour NOS	BB5R000	Neoplasm--NOS
[M]Carcinoid tumour, argentaffin, NOS	BB5R200	Neoplasm--NOS
[M]Carcinoid tumour, malignant	BB5R100	Neoplasm--NOS
[M]Carcinoid tumours	BB5R.00	Neoplasm--NOS
[M]Carcinoma in pleomorphic adenoma	BBLG.00	Neoplasm--NOS
[M]Carcinoma NOS	BB12.00	Neoplasm--NOS
[M]Carcinoma, anaplastic type, NOS	BB19.00	Neoplasm--NOS
[M]Carcinoma, diffuse type	BB58.00	Neoplasm--NOS
[M]Carcinoma, undifferentiated type, NOS	BB18.00	Neoplasm--NOS
[M]Carcinomatosis	BB14.00	Neoplasm--NOS
[M]Carcinosarcoma NOS	BBL9.00	Neoplasm--NOS
[M]Carcinosarcoma, embryonal type	BBLA.00	Neoplasm--NOS
[M]Ceruminous adenoma	BB6A000	Neoplasm--NOS
[M]Ceruminous adenoma and adenocarcinoma	BB6A.00	Neoplasm--NOS
[M]Chondroid syringoma	BBL3.11	Neoplasm--NOS
[M]Clear cell adenocarcinoma NOS	BB5X100	Neoplasm--NOS
[M]Clear cell adenofibroma	BB5Z.00	Neoplasm--NOS
[M]Clear cell adenoma	BB5X000	Neoplasm--NOS
[M]Clear cell adenoma or adenocarcinoma NOS	BB5Xz00	Neoplasm--NOS
[M]Clear cell adenomas and adenocarcinomas	BB5X.00	Neoplasm--NOS
[M]Clear cell hidradenoma	BB63.11	Neoplasm--NOS
[M]Clear cell sarcoma of kidney	BBLJ.00	Neoplasm--NOS
[M]Complex mixed and stromal neoplasms	BBL..00	Neoplasm--NOS
[M]Complex mixed or stromal neoplasm NOS	BBLz.00	Neoplasm--NOS
[M]Cylindroma NOS	BB5J.13	Neoplasm--NOS
[M]Cystic, mucinous and serous neoplasms	BB8..00	Neoplasm--NOS
[M]Cystic, mucinous or serous neoplasm NOS	BB8z.00	Neoplasm--NOS
[M]Dedifferentiated liposarcoma	BBJH.00	Neoplasm--NOS
[M]Dermoid cyst	BBQ8.00	Neoplasm--NOS
[M]Dermoid cyst with malignant transformation	BBQ9.00	Neoplasm--NOS
[M]Dermoid NOS	BBQ8.11	Neoplasm--NOS
[M]Eccrine acrospiroma	BB63.00	Neoplasm--NOS
[M]Eccrine papillary adenoma	BB6B.00	Neoplasm--NOS
[M]Eccrine poroma	BB63.12	Neoplasm--NOS
[M]Eccrine spiradenoma	BB64.00	Neoplasm--NOS
[M]Embryonal sarcoma	BBLD.00	Neoplasm--NOS
[M]Embryonal teratoma	BBQ7211	Neoplasm--NOS
[M]Endometrial stromal nodule	BBLF.00	Neoplasm--NOS
[M]Endosalpingioma	BBS3.00	Neoplasm--NOS
[M]Fibroadenoma NOS	BBM1.00	Neoplasm--NOS
[M]Fibrolipoma	BBJ2.00	Neoplasm--NOS
[M]Fibroma molle	BBJ2.11	Neoplasm--NOS
[M]Fibromyxolipoma	BBJ4.00	Neoplasm--NOS
[M]Gangliocytic paraganglioma	BBDE.00	Neoplasm--NOS

Cancer description	Med Code	Cancer type
[M]Germ cell neoplasm NOS	BBQz.00	Neoplasm--NOS
[M]Germ cell neoplasms	BBQ..00	Neoplasm--NOS
[M]Giant cell and spindle cell carcinoma	BB1B.00	Neoplasm--NOS
[M]Giant cell carcinoma	BB1C.00	Neoplasm--NOS
[M]Giant cell tumour NOS	BBXz.00	Neoplasm--NOS
[M]Giant cell tumour of soft parts NOS	BBX2.00	Neoplasm--NOS
[M]Giant cell tumours	BBX..00	Neoplasm--NOS
[M]Glomangioma	BBDD.00	Neoplasm--NOS
[M]Glomangiomyoma	BBDF.00	Neoplasm--NOS
[M]Glomangiosarcoma	BBDB.00	Neoplasm--NOS
[M]Glomus tumour	BBDC.00	Neoplasm--NOS
[M]Hibernoma	BBJD.00	Neoplasm--NOS
[M]Hidradenoma NOS	BB61011	Neoplasm--NOS
[M]Hidrocystoma	BB65.00	Neoplasm--NOS
[M]Hypernephroid tumour	BB5Y.00	Neoplasm--NOS
[M]Immature teratoma	BBQ7212	Neoplasm--NOS
[M]Infiltrating lipoma	BBJ9.11	Neoplasm--NOS
[M]Inflammatory carcinoma	BB9H.00	Neoplasm--NOS
[M]Intraepithelial carcinoma NOS	BB11.11	Neoplasm--NOS
[M]Intramuscular lipoma	BBJ9.00	Neoplasm--NOS
[M]Klatskin's tumour	BB5y200	Neoplasm--NOS
[M]Linitis plastica	BB55.00	Neoplasm--NOS
[M]Lipoadenoma	BB5e.00	Neoplasm--NOS
[M]Lipoma NOS	BBJ0.00	Neoplasm--NOS
[M]Lipomatous neoplasms	BBJ..00	Neoplasm--NOS
[M]Lipomatous neoplasms NOS	BBJz.00	Neoplasm--NOS
[M]Liposarcoma NOS	BBJ1.00	Neoplasm--NOS
[M]Liposarcoma, well differentiated type	BBJ3.00	Neoplasm--NOS
[M]Malignant mastocytosis	BBp2.00	Neoplasm--NOS
[M]Malignant teratoma, intermediate type	BBQ7500	Neoplasm--NOS
[M]Malignant teratoma, undifferentiated type	BBQ7400	Neoplasm--NOS
[M]Malignant tumour, fusiform cell type	BB0A.00	Neoplasm--NOS
[M]Malignant tumour, giant cell type	BB09.00	Neoplasm--NOS
[M]Malignant tumour, small cell type	BB08.00	Neoplasm--NOS
[M]Mast cell tumours	BBp..00	Neoplasm--NOS
[M]Mastocytoma NOS	BBp0.00	Neoplasm--NOS
[M]Mature teratoma	BBQ7012	Neoplasm--NOS
[M]Mesenchymoma NOS	BBLCz00	Neoplasm--NOS
[M]Mesenchymomas	BBLC.00	Neoplasm--NOS
[M]Mesodermal mixed tumour	BBL6.00	Neoplasm--NOS
[M]Microcystic adenoma	BB50000	Neoplasm--NOS
[M]Miscellaneous tumour NOS	BBaz.00	Neoplasm--NOS
[M]Miscellaneous tumours	BBa..00	Neoplasm--NOS
[M]Mixed germ cell tumour	BBQB.00	Neoplasm--NOS
[M]Mixed tumour NOS	BBL3.12	Neoplasm--NOS
[M]Mixed tumour, malignant, NOS	BBL4.00	Neoplasm--NOS
[M]Mixed type liposarcoma	BBJ8.00	Neoplasm--NOS
[M]Monomorphic adenoma	BB59.00	Neoplasm--NOS
[M]Morphology of neoplasms	BB...00	Neoplasm--NOS
[M]Mucocarcinoid tumour, malignant	BB5R600	Neoplasm--NOS

Cancer description	Med Code	Cancer type
[M]Mucoepidermoid carcinoma	BB71.00	Neoplasm--NOS
[M]Mucoepidermoid neoplasms	BB7..00	Neoplasm--NOS
[M]Mucoepidermoid tumour	BB70.00	Neoplasm--NOS
[M]Mullerian mixed tumour	BBL5.00	Neoplasm--NOS
[M]Myelolipoma	BBJC.00	Neoplasm--NOS
[M]Myoepithelioma	BBLB.00	Neoplasm--NOS
[M]Myxoid liposarcoma	BBJ5.00	Neoplasm--NOS
[M]Myxolipoma	BBJ4.11	Neoplasm--NOS
[M]Myxoliposarcoma	BBJ5.12	Neoplasm--NOS
[M]Neoplasm morphology NOS	BBz..00	Neoplasm--NOS
[M]Neoplasm, malignant	BB02.00	Neoplasm--NOS
[M]Neoplasms NOS	BB0..00	Neoplasm--NOS
[M]No microscopic confirmation of tumour	BBy..00	Neoplasm--NOS
[M]Nodular hidradenoma	BB61012	Neoplasm--NOS
[M]Oncocytic adenoma	BB5W012	Neoplasm--NOS
[M]Oncocytoma	BB5W013	Neoplasm--NOS
[M]Oxyphilic adenocarcinoma	BB5W100	Neoplasm--NOS
[M]Papillary hydradenoma	BB66.00	Neoplasm--NOS
[M]Papillary syringadenoma	BB67.00	Neoplasm--NOS
[M]Paraganglioma or glomus tumour NOS	BBDz.00	Neoplasm--NOS
[M]Pericanalicular fibroadenoma	BBM3.00	Neoplasm--NOS
[M]Pleomorphic adenoma	BBL3.00	Neoplasm--NOS
[M]Pleomorphic carcinoma	BB1A.00	Neoplasm--NOS
[M]Pleomorphic lipoma	BBJF.00	Neoplasm--NOS
[M]Pleomorphic liposarcoma	BBJ7.00	Neoplasm--NOS
[M]Pneumoblastoma	BBLA.11	Neoplasm--NOS
[M]Polygonal cell carcinoma	BB1F.00	Neoplasm--NOS
[M]Pseudosarcomatous carcinoma	BB1E.00	Neoplasm--NOS
[M]Pulmonary blastoma	BBLM.00	Neoplasm--NOS
[M]Rhabdoid sarcoma	BBLH.00	Neoplasm--NOS
[M]Scirrhous adenocarcinoma	BB54.00	Neoplasm--NOS
[M]Sclerosing stromal tumour	BBCG.00	Neoplasm--NOS
[M]Sebaceous adenocarcinoma	BB69100	Neoplasm--NOS
[M]Sebaceous adenoma	BB69000	Neoplasm--NOS
[M]Sebaceous adenoma and adenocarcinoma	BB69.00	Neoplasm--NOS
[M]Soft fibroma	BBJ2.12	Neoplasm--NOS
[M]Solid carcinoma NOS	BB5P.00	Neoplasm--NOS
[M]Spheroidal cell carcinoma	BB1G.00	Neoplasm--NOS
[M]Spindle cell carcinoma	BB1D.00	Neoplasm--NOS
[M]Spindle cell lipoma	BBJA.00	Neoplasm--NOS
[M]Spiradenoma NOS	BB64.11	Neoplasm--NOS
[M]Superficial spreading adenocarcinoma	BB56.00	Neoplasm--NOS
[M]Sweat gland adenocarcinoma	BB61200	Neoplasm--NOS
[M]Sweat gland adenoma	BB61000	Neoplasm--NOS
[M]Sweat gland adenoma and adenocarcinomas	BB61.00	Neoplasm--NOS
[M]Sweat gland tumour NOS	BB61100	Neoplasm--NOS
[M]Syringadenoma NOS	BB61013	Neoplasm--NOS
[M]Syringoma NOS	BB68.00	Neoplasm--NOS
[M]Teratoblastoma, malignant	BBQ7213	Neoplasm--NOS

Cancer description	Med Code	Cancer type
[M]Teratoma NOS	BBQ7100	Neoplasm--NOS
[M]Teratoma NOS	BBQ7z00	Neoplasm--NOS
[M]Teratoma, malignant, NOS	BBQ7200	Neoplasm--NOS
[M]Teratomas	BBQ7.00	Neoplasm--NOS
[M]Trabecular adenoma	BB5E.00	Neoplasm--NOS
[M]Tubular androblastoma NOS	BBC9.00	Neoplasm--NOS
[M]Tumour cells, malignant	BB07.00	Neoplasm--NOS
[M]Tumour morphology	BB...11	Neoplasm--NOS
[M]Tumourlet	BB1H.00	Neoplasm--NOS
[M]Unspecified epithelial neoplasm	BB1z.00	Neoplasm--NOS
[M]Unspecified tumour cell NOS	BB0z.00	Neoplasm--NOS
[M]Vipoma	BB5y100	Neoplasm--NOS
[X]Malignant neoplasm of mesothelial and soft tissue	Byu5.00	Neoplasm--NOS
[X]Malignant neoplasm of other specified sites	ByuC000	Neoplasm--NOS
[X]Malignant neoplasm without specification of site	ByuC800	Neoplasm--NOS
[X]Malignant neoplasms/independent (primary) multiple sites	ByuE.00	Neoplasm--NOS
[X]Malignant neoplasms/independent(primary)multiple sites	ByuE000	Neoplasm--NOS
[X]Mesothelioma, unspecified	Byu5100	Neoplasm--NOS
[X]Myelodysplastic syndrome, unspecified	ByuHD00	Neoplasm--NOS
[X]Neoplasms of uncertain and unknown behaviour	ByuH.00	Neoplasm--NOS
Cancers	B....11	Neoplasm--NOS
H/O: cancer	142..11	Neoplasm--NOS
H/O: malignancy	142..13	Neoplasm--NOS
H/O: malignant neoplasm (*)	142..00	Neoplasm--NOS
H/O: neoplasm	142..15	Neoplasm--NOS
Malignant neoplasm of abdomen	B552.00	Neoplasm--NOS
Malignant neoplasm of back NOS	B55y000	Neoplasm--NOS
Malignant neoplasm of inguinal region NOS	B553000	Neoplasm--NOS
Malignant neoplasm of lower limb NOS	B555.00	Neoplasm--NOS
Malignant neoplasm of other and ill defined site NOS	B55z.00	Neoplasm--NOS
Malignant neoplasm of other and ill-defined sites	B55..00	Neoplasm--NOS
Malignant neoplasm of other specified sites	B55y.00	Neoplasm--NOS
Malignant neoplasm of pelvis	B553.00	Neoplasm--NOS
Malignant neoplasm of pelvis NOS	B553z00	Neoplasm--NOS
Malignant neoplasm of presacral region	B553100	Neoplasm--NOS
Malignant neoplasm of specified site NOS	B55yz00	Neoplasm--NOS
Malignant neoplasm of trunk NOS	B55y100	Neoplasm--NOS
Malignant neoplasm of unspecified site NOS	B59z.00	Neoplasm--NOS
Malignant neoplasm of upper limb NOS	B554.00	Neoplasm--NOS
Neop of uncertain behaviour of other specified sites NOS	B93yz00	Neoplasm--NOS
Neop uncertain behaviour of digestive and respiratory system	B90..00	Neoplasm--NOS
Neop uncertain behaviour other and unspec sites and tissues	B93..00	Neoplasm--NOS
Neop uncertain behaviour other unspec site and tissue NOS	B93z.00	Neoplasm--NOS
Neoplasm of uncertain behaviour NOS	B9z..00	Neoplasm--NOS
Neoplasm of uncertain behaviour of coccygeal body	B923300	Neoplasm--NOS
Neoplasm of uncertain behaviour of glomus jugulare	B923100	Neoplasm--NOS
Neoplasm of uncertain behaviour of paraganglia NOS	B923z00	Neoplasm--NOS
Neoplasm of uncertain behaviour otherwise specified	B9y..00	Neoplasm--NOS
Neoplasm of unspecified nature	BA0..00	Neoplasm--NOS
Neoplasm of unspecified nature NOS	BA0z.00	Neoplasm--NOS

Cancer description	Med Code	Cancer type
Neoplasm of unspecified nature NOS	BAz..00	Neoplasm--NOS
Neoplasm of unspecified nature of other specified sites	BA0y.00	Neoplasm--NOS
Neoplasms	B....00	Neoplasm--NOS
Neoplasms NOS	Bz...00	Neoplasm--NOS
Neoplasms of uncertain behaviour	B9...00	Neoplasm--NOS
Neoplasms otherwise specified	By...00	Neoplasm--NOS
Primary malignant neoplasm of unknown site	B593.00	Neoplasm--NOS
Unspecified nature neoplasm	BA...00	Neoplasm--NOS
[M]Adenocarcinoma, metastatic, NOS	BB53.00	Metastasis
[M]Carcinoma, metastatic, NOS	BB13.00	Metastasis
[M]Epithelioma, malignant	BB16.00	Metastasis
[M]Large cell carcinoma NOS	BB17.00	Metastasis
[M]Metastatic signet ring cell carcinoma	BB85100	Metastasis
[M]Neoplasm, malig, uncertain whether primary or metastatic	BB04.00	Metastasis
[M]Neoplasm, metastatic	BB03.00	Metastasis
[M]Secondary carcinoma	BB13.11	Metastasis
[M]Secondary neoplasm	BB03.11	Metastasis
[M]Squamous cell carcinoma, metastatic NOS	BB2B.00	Metastasis
[M]Squamous cell carcinoma, small cell, non-keratinising	BB2E.00	Metastasis
[M]Tumour embolism	BB03.13	Metastasis
[X]2ndry malignant neoplasm/oth+unspec parts/nervous system	ByuC600	Metastasis
[X]Malignant neoplasm of ill-defined, secondary and unspeci	ByuC.00	Metastasis
[X]Secondary malignant neoplasm of other specified sites	ByuC700	Metastasis
[X]Secondary malignant neoplasm/oth+unspc respiratory organs	ByuC300	Metastasis
[X]Secondary malignant neoplasm/oth+unspcfd digestive organs	ByuC400	Metastasis
Carcinoma of other and unspecified sites	B5...11	Metastasis
Carcinomatosis	B590.11	Metastasis
Cerebral metastasis	B583200	Metastasis
Disseminated malignancy NOS	B590.00	Metastasis
Kaposi's sarcoma of multiple organs	B592X00	Metastasis
Liver metastases	B577.11	Metastasis
Lymph node metastases	B56..11	Metastasis
Malignant ascites	B576200	Metastasis
Malignant neoplasm of other and unspecified site NOS	B5z..00	Metastasis
Malignant neoplasm of other and unspecified site OS	B5y..00	Metastasis
Malignant neoplasm of other and unspecified sites	B5...00	Metastasis
Malignant neoplasm of unspecified site	B59..00	Metastasis
Malignant neoplasms of independent (primary) multiple sites	B592.00	Metastasis
Metastases of respiratory and/or digestive systems	B57..11	Metastasis
Other malignant neoplasm NOS	B591.00	Metastasis
Pathological fracture due to metastatic bone disease	B585000	Metastasis
Secondary and unspec malig neop ant mediastinal lymph nodes	B561300	Metastasis
Secondary and unspec malig neop anterior cervical LN	B560800	Metastasis
Secondary and unspec malig neop axilla and upper limb LN	B563.00	Metastasis
Secondary and unspec malig neop axilla and upper limb LN NOS	B563z00	Metastasis
Secondary and unspec malig neop axillary lymph nodes	B563000	Metastasis
Secondary and unspec malig neop bronchopulmonary lymph nodes	B561800	Metastasis
Secondary and unspec malig neop circumflex iliac LN	B565200	Metastasis

Cancer description	Med Code	Cancer type
Secondary and unspec malig neop common iliac lymph nodes	B562300	Metastasis
Secondary and unspec malig neop deep cervical LN	B560900	Metastasis
Secondary and unspec malig neop deep parotid lymph nodes	B560400	Metastasis
Secondary and unspec malig neop external iliac lymph nodes	B562400	Metastasis
Secondary and unspec malig neop inferior mesenteric LN	B562200	Metastasis
Secondary and unspec malig neop infraclavicular lymph nodes	B563200	Metastasis
Secondary and unspec malig neop inguinal and lower limb LN	B564.00	Metastasis
Secondary and unspec malig neop internal mammary lymph nodes	B561000	Metastasis
Secondary and unspec malig neop intra-abdominal LN NOS	B562z00	Metastasis
Secondary and unspec malig neop intra-abdominal lymph nodes	B562.00	Metastasis
Secondary and unspec malig neop intrapelvic LN NOS	B565z00	Metastasis
Secondary and unspec malig neop intrapelvic lymph nodes	B565.00	Metastasis
Secondary and unspec malig neop intrathoracic LN NOS	B561z00	Metastasis
Secondary and unspec malig neop intrathoracic lymph nodes	B561.00	Metastasis
Secondary and unspec malig neop lymph nodes head/face/neck	B560.00	Metastasis
Secondary and unspec malig neop lymph nodes multiple sites	B56y.00	Metastasis
Secondary and unspec malig neop lymph nodes NOS	B56z.00	Metastasis
Secondary and unspec malig neop of inguinal and leg LN NOS	B564z00	Metastasis
Secondary and unspec malig neop of superficial parotid LN	B560000	Metastasis
Secondary and unspec malig neop paratracheal lymph nodes	B561500	Metastasis
Secondary and unspec malig neop pectoral lymph nodes	B563300	Metastasis
Secondary and unspec malig neop post mediastinal lymph nodes	B561400	Metastasis
Secondary and unspec malig neop pulmonary lymph nodes	B561900	Metastasis
Secondary and unspec malig neop submandibular lymph nodes	B560500	Metastasis
Secondary and unspec malig neop submental lymph nodes	B560700	Metastasis
Secondary and unspec malig neop superfic tracheobronchial LN	B561600	Metastasis
Secondary and unspec malig neop superficial cervical LN	B560200	Metastasis
Secondary and unspec malig neop superficial mesenteric LN	B562100	Metastasis
Secondary and unspec malignant neoplasm mastoid lymph nodes	B560100	Metastasis
Secondary and unspec malignant neoplasm occipital lymph node	B560300	Metastasis
Secondary and unspecified malignant neoplasm of lymph nodes	B56..00	Metastasis
Secondary cancer of the cervix	B58y211	Metastasis
Secondary carcinoma of other specified sites	B58..11	Metastasis
Secondary carcinoma of respiratory and/or digestive systems	B57..12	Metastasis
Secondary malig neop of large intestine or rectum NOS	B575z00	Metastasis
Secondary malig neop of respiratory and digestive systems	B57..00	Metastasis
Secondary malig neop of respiratory or digestive system NOS	B57z.00	Metastasis
Secondary malig neop of retroperitoneum and peritoneum	B576.00	Metastasis
Secondary malig neop of small intestine or duodenum NOS	B574z00	Metastasis
Secondary malignant neoplasm of adrenal gland	B587.00	Metastasis
Secondary malignant neoplasm of bladder	B581100	Metastasis
Secondary malignant neoplasm of bone and bone marrow	B585.00	Metastasis
Secondary malignant neoplasm of brain	B583000	Metastasis
Secondary malignant neoplasm of brain and spinal cord	B583.00	Metastasis
Secondary malignant neoplasm of brain or spinal cord NOS	B583z00	Metastasis
Secondary malignant neoplasm of breast	B58y000	Metastasis
Secondary malignant neoplasm of cervix uteri	B58y200	Metastasis

Cancer description	Med Code	Cancer type
Secondary malignant neoplasm of colon	B575000	Metastasis
Secondary malignant neoplasm of duodenum	B574000	Metastasis
Secondary malignant neoplasm of kidney	B580.00	Metastasis
Secondary malignant neoplasm of large intestine and rectum	B575.00	Metastasis
Secondary malignant neoplasm of liver	B153.00	Metastasis
Secondary malignant neoplasm of liver	B577.00	Metastasis
Secondary malignant neoplasm of lung	B570.00	Metastasis
Secondary malignant neoplasm of mediastinum	B571.00	Metastasis
Secondary malignant neoplasm of other digestive organ	B57y.00	Metastasis
Secondary malignant neoplasm of other part of nervous system	B584.00	Metastasis
Secondary malignant neoplasm of other respiratory organs	B573.00	Metastasis
Secondary malignant neoplasm of other specified site NOS	B58yz00	Metastasis
Secondary malignant neoplasm of other specified site NOS	B58z.00	Metastasis
Secondary malignant neoplasm of other specified sites	B58..00	Metastasis
Secondary malignant neoplasm of other specified sites	B58y.00	Metastasis
Secondary malignant neoplasm of other urinary organ NOS	B581z00	Metastasis
Secondary malignant neoplasm of other urinary organs	B581.00	Metastasis
Secondary malignant neoplasm of ovary	B586.00	Metastasis
Secondary malignant neoplasm of penis	B58y700	Metastasis
Secondary malignant neoplasm of peritoneum	B576100	Metastasis
Secondary malignant neoplasm of pleura	B572.00	Metastasis
Secondary malignant neoplasm of prostate	B58y500	Metastasis
Secondary malignant neoplasm of retroperitoneum	B576000	Metastasis
Secondary malignant neoplasm of skin	B582.00	Metastasis
Secondary malignant neoplasm of skin NOS	B582z00	Metastasis
Secondary malignant neoplasm of skin of breast	B582600	Metastasis
Secondary malignant neoplasm of skin of face	B582100	Metastasis
Secondary malignant neoplasm of skin of head	B582000	Metastasis
Secondary malignant neoplasm of skin of hip and leg	B582500	Metastasis
Secondary malignant neoplasm of skin of neck	B582200	Metastasis
Secondary malignant neoplasm of skin of shoulder and arm	B582400	Metastasis
Secondary malignant neoplasm of skin of trunk	B582300	Metastasis
Secondary malignant neoplasm of small intestine and duodenum	B574.00	Metastasis
Secondary malignant neoplasm of spinal cord	B583100	Metastasis
Secondary malignant neoplasm of testis	B58y600	Metastasis
Secondary malignant neoplasm of tongue	B58y900	Metastasis
Secondary malignant neoplasm of unknown site	B594.00	Metastasis
Secondary malignant neoplasm of ureter	B581000	Metastasis
Secondary malignant neoplasm of urethra	B581200	Metastasis
Secondary malignant neoplasm of uterus	B58y100	Metastasis
Secondary malignant neoplasm of vagina	B58y300	Metastasis
Secondary malignant neoplasm of vulva	B58y400	Metastasis
Secondary unspec malig neop lymph nodes head/face/neck NOS	B560z00	Metastasis
[M]Adenocarcinoma in situ	BB51.00	In Situ
[M]Adenocarcinoma in situ in adenomatous polyp	BB5L200	In Situ
[M]Adenocarcinoma in situ in tubulovillous adenoma	BB51100	In Situ
[M]Adenocarcinoma in situ in villous adenoma	BB51000	In Situ
[M]Bowen's disease	BB2L.00	In Situ
[M]Carcinoma in situ NOS	BB11.00	In Situ

Cancer description	Med Code	Cancer type
[M]Epidermoid carcinoma in situ	BB29.11	In Situ
[M]Intraductal carcinoma and lobular carcinoma in situ	BB9E000	In Situ
[M]Intraepit neop,grade III,of cervix, vulva and vagina	BB2N.00	In Situ
[M]Lobular carcinoma in situ	BB9E.00	In Situ
[M]Papillary carcinoma in situ	BB21.00	In Situ
[M]Queyrat's erythroplasia	BB2K.00	In Situ
[M]Squamous cell ca-in-situ, questionable stromal invasion	BB2H.00	In Situ
[M]Squamous cell carcinoma in situ NOS	BB29.00	In Situ
[M]Transitional cell carcinoma in situ	BB42.00	In Situ
[M]Verrucous carcinoma NOS	BB24.00	In Situ
[M]Verrucous epidermoid carcinoma	BB24.11	In Situ
[M]Verrucous squamous cell carcinoma	BB24.12	In Situ
[X]Carcinoma in situ of oth+unspecified male genital organs	ByuFC00	In Situ
[X]Carcinoma in situ of other specified digestive organs	ByuF100	In Situ
[X]Carcinoma in situ of skin, unspecified	ByuF900	In Situ
[X]Carcinoma in situ/other+unspecified parts of intestine	ByuF000	In Situ
[X]Melanoma in situ, unspecified	ByuFF00	In Situ
[X]Other carcinoma in situ of breast	ByuFG00	In Situ
Anal intraepithelial neoplasia grade III	B805000	In Situ
Bowen's disease	B8...11	In Situ
Ca-in-situ of G.I. tract	B80..11	In Situ
Carcinoma in situ	B8...00	In Situ
Carcinoma in situ NOS	B8z..00	In Situ
Carcinoma in situ of adrenal gland	B8yy100	In Situ
Carcinoma in situ of ampulla of Vater	B808600	In Situ
Carcinoma in situ of anal canal	B805.00	In Situ
Carcinoma in situ of anus NOS	B806.00	In Situ
Carcinoma in situ of appendix	B803500	In Situ
Carcinoma in situ of aryepiglottic fold	B810600	In Situ
Carcinoma in situ of ascending colon	B803600	In Situ
Carcinoma in situ of biliary system	B808.11	In Situ
Carcinoma in situ of bladder	B837.00	In Situ
Carcinoma in situ of body of stomach	B802200	In Situ
Carcinoma in situ of body of uterus	B832.11	In Situ
Carcinoma in situ of breast	B830.00	In Situ
Carcinoma in situ of breast and genitourinary system	B83..00	In Situ
Carcinoma in situ of bronchus and lung	B812.00	In Situ
Carcinoma in situ of bronchus or lung NOS	B812z00	In Situ
Carcinoma in situ of caecum	B803400	In Situ
Carcinoma in situ of cardia of stomach	B802000	In Situ
Carcinoma in situ of carina of bronchus	B812000	In Situ
Carcinoma in situ of cervix uteri	B831.00	In Situ
Carcinoma in situ of cheek	B800500	In Situ
Carcinoma in situ of colon	B803.00	In Situ
Carcinoma in situ of colon NOS	B803z00	In Situ
Carcinoma in situ of common bile duct	B808500	In Situ
Carcinoma in situ of cricoid cartilage	B810100	In Situ
Carcinoma in situ of cystic duct	B808400	In Situ
Carcinoma in situ of descending colon	B803200	In Situ
Carcinoma in situ of digestive organs	B80..00	In Situ

Cancer description	Med Code	Cancer type
Carcinoma in situ of duodenum	B807000	In Situ
Carcinoma in situ of ear	B822.11	In Situ
Carcinoma in situ of endocervix	B831000	In Situ
Carcinoma in situ of endometrium	B832000	In Situ
Carcinoma in situ of epiglottis	B810200	In Situ
Carcinoma in situ of ethmoidal sinus	B81y700	In Situ
Carcinoma in situ of Eustachian tube	B81y400	In Situ
Carcinoma in situ of exocervix	B831100	In Situ
Carcinoma in situ of eye	B8y0.00	In Situ
Carcinoma in situ of fallopian tube	B833100	In Situ
Carcinoma in situ of female genital organs NOS	B833z00	In Situ
Carcinoma in situ of floor of mouth	B800400	In Situ
Carcinoma in situ of gall bladder	B808300	In Situ
Carcinoma in situ of glottis	B810811	In Situ
Carcinoma in situ of gums	B800300	In Situ
Carcinoma in situ of hepatic duct	B808200	In Situ
Carcinoma in situ of hepatic flexure of colon	B803000	In Situ
Carcinoma in situ of hypopharynx	B800900	In Situ
Carcinoma in situ of ileum	B807200	In Situ
Carcinoma in situ of intrahepatic bile ducts	B808100	In Situ
Carcinoma in situ of jejunum	B807100	In Situ
Carcinoma in situ of larynx	B810.00	In Situ
Carcinoma in situ of larynx NOS	B810z00	In Situ
Carcinoma in situ of lip	B800000	In Situ
Carcinoma in situ of lip, oral cavity and pharynx NOS	B800z00	In Situ
Carcinoma in situ of liver	B808000	In Situ
Carcinoma in situ of liver or biliary system NOS	B808z00	In Situ
Carcinoma in situ of lower 1/3 oesophagus	B801200	In Situ
Carcinoma in situ of lower lobe bronchus and lung	B812400	In Situ
Carcinoma in situ of main bronchus	B812100	In Situ
Carcinoma in situ of maxillary sinus	B81y600	In Situ
Carcinoma in situ of middle 1/3 oesophagus	B801100	In Situ
Carcinoma in situ of middle lobe bronchus and lung	B812300	In Situ
Carcinoma in situ of nasal cavity	B81y100	In Situ
Carcinoma in situ of nasal sinuses	B81y.11	In Situ
Carcinoma in situ of nasopharynx	B800700	In Situ
Carcinoma in situ of oesophagus	B801.00	In Situ
Carcinoma in situ of oesophagus NOS	B801z00	In Situ
Carcinoma in situ of oral cavity	B800.11	In Situ
Carcinoma in situ of oropharynx	B800800	In Situ
Carcinoma in situ of other and unspecified parts of uterus	B832.00	In Situ
Carcinoma in situ of other and unspecified sites	B8y..00	In Situ
Carcinoma in situ of other and unspecified small intestine	B807.00	In Situ
Carcinoma in situ of other specified part respiratory system	B81y.00	In Situ
Carcinoma in situ of other specified site	B8yy.00	In Situ
Carcinoma in situ of other specified site NOS	B8yyz00	In Situ
Carcinoma in situ of other specified sites of skin	B82y.00	In Situ
Carcinoma in situ of ovary	B833000	In Situ
Carcinoma in situ of palate	B800600	In Situ
Carcinoma in situ of pancreas	B80z000	In Situ

Cancer description	Med Code	Cancer type
Carcinoma in situ of parathyroid gland	B8yy200	In Situ
Carcinoma in situ of penis	B835.00	In Situ
Carcinoma in situ of perianal skin	B825800	In Situ
Carcinoma in situ of pharynx	B800.12	In Situ
Carcinoma in situ of pituitary gland	B8yy300	In Situ
Carcinoma in situ of pleura	B81y000	In Situ
Carcinoma in situ of prostate	B834.00	In Situ
Carcinoma in situ of pyloric antrum	B802300	In Situ
Carcinoma in situ of pyloric canal	B802400	In Situ
Carcinoma in situ of rectosigmoid junction	B804000	In Situ
Carcinoma in situ of rectum	B804100	In Situ
Carcinoma in situ of rectum and rectosigmoid junction	B804.00	In Situ
Carcinoma in situ of rectum or rectosigmoid junction NOS	B804z00	In Situ
Carcinoma in situ of respiratory organ NOS	B81z.00	In Situ
Carcinoma in situ of respiratory system	B81..00	In Situ
Carcinoma in situ of salivary glands	B800200	In Situ
Carcinoma in situ of scalp	B824000	In Situ
Carcinoma in situ of scalp and skin of neck	B824.00	In Situ
Carcinoma in situ of scrotum	B836300	In Situ
Carcinoma in situ of sigmoid colon	B803300	In Situ
Carcinoma in situ of skin	B82..00	In Situ
Carcinoma in situ of skin NOS	B82z.00	In Situ
Carcinoma in situ of skin of abdominal wall	B825400	In Situ
Carcinoma in situ of skin of auricle	B822000	In Situ
Carcinoma in situ of skin of axilla	B825200	In Situ
Carcinoma in situ of skin of back	B825300	In Situ
Carcinoma in situ of skin of breast	B825000	In Situ
Carcinoma in situ of skin of cheek	B823300	In Situ
Carcinoma in situ of skin of chest wall NOS	B825100	In Situ
Carcinoma in situ of skin of eyebrow	B823100	In Situ
Carcinoma in situ of skin of eyelid including canthus	B821.00	In Situ
Carcinoma in situ of skin of foot	B827400	In Situ
Carcinoma in situ of skin of forehead skin	B823000	In Situ
Carcinoma in situ of skin of groin	B825500	In Situ
Carcinoma in situ of skin of hand	B826300	In Situ
Carcinoma in situ of skin of hip	B827000	In Situ
Carcinoma in situ of skin of jaw	B823600	In Situ
Carcinoma in situ of skin of knee	B827200	In Situ
Carcinoma in situ of skin of leg	B827.11	In Situ
Carcinoma in situ of skin of lip	B820.00	In Situ
Carcinoma in situ of skin of lower arm	B826200	In Situ
Carcinoma in situ of skin of lower leg	B827300	In Situ
Carcinoma in situ of skin of lower limb and hip	B827.00	In Situ
Carcinoma in situ of skin of lower limb or hip NOS	B827z00	In Situ
Carcinoma in situ of skin of neck	B824100	In Situ
Carcinoma in situ of skin of nose	B823400	In Situ
Carcinoma in situ of skin of other parts of face	B823.00	In Situ
Carcinoma in situ of skin of other parts of face NOS	B823z00	In Situ
Carcinoma in situ of skin of perineum	B825600	In Situ
Carcinoma in situ of skin of shoulder	B826000	In Situ

Cancer description	Med Code	Cancer type
Carcinoma in situ of skin of temple	B823500	In Situ
Carcinoma in situ of skin of thigh	B827100	In Situ
Carcinoma in situ of skin of trunk NOS	B825z00	In Situ
Carcinoma in situ of skin of trunk, excluding scrotum	B825.00	In Situ
Carcinoma in situ of skin of upper arm	B826100	In Situ
Carcinoma in situ of skin of upper limb and shoulder	B826.00	In Situ
Carcinoma in situ of skin of upper limb or shoulder NOS	B826z00	In Situ
Carcinoma in situ of sphenoidal sinus	B81y900	In Situ
Carcinoma in situ of sphincter of Oddi	B808700	In Situ
Carcinoma in situ of spleen	B80z100	In Situ
Carcinoma in situ of splenic flexure of colon	B803700	In Situ
Carcinoma in situ of stomach	B802.00	In Situ
Carcinoma in situ of stomach NOS	B802z00	In Situ
Carcinoma in situ of testis	B836000	In Situ
Carcinoma in situ of thyroid cartilage	B810000	In Situ
Carcinoma in situ of thyroid gland	B8yy000	In Situ
Carcinoma in situ of tongue	B800100	In Situ
Carcinoma in situ of trachea	B811.00	In Situ
Carcinoma in situ of transverse colon	B803100	In Situ
Carcinoma in situ of upper lobe bronchus and lung	B812200	In Situ
Carcinoma in situ of urinary organs NOS	B83z.00	In Situ
Carcinoma in situ of vagina	B833200	In Situ
Carcinoma in situ of vestibular fold	B810700	In Situ
Carcinoma in situ of vocal fold - glottis	B810800	In Situ
Carcinoma in situ of vulva	B833300	In Situ
Carcinoma in situ other and unspecified female genital organ	B833.00	In Situ
Carcinoma in situ other and unspecified small intestine NOS	B807z00	In Situ
Carcinoma in situ skin of ear and external auricular canal	B822.00	In Situ
Carcinoma in situ skin of ear/external auricular canal NOS	B822z00	In Situ
Cervical intraepithelial neoplasia	B831.12	In Situ
Cervical intraepithelial neoplasia grade III	B831.13	In Situ
CIN III - carcinoma in situ of cervix	B831.11	In Situ
Erythroplasia	B8...12	In Situ
High grade prostatic intraepithelial neoplasia	B834000	In Situ
Intraductal carcinoma in situ of breast	B830100	In Situ
Lobular carcinoma in situ of breast	B830000	In Situ
Melanoma in situ of back	B828900	In Situ
Melanoma in situ of back of hand	B828800	In Situ
Melanoma in situ of eyelid, including canthus	B828100	In Situ
Melanoma in situ of lip	B828000	In Situ
Melanoma in situ of lower limb, including hip	B828600	In Situ
Melanoma in situ of other and unspecified parts of face	B828X00	In Situ
Melanoma in situ of scalp	B828700	In Situ
Melanoma in situ of scalp and neck	B828300	In Situ
Melanoma in situ of skin	B828.00	In Situ
Melanoma in situ of trunk	B828400	In Situ
Melanoma in situ of upper limb, including shoulder	B828500	In Situ
Melanoma in situ, unspecified	B828W00	In Situ
Queyrats's erythroplasia	B8...13	In Situ
Vulval intraepithelial neoplasia	B833311	In Situ

20.18 Atrial fibrillation

Atrial fibrillation description	Med Code
Atrial fibrillation	G573000
Atrial fibrillation and flutter	G573.00
Atrial fibrillation and flutter NOS	G573z00
Non-rheumatic atrial fibrillation	G573300
Paroxysmal atrial fibrillation	G573200
Permanent atrial fibrillation	G573400
Persistent atrial fibrillation	G573500

20.19 Dementia

Dementia description	Med Code
[X] Presenile dementia NOS	Eu02z11
[X] Presenile psychosis NOS	Eu02z12
[X] Primary degenerative dementia NOS	Eu02z13
[X] Senile dementia NOS	Eu02z14
[X] Senile dementia, depressed or paranoid type	Eu02z16
[X] Senile psychosis NOS	Eu02z15
[X] Unspecified dementia	Eu02z00
[X]Alzheimer's dementia unspec	Eu00z11
[X]Alzheimer's disease type 1	Eu00111
[X]Alzheimer's disease type 2	Eu00013
[X]Arteriosclerotic dementia	Eu01.11
[X]Delirium superimposed on dementia	Eu04100
[X]Dementia in Alzheimer's dis, atypical or mixed type	Eu00200
[X]Dementia in Alzheimer's disease	Eu00.00
[X]Dementia in Alzheimer's disease with early onset	Eu00000
[X]Dementia in Alzheimer's disease with late onset	Eu00100
[X]Dementia in Alzheimer's disease, unspecified	Eu00z00
[X]Mixed cortical and subcortical vascular dementia	Eu01300
[X]Multi-infarct dementia	Eu01100
[X]Other Alzheimer's disease	Fyu3000
[X]Other vascular dementia	Eu01y00
[X]Predominantly cortical dementia	Eu01111
[X]Presenile dementia,Alzheimer's type	Eu00011
[X]Primary degen dementia of Alzheimer's type, senile onset	Eu00113
[X]Primary degen dementia, Alzheimer's type, presenile onset	Eu00012
[X]Senile dementia,Alzheimer's type	Eu00112
[X]Subcortical vascular dementia	Eu01200
[X]Vascular dementia	Eu01.00
[X]Vascular dementia of acute onset	Eu01000
[X]Vascular dementia, unspecified	Eu01z00
Alzheimer's disease	F110.00
Alzheimer's disease with early onset	F110000
Alzheimer's disease with late onset	F110100
Arteriosclerotic dementia	E004.00
Arteriosclerotic dementia NOS	E004z00
Arteriosclerotic dementia with delirium	E004100
Arteriosclerotic dementia with depression	E004300

Dementia description	Med Code
Arteriosclerotic dementia with paranoia	E004200
Dementia annual review	6AB..00
Dementia monitoring	66h..00
Dementia monitoring administration	9Ou..00
Dementia monitoring first letter	9Ou1.00
Dementia monitoring second letter	9Ou2.00
Dementia monitoring telephone invite	9Ou5.00
Dementia monitoring third letter	9Ou3.00
Dementia monitoring verbal invite	9Ou4.00
Excepted from dementia quality indicators: Informed dissent	9hD1.00
Excepted from dementia quality indicators: Patient unsuitabl	9hD0.00
Exception reporting: dementia quality indicators	9hD..00
H/O: dementia	1461.00
Language disorder of dementia	ZS7C500
Multi infarct dementia	E004.11
Other senile and presenile organic psychoses	E00y.00
Presbyophrenic psychosis	E00y.11
Presenile dementia	E001.00
Presenile dementia NOS	E001z00
Presenile dementia with delirium	E001100
Presenile dementia with depression	E001300
Presenile dementia with paranoia	E001200
Senile and presenile organic psychotic conditions	E00..00
Senile dementia	E00..11
Senile dementia with delirium	E003.00
Senile dementia with depression	E002100
Senile dementia with depressive or paranoid features	E002.00
Senile dementia with depressive or paranoid features NOS	E002z00
Senile dementia with paranoia	E002000
Senile or presenile psychoses NOS	E00z.00
Senile/presenile dementia	E00..12
Uncomplicated arteriosclerotic dementia	E004000
Uncomplicated presenile dementia	E001000
Uncomplicated senile dementia	E000.00

20.20 Palliative care

Terminal illness / Palliative care description	Med Code
[V]Palliative care	ZV57C00
Anticipatory palliative care	8BAe.00
DS 1500 Disability living allowance completed	9EB5.00
GSF supportive care stage 1 - advancing disease	8CM1000
GSF supportive care stage 2 - increasing decline	8CM1100
GSF supportv care stge 3 - last days: cat C - wks prognosis	8CM1200
GSF supportv care stge 3 - last days: cat D - days prognosis	8CM1300
Has end of life advanced care plan	8CME.00
Last days of life	2JE..00
Liverpool care pathway for the dying	8CM4.00
On end of life care register	9Ng7.00
On gold standards palliative care framework	8CM1.00

Terminal illness / Palliative care description	Med Code
Palliative treatment	8BJ1.00
Refer for terminal care	8H7L.00
Refer to terminal care consult	8H6A.00
Referral to community palliative care team declined	8IEE.00
Referral to palliative care service	8H7g.00
Referred to community specialist palliative care team	8HH7.00
Specialist palliative care	8BAP.00
Specialist palliative care treatment - daycare	8BAS.00
Specialist palliative care treatment - outpatient	8BAT.00
Terminal care	8BA2.00
Terminal illness - late stage	1Z01.00

21 Investigation of the age at which SMI is diagnosed:

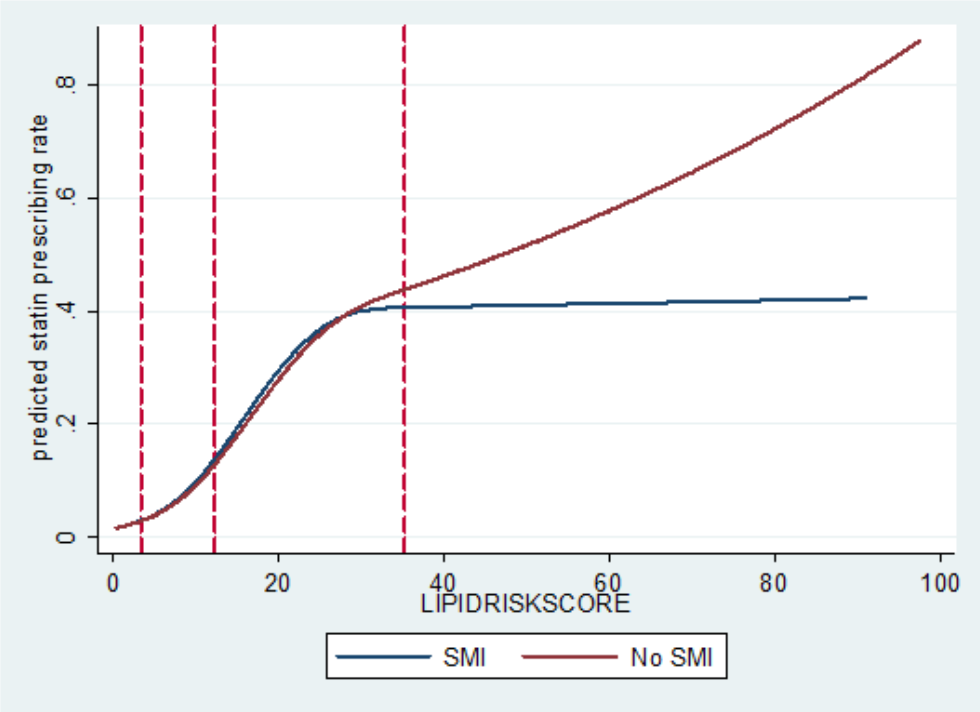
The selected age limits (30 and 99 years) are supported by exploratory work evaluating the ages at which rates of new diagnoses of SMI are made in people who were registered at or before their 18th, 20th, 25th or 30th birthday. This work showed that the majority of people who were registered with a THIN practice from an early age (and had a recording of SMI) had a first diagnosis of bipolar disorder or schizophrenia recorded before the age of thirty. This is also supported by other studies in UK primary care, which found that over 70% of people with schizophrenia were first diagnosed by the age of 30 years (Roberts et al., 2007). Furthermore, rates of recording of new cases of SMI in UK primary care are highest in people aged 16-34 years of age(Hardoon et al., 2013). Obtaining a firm diagnosis of SMI may take a substantial length of time: therefore the recorded age of onset is likely to be older than the actual age that the illness first began. When combined with a preference for using an age limit that is compatible with most CVD risk scores, setting the minimum age at entry into the cohort at 30 years is justified.

22 Association between estimated CVD risk and statin prescribing within the subset of people who had all components of physical health check recorded

There was some evidence of interaction between the spline functions and the presence or absence of SMI for people with schizophrenia (p=0.001) but not bipolar disorder (p=0.12). Visualisation of the predicted values from the regression model for the schizophrenia cohort (Figure 22-1) suggested that prescribing rates were might be different in people with schizophrenia compared to people without SMI only at risk scores above 30%. However, it should be noted that almost 90% of the people included in the analysis had a risk score that was below 30%,

meaning that the fit of the spline at values above 30% is based on a relatively small subset of data.

Figure 22-1: Predicted rate of statin prescribing and estimated CVD risk score for people with schizophrenia and comparison people without SMI



The dashed vertical lines indicate the placement of the knots within the regression spline at the 10th, 50th and 90th percentiles of data: the spline function is cubic between knots and linear before the first knot and after the last knot

23 Statin prescribing for primary prevention of CVD in people with and without SMI

23.1 Abstract submitted to Primary Care Mental Health Annual Conference

Introduction: Cardiovascular disease (CVD) screening rates in people with severe mental illness (SMI) have increased since the introduction of the Quality and Outcomes Framework. However, the impact on statin prescribing is unknown.

Aim: to describe differences in new statin prescriptions in UK GP patients with and without SMI who do not have a pre-existing CVD condition.

Method: A cohort was constructed using primary care data from The Health Improvement Network for the period January 2007-December 2012. Individuals aged 30-99 years with a schizophrenia or bipolar disorder diagnosis were selected and age and gender frequency-matched to ten control patients in the same

practice who did not have an SMI diagnosis. Individuals were excluded if they had pre-existing CVD or a previous statin prescription. Prescribing differences between individuals with SMI and controls were investigated in Poisson regression models with new statin prescription as the outcome. Models were adjusted for calendar time (with year as a categorical variable) or estimated CVD risk, which was incorporated as a restricted cubic spline.

Results: A total of 8,530 individuals with schizophrenia and 7,561 with bipolar disorder and ten-times as many controls were included in the study. Time-adjusted IRRs for statin prescribing amongst 30-59 year olds were; 1.92 (95% CI: 1.74-2.11) for schizophrenia and 1.98 (95% CI: 1.78-2.2) for bipolar disorder compared to controls without SMI. However, individuals aged 60-99 years with schizophrenia (but not bipolar disorder) had lower rates of statin prescribing than controls; IRR 0.75 (95% CI: 0.67-0.84). After adjusting for estimated CVD risk, individuals with schizophrenia (but not bipolar disorder) were less frequently prescribed statins than controls; IRR 0.93 (95% CI: 0.87-0.98).

Conclusion: There is evidence of disparity in prescribing for older Individuals with schizophrenia, and after accounting for estimated CVD risk, relative to controls without SMI.

23.2 Abstract submitted to SAPC

Title: Patterns of statin prescribing for the primary prevention of cardiovascular disease in people with severe mental illness

The Problem: Severe mental illness (SMI) such as bipolar disorder and schizophrenia is associated with excess cardiovascular disease (CVD) morbidity and mortality, which has significant financial and social cost implications. This healthcare need is recognised within UK primary care and, since the introduction of GP incentives in 2004, rates of CVD screening have increased amongst individuals with SMI. However, the impact on statin prescribing is unknown.

The Approach: We used data from The Health Improvement Network (THIN) primary care database from 2007 to 2012 to describe differences in new statin prescriptions in UK patients with and without SMI with no pre-existing CVD conditions. Individuals aged 30-99 years with a diagnosis of schizophrenia or bipolar disorder were selected and age and gender frequency-matched to ten control patients in the same practice who did not have an SMI diagnosis. Individuals were excluded if they had pre-existing CVD or a previous statin prescription. Prescribing differences between individuals with SMI and controls were investigated in Poisson regression models with new statin prescription as the outcome. Models were adjusted for calendar time or estimated CVD risk.

Findings: A total of 8,530 individuals with schizophrenia and 7,561 with bipolar disorder were included in the study: 85,088 and 74,446 frequency-matched controls without SMI were also selected for comparison with individuals with schizophrenia or bipolar disorder (respectively). Time-adjusted incidence rate ratios (IRR) for statin prescribing amongst 30-59 year olds were; 1.92 (95% CI: 1.74-2.11) for schizophrenia and 1.98 (95% CI: 1.78-2.20) for bipolar disorder compared to controls without SMI. Individuals aged 60-99 years with schizophrenia had lower rates of statin prescribing than controls; IRR 0.75 (95% CI: 0.67-0.84), but there were no such difference for bipolar disorder; IRR 0.99 (95% CI: 0.88-1.11). After adjusting for estimated CVD risk, individuals with schizophrenia (but not bipolar disorder) were less frequently prescribed statins than controls; IRR 0.93 (95% CI: 0.87-0.98).

Consequences: The introduction of GP incentives for CVD screening has successfully increased statin prescribing amongst younger individuals with SMI. However, evidence of disparity in statin prescribing is apparent for older individuals with schizophrenia (relative to controls without SMI) may suggest an unmet need for statin prescribing in this group. Further work is required to ascertain the impact of CVD interventions in people with SMI, and how the uptake of effective measures can be improved.

23.3 Abstract submitted to the International Society for Pharmaco-Epidemiology Annual Conference

Title: Patterns of statin prescribing for the primary prevention of cardiovascular disease in people with severe mental illness

Background: Severe mental illness (SMI) such as bipolar disorder and schizophrenia is associated with excess cardiovascular disease (CVD) morbidity and mortality, which may indicate an unmet need for interventions to prevent CVD. Statins are the most commonly prescribed CVD drug, but uptake is unknown for individuals with SMI.

Objectives: To quantify differences in new statin prescribing for primary CVD prevention between individuals with and without SMI

Methods: We used data from The Health Improvement Network (THIN) primary care database from 2007 to 2012 to describe differences in new statin prescriptions in UK patients with and without SMI with no pre-existing CVD conditions. Individuals aged 30-99 years with a schizophrenia or bipolar disorder diagnosis were selected and age and gender frequency-matched to ten control patients in the same practice who did not have an SMI diagnosis. Prescribing differences between individuals with SMI and controls were investigated in Poisson regression models with new statin prescription as the outcome. Models were adjusted for calendar time or estimated CVD risk.

Results: A total of 8,530 individuals with schizophrenia and 7,561 with bipolar disorder and ten-times as many controls were included in the study. Time-adjusted Incidence Rate Ratios (IRR) for statin prescribing amongst 30-59 year olds were; 1.92 (95% CI: 1.74-2.11) for schizophrenia and 1.98 (95% CI: 1.78-2.2) for bipolar disorder compared to controls without SMI. Individuals aged 60-99 years with schizophrenia had lower rates of statin prescribing than controls; IRR 0.75 (95% CI: 0.67-0.84), but there were no such difference for bipolar disorder; IRR 0.99 (95% CI: 0.88-1.11). After adjusting for estimated CVD risk, individuals with schizophrenia (but not bipolar disorder) were less frequently prescribed statins than controls; IRR 0.93 (95% CI: 0.87-0.98).

Conclusions: Evidence of disparity in statin prescribing is apparent for older individuals with schizophrenia (relative to controls without SMI), suggesting an unmet need for statin prescribing in this group.

24 The effectiveness of statins for primary prevention of CVD in people with SMI: a staggered cohort study in THIN

24.1 Abstract submitted to Public Health England's Applied Epidemiology Scientific Conference 2016

Reducing inequalities in cardiovascular health in people with severe mental illness: evaluating the real-life impact of statin prescribing

Cardiovascular disease (CVD) is the leading cause of death amongst people with severe mental illness (SMI) and drives substantial portion of the 15-20 year deficit in life expectancy experienced by this group relative to the general population. Statins form a core part of CVD prevention in the general population, but the evidence-base for people with SMI is unclear. We aimed to estimate the effectiveness of statins for primary prevention of CVD amongst people with SMI using data from The Health Improvement Network, which captures primary care data on 6% of the UK population.

The average treatment effect of statin prescribing was estimated using a staggered cohort design that compared people with SMI who did (statin users), or did not (statin non-users), receive a statin prescription within a two year period between January 2002 and December 2010. Combined first myocardial infarction (MI) and stroke events were the primary outcome. All-cause mortality and change in total cholesterol concentration were evaluated as secondary outcomes. The association between statin prescribing and the outcomes were estimated using a Poisson regression model (or linear regression for cholesterol), that incorporated an extensive array of covariates identified from the literature. Unobserved covariate data on total cholesterol, blood pressure, weight, height and smoking status were estimated using multiple imputation.

A total of 2,944 statin users and 42,886 statin non-users were identified across the series of cohorts. Statin prescribing was associated with statistically significant reductions in total cholesterol (of 1.2mmol/L for up to 2 years, $p<0.001$) and non-significant reductions in the rate of MI and stroke (IRR 0.89; 95% CI; 0.68-1.15) and all-cause mortality 0.89 (95% CI; 0.78, 1.02).

Our results are broadly similar to those for the general population and provide new assurance that statin prescribing may help reduce cardiovascular health inequalities amongst people with SMI.

25 Example MI impute dryrun output (for imputation of cholesterol data for the baseline year 2002)

```
Conditional models:
log_chol2002: regress log_chol2002 log_height i.eversmoke log_sys2004
log_sys2003 log_sys2002 log_sys2001 log_sys2000 log_weight2004
log_weight2003 log_weight2002 log_chol2004 log_weight2001 log_chol2003
log_weight2000 log_chol2001 log_chol2000 Jan2002 cvd NA i.ageband sex
TYPEGROUP BL_diabetes BL_heavydrink BL_antihyp BL_nonstatin BL_antipsy
BL_antidep BL_moods BL_copd BL_hypothy BL_cancer BL_ckd BL_FH , noisily
```

26 Example MI impute output

```
Multivariate imputation                     Imputations =       10
Chained equations                                 added =       10
Imputed: m=1 through m=10                       updated =        0

Initialization: monotone                     Iterations =      100
burn-in =       10

        log_chol2004: linear regression
        log_chol2003: linear regression
        log_chol2000: linear regression
        log_chol2001: linear regression
        log_chol2002: linear regression
        log_height: linear regression
        log_weight2000: linear regression
        log_weight2004: linear regression
        log_weight2001: linear regression
        log_weight2003: linear regression
        log_weight2002: linear regression
        log_sys2000: linear regression
        log_sys2004: linear regression
        log_sys2001: linear regression
        log_sys2003: linear regression
        log_sys2002: linear regression
        eversmoke: logistic regression


Observations per m
-----------------------------------------------
               Variable    Complete   Incomplete   Imputed      Total

        log_chol2004        1630         6414      6414       8044
        log_chol2003        1312         6732      6732       8044
        log_chol2000         400         7644      7644       8044
        log_chol2001         688         7356      7356       8044
        log_chol2002         964         7080      7080       8044
        log_height          7402          642       642       8044
        log_weight2000      1289         6755      6755       8044
        log_weight2004      2361         5683      5683       8044
        log_weight2001      1592         6452      6452       8044
        log_weight2003      2033         6011      6011       8044
        log_weight2002      1635         6409      6409       8044
        log_sys2000         2501         5543      5543       8044
        log_sys2004         4245         3799      3799       8044
        log_sys2001         3068         4976      4976       8044
```

```
log_sys2003         3926          4118        4118        8044
log_sys2002         3409          4635        4635        8044
eversmoke           6772          1272        1272        8044

(complete + incomplete = total; imputed is the minimum across m of the
number of filled-in observations.)
(saving in Stata 13 format)
(FYI, saveold has options version(12) and version(11) that write files in
older Stata formats)

file N:\Ruth\Stata\THIN\Multi trial study\FINAL COMBINED DATASETS AND LOG
FILES/Jan2002_FULLIMPUTED_test.dta saved
```

Table 8: Output from multivariable logistic regression model for associations between covariates and either statin prescribing or CVD events in complete cases

COMPLETE CASES		Statin Prescribing			CVD events		
		OR	95% CI		OR	95% CI	
Age band	40-44	1.00	--	--	1.00	--	--
	45-49	0.97	0.75	1.24	3.64	1.66	7.95
	50-54	1.54	1.22	1.96	3.81	1.76	8.28
	55-59	1.98	1.56	2.53	4.82	2.24	10.36
	60-64	1.93	1.50	2.48	5.87	2.73	12.64
	65-69	2.19	1.66	2.87	8.43	3.92	18.13
	70-74	1.85	1.35	2.52	10.80	4.94	23.64
	75-79	2.04	1.42	2.93	9.74	4.21	22.57
	80-84	0.96	0.59	1.57	11.45	4.61	28.40
Sex	Male	1.00	--	--	1.00	--	--
	Female	0.55	0.48	0.63	0.73	0.57	0.93
	Diabetes	5.11	4.42	5.90	1.29	1.00	1.66
	Cholesterol	2.59	2.43	2.77	1.08	0.98	1.20
	Systolic BP	1.01	1.01	1.02	1.02	1.01	1.03
	BMI	1.03	1.02	1.04	1.01	0.99	1.03
Smoking status	Never	1.00	--	--	1.00	--	--
	Ex	1.20	0.97	1.49	1.36	0.96	1.94
	Current	1.75	1.50	2.04	1.33	1.00	1.77
SMI type	Bipolar	1.00	--	--	1.00	--	--
	Schizophrenia	1.00	0.86	1.16	0.96	0.73	1.26
Cohort	2002/3	1.00	--	--	1.00	--	--
	2004/5	2.18	1.64	2.89	0.68	0.47	0.98
	2006/7	2.29	1.74	3.00	0.52	0.36	0.75
	2008/9	1.75	1.33	2.30	0.33	0.22	0.50
	2009/10	1.16	0.89	1.53	0.16	0.10	0.25
Consultation rate	<4	1.00	--	--	1.00	--	--
	4-6	1.14	0.89	1.47	1.23	0.73	2.08
	7-12	1.26	0.99	1.60	1.26	0.77	2.07
	>13	1.38	1.08	1.76	1.40	0.85	2.30
Antipsychotic	None	1.00	--	--	1.00	--	--
	1	0.95	0.80	1.13	0.95	0.70	1.28
	2	0.97	0.83	1.12	0.97	0.73	1.28

COMPLETE CASES		Statin Prescribing			CVD events		
		OR	95% CI		OR	95% CI	
Townsend Deprivation score	1	1.00	--	--	1.00	--	--
	2	0.99	0.79	1.24	1.09	0.73	1.63
	3	1.01	0.82	1.26	1.56	1.07	2.27
	4	0.93	0.75	1.15	1.05	0.71	1.55
	5	1.16	0.93	1.44	1.00	0.66	1.50
	Antihypertensive	1.52	1.31	1.75	0.86	0.66	1.10
	Antidepressant	1.23	1.07	1.40	1.63	1.29	2.08
	Mood stabiliser	0.86	0.73	1.00	1.07	0.81	1.42
	Asthma	1.09	0.89	1.34	1.37	0.96	1.94
	COPD	1.09	0.78	1.51	2.35	1.55	3.56
	FH	10.27	7.09	14.87	1.16	0.66	2.03
	AF	0.98	0.52	1.84	0.58	0.17	1.94
	Cancer	0.61	0.36	1.04	0.65	0.26	1.65
	Hypothyroidism	0.99	0.55	1.80	0.48	0.11	2.05
	CKD	0.87	0.67	1.13	1.22	0.79	1.87
	Heavy drinking	0.77	0.64	0.92	0.59	0.40	0.86
	Non statin use	1.11	0.68	1.82	0.97	0.38	2.49

Table 9: Output from multivariable logistic regression model for associations between covariates and either statin prescribing or CVD events in the full dataset (with imputed values)

IMPUTED DATA		Statin Prescribing			CVD events		
		OR	95% CI		OR	95% CI	
Age band	40-44	1.00	--	--	1.00	--	--
	45-49	1.18	0.98	1.42	2.00	1.57	2.56
	50-54	1.66	1.40	1.98	2.47	1.94	3.15
	55-59	2.11	1.77	2.51	3.21	2.53	4.07
	60-64	2.41	2.01	2.88	4.43	3.49	5.61
	65-69	2.71	2.24	3.28	6.18	4.87	7.85
	70-74	2.30	1.85	2.85	7.64	5.97	9.77
	75-79	1.78	1.39	2.28	7.05	5.42	9.16
	80-84	0.98	0.70	1.37	7.82	5.89	10.38
Sex	Male	1.00	--	--	1.00	--	--
	Female	0.56	0.50	0.61	0.71	0.64	0.79
	Diabetes	7.20	6.49	7.99	1.31	1.13	1.51
	Cholesterol	2.25	2.15	2.36	1.06	1.00	1.13
	Systolic BP	1.01	1.01	1.02	1.01	1.01	1.01
	BMI	1.04	1.04	1.05	1.01	1.00	1.02
Smoking status	Never	1.00	--	--	1.00	--	--
	Ex	1.27	1.10	1.47	1.12	0.96	1.30
	Current	1.58	1.41	1.76	1.38	1.23	1.54
SMI type	Bipolar	1.00	--	--	1.00	--	--
	Schizophrenia	1.01	0.91	1.13	0.83	0.74	0.93

IMPUTED DATA		Statin Prescribing			CVD events		
		OR	95% CI		OR	95% CI	
Cohort	2002/3	1.00	--	--	1.00	--	--
	2004/5	2.12	1.78	2.53	0.71	0.63	0.81
	2006/7	2.84	2.39	3.37	0.48	0.42	0.56
	2008/9	2.49	2.09	2.97	0.33	0.28	0.38
	2009/10	2.15	1.80	2.57	0.15	0.13	0.19
Consultation rate	<4	1.00	--	--	1.00	--	--
	4-6	1.79	1.53	2.11	1.01	0.87	1.17
	7-12	2.34	2.00	2.73	1.10	0.96	1.27
	>13	2.87	2.46	3.35	1.10	0.95	1.27
Antipsychotic	None	1.00	--	--	1.00	--	--
	1	0.94	0.84	1.06	1.01	0.89	1.14
	2	1.11	1.00	1.23	1.05	0.94	1.18
Townsend Deprivation score	1	1.00	--	--	1.00	--	--
	2	0.96	0.82	1.12	1.21	1.03	1.42
	3	1.01	0.87	1.18	1.41	1.21	1.65
	4	0.91	0.78	1.06	1.22	1.04	1.43
	5	1.13	0.97	1.32	1.27	1.07	1.50
	Antihypertensive	2.35	2.12	2.60	1.31	1.17	1.47
	Antidepressant	0.96	0.83	1.11	1.18	1.00	1.38
	Mood stabiliser	1.04	0.83	1.31	1.15	0.93	1.43
	Asthma	1.03	0.94	1.13	1.12	1.01	1.23
	COPD	0.85	0.76	0.94	1.00	0.89	1.12
	FH	38.39	28.99	50.83	1.42	0.95	2.12
	AF	1.22	0.83	1.79	1.04	0.71	1.53
	Cancer	0.64	0.43	0.94	0.69	0.46	1.02
	Hypothyroidism	1.14	0.74	1.76	1.21	0.76	1.94
	CKD	1.29	1.06	1.57	1.17	0.90	1.51
	Heavy drinking	0.95	0.83	1.07	0.98	0.85	1.14
	Non statin use	1.81	1.24	2.66	0.99	0.51	1.89

Table 6: Output from multivariable linear regression model for associations between statin prescribing and total cholesterol at 1 year after the index date (complete cases)

Factor		Coefficient	Std. Err.	P>t	95% CI	
Statin prescription		-1.29	0.03	0.00	-1.35	-1.23
Cholesterol at baseline		-0.36	0.01	0.00	-0.39	-0.34
Age band	40-44	baseline	--	--	--	
	45-49	-0.05	0.04	0.26	-0.13	0.04
	50-54	-0.05	0.04	0.25	-0.13	0.03
	55-59	-0.02	0.05	0.70	-0.11	0.07
	60-64	-0.06	0.05	0.17	-0.15	0.03
	65-69	-0.13	0.05	0.01	-0.23	-0.03

Factor		Coefficient	Std. Err.	P>t	95% CI	
	70-74	-0.11	0.06	0.05	-0.22	0.00
	75-79	-0.20	0.07	0.00	-0.33	-0.07
	80-84	-0.13	0.08	0.10	-0.27	0.02
Sex	Male	baseline	--	--	--	
	Female	0.09	0.02	0.00	0.05	0.14
	Diabetes	-0.11	0.03	0.00	-0.16	-0.06
	Systolic BP	0.00	0.00	0.17	0.00	0.00
	BMI	0.00	0.00	0.05	-0.01	0.00
Smoking status	Never	baseline	--	--	--	
	Ex	-0.02	0.04	0.53	-0.10	0.05
	Current	0.02	0.03	0.51	-0.04	0.07
SMI type	Bipolar	baseline	--	--	--	
	Schizophrenia	-0.04	0.03	0.19	-0.09	0.02
Cohort	2002/3	baseline	--	--	--	
	2004/5	-0.11	0.06	0.07	-0.22	0.01
	2006/7	-0.11	0.06	0.05	-0.23	0.00
	2008/9	-0.06	0.06	0.33	-0.17	0.06
	2009/10	-0.05	0.06	0.34	-0.16	0.06
Consultation rate	<4	baseline	--	--	--	
	04-Jun	0.00	0.05	0.95	-0.09	0.10
	07-Dec	-0.03	0.04	0.53	-0.12	0.06
	>13	-0.01	0.04	0.80	-0.10	0.08
Antipsychotic	None	baseline	--	--	--	
	1	-0.05	0.03	0.16	-0.11	0.02
	2	-0.06	0.03	0.03	-0.12	-0.01
Townsend score for deprivation	1	baseline	--	--	--	
	2	-0.02	0.04	0.67	-0.10	0.06
	3	-0.07	0.04	0.07	-0.15	0.00
	4	-0.08	0.04	0.04	-0.15	0.00
	5	-0.03	0.04	0.42	-0.11	0.04
	Antihypertensive	-0.05	0.03	0.06	-0.10	0.00
	Antidepressant	0.03	0.02	0.20	-0.02	0.08
	Mood stabiliser	0.03	0.03	0.33	-0.03	0.08
	Asthma	0.08	0.04	0.03	0.01	0.15
	COPD	-0.03	0.05	0.53	-0.14	0.07
	FH	-0.06	0.07	0.42	-0.21	0.09
	AF	0.00	0.12	1.00	-0.24	0.24
	Cancer	-0.05	0.11	0.67	-0.26	0.17
	Hypothyroidism	-0.24	0.10	0.02	-0.44	-0.04
	CKD	-0.02	0.04	0.64	-0.10	0.06
	Heavy drinking	0.04	0.03	0.22	-0.02	0.10
	Non statin use	0.20	0.10	0.05	0.00	0.39
	_cons	1.96	0.16	0.00	1.64	2.27

Table 7: Output from multivariable linear regression model for associations between statin prescribing and total cholesterol at 2 years after the index date (complete cases)

Factor		Coefficient	Std. Err.	P>t	95% CI	
Statin prescription		-1.19	0.04	0.00	-1.26	-1.12
Cholesterol at baseline		-0.41	0.01	0.00	-0.44	-0.38
Age band	**40-44**	baseline	--	--	--	
	45-49	-0.01	0.05	0.86	-0.10	0.08
	50-54	-0.04	0.05	0.36	-0.13	0.05
	55-59	-0.01	0.05	0.79	-0.10	0.08
	60-64	-0.02	0.05	0.73	-0.11	0.08
	65-69	-0.15	0.05	0.01	-0.26	-0.04
	70-74	-0.19	0.06	0.00	-0.31	-0.08
	75-79	-0.19	0.08	0.02	-0.35	-0.03
	80-84	-0.28	0.08	0.00	-0.44	-0.12
Sex	**Male**	baseline	--	--	--	
	Female	0.14	0.03	0.00	0.09	0.19
	Diabetes	-0.14	0.03	0.00	-0.20	-0.08
	Systolic BP	0.00	0.00	0.03	0.00	0.00
	BMI	-0.01	0.00	0.00	-0.01	0.00
Smoking status	**Never**	baseline	--	--	--	
	Ex	-0.05	0.04	0.18	-0.13	0.02
	Current	-0.06	0.03	0.05	-0.12	0.00
SMI type	**Bipolar**	baseline	--	--	--	
	Schizophrenia	-0.03	0.03	0.27	-0.09	0.03
Cohort	**2002/3**	baseline	--	--	--	
	2004/5	-0.08	0.07	0.26	-0.23	0.06
	2006/7	0.03	0.07	0.69	-0.11	0.17
	2008/9	0.04	0.07	0.57	-0.10	0.18
	2009/10	0.13	0.07	0.07	-0.01	0.26
Consultation rate	**<4**	baseline	--	--	--	
	04-Jun	0.03	0.05	0.55	-0.06	0.12
	07-Dec	0.05	0.04	0.28	-0.04	0.13
	>13	0.04	0.04	0.31	-0.04	0.13
Antipsychotic	**None**	baseline	--	--	--	
	1	-0.06	0.04	0.07	-0.13	0.01
	2	-0.07	0.03	0.02	-0.13	-0.01
Townsend score for deprivation	**1**	baseline	--	--	--	
	2	-0.01	0.04	0.78	-0.10	0.07
	3	-0.12	0.04	0.01	-0.20	-0.04
	4	-0.06	0.04	0.12	-0.14	0.02
	5	-0.07	0.04	0.09	-0.15	0.01
	Antihypertensive	-0.03	0.03	0.35	-0.09	0.03
	Antidepressant	0.02	0.03	0.51	-0.03	0.07
	Mood stabiliser	-0.03	0.03	0.35	-0.09	0.03
	Asthma	0.10	0.04	0.02	0.02	0.19

Factor	Coefficient	Std. Err.	P>t	95% CI	
COPD	-0.09	0.06	0.13	-0.22	0.03
FH	0.04	0.09	0.63	-0.13	0.21
AF	-0.08	0.10	0.43	-0.27	0.11
Cancer	0.00	0.13	0.99	-0.25	0.25
Hypothyroidism	-0.03	0.14	0.84	-0.31	0.25
CKD	-0.03	0.04	0.54	-0.11	0.06
Heavy drinking	0.04	0.04	0.30	-0.03	0.11
Non statin use	0.08	0.09	0.37	-0.09	0.25
_cons	2.05	0.17	0.00	1.71	2.39

Table 25: Summary of the number and unadjusted rate of CVD outcomes and all-cause mortality in the main analysis

Type of outcome	Complete cases						Full population					
	Statin -			Statin +			Statin -			Statin +		
	N	rate*	95% CI	N	rate*	95% CI	N	rate*	95% CI	N	rate*	95% CI
MI and Stroke	106	4.91	(4.06, 5.94)	45	5.43	(4.05, 7.27)	927	4.17	(3.91, 4.45)	83	5.74	(4.62, 7.11)
MI	37	1.71	(1.24, 2.37)	19	2.29	(1.46, 3.59)	316	1.42	(1.27, 1.59)	31	2.14	(1.51, 3.05)
stroke	69	3.20	(2.52, 4.05)	26	3.14	(2.13, 4.61)	611	2.75	(2.54, 2.98)	52	3.60	(2.74, 4.72)
All-cause mortality	363	16.75	(15.1, 18.6)	146	17.54	(14.9, 20.6)	4287	19.26	(18.7, 19.8)	284	19.57	(17.4, 22.0)

*Crude rate per 1000 person years

Table 9: Analysis of complete case data in the main analysis. Estimates presented alongside imputed data results

Section of Main Analysis		N=6915 Complete case analysis			N=45824 Imputed data analysis		
VARIABLES IN THE ADJUSTED MODEL		**IRR**	**95% CI**		**IRR**	**95% CI**	
Impact of adding additional variables into the model	Crude	1.11	0.78	1.58	1.39	1.11	1.74
	Age + Sex	1.06	0.75	1.51	1.16	0.93	1.46
	Diabetes	1.01	0.70	1.44	1.04	0.82	1.31
	Cholesterol	1.06	0.72	1.56	0.98	0.77	1.25
	BMI	1.03	0.70	1.53	0.96	0.75	1.22
	Sys BP	0.99	0.67	1.46	0.92	0.72	1.18
	Smoker	0.96	0.65	1.42	0.89	0.70	1.14
	SMI type	0.96	0.65	1.43	0.89	0.70	1.14
	Year	0.92	0.62	1.37	0.92	0.72	1.18
	Fully adjusted*	**0.88**	**0.58**	**1.36**	**0.89**	**0.68**	**1.15**
COHORT-SPECIFIC ESTIMATES		**IRR**	**95% CI**		**IRR**	**95% CI**	
Cohort (fully adjusted*)	2002/3	0.41	0.02	7.08	0.68	0.35	1.32
	2004/5	0.91	0.40	2.06	1.19	0.75	1.88
	2006/7	0.98	0.43	2.24	0.99	0.58	1.69
	2008/9	0.71	0.24	2.07	0.70	0.35	1.41
	2010/11	2.70	0.64	8.35	0.77	0.26	2.31
PRIMARY OUTCOME		**IRR**	**95% CI**		**IRR**	**95% CI**	
(fully adjusted*)	MI and Stroke	0.88	0.58	1.36	0.89	0.68	1.15
SECONDARY OUTCOMES		**IRR**	**95% CI**		**IRR**	**95% CI**	
(fully adjusted*)	All cause mortality	1.02	0.82	1.27	0.89	0.78	1.02
	Stroke	0.85	0.49	1.48	0.96	0.68	1.34
	MI	0.93	0.47	1.83	0.75	0.48	1.15
SUB-GROUP ANALYSES (fully adjusted*)		**IRR**	**95% CI**		**IRR**	**95% CI**	
SMI type	Bipolar disorder	0.78	0.38	1.61	0.89	0.60	1.32
	Schizophrenia	0.90	0.53	1.52	0.85	0.60	1.20
Gender	Men	0.95	0.53	1.72	0.96	0.65	1.42
	Women	0.86	0.46	1.61	0.84	0.58	1.20
CVD risk strata	≥10%	0.96	0.60	1.53	0.93	0.69	1.26
	≥15%	1.03	0.65	1.62	0.90	0.67	1.21
	≥20%	1.00	0.63	1.60	0.82	0.59	1.13
	≥25%	0.91	0.55	1.50	0.73	0.52	1.05

* Final model covariates (baseline): age and sex, diabetes, total cholesterol concentration, BMI, systolic blood pressure (Sys BP), smoking status, SMI type, cohort time period, antihypertensive use, antidepressant use, quartile of consultation rate, antipsychotic use and type, mood-stabiliser use, Townsend score, asthma, COPD, hypothyroidism, CKD, AF, familial hypercholesterolaemia, heavy drinking, non-statin lipid modification, cancer