Multimorbidity and Cardiovascular Disease in the United Kingdom



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Abstract

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Background: Multimorbidity, the presence of two or more conditions in the same individual, is common, particularly in populations with cardiovascular disease. Addressing the evidence gaps in temporal trends, effects on treatment, and associations with relative mortality risk in the field of multimorbidity will inform health service planning, resourcing and delivery of quality patient care for an increasingly multimorbid population.

Aims: The aim of this thesis was to examine multimorbidity and cardiovascular disease using the United Kingdom's Clinical Practice Research Datalink. To achieve this aim, the specific objectives of this thesis were to:

1. Select an appropriate framework for measuring multimorbidity, including selection of conditions, in the Clinical Practice Research Datalink
2. Prepare data in the Clinical Practice Research Datalink for analysis, including phenotyping of the selected chronic conditions
3. Investigate patterns and temporal trends of comorbidities in incident cardiovascular disease
4. Examine the association between multimorbidity and blood pressure & antihypertensive prescription
5. Investigate the association between multimorbidity and mortality in patients with cardiometabolic comorbidities

Methods: First, a literature review was conducted to select an appropriate method of measuring multimorbidity applicable to the Clinical Practice Research Datalink. Second, raw data in the Clinical Practice Research Datalink was extracted and converted to data for analysis, including phenotyping of chronic conditions. Third, age/sex-standardised prevalences of comorbidities were calculated for patients with incident cardiovascular disease, with stratification by age, sex and socioeconomic status. Fourth, a landmark cohort analysis using linear and Poisson regression investigated the association between number & type of comorbidity, and blood pressure & prescription of antihypertensives . Finally, a cohort study using Cox proportional hazards regression examined the association between cardiometabolic comorbidities and mortality, with adjustment for a range of additional comorbidities.

Results: The method of measuring multimorbidity was highly heterogeneous, and a pragmatic approach of examining multimorbidity by number of conditions, specific comorbid conditions, and condition groups, was chosen for subsequent analyses. Data in the Clinical Practice Research Datalink was extracted and processed for analytical use, including phenotyping of 60 chronic conditions. The prevalence of patients with multimorbidity in incident cardiovascular disease increased between 2000 to 2014. Furthermore, 4 out of the top 10 comorbidities were non-cardiovascular conditions, and patterns of comorbidities differed by age group and sex. The presence of comorbidity was associated with lower blood pressure in hypertensive patients, largely driven by a lower blood pressure at diagnosis, even when differences in health service use were accounted for. The mortality risk of patients with multiple cardiometabolic comorbidity was partly explained by additional comorbidities, and the combined risk of concomitant cardiometabolic conditions was less than the additive risk of the individual conditions.

Conclusion: Overall, this thesis provides descriptive and analytical evidence for the increasing burden and impact of multimorbidity in cardiovascular disease. Clinical practice, policy and research in cardiovascular disease needs to move away from a single-disease paradigm and incorporate an integrated, coordinated approach to care for an increasingly multimorbid population.

Publications

Publications contributing to DPhil thesis

Tran J, Norton R, Conrad N, Rahimian F, Canoy D, Nazarzadeh M, Rahimi K. (2018) Patterns and temporal trends of comorbidity among adult patients with incident cardiovascular disease in the UK between 2000 and 2014: A population-based cohort study. PLOS Medicine. 2018;15(3):e1002513.

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The Academy of Medical Sciences working group for multimorbidity (2018)

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Tran J, A Kiran, K Rahimi. (2016) Multimorbidity in the UK, *European Society of Cardiology Congress*

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List of Abbreviations

ACC	American College of Cardiology
ACG	Adjusted Clinical Groups
AHA	American Heart Association
AIDS	acquired immunodeficiency syndrome
AMS	Academy of Medical Sciences
BMI	body mass index
BNF	British National Formulary
BP	blood pressure
CALIBER	ClinicAl disease research using LInked Bespoke studies and Electronic health Records
CCI	Charlson Comorbidity Index
CDC	Centers for Disease Control and Prevention
CDS	Chronic Disease Score
CI	confidence interval
CIRS	Cumulative Index Illness Rating Scale
CKD	chronic kidney disease
COPD	chronic obstructive pulmonary disease
CPRD	Clinical Practice Research Datalink
CRD	current registration date
CVD	cardiovascular disease
DALY	disability-adjusted life-years
DBP	diastolic blood pressure
DM	diabetes mellitus
DUSOI	Duke Severity Illness Checklist
EHR	Electronic health record
EMIS	Egton Medical Information Systems
ENT	ear, nose and throat
ERFC	Emerging Risk Factors Collaboration
GBD	Global burden of Disease
GP	General Practitioner
HES	Hospital episode statistics

HHS	Health and Human Services
HIV	human immunodeficiency virus
HR	hazards ratio
ICD	International Classification of Diseases
IHD	ischaemic heart disease
IMD	Index of Multiple Deprivation
ISAC	Independent Scientific Advisory Committee
IT	information technology
LSOA	Lower-layer Super Output Areas
MHRA	Medicines and Healthcare products Regulatory Agency
MI	myocardial infarction
NCD	non-communicable disease
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
ONS	Office of National Statistics
PAD	peripheral arterial disease
PPV	positive predictive value
PY	person-years
QOF	Quality and Outcomes Framework
RCT	randomised controlled trial
RECORD	REporting of studies Conduction using Observational Routinely collected Data
SBP	systolic blood pressure
SD	standard deviation
SES	socioeconomic status
TC	total cholesterol
TGI	The George Institute for Global Health
TIA	transient ischaemic attack
UK	United Kingdom
US	United States
UTS	up-to-standard
VTE	venous thromboembolism
WHO	World Health Organisation
YLL	years of life lost
YOB	year of birth

1 Introduction

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1.1 Introduction

> *"Multimorbidity cuts across the vertical paradigms in which most health research and policy is envisaged, supported and carried out, reflecting not only specialist interests in particular problems and diseases, but also the tendency of research to focus on easily defined issues.*— Stewart Mercer [1]

Multimorbidity can be defined as the presence of two or more conditions in the same individual [2]. It is a highly prevalent public health issue, with estimates that it affects up to 72% of the general population [3]. The burden of multimorbidity is expected to rise, driven by several factors, including the ageing population, changes in lifestyle and environmental risks, healthcare advances, and changes to health literacy and health-seeking behaviour [4]. There is an urgent and increasing need to further understand the burden, risk factors and consequences of multimorbidity to guide health service planning, resourcing and delivery of quality patient care [3].

This thesis specifically examines multimorbidity in relation to cardiovascular disease (CVD). This group of diseases includes ischaemic heart disease and stroke, and is the leading cause of mortality and morbidity worldwide, causing 17.9 million deaths globally [5]. More than two thirds of people with CVD are also multimorbid [6, 7, 8].

Multimorbidity and CVD were investigated in this thesis using the Clinical Practice Research Datalink (CPRD). The CPRD is a linked primary care database in the UK that is one of largest prospective databases of routinely-collected health records in the world [9]. It contains a breadth of clinical, demographic and health service variables [9]. The data are longitudinal, providing information on a large population that is broadly representative of the UK [9]. It is likely that electronic health records (EHR), such as the CPRD, will increasingly be standardised and adopted for research purposes in the future to further epidemiological research [10].

1.2 Aim of thesis

The overall aim of this thesis was to examine multimorbidity and CVD using the CPRD.

1.2.1 Objectives

1. Select an appropriate framework for measuring multimorbidity, including selection of conditions, in the CPRD

2. Prepare data in the CPRD for analysis, including phenotyping of the selected chronic conditions

3. Investigate patterns and temporal trends of comorbidities in incident cardiovascular disease

4. Examine the association between multimorbidity and blood pressure & antihypertensive prescription

5. Investigate the association between multimorbidity and mortality in patients with cardiometabolic comorbidities

1.3 Structure of thesis

First, I completed a literature review to identify an appropriate framework to study multimorbidity, including a method of measurement and selection of chronic conditions. Second, I detail the extraction and conversion of data into a format for analysis, including the phenotyping of 60 chronic conditions. Using the first two methodological foundations, I completed three analytical studies. The first study examined patterns and temporal trends of comorbidity prevalence in incident cardiovascular disease. The second study investigated the association between multimorbidity and blood pressure in hypertensive patients. Finally, the third study examined the risk of mortality in patients with cardiometabolic conditions and the contribution of a range of additional comorbidities. I conclude the thesis

with a synthesis of findings, overall strengths and weaknesses, implications and future directions for research.

The remainder of this section will provide a summary of each chapter.

Chapter 2 is an overview of the background relevant to this thesis, providing an introduction to multimorbidity, CVD and electronic health records (EHR). It explores multimorbidity within a research context, and further explores the impact and importance of multimorbidity, covering the burden, clinical and public health implications, and the role of multimorbidity in primary care and future research. This chapter then covers CVD, which is the common binding theme in this thesis on multimorbidity. Finally, a brief overview of EHR provides context for the subsequent methodological and analytical chapters.

Chapter 3 is the first methods chapter that presents a literature review on methods of measuring multimorbidity, including selection of conditions. Methods of measurement were identified from the literature and assessed for applicability to the CPRD. A list of 60 conditions was selected that were clinically significant and highly prevalent.

Chapter 4 is the second methods chapter that describes the CPRD and the process of converting raw data into data for subsequent analyses. An overview of the CPRD and linked databases is described, including the research protocol and ethical approval for using patient data. The chapter then outlines extraction of data for variables used throughout this thesis, including the phenotyping of conditions used to examine multimorbidity.

Chapter 5 is an analytical chapter that examines the pattern and temporal trends of comorbidity in patients with incident CVD. It shows that the age/sex-standardised incidence of non-fatal CVD has decreased by a third between 2000-2014, but the burden of multimorbidity and comorbidity has increased. Although part of the increase was accounted for by an ageing population, even in age/sex-standardised analysis, the prevalence of those with 5 or more comorbidities increased four times from 6.3% to 24.3% between 2000 and 2014. On average, older patients, women and socioeconomically-deprived groups had higher numbers of comorbidities, but

the type of comorbidities differed by age and sex. Cardiometabolic comorbidities contributed substantially to the burden of comorbidities, but 4 out of 10 major comorbidities were non-cardiometabolic.

Chapter 6 investigated the association between comorbidities and blood pressure (BP) in patients with incident hypertension. The trajectory of BP was driven by BP at diagnosis. Mean systolic BP (SBP) decreased with time after diagnosis across all patient groups, but patients with higher numbers of comorbidities consistently maintained lower SBP. The differences in SBP by number of comorbidities was even more pronounced in years preceding hypertension diagnosis. The association between higher number of comorbidities and lower SBP changed minimally when treatment intensity and prior health service exposure were accounted for. After adjustments, each comorbidity was associated with approximately 1 mmHg lower SBP during follow-up. Analysis by type of comorbidity showed that adjusted mean SBP was lower across all groups of comorbidities. There was also a positive relationship between the number of comorbidities and number of antihypertensive classes prescribed during follow-up.

Chapter 7 examined the association between cardiometabolic comorbidities and mortality risk, and the contribution of additional comorbidities. In this large-scale cohort study, patients with cardiometabolic comorbidities myocardial infarction (MI), stroke and diabetes had an increased relative mortality risk compared to those with none of these conditions. Taking additional comorbidities into account with adjustment, hazard ratios (HRs) were decreased, suggesting that relative mortality risk in all patient groups were partly explained by baseline additional comorbidities. The relative mortality risk associated with each type of additional comorbidity varied by comorbidity type, with cancers making up the majority of conditions with the highest mortality risk.

Chapter 8 synthesises the overall findings of the thesis. It discusses the contribution of findings to current literature, the strengths and limitations, implications and directions for future research.

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2.1 Chapter overview

This chapter provides an overview of three core areas that are critical to this thesis. Firstly, the research landscape of multimorbidity is described. Secondly, the chapter summarises the burden of cardiovascular diseases (CVD) with a specific focus on

hypertension, ischaemic heart disease, stroke and diabetes. Thirdly, electronic health records (EHRs), the key type of data used in this thesis, is briefly described.

2.2 Multimorbidity

2.2.1 What is multimorbidity

Multimorbidity can be defined as the presence of two or more conditions in the same individual [2]. The definition can vary between studies, as there is no standard definition of multimorbidity [3]. This operational definition is helpful for epidemiological research. However, in the clinical context, the specific number is not as important as the concept of a patient with multiple conditions that can impact their long-term prognosis, healthcare utilisation and care trajectory [11].

Moreover, multimorbidity is not a homogeneous concept; it is more important to identify the specific long-term conditions and their interactions rather than to classify patients as "multimorbid," because different combinations can have wide-ranging impacts on the individual patient and the health care system [12]. For example, a 25 year old female with exercise-induced asthma and anaemia is different to a 60 year old renal transplant patient with reduced ejection fraction heart failure; each combination of conditions have different implications on the patient's quality of life and how amenable they are to medical intervention. There is increasing recognition that multimorbidity is not simply the sum of a combination of chronic conditions; it has wide-ranging effects on the individual, the health care system and society [13].

2.2.2 Why care about multimorbidity?

Multimorbidity is highly prevalent. It has become the norm rather than the exception, with almost a quarter of all patients in the UK reported to be multimorbid in 2007 [14], and predictions that more than 50% of people aged between 65-74 years old will be multimorbid by 2035 [15]. The burden of multimorbidity is expected to increase even more in the future. There are several contributing factors, including the drivers of non-communicable diseases, such as the ageing population, lifestyle and environmental risks, healthcare advances and changes to health literacy and

health-seeking behaviour [4]. Hence, there is increasing interest in multimorbidity from health services researchers and policy-makers to help health service planning, resourcing and delivery of quality patient care [3].

There is a lack of robust evidence in multimorbidity, despite the recent trend in increasing research in this field. In the 20 years since 1993, the number of publications related to multimorbidity, or the related term of comorbidity, has increased more than 20-fold [16]. Yet, there is limited descriptive data on multimorbidity prevalence and temporal trends at the local, national and international level [12]. There is even less evidence on interventions and their effectiveness in managing multimorbidity [16]. Furthermore, much of the existing evidence is based on studies with low power, inadequate adjustment for confounders and other methodological weaknesses, such as excluding mental illness from the conditions under study [3]. As such, there is an urgent need to close the evidence gap on the risk factors, burden, management and outcomes of multimorbidity. The ability for policy-makers to plan health services for an increasingly multimorbid population are being hampered by inadequate evidence and gaps in the literature [12].

2.2.3 How common is multimorbidity

It is difficult to describe the burden of multimorbidity, as different definitions and contexts for multimorbidity have led to heterogeneity of reported results on the multimorbidity burden. However, regardless of how it is defined and in what context, multimorbidity is common and increasing [3, 13].

Reported prevalence of multimorbidity in observational studies ranges from 13% to 95% worldwide [17, 18]. The Global Burden of Disease (GBD) study in 2013 used data from 188 countries and concluded 32% of adults aged 20-64 years old had 5 or more conditions based on 301 acute and chronic conditions [19]. There is a growing body of literature describing multimorbidity in various geographical contexts including the United Kingdom (UK), Scandinavia, China and the United States (US) [14, 20, 21, 22, 23]. The largest of these studies is a US study of 31 million Medicare beneficiaries enrolled in health services in 2008. It examined 15

chronic conditions and reported that the prevalence of multimorbidity (defined as the presence of two or more conditions) ranged from 50% among those less than 65 years old to 82% among those aged 85 years or older year [24, 25]. In the UK, prevalence estimates range from 16% to 58%, depending on the method used to define multimorbidity [26]. The difference in prevalence reported by studies is likely to reflect a number of factors, including differences in context, as well as the definition of multimorbidity, which is investigated further in chapter 3.

Despite the variability in reported prevalence of multimorbidity, there is general consensus that multimorbidity is more common with older age [27, 28, 29]. Age is considered a risk factor for developing multimorbidity [30] and the prevalence of multimorbidity is generally higher than the prevalence of common single diseases of old age e.g. heart failure [31, 8]. However, it is important to note that multimorbidity is not exclusive to old age - the absolute number of people who are multimorbid under the age of 65 often exceeds those over 65 [32], in part due to fewer people surviving into old age [13].

There is also evidence to suggest that women are more likely to be multimorbid (defined as having two or more conditions), compared to men [33]. Multimorbid women are also more likely to have higher numbers of conditions, and be diagnosed with a mental health disorder compared to men [14, 8].

Multimorbidity is also differs by socio-economic status [34]. People who are more socially deprived, whether measured by education, financial circumstances or childhood upbringing, are more likely to have multimorbidity, and develop it up to 15 years earlier than those who are not socially deprived [14]. There is also a strong association of mental health disorders with multimorbidity in people from socially deprived populations [35].

2.2.4 The impact of multimorbidity

The burden of multimorbidity has increased in recent years [36, 37, 21, 38, 39]. Multimorbidity has deleterious effects on patients, and the health care system, leading to higher health service utilisation and health care costs [14, 40, 41].

Individual patients

Mutimorbidity creates complexity for individual patients [11]. Multimorbid patients have multiple conditions, requiring higher numbers of health care consultations, larger number of medications, and more time to monitor and manage at home [42]. Additionally, each condition often interacts with other conditions, treatment, and other environmental factors to further worsen health outcomes [43]. Patients also need to balance managing and coping with multimorbidity, with other life priorities, which can affect their quality of life and personal relationships [11, 3].

Multimorbidity is associated with a higher relative mortality risk. Multimorbidity and higher numbers of conditions are associated with a higher relative risk of mortality, independent of age and socioeconomic status [44]. The pattern differs by comorbidity type - patients with certain conditions, such as heart failure and cancer, are at increased risk of death [13]. The largest study examining the interaction of diabetes, stroke and myocardial infarction and mortality risk reported an increased risk with the co-existence of all three conditions, and a 15 year reduction in life expectancy at age 60 [45].

The association between multimorbidity and hospitalisation follows a similar pattern to multimorbidity and mortality. Patients with higher numbers of conditions are at increased risk of avoidable hospital admissions, independent of age [27]. This risk is also influenced by comorbidity type, for example, the presence of mental illness increases the risk of hospitalisation [46]. Hospitalisations for multimorbid patients are not only driven by the higher number of conditions, but can also be a result of treatment burden or complications, such as medication errors [13].

Multimorbidity is also associated with poorer quality of life and reduction in functional status [47, 43, 28, 48]. Higher numbers of conditions are associated with lower quality of life [48] The pattern is highly specific to comorbidity type. Many different groups of conditions have strong negative effects on quality of life, and in particular, the combination of cardiac and respiratory conditions interact to further worsen quality of life [49]. Specific conditions such as arthritis, back pain and obesity, are common in limiting physical function [50, 51] and mental illness

is both a determinant and consequence of lower functional status and quality of life in multimorbid patients [13]. Furthermore, physical and mental limitations also place an increased burden on carers, often informal and uncompensated, which places further strain on multimorbid patients [52].

The treatment burden for patients and their carers is a particular issue in multimorbidity. Patients manage competing demands between different conditions, as well as between health care management and other personal demands [3]. The increased treatment burden associated with multiple conditions, even if they are concordant (i.e. share common management strategies) is not only time-consuming and psychologically draining for patients, but also leads to poorer health outcomes from poorer self-management, complications (such as adverse drug reactions from polypharmacy), and financial strain [53, 54]. The medical and non-medical treatment burden on multimorbid patients suggests that a re-organisation of care and priorities for patients, as well as further research to understand the impact and implications of treatment adherence, is needed to improve care for multimorbid patients [55].

Health systems

Multimorbidity has been described as "the biggest challenge facing the NHS [National Health Service]" [56]. The UK's combined health services, the NHS, and most other health care systems worldwide, have been designed to manage individual conditions. For multimorbid patients, organising effective care is challenging, as their conditions and treatments interact in complex ways that diverge from single-disease guidelines. This often results in fragmented care, where a holistic view of how conditions and treatments impact on a patient's quality of life are sidelined [56].

Patients with multimorbidity have competing priorities, which require a collaborative approach both between health care providers, and between patient and provider. Providers often have to prioritise different health care demands and consolidate clinical guidelines for individual conditions in order to pave a path of integrated care, especially within a system that incentivises and guides the sequential treatment of individual conditions [57]. Interventional studies looking

at improving multimorbidity care have focused on simplifying this process and focusing on patient-centred outcomes, such as quality of life, symptom burden and well-being, as opposed to condition-specific outcomes [47]. Some of these interventions have included coordination of care and communication, as it has been reported that miscommunication, or lack of coordination of communication leading to conflicting messages or duplication of care, can lead to patient perception of lower quality of care [58].

Suboptimal coordination of care leads to unnecessary and high health care resource usage amongst multimorbid patients [13]. Multimorbid patients, regardless of how they are defined, use up a disproportionate amount of healthcare resources. For example, in the US Medicare population of people aged 65 and over, those with 5 or more conditions are 20% of the Medicare population but use 66% of healthcare resources [59]. Healthcare utilisation and associated costs have been shown to increase in direct proportion to the number of co-existing conditions. In a study of patients over 50 years old in West Ireland, the total cost of health care for a patient with more than 4 chronic conditions was around €4000 over 12 months, compared with around €800 for a patient with no chronic conditions [60].

There are increasing efforts to promote effective care for multimorbid patients. The World Health Organisation (WHO) has published a technical report on multimorbidity as part of their series on improving safety in primary care [61]. The report is a response to the safety issues associated with multimorbid patients receiving care, which include polypharmacy, failed care coordination, and the need for clear communication and a patient-centred approach. The solutions proposed cover the need to take a systems-based approach, improve universal access to primary care services, promoting generalism rather than medical specialism, and creating multimorbidity-specific guidelines [61]. The National Institute for Health and Clinical Excellence (NICE) published guidelines on multimorbidity in 2016, which provide an overview of how to optimise care for patients with multimorbidity by mitigating the risk of potential adverse events created by the health care system, such as unplanned hospital admissions and polypharmacy

[62]. It includes recommendations on tailoring a care approach to the patient's specific needs, by identifying patients who would benefit most from the tailored approach, and assessment of frailty [62]. The NHS England's Long-Term Conditions Unit published practical advice on making the most of the NICE guideline for the multimorbid patient in clinical practice, which places emphasis on a few key concepts, such as focusing on patient-centred care, and not forgetting about carers or younger multimorbid patients, especially in more deprived areas [56].

2.2.5 Multimorbidity in primary care

Many studies of multimorbidity to date have been conducted using data obtained from general practice records. General practitioners encounter a broad range of medical conditions and are the gatekeepers for speciality care in the UK, delivering continuous care to their patients and receiving comprehensive information on the health status of their patients from tertiary and speciality care referrals [63]. Hence, general practice is a suitable setting to study multimorbidity [63]. The largest study on multimorbidity in the UK to date conducted by Barnett et. al reported 23.2% of patients were multimorbid, based on approximately 1.75 million patients in the Scottish Clinical Practice Research Datalink (CPRD) (more details in chapter 4), a linked database of general practice electronic health records (EHR) [14].

2.2.6 The future of multimorbidity research

Despite the extensive evidence that multimorbidity presents a challenge to current and future healthcare, there are many research gaps that need to be addressed to inform clinical practice, research and policy [3]. Key priority areas that have been identified for further research include: going beyond cross-sectional studies to examine longitudinal trends, studying patterns of multimorbidity using a broad range of conditions, and extending study populations beyond the elderly who commonly experience multimorbidity [3]. The current body of literature provides an incomplete picture of the burden, risk factors and consequences of multimorbidity to guide future directions for practice, policy and research.

This thesis explores some of the evidence gaps in multimorbidity related to cardiovascular diseases.

2.2.7 Conceptualisation of multimorbidity

In this next section, I will diverge and explain my conceptualisation of multimorbidity using an analogy. The idea has evolved during the course of my DPhil and has been used as a tool to provide clarity of the concept in my presentations. Although multimorbidity is a simple concept that is well-recognised, it is not well defined and highly heterogeneous.

Multimorbidity is like cake. A cake can be defined as a sweet food, made from a range of ingredients, including flour, eggs and sugar. This definition is paradoxically as vague as it is specific, as there is no clear boundary between cake and non-cake, but there is a recognition about general features of what might define a cake. A cake cannot be defined by its flavour, constituent parts, or the way it looks, but it can be recognised using a combination of these characteristics. There are so many variations of ingredients, methods and definitions of cake that the categorisation of an item of food as cake can be ambiguous. When is a chocolate cake a cake as opposed to a brownie? Yet, most people recognise (and enjoy eating) cake when they see it.

Clinical profiles:

- *Patient A: the chocolate cake (a common scenario)*

  Patient A is a 75 year-old man with ischaemic heart disease, diabetes, depression and arthritis.

- *Patient B: lemon drizzle (a little less common)*

  Patient B is a 50 year-old woman with breast cancer (now resolved), deep vein thrombosis and hypertension.

- *Patient C: flourless courgette cake (is it a cake?)*

  Patient C is a 25 year-old woman with rheumatoid arthritis, anxiety and depression.

A similar complexity can be observed in defining multimorbidity. Patients with multimorbidity are extremely heterogenous (refer to Clinical Profiles above), the conditions that make up multimorbidity also vary, and there is no standard

trajectory of how multimorbidity develops. Yet it is easily recognisable in the clinical, research and policy setting, and it requires special attention from care providers and policymakers for how care is provided [11].

2.3 Cardiovascular disease

2.3.1 Overview

Cardiovascular disease (CVD) is the leading cause of mortality and morbidity worldwide, causing 17.9 million deaths globally [5]. Despite the reduction in overall mortality from CVD, it still has a substantial burden, accounting for approximately 30% of deaths in the UK and costs the NHS £6.8 billion (2012-2013) [64]. More than two thirds of people with CVD are also multimorbid [6, 7, 8].

It is estimated that 57% of CVD deaths can be attributed to the big four modifiable risk factors: high blood pressure, smoking, high cholesterol and obesity [65]. Hypertension, defined as systolic blood pressure (SBP) $\geq$140 and diastolic blood pressure (DBP) $\geq$90, is the leading risk factor for CVD and is prevalent in 20% of people worldwide and 31% of people in England [66, 67, 68, 69]. More than two thirds of people with hypertension also have comorbidities [70].

Despite the high prevalence of multimorbidity in patients with CVD and hypertension, little is known about the impact of multimorbidity in causing CVD or affecting prognosis of treatment [6].

This section will now examine the major cardiovascular diseases and risk factors that are studied in this thesis, namely hypertension, ischaemic heart disease, stroke & transient ischaemic attack (TIA), and diabetes mellitus.

2.3.2 Hypertension

Hypertension has long been recognised as a leading risk factor for CVD morbidity and mortality [71]. In 2013, the Global Burden of Disease (GBD) study placed renewed emphasis on the large burden of hypertension worldwide [68]. Hypertension alone accounts for 9.4 million global deaths per year [72]. Specifically for CVD, hypertension is responsible for 45% of deaths due to ischaemic heart disease and 51% of deaths due to stroke [72]. The associated burden of hypertension-related mortality and morbidity has increased between 1990 and 2015 [73].

Hypertension has been dubbed "the silent killer," as it rarely causes symptoms in the early stages of disease, and hence there is a large burden of undiagnosed hypertension worldwide [74, 72]. It has been shown that early diagnosis, treatment and control of hypertension has significant health benefits for individuals and society, for example, reducing the use of costly interventions such as cardiac bypass surgery and dialysis from ischaemic heart disease and chronic kidney disease respectively [72].

There has been a recent trend to investigate whether the diagnostic threshold for hypertension needs to be reduced (i.e. below the current threshold of SBP 140mmHg), to adequately address the burden of disease related to hypertension. The American Heart Association (AHA) reduced the hypertension diagnostic threshold to SBP 130mmHg from SBP 140mmHg in November 2017, and has faced support as well as opposition for this decision [75]. In 2015, it was estimated that the number of people worldwide with SBP above 110mmHg was 3.5 billion and SBP above 140mmHg was 874 million [73]. It has been estimated that implementation of the 2017 AHA guidelines with a reduced hypertension diagnostic threshold would mean that more than 50% of people in the US and China aged between 45-75 years old would be considered hypertensive [76]. Although this increases the burden of hypertension, there is evidence that this could be beneficial, as lowering the diagnostic threshold from 140mmHg to 120mmHg using more intensive BP (blood pressure) treatment has been shown to lead to a lower number of fatal and non-fatal cardiovascular events [77].

2.3.3 Ischaemic heart disease

Ischaemic heart disease (IHD) is a leading cause of death globally [78]. In 2008, IHD was responsible for 7.25 million deaths, which was more than an eighth of global mortality [79]. The majority of patients with IHD, also have at least one other comorbidity [8].

Although overall the age-standardised mortality rate of IHD is decreasing, it remains a significant contributor to the global burden of disease. IHD is responsible for 6.8% and 5.3% of disability-adjusted life years in men and women respectively [65].

In the UK, mortality from IHD has declined, but prevalence has remained constant at about 3-4%, which has led to increased hospital admissions and prescriptions [64].

Recent literature has shown that in addition to the key risk factors, inflammation also plays a key role in IHD [80]. An RCT using the anti-inflammatory agent canakinumab to treat atherosclerotic disease has been shown to effectively reduce the rate of cardiovascular events [81]. Inflammation, or a pro-inflammatory environment, has also been implicated as an underlying pathophysiological mechanism for the clustering of chronic conditions in multimorbid patients more than would be expected from chance alone, and has also been shown to mediate the effects of multimorbidity on physical limitations [82, 83].

2.3.4 Stroke

Cerebrovascular disease, that is, stroke (ischaemic and haemorrhagic) and transient ischaemic attack (TIA), were the second largest cause of disability-adjusted life-years (DALYs) in 2015. It accounts for 6.33 million deaths worldwide, 57% of which are due to ischaemic, rather than haemorrhagic stroke. Stroke is predominantly a disease of older age groups, with prevalence rising after 40 years old, and mortality rising after 50 years of age [84].

Despite a decrease in age-standardised incidence, prevalence, mortality and DALYs from stroke between 1990 and 2013, stroke continues to rank highly in its contribution to the global burden of disease [85]. The overall absolute stroke burden has increased globally in all sub-groups of age and sex [86]. There is increasing need to up-scale primary prevention of stroke as well as address the ongoing management of patients with stroke [87].

A key issue in patients with stroke is multimorbidity and polypharmacy. In a Scottish study of 36,000 people with stroke, it was found that 94.2% of people had at least one additional comorbidity, which was almost double the prevalence in those without stroke [88]. These stroke patients were also up to 15 times more likely to be prescribed more than 11 medications compared to those without stroke

[88]. It has also been found that the number of comorbidities in stroke patients is associated with mortality [89].

2.3.5 Diabetes mellitus

Diabetes mellitus affected an estimated 422 million adults worldwide in 2014, and this is expected to rise to 552 million by 2030 [90, 91]. Diabetes leads to multiple complications, including IHD, stroke, renal failure, peripheral neuropathy, peripheral arterial disease and retinal eye disease, that predispose to premature mortality [91]. The excess mortality attributable to diabetes was estimated to be 3.8 million deaths in 2010, but it is likely that the contribution of diabetes to premature mortality worldwide is underestimated, because most diabetics die from another cause related to rather than from diabetes directly - approximately half die from a cardiovascular cause and 10% from a renal cause [92].

Comorbidity and diabetes is a growing area of interest amongst researchers. It is estimated that most patients with diabetes have at least one other comorbidity, and up to 40% have at least three [93]. Piette et al. have proposed typologies for understanding comorbid conditions in diabetes that can also be used for other index conditions (i.e. main condition to reference other comorbid conditions). One important concept is categorising concordant and discordant conditions; concordant conditions are likely to share a similar pathophysiological mechanism and management plan, whereas discordant conditions may not share underlying risk factors and diverge from shared pathophysiology and management [93]. It is well-recognised that diabetes guidelines often account for concordant conditions, but do not make specific recommendations for discordant conditions [94]. As a result, patients with multimorbidity may not receive the appropriate care; for example, women with diabetes are less likely to receive hormone replacement therapy compared to those without diabetes [95].

2.4 Electronic health records

Electronic health records (EHRs) can be defined as a platform that contains individual patient and provider data that is captured during a health care encounter [96]. The EHR captures and integrates data on aspects of patient health care over time in a computer-readable form. They can contain various types of data, including structured data of prescriptions that includes dosages and dates captured in e-prescribing systems, to unstructured free-text in clinical notes [97].

The accessibility, functionality and research application of EHRs have increased markedly. This is partly in response to the increasing difficulties associated with traditional epidemiological methods such as randomised controlled trials and cohort studies, where cost, time and resources are key limiting factors to collecting data for these studies [96]. EHRs can be a cost-effective means to conduct research on data that is already collected in routine clinical encounters, incurring significantly less cost than prospective data collection [98]. As the EHR often contains a breadth of information, one source can be used for multiple studies with new hypotheses or analytical methods [99], which further increases its intrinsic value. Furthermore, declining research support and reduced population participation rates in research studies have led epidemiologists to look for alternative sources of data [100]. EHRs offer a timely opportunity as they have become more accessible with improvements in health information technology [97]. EHRs are generally also longitudinal with less restriction on follow-up time, involve large generalisable populations, and contain data rich in depth and breadth [96]. EHRs have been used for a diverse mix of studies in epidemiology, including re-evaluating results from smaller studies, investigating sub-populations, examining the impact of environmental and social factors, predictive modelling, and investigating stigmatised conditions such as mental illnesses [96]. It is likely that the capture and standardisation of EHRs will accelerate in the future to further benefit epidemiological research [10].

The large sample sizes in EHRs enables the study of subgroups, as well as multiple risk factors and outcomes making it an ideal source for studying multimorbidity. Comorbidity and multimorbidity research has taken advantage of the structured,

longitudinal and comprehensive nature of the EHR in data-driven statistics to draw conclusions about how conditions cluster in large cohorts [101, 97]. Previously, small sample sizes and a small set of target conditions have limited studies on the correlation between conditions [97]. There have been many examples of EHRs being used to provide valuable additions to research into multimorbidity. A study using longitudinal EHRs found that depression and type II diabetes each increased the risk of myocardial infarction by approximately 30% [102], the CALIBER group has conducted a study examining 12 CVD conditions and their differential association with SBP and DPB [103], and a Scottish study demonstrated an association between social deprivation and multimorbidity [14]. The EHR is also an ideal data source to identify cases with chronic conditions that require ongoing care. The EHR contains the patient's entire health record, including diagnoses, tests and treatments, and it captures data that are often not captured completely in traditional observational studies. This practitioner-recorded data is also often more accurate and reliable than self-report data [96]. The combination of large sample sizes and rich breadth of data available in EHRs make it ideal for studying multimorbidity.

Despite the many benefits, there are also considerations that researchers must account for when using EHRs for research. There are issues with the consistency and quality of EHRs, including missing data, incorrect data and differences in recording of data over time. There can be differences within and between different practitioners and/or practices. There are, however, practical approaches to dealing with the disadvantages of EHRs. For example, imputation of EHR data, specifically blood pressure, cholesterol, BMI and smoking status, is a viable solution to use in cardiovascular risk prediction [104]. It has also been shown that one EHR source is not adequate to identify all patients with a condition; case identification is improved by combining multiple EHR sources, or use of algorithms and/or more specific diagnostic codes (refer to subsection 4.2.4) [105, 106, 107]. These are all factors that I have taken into consideration and are described further in this thesis.

2.5 Summary

The burden of multimorbidity and cardiovascular disease is increasing and challenging current health care systems to provide more integrated, patient-centred care. There is an urgent need to close the evidence gap on the risk factors, burden, management and outcomes of multimorbidity to plan health services for an increasingly multimorbid population. EHRs that provide a breadth of variables and longitudinal data on large populations, offer a unique opportunity to study multimorbidity and cardiovascular diseases.

3
Multimorbidity framework

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3.1 Background

Multimorbidity is commonly defined as the presence of two or more conditions within one individual [2]. However, there is no universally agreed way of defining multimorbidity beyond the operational "two or more" definition. For instance, some

papers use a simple count of conditions, and others use weighted condition diagnoses as well as symptoms and syndromes [3]. Additionally, different tools to measure multimorbibidity are tailored towards a specific purpose, such as to predict mortality or to assess quality of life [3]. Previous reviews have examined the variation in the definition of multimorbidity, and concluded that different definitions are required for different studies, as the method of measuring multimorbidity depends on the research question and data available [108, 109].

Additionally, multimorbidity is also described in the literature using a variety of terms including multiple chronic conditions, polychronicity and pluripathology [110], which make it difficult to track multimorbidity research historically. It is also important to note that multimorbidity is related, yet distinctly different to several terms:

- Comorbidity: co-occurrence of additional conditions alongside an index condition [111]
- Frailty: a syndrome of reduced physiological reserves and ability to respond to stressors [112]
- Syndemics: two or more conditions that adversely interact with each other and are worsened by environmental and socio-economic-political context [113]

In this thesis, the terms multimorbidity and comorbidity are used as defined above; the scope of this thesis does not cover other related terms.

The lack of standardised definition for multimorbidity has led to gaps and inconsistencies in evidence in this field. These include the burden, causes, prevention and treatment of multimorbidity [3]. For example, the prevalence of multimorbidity (defined as two or more conditions in the same individual) ranges from 13% to 95% worldwide [17, 18]. Systematic reviews and meta-analyses that have attempted to summarise the evidence, and conclude that standardisation of the definition of multimorbidity is key to better understanding to inform policy, research and practice [114, 17].

The Academy Medical Sciences (AMS) working group for multimorbidity has attempted to standardise a minimum operating definition for multimorbidity. The proposed definition is: "[the] co-existence of two or more chronic conditions, each of which is either: A physical non-communicable disease of long duration...A mental health condition of long duration...An infectious disease of long duration" [3]. Parts of this chapter have contributed to the AMS working group papers and report that formulated this definition [3]. This chapter furthers the AMS definition by providing detailed justification for the selected method of measuring multimorbidity that served as a foundation for subsequent analyses in this thesis.

The overall aim for this chapter was to review the literature to provide a scientific foundation for a pragmatic way of investigating multimorbidity in the Clinical Practice Research Datalink (CPRD) (refer to chapter 4) for more details), the data used for analyses in this thesis.

3.2 Aims

Identify an appropriate framework for researching multimorbidity in the CPRD:

1. Method of measuring multimorbidity
2. Selection of conditions to include in the definition

3.3 Methods

A review of the literature on multimorbidity was conducted to identify frameworks for multimorbidity up until August 2015.

3.3.1 Search

The search protocol was based upon a previously published search strategy, that was iteratively developed to reach acceptable sensitivity and specificity levels, and cross-checked with personal communication and reference lists from major articles in order to capture all relevant studies [109]. This search strategy included the MeSH terms multimorbidity and comorbidity (details in Table 3.1). The search

was supplemented with a snowball method of backward and forward searches for eligible papers, which increased sensitivity, as terminology for multimorbidity has not been consistently used in the literature [110].

3.3.2 Eligibility criteria

Studies were eligible if they were primary studies reporting on multimorbidity and a wide range of determinants or outcomes, including prevalence, risk factors, disability and functional decline, mortality, quality of life and health care utilisation. 'Guidance publications' were also included, which were defined as those that were intended to provide researchers, practitioners or policy-makers guidance on multimorbidity research or practice. Exclusion criteria applied were: 1) articles not reporting original research (e.g. editorials, non-research letters, letters to editor, case-reports, protocols), excluding 'guidance publications,' 2) not written in English language, and 3) patients studied were not over 18 years old, as our cut of the CPRD only included adult patients.

3.3.3 Data sources

The searches were conducted on 1st October 2015 using MEDLINE and EMBASE since their inception of coverage from 1950 and 1980 respectively.

3.3.4 Study selection & Data extraction

Article titles were screened and then resulting abstracts against the inclusion and exclusion criteria. Full texts were then extracted for further screening and for each selected article, I extracted data on the definition of multimorbidity, definition of conditions included, list of conditions included (if specified), and rationale of using the specified definition, as well as publication year, author and research objective. Eligibility of each study was assessed and discussed with a second researcher (supervisor AK).

Table 3.1: Search terms for "multimorbidity"

1. (multimorbid$ or multi-morbid$).tw.
2. (multiple adj2 diseas$).tw.
3 (multiple adj2 illness$).tw.
4. (multiple adj2 diagnos$).tw.
5. (multiple adj2 condition).tw.
6. (multiple adj2 morbid$).tw.
7. (coexisting adj2 diseas$).tw.
8. (coexisting adj2 illness$).tw.
9. (coexisting adj2 diagnos$).tw.
10. (coexisting adj2 condition$).tw.
11. (coexisting adj2 morbid$).tw.
12. (co-existing adj2 diseas$).tw.
13. (co-existing adj2 illness$).tw.
14. (co-existing adj2 diagnos$).tw.
15. (co-existing adj2 morbid$).tw.
16. (concurrent adj2 diseas$).tw.
17. (concurrent adj2 illness$).tw.
18. (concurrent adj2 diagnos$).tw.
19. (concurrent adj2 condition$).tw.
20. (concurrent adj2 morbid$).tw.
21. (comorbid adj2 diseas$).tw.
22. (comorbid adj2 illness$).tw.
23. (comorbid adj2 diagnos$).tw.
24. (comorbid adj2 condition$).tw.
25. (comorbid adj2 morbid$).tw.
26. (co-morbid adj2 diseas$).tw.
27. (co-morbid adj2 illness$).tw.
28. (co-morbid adj2 diagnos$).tw.
29. (co-morbid adj2 condition$).tw.
30. (co-morbid adj2 morbid$).tw.
31. (multiple comorbid$ or multiple co-morbid$ or case-mix$ or casemix$ or comorbid* or co-morbid*).tw.

Search terms shown are for EMBASE strategy and are derived from [109]

3.3.5 Assessment and reporting of studies

I assessed the studies, looking for common characteristics among definitions and assessing for usability in the CPRD (refer to chapter 4 for more information), and pragmatic considerations such as cost (e.g. licenses to use software) and ease of accessing the tools to use the multimorbidity framework. I decided the best way

to present results would be in a summary table of the full text articles included, and a narrative review emphasising the main insights gained from the literature. As this literature review served as a scoping exercise to inform further work, bias or quality of each study was not explicitly assessed.

3.4 Results

3.4.1 Selected literature & characteristics

The literature search for articles related to multimorbidity and comorbidity yielded 1242 articles, of which 170 were potentially relevant and reviewed in full text, leading to inclusion of 74 studies (Figure 3.1[115]). The summary table of included studies can be found in section A.1.

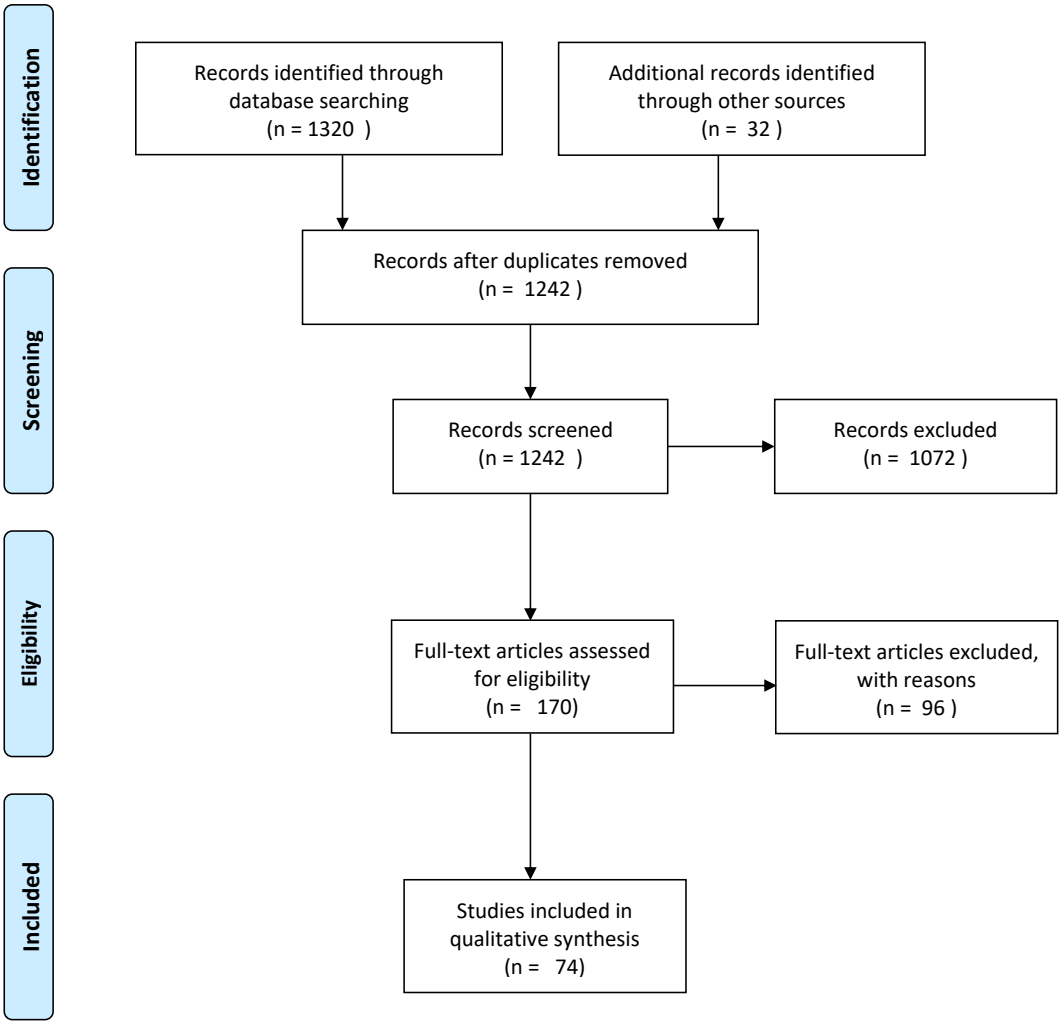
3.4.2 Measurement of multimorbidity

The majority of papers used one method to measure multimorbidity. Some of these papers tested several methods of measurement before selecting a final method of measurement. Other papers also used several methods to measure multimorbidity.

The majority (n = 49) of publications defined multimorbidity as the presence of two or more conditions in the same individual. There were some publications (n=5), like The King's Fund report [116], that defined multimorbidity as three or more conditions. One article made a distinction between 'complex multimorbidity' (defined as three or more conditions) and simple multimorbidity (defined as two or more conditions) [117]. Disease counts were the most commonly used approach to the definition of multimorbidity [114, 118] but several other approaches were used including: the Charlson index, a weighted comorbidity scale used to assess inpatient mortality risk [119]; the Cumulative Illness Rating Scale that is structured around body systems [120]; the Index of Co-existing Diseases that incorporates both disease severity and disability [121]; and the Kaplan Index developed specifically for patients with diabetes [122, 93].

A particular note must also be made about the Global Burden of Disease (GBD) study, a key study in chronic disease research, and one of the world's largest

Figure 3.1: PRISMA flow diagram for study screening and inclusion



PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses [115]

epidemiological studies examining several hundreds of diseases using a hierarchical structure [123]. This study has provided a significant contribution to scientific understanding of the global and disease-specific burden of disease. The GBD provides prevalences and rankings of single diseases, stratified by several variables such as country, sex and age, but does not specifically measure multimorbidity.

Table 3.2 summarises the main findings of more common frameworks to measure multimorbidity and assessed them in relation to the application to the CPRD. Two of the measures (CIRS and DUSOI) were not possible to assess using the CPRD as they

required a subjective clinical assessment of patient severity based on information that was not recorded consistently in the CPRD (e.g. impairment on activities of daily living, symptoms). Other methods of measurement used data that was available and reliable in the CPRD. The Charlson comorbidity index (CCI) uses age, which can be derived from data in the CPRD, and also clinical diagnoses, which have been shown to be highly reliable, valid and representative of the UK population in the CPRD [124]. The CDS/RxRisk model uses pharmacy data, of which prescriptions (but not over-the-counter medications) are reliably recorded in the CPRD. Most methods of measurement were free to access, except for the Adjusted Clinical Groups (ACG) system, which required a fee to access the licensed software.

Table 3.2: Summary of literature and applicability to the CPRD

Measure	Information needed	Data available in the CPRD	Cost	Purpose	Derivation study
Disease count	Disease can be defined as: clinician-diagnosed (e.g. medical records, clinician diagnosis), self-report (e.g. patient questionnaire/interviews)	clinical diagnoses	free	variable	N/A
Charlson Comorbidity Index (CCI) [119]	17 to 22 disease categories (dependent on version), including age	clinical diagnoses, age	free	predict 1-year mortality among patients admitted to hospital	Derived in 559 US medical inpatients; Validated in 685 women receiving treatment for breast cancer

Measure	Information needed	Data available in the CPRD	Cost	Purpose	Derivation study
Chronic Disease Score (CDS) / RxRisk Model [125]	pharmacy data	prescriptions	free	To develop a stable measure of chronic disease status using routine pharmacy data rather than chart review	Original CDS15: adult HMO enrollees from a single US HMO; Revised CDS16 derived and validated in 254,694 adult members of a US HMO; RxRisk17 derived and validated in large samples of US HMO enrollees

Measure	Information needed	Data available in the CPRD	Cost	Purpose	Derivation study
Adjusted Clinical Groups (ACG) System [26, 118]	ICD and Read codes for diagnosis codes, age, sex	clinical diagnoses, age, sex	ACG software only available with a license with a fee	predict morbidity burden and use of health care resources	Derived and validated in US using large HMO databases; Validation sample also included 30,000 Medicaid recipients
Cumulative Index Illness Rating Scale (CIRS) [120]	rating of 14 body systems by trained assessors directly during clinical consultation or from medical records	no - subjective rating of severity (impact on activities of daily living) of each body system	free	assess the medical burden of chronic illness	Hospitalized men in the US and subsequently older adults in ambulatory settings

Measure	Information needed	Data available in the CPRD	Cost	Purpose	Derivation study
Duke Severity Illness Checklist (DUSOI) index [126]	measurement of a person's illness severity filled in during clinical consultation or from medical records	no - subjective rating of severity (based on symptoms, complications, prognosis, treatability) of each health problem	free	quantify the burden of illness as measured by the physician	Developed in 249 adult patients attending a family practice in the US

Note: only selected methods of measuring multimorbidity and key references are provided in this table

Several frameworks were assessed. Based on the applicability to the CPRD three methods (disease counts, CCI and CDS) were appropriate as they were all free and used data that is obtainable from the CPRD [119, 125]. Other methods of measuring multimorbidity or disease burden, would not have been possible to measure reliably in the CPRD. Disease counts and CCI used clinical diagnoses, and the CDS used prescription data as a proxy for diagnoses. As symptom and severity data, as well as over-the-counter prescription data are not well-recorded in the CPRD, the definition was restricted to clinical diagnoses only, as this was available and reliable in the CPRD [124], and would allow differentiation of prescription data from the multimorbidity definition so that it could be included as a covariate, outcome or criteria for patient selection in planned analysis. To improve breadth of applicability, the use of CCI was not considered as the method uses weight count of conditions and was derived from a study investigating in the 1970s [119]. Given all the evidence and practical considerations, unweighted disease counts, was chosen as the method of measuring multimorbidity in this thesis. This method of measurement, when applied to the CPRD would be simple and reliable, and would also allow investigation of the impact of multimorbidity by number of conditions as well as by specific comorbidities (including concordant-discordant combinations, explained below) to inform practice and policy.

3.4.3 Selected conditions

The decision about the list conditions to include to measure multimorbidity was also critical to this thesis.

There has been a wide variation in the conditions included to define multimorbidity in previous literature. The NICE guidelines have specified that "multimorbidity refers to the presence of two or more long-term health conditions, which can include: defined physical and mental health conditions such as diabetes or schizophrenia, ongoing conditions such as learning disability, symptom complexes such as frailty or chronic pain, sensory impairment such as sight or hearing loss, alcohol and substance misuse." Most original research studies focused on chronic conditions,

with some citing the O'Halloran rubric for chronic conditions in primary care [127, 128, 129]. Several US studies used a variation of a list of 20 conditions that the U.S. Department of Health and Human Services proposed in 2010 for studying chronic conditions and multimorbidity [130, 30, 38, 131]. Similarly, some studies in the UK used the Quality and Outcomes Framework (QOF) list of conditions for General Practice [132, 26], combined with other nationally-prioritised conditions [14]. There was also a common trend of using highly prevalent and/or clinically important conditions, with no further details provided on how those criteria were determined [133, 29, 134, 135]. Not all studies limited the definition of multimorbidity to 'conditions' with some using classification chapters, medical specialties [129], or scales e.g. CCI, ACG clusters, CIRS [132, 120].

Most definitions of multimorbidity dealt exclusively with chronic conditions, definitions of which varied with respect to duration, functional limitations and medical treatments received [136]. There was controversy over which conditions could be defined as a 'chronic condition'. Some of the conditions for which there was particular debate included: certain infectious diseases (e.g. HIV) that can be of long duration when treated appropriately (e.g. with antiretroviral therapy); non-specific clinical syndromes defined by signs and symptoms (e.g. dizziness or breathlessness); and, common conditions associated with ageing (e.g. falls, fractures, osteopenia). Some conditions such as hypertension, were considered risk factors rather than chronic diseases, and were not included in chronic conditions lists as they predispose to multiple individual diseases that frequently co-exist such as coronary, cerebrovascular, renal and retinal diseases, and hence would be could be "double-counted" alongside these conditions. Furthermore, conditions like diabetes, that lead to several conditions such as chronic renal failure, peripheral neuropathy and retinopathy, were considered as multiple conditions in some studies [21, 137, 138, 139, 140, 141, 38, 131].

Additionally, some definitions of multimorbidity used clusters of diseases instead of individual conditions as the smallest unit used to contribute to the definition of multimorbidity. For example, some studies used clusters of similar diseases

(e.g. a cluster of cardiovascular diseases) [142, 114], while others used clusters of diseases considered to be national priorities [21, 38, 131]. The number of conditions considered to constitute a cluster also varied, starting from three conditions in some smaller cohort studies [20]. The system of classification to define these combinations of diseases also varied, for example, clustering by body system (e.g. circulatory, respiratory, psychological), common triads, or "clinically-meaningful groups" [143, 144]. Several studies also investigated specific comorbidities (i.e. a disease with reference to an index condition)[145, 146, 147, 36], and combinations of conditions, including concordant-discordant combinations [148, 149, 150].

The concept of concordant and discordant conditions was first studied in relation to diabetes [93]. Concordant conditions are those that share a common aetiology and frequently co-exist e.g. ischaemic heart disease and diabetes, whereas discordant conditions seem to be unrelated and may require very different management [3]. Some studies referred to concordance of conditions, but there were no studies that explicitly used concordance in their method of selecting conditions and measuring multimorbidity. One of the simplest ways to group concordant and discordant conditions was to use a body-systems categorisation e.g. cardiovascular diseases include ischaemic heart disease, stroke and peripheral arterial disease [93]. I used this method of grouping of conditions for this thesis.

Based on this review, I chose a list of 60 chronic conditions (Table 3.3) for their clinical and public health importance based on three sources. Firstly, the Quality and Outcomes Framework (QOF) conditions [151], identified as priority areas for GPs by the NHS, have been used in several epidemiological studies [26, 132, 14]. Secondly, the Charlson Comorbidity Index measures comorbidity with different diseases weighted according to perceived morbidity burden and has been shown to strongly associate with mortality in a range of contexts and remains one of the most commonly used measures of comorbidity and multimorbidity [119, 118, 152, 109, 128, 153]. Thirdly, the US Department of Health and Human Services (HHS) list of chronic conditions is part of a strategic framework for Multiple Chronic Conditions [136]. These sources were combined to derive a list of 60 unique

conditions that provides comprehensive coverage of chronic conditions that have been widely studied. Most of these conditions also overlap with the GBD, and can be examined as specific comorbidities, groups of conditions, or disease counts and tailored towards more specific research questions in this thesis.

Table 3.3: Conditions selected

Atrial Fibrillation
Other Cardiac ArrhythmiasΩ
Coronary Heart Disease*Ω
Heart Failure*#Ω
Hypertension*Ω
HyperlipidaemiaΩ
Peripheral Arterial Disease*#
Aortic aneurysm
Stroke/TIA*#
Asthma*Ω
Chronic Obstructive Pulmonary disease*#Ω
Obesity (age 16+)*
Cancer*Ω- subcategorized into cancer types by origin
Chronic Kidney Disease (age 18+)*Ω
Diabetes mellitus (age 17+)*Ω
Dementia*#Ω
Depression (age 18+)*Ω
Epilepsy (age 18+)*
Learning disability*, including Autism Spectrum DisorderΩ
SchizophreniaΩ
Substance abuseΩ
Osteoporosis (age 50+)*Ω
Rheumatoid arthritis (age 16+)*
Other ArthritisΩ
Connective tissue disease #
Peptic ulcer disease*
Mild liver disease #
Hemiplegia #
Moderate or severe liver disease #
HIV/AIDS #
Anaemia

* Quality Outcomes Framework (QOF) 2013-2014; # CCI; Ω20 Chronic conditions defined by the US department of Health and Human Services

3.5 Discussion

3.5.1 Summary of main results

The multiplicity of related terms, definitions and usage of multimorbidity make it difficult to both navigate the literature and make relevant comparisons to inform future research on multimorbidity. My goal was to understand the current available frameworks and select, (a) a method of measuring multimorbidity, and (b) a condition list, for use in the CPRD for this thesis. I have chosen three reputable sources to derive sixty conditions that cover a group of common and clinically-significant conditions that will be useful in informing practice, policy and research for multumorbidity. This list of conditions can be used to investigate multimorbidity by disease counts, specific comorbidities and groups of conditions in the CPRD.

3.5.2 Comparison with existing literature

There were two main systematic reviews on this topic that have been conducted to date, which were highly informative to this review. Diedrichs et al conducted a systematic review using MEDLINE until August 31 2009 and focused on multimorbidity measures that were either weighted or measured in terms of effect on outcome. They assessed 39 articles and found a high level of heterogeneity, but a common focus on highly prevalent conditions and conditions with high impact on patients [108]. Huntley et al conducted a systematic review using MEDLINE and EMBASE until December 2009 and focused on multimorbidity measures appropriate for use in community and primary care populations. They assessed 194 articles and also found a high discrepancy between measures used, determined both by the research question and data available [109]. Compared to this review, Huntley included more studies as the criteria for inclusion was much broader than the review in this thesis. Both previous reviews also extracted more information from articles, with the view to helping advance multimorbidity research through accessible information for researchers. For example, Diedrichs extracted and examined additional characteristics, such as which diseases most

frequently occurred in different multimorbidity measurements. Although an update of these reviews to include more recent publications with the full systematic review methodology (including assessment and extraction of studies by a second reviewer and assessment of quality and bias) may have been helpful, a full systematic review was beyond the scope of work performed here; the primary aim of which was to develop a framework for the original research presented in the subsequent chapters.

Since the completion of this literature review, an expert panel review of measuring multimorbidity has been published [154] and further demonstrates the lack of progress towards consensus, as well as the complexity of the issue. Fifteen experts agreed that "there is no single multimorbidity measure that is suitable for all research studies" and described four factors that should be considered in selecting a measure for a particular study, namely the fit with the study purpose, the selections included in the measure, consideration of "commonly missed" factors such as social deprivation and mental illnesses and consideration of episodic conditions [154]. The literature review in this chapter addresses the first three factors. Firstly, the literature review examined previous studies to determine a best-fit measurement of multimorbidity for the overall thesis, and subsequently for each analysis. Secondly, the list of included conditions was based on previous lists, and also excluded social factors as a "condition", but included mental illnesses (addressing the third factor). Finally, episodic conditions i.e. those that may fluctuate between active and inactive states, were dealt with as a fundamental characteristic of the condition (further details in section 4.2.4). Although research and discussion on the definition of multimorbidity has increased, the importance of defining an appropriate definition tailored to the research question remains a key step.

3.5.3 Strengths and limitations

The strength of this review was the targeted, efficient approach to provide a foundation for further work. The review was exhaustive and likely screened most of the available literature on multimorbidity, which was not only useful to provide a specific framework for multimorbidity, but also identified gaps in the literature

that could be addressed using the CPRD. The final analysis plans for chapter 5, chapter 6 and chapter 7 were informed by the understanding of the multimorbidity research landscape presented here. At the same time, the review used a pragmatic approach towards screening and data extraction to allow for the generation of quick results. Additionally, the available options were assessed specifically against the data available in the CPRD to further direct the targeted approach.

This broad but pragmatic approach also had several limitations. The broad scope of the aim meant that the method of measurement and conditions selected were applicable to multiple research questions. The analytical chapters of this thesis used the list of conditions from this chapter as a foundation, and this list was developed and shaped further for the specific research questions in chapter 5, chapter 6 and chapter 7. Furthermore, screening and data extraction by multiple independent researchers would have strengthened the methodology, but was not necessary for the purposes of this review. In the broader context of multimorbidity research, the approach used in this chapter is sufficient for the purposes of this thesis and more extensive than performed for most studies examining multimorbidity, which provide little or no rationale for the method and selection of conditions in the definition of multimorbidity.

3.6 Conclusion

There are many different ways to measure multimorbidity using different selected conditions. Based on the results of this review, I chose a list of 60 clinically significant and highly prevalent conditions in the UK as a foundation for this DPhil thesis, which enables the investigation of multimorbidity by number of conditions, specific comorbidities and groups of conditions.

4

Data Sources: The Clinical Practice Research Datalink and linked datasets

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4.1 Background

Clinical Practice Research Datalink (CPRD) is a joint UK Government initiative of the Medicines and Healthcare products Regulatory Agency (MHRA) and National Institute for Health Research (NIHR) to drive healthcare research through the use of electronic health records (EHRs) [124]. The CPRD database contains anonymised patient data from 674 general practices in the UK, covering approximately 7% of

the current UK population, and broadly representative of the UK population by age, sex and ethnicity [155, 156, 124, 9]. As of April 2018, the CPRD contained over 20 million individual patient records, with approximately 5 million actively registered patients [157]. The CPRD-GOLD (herein referred to as CPRD) data are derived from general practices that use the Vision electronic health record system software [158] (this is different from the CPRD-Aurum database that contains data from the Egton Medical Information Systems electronic record system (EMIS-Web) software, that has a different architecture and coding to CPRD-GOLD [157]). The dataset is one of the most comprehensive prospective primary care databases in the world, the validity of which has previously been reviewed elsewhere [159, 124].

The CPRD has been used in over 2000 articles [157], which includes large observational studies on the association between blood pressure and cardiovascular disease [103], heart failure incidence over time [31], and the association between body-mass-index and cancer [160]. The dataset has contributed to the exponential growth in the use of primary care databases in publications since the early 1990s [161].

It contains data on a wide range of variables, including diagnoses, prescriptions, investigations and vaccinations [162]. As data are prospectively recorded as part of routine care, it is not subject to certain types of bias inherent in traditional observational studies, such as recall bias in cross-sectional surveys, and differential interviewer bias related to outcome or exposure [163].

The research in this thesis was conducted with linked electronic health records from the CPRD, with data available since its inception on 1st January 1985 to 30th September 2015. The specific data cut (i.e. subset of the CPRD data) used for this thesis was obtained under an Independent Scientific Advisory Committee (ISAC) protocol.

This chapter provides details on methods common to the analyses in chapter 5, chapter 6 and chapter 7. Additional detail and variations on the data used for each analysis are provided in the methods sections of each chapter.

4.1.1 Structure of the CPRD

The following section provides an overview of the structure of the CPRD to enable understanding of the phenotyping and data extraction process described later in this chapter.

The CPRD are routinely-collected records from primary care. General Practitioners (GPs) use the Vision software to record data, and this data is collated into the primary care dataset, the CPRD. Basic patient demographic information is contained in the *Patient* files in the CPRD. GPs enter clinical diagnoses into the software, and these are coded as Read codes in the *Clinical* files in the CPRD. *Additional Clinical* files in the CPRD contain clinical measurements such as blood pressure, height and weight. *Therapy* files contain all electronically prescribed medications [164]. Further details on the structure of the CPRD files is provided in section A.2.

The structure of the CPRD is not straightforward, and hence, a considerable amount of time was on spent data cleaning and managing, to prepare data for analysis in this thesis. There can be multiple ways to extract the same data from the CPRD, which can result in slightly different resulting datasets, and hence, all variables used in this thesis are described in detail below in section 4.2 to provide enough detail for studies in this thesis to be replicated.

4.1.2 Linked databases

Overview

The UK's NHS provides a unique environment for EHR where a patient's entire care journey can be mapped from primary care to secondary care and also linked to the mortality and disease registries. The CPRD was the first to link primary care data with a broad range of health-related datasets using data from England [165]. Each patient's unique NHS identifier enables reliable record linkage between linked datasets, and the matching probability is enhanced by using other patient characteristics [157, 163]. Linkage carried out independently by ClinicAl disease research using LInked Bespoke studies and Electronic health Records (CALIBER)

by deterministic matching using NHS number, birthdate and sex has demonstrated 96% successful matching [156].

The CPRD links primary care records with Hospital Episode Statistics (HES), and mortality data from national death registries (Office of National Statistics (ONS)) and Index of Multiple Deprivation (IMD). It is also linked to disease registries e.g. the Myocardial Infarction National Audit Project, that are not used in this thesis. Linkage is only available for English practices, due to the differences in NHS admission datasets created in Wales, Scotland and Northern Ireland [157]. It is available for patients who have consented to participate, and practices who have not opted out, and this proportion varies by data cut and time period of capture used for analysis [157]. As of June 2018, CPRD linkage included patients from 411 out of 674 practices, representing 75% of English practices in the CPRD in England, and covering approximately 10.5 million patients [157, 165]. In the data cut used in this thesis, approximately 50% of patients were eligible for linkage.

Linkage is performed by NHS Digital (also known as Health and Social Care Information Centre as a legal entity), the statutory body that is allowed to receive identifiable patient data, and the national provider of data and information technology (IT) systems related to health and social care in England. NHS Digital use a deterministic linkage strategy, a method that uses rules based on an agreement between different variables. Identifier variables from the CPRD are matched with identifiers from external data to be linked via eight progressive steps created from combinations of NHS number, date of birth, postcode and sex. The "match rank" is the step at which the record is matched, and further matching for an observation is not possible once matched. The majority of patients (67.6% in June 2018) are matched in the first step, which requires an exact match of NHS number, sex, date of birth and postcode [165]. Using a multi-step process requiring several identifiers reduces the risk of bias as a result of false or missing matches [166]. Furthermore, the NHS number as a unique identifier has been shown to be valid for more than 94% of HES and 99% of primary care records in England [167], and hence the

match quality using NHS number and a deterministic approach is one of the most robust linkages of EHR in the world [165].

The availability of linked datasets creates two decision points for researchers: 1) which linked datasets to use, and, 2) what time period covering the period of linkage to use. These decisions can impact the population selected, and studies are prone to systematic bias if these considerations are not taken into account. For example, the mortality rate from venous thromboembolism (VTE) in primary care is half of that recorded in secondary care [168], suggesting that care settings deal with very different patient populations that should be accounted for in analyses. Furthermore, when mortality rate from VTE is estimated using all linked data in CPRD, HES and ONS mortality, irrespective of coverage period, an even lower mortality rate compared to using only one data source was reported, likely due to cases missed from patients who were not linked [165].

Hospital episode statistics

Hospital episode statistics (HES) are a dataset of national hospital admissions in the UK (www.hscic.gov.uk/hes). There are two coding systems used: diagnoses are coded using International Statistical Classification of Diseases and Health-Related Problems, Tenth Edition (ICD-10, herein referred to as ICD) and procedures are coded using Office of Population Censuses and Surveys' Classification of Interventions and Procedures version 4. In this thesis, ICD codes were used to identify condition diagnoses. Procedures were not requested for the data cut for this thesis, as they were not required in planned analyses or algorithms to identify condition diagnoses for multimorbidity.

Office of National Statistics mortality data

The Office of National Statistics (ONS) provides cause-specific mortality for all deaths in the UK. All deaths are recorded with date of death, a primary cause of death, and up to 15 secondary causes of death. Neonatal causes of death (up to 8 total causes) are also included in ONS, but were not used in this thesis as

this thesis focused on a population aged 16 years or older. The causes of death are recorded using ICD codes [169].

Index of Multiple Deprivation

Social deprivation is recorded using the 2007 Index of Multiple Deprivation (IMD) in the CPRD [170]. The IMD is one of the most commonly used measures for socioeconomic status in epidemiological research [170, 171]. It covers seven dimensions: income, employment, education, health, crime, housing and living environment, and is calculated using small neighbourhoods defined by boundaries that remain fixed over time, so that comparisons for temporal trends are possible. These small areas, also known as Lower-layer Super Output Areas (LSOA), each contain approximately 1000-3000 people [170]. This small-area approach derives small mean populations across each small neighbourhood, so that population homogeneity is better than deriving larger population means for social deprivation [170].

4.1.3 Ethics

Scientific approval for the research in this thesis was given by the CPRD Independent Scientific Advisory Committee (ISAC) (protocol number 16_049R, available at https://www.researchgate.net/profile/Jenny_Tran20), and no additional informed consent was required as there was no individual patient involvement [157]. The ethics approval for the CPRD is provided by the UK's Health Research Authority Research Ethics Committee and covers the use of patient data for observational public health research [165]. All data provided to The George Institute for Global Health (TGI) was for patients who matched the selection criteria in the ISAC protocol used to apply for the data cut.

The data in the CPRD is provided from general practices who opt-in and patients in these practices who have not opted-out. The participating practice contributes de-identified data of all patients who have not opted-out. Each practice can also choose whether they consent to further data linkage [165].

4.1.4 External influencers of data quality

The Quality and Outcomes Framework (QOF) is a GP pay-for-performance incentive scheme that aims to improve quality of care of long-term conditions in the NHS in the UK [172]. Data recording and health outcomes are expected to improve after the introduction of QOF. However, only modest changes in emergency admissions, diabetes care, and consultation rates for severe mental illness, have been observed [173]. It has also been shown that the introduction of the QOF indicators led to an increase in diagnoses and clinical measurements, but not guideline-indicated prescriptions for management of conditions [174]. The impact of QOF on the CPRD is variable and must be assessed critically for each study.

The quality of data available in the CPRD varies over time, and the QOF is a key determinant of data quality in the CPRD. In this thesis, a start date of the 1stof January 2000 was chosen as a compromise between maximising population size and available quality data. Based on analyses of the cut of CPRD available to the TGI, the CPRD population increased over time and peaked in 2007. The QOF started in 2004, and has been shown to impact the quality of GP recording of condition diagnoses [172, 175]. In analyses performed in this thesis, the effects of QOF on diagnoses and quality of care were visible from 2005. However, in sensitivity analyses comparing open cohorts in 2000 to 2004, the relative trends in diagnoses were not compromised by the introduction of QOF and therefore it was deemed appropriate to use data from 2000 onwards to maximise population sample size for the analyses in this thesis (refer to chapter 5 for further details).

Futhermore, changes to QOF have the potential to influence clinical condition phenotyping, sometimes necessitating changes in code lists over time [161]. For example, there was a change in QOF in 2006, which included a change in the identification of diabetes patients to a more restricted code list (from *any* diabetes code to only codes that specified type I or type II diabetes), meaning that almost 200 codes previously used to identify diabetes were no longer used [176]. This demonstrates the need for code lists to be more sensitive (inclusive) rather than specific, and supports approaches that are universal and not dependent on policies

or guidelines. Therefore, the condition code lists used in this thesis extend beyond those provided by QOF, as described in subsection 4.2.4.

4.2 Converting CPRD and linked data to research data

One of the core challenges of using the CPRD for research is that EHR data are not in a format appropriate for research. Data capture often varies within and between different health care settings and health care providers, with varying levels of detail and specificity [163]. Combining data from different sources to extract clinical information is challenging, but valuable. For example, linkage of multiple sources of EHR data improves the identification of cases of acute myocardial infarction [177].

"Phenotyping" is the process of combining data sources (e.g. CPRD, HES, ONS mortality data) to identify patients, disease onset, severity and detailed clinical information. This involves identifying relevant codes and how they should be combined. There is currently no widely accepted framework to guide this process, nor are there standards for how these phenotypes are described in the literature, even for commonly used databases like the CPRD [177]. The process of creating research-ready data for analysis from the CPRD varies in complexity. Some variables, e.g. sex, are provided as a variable in the CPRD and may require one step to translate into valuable information (sex coded as 1 equals male), whereas other variables, such as diagnosis of diabetes, requires a custom code list and algorithm for case ascertainment.

The remainder of this chapter will detail how data are extracted from the CPRD for each variable used.

4.2.1 Selection of study population with quality data

Patients over 16 years old were included in each of the analytical studies (chapter 5, chapter 6, chapter 7). Patients were included only if they had linkage to HES, as using diagnostic codes from multiple records (primary care and secondary care) improves capture of condition diagnoses [177].

Only data that met the CPRD standard for research quality were included. The research quality was determined by an acceptable standard for both patients and practices. For patients, the criteria for quality data was met by the acceptability metric, which is derived from a combination of registration status, recording of events and valid age and gender [9]. For practices, quality data was determined by capturing data starting from the practice up-to-standard (UTS) date, which is based on continuity of recording and recorded deaths [9]. Data was extracted from the *Patient* and *Practice* files as necessary.

Based on the patient and practice quality data criteria, dates for inclusion of data were determined for the overall population and each individual patient. Overall, the period of study was chosen to start from 1stJan 2000 to 31stDecember 2014, as these dates were within the coverage period guaranteed by the linked datasets used, which would improve capture of condition diagnoses [177]. This study period also provided a higher likelihood of providing complete data on all patients, as data was available in our data cut until the end of 2015, but there is a known lag time for practices to provide data to CPRD for inclusion [164].

For each patient, period of quality data capture was also determined using the following algorithms.

The start date was the latest date of:

- 12 months after a patient's current registration date (CRD)*
- the practice's "up-to-standard" date
- start of the study on the 1st of January 2000

The end date was the earliest date of:

- transfer out of practice date
- last collection date of the practice
- 2 years before date of death**

- end of the study on the 31st December 2014

*During the first year of follow-up, historical diagnoses are often recorded, which can lead to an over-estimation of disease, especially incident diagnoses [178]; **There is bias in recording and management associated with end-of-life care [179]. This criteria was implemented unless death was the outcome measured, as in chapter 7

4.2.2 Demographic variables

Age

Calculation of age for each patient was dependent on two variables: year of birth and selected year for age calculation. Year of birth was extracted from the *Patient* file set, "yob" column. As indicated by the CPRD, year of birth was calculated by adding 1800 to the value in "yob" [164]. The selected year for age calculation differed for each analysis. For chapter 5, year for age calculation was the year of incident diagnosis of hypertension. For chapter 6, age was calculated using year of incident diagnosis of hypertension for time 0, and then for each year of follow-up thereafter. For chapter 7, age was calculated for the year 2005. Exact dates i.e. months and day of month, were not used to calculate age in years.

Sex

Sex was extracted from the *Patient* file set, with 1=male, 2=female. There were no patients with indeterminate gender in the data cut used in this thesis.

Socioeconomic status

Although patient-level socioeconomic status was listed as a column in the *Patient* file, at the time of receipt of the data cut, this data was not yet available. Therefore, Index of Multiple Deprivation fifths were extracted from the linked files, where 1=least deprived fifth and 5=most deprived fifth.

Ethnicity

Ethnicity was extracted from the linked data "HES_patient.txt" under the "ethnos" column. The majority of ethnicity extracted was "White" (>95% of non-missing entries) and "Unknown"; other categories included "Indian," "Pakistani," "Black_African" and "Chinese" [180].

4.2.3 Clinical variables

Smoking

Smoking was extracted from the *Additional Clinical* file sets, using the subset of data enttype=4, which describes "Smoking." Smoking status was categorised into "Current smoker" (column1=1), "Ex-smoker" (column1=3), "Never smoked" (column1=2) or "Missing" (column1=0).

Body mass index

Body mass index (BMI) was extracted from the *Additional Clinical* file sets, using the subset of data enttype=13. In these data, data3 (data column 3) was used directly, which was recorded BMI. Sensitivity analyses were performed using enttype=13 (Weight) and enttype=14 (Height) and calculating BMI using (weight in kg)/(height in meters)^2. However, almost all entries for Height were missing, so the calculated BMI from raw values were not used. BMI was stratified according to the WHO categories: "underweight" (<18.5 kg/m2), "normal" (18.5-24.9 kg/m^2), "overweight" (25-29.9 kg/m^2), and "obese" ($\geq$30 kg/m^2) [181]. Invalid readings were removed if BMI$\leq$10 or BMI$\geq$200. Read or ICD codes for categories of BMI were not used to extract BMI as a clinical variable.

Blood pressure

Blood pressure was extracted from the *Additional Clinical* file sets, using the subset of data enttype=1. Data1 and data2 were used, which were DBP and SBP, respectively, and all readings were assumed to be in mmHg. Invalid readings were removed if SBP$\leq$50, SBP$\geq$300, DBP$\leq$10, DBP$\geq$200.

Cholesterol

Cholesterol was extracted from the *Additional Clinical* file sets, using a subset of data enttype=163 for total serum cholesterol (TC) and all readings were converted into mmol/L. Invalid readings were removed if TC$\leq$1 or TC$\geq$25.

Prescriptions

Prescription data was extracted from the *Therapy* file set, with identification of drugs using the "prodcode" number. In the "prod_bnfcode.txt" file, each "prodcode" is a row with detailed data to identify the specific formulation of the drug and includes "bnfcode," "bnfchapter," "drugsubstance" and "strength." The "bnfcode" and "bnfchapter" data fields refer to the British National Formulary codes that details all medicines prescribed in the UK [182].

Mortality

Mortality data was extracted from the "death_patient.txt" file, which is linked ONS data. "dod" in the "death_patient.txt" file were compared to the "deathdate" in the *Patient* file set, and differences were noted. As "deathdate" in the patient file is derived from an algorithm, this was judged to be less accurate and the "dod" was preferentially used [164]. The primary cause of death was also extracted using the "cause" column in the "death_patient.txt" file.

Conditions

Condition diagnoses were extracted using the code lists described in subsection 4.2.4. Medcode lists were used to extract data from the *Clinical* file sets. ICD lists were used to extract data from the linked HES_patient_diagnoses.txt file. The date of diagnosis used was the "eventdate" recorded in the *Clinical* file sets and the "admidate" (admission date) recorded in HES files.

4.2.4 Phenotyping conditions

The aim of phenotyping condition diagnoses for this thesis was to identify patients with a condition with sufficient validity. There has been much investigation into the validity of diagnoses recorded by general practitioners in the CPRD for a range of comorbidities; the average positive predictive value is 89%, with 92% completeness when compared to national registries, and is further improved with the use of multiple sources of data [177].

Diagnostic or clinical codes are a common format of data for clinical entities in EHR databases. In UK primary care, Read codes are the most commonly used (in the CPRD, Read codes are mapped to medcodes), and in secondary care settings (including HES that are linked to the CPRD), ICD codes are used [161].

Part of the phenotyping process for conditions is drawing up code lists that identify the condition of interest. This is often a time-consuming and complicated multi-step process that involves searching code dictionaries, collating results and classifying them with input from a clinician [161]. Code lists not only vary by the specific research question, but can also impact the results of the study [183]. For example, differences in code-lists between studies in rheumatoid arthritis have demonstrated a more than sevenfold difference in prevalence [184, 185]. Some studies perform sensitivity analyses using different code lists to account for variation in results from code lists [124, 186].

In this thesis, for each condition, a list of diagnostic codes from hospital (ICD) and primary care (medcode and Read) coding schemes was used to identify diagnoses. The steps were performed in the following order:

1. Compile initial comprehensive code lists from:
    - Previous work completed at TGI
    - Code repositories including CALIBER[156] and ClinicalCodes[161]
    - Other research studies with published code lists
    - Medical dictionary keyword searches

2. Screening of code lists by compiler with clinical expertise
3. Independent review of code lists by two additional clinicians, with expertise in general practice and EHR
4. Adapt for specific research question
5. Implementation in the CPRD
6. Review and revise
7. Reporting of research

Compiling initial code lists

Previous work done at TGI provided an initial source of comprehensive codes for the following conditions:

- atrial fibrillation [187]
- ischaemic heart disease [187, 188]
- stroke/TIA [189]
- dementia [189]
- diabetes [190]
- peripheral arterial disease [188]

These conditions were phenotyped by compiling previously published code lists and were subsequently validated by a clinical expert.

I updated these condition code lists (where available) by using additional code lists from newly published studies. Although studies have been conducted on most of the conditions selected for this thesis, the large majority of those code lists were not readily available (less than 10% of primary research using EHR publish their clinical codes)[161]. The two main sources of further code lists were repositories. ClinicalCodes is an online repository of clinical code lists for research

in electronic health records. It is motivated by the idea that a repository where researchers can upload and download clinical codes will help validate and replicate EHR studies, improve code lists and compare disease phenotypes across different studies [161]. Another source was the CALIBER database, which has created and evaluated a framework for cardiovascular diseases [156]. Their multi-step process involves creating an iterative phenotype by drawing on domain expertise, implementing the phenotype, validating and then distributing to the scientific community by publishing their phenotyping algorithms on a central repository (www.caliberresearch.org/portal) [156].

Finally, to ensure capture of all potential codes, a manual search of keywords in the dictionary for medcodes and ICD codes was performed for each condition. Additional code lists were added to the iterative initial code list if not present.

The episodic nature of chronic conditions was considered when compiling code lists, as has been suggested by expert panel review [154]. Fluctuation between active and inactive states of disease were accepted as a natural characteristic of chronic conditions, and patients were assumed to have the condition of interest if they had a recording of a prevalent or incident disease code as per the final condition list. Codes that indicated that a condition was inactive, treated or resolved, were excluded from these code lists and not used in this thesis because the coding of incident or prevalent diagnosis is relatively reliable and has been validated in the CPRD, whereas the coding of termination of disease is not as common and has not been broadly validated [124].

Screening of code lists

The initial code lists prioritised sensitivity rather than specificity, i.e. the objective was to capture all potential codes. Screening of the initial code lists was performed to cut down the list to be more specific. First, acute conditions were removed from the list, for example, acute renal failure was removed from the chronic kidney disease code list. Second, each code was ranked for specificity (based on the description) of indicating a diagnosis of the condition of interest (0=not specific, 1=likely specific,

2=specific). Codes categorised as specificity=0 were removed, specificity=1 were manually reviewed, and specificity=2 were automatically included in the subsequent list. Third, codes were categorised into "incident" (incident=1) and "non-incident" (incident=0), to indicate whether the code could be the first diagnosis. For example, "H/O: hypertension" (medcode 2666) was classified as non-incident, and "Systolic hypertension" (medcode 4372) was classified as incident. This third step was informative for analyses where incident, and not prevalent, condition diagnoses were required. Fourth, codes were also subcategorised where appropriate. For example, chronic kidney disease was divided into "mild", "moderate", "severe", and "unspecified."

Independent review

The code lists were independently reviewed by a clinician with EHR expertise (Professor Kazem Rahimi). Code lists that were not derived from at least one previously published source (i.e. previously published study, code repository) were also reviewed by a GP familiar with GP coding (Dr Daniel Lasserson). Discrepancies were resolved by discussion and final decisions were indicated by include=1.

Adapt, implement, revise

Each code list was reviewed in the context of specific analyses (presented in chapter 5. chapter 6 and chapter 7) and tailored for the research question. For example, only incident diagnoses of ischaemic heart disease and stroke/TIA were used to identify the patient population in chapter 5. If necessary, these code lists were revised for the research study. For instance, pregnancy-related hypertensive disease codes were removed from the hypertension code lists for chapter 6.

Reporting in publication

Published studies were reported in accordance with the RECORD criteria, which included reporting of phenotyping algorithms and code lists [191].

4.2.5 Final code lists

The final code lists of ICD codes can be found online (more details in section A.6), making them accessible for other researchers to download and use the codes in a computer-ready format. They are not included in the supplementary appendix due to the large size of all codes (more than 1000 pages).

5

Multimorbidity in incident cardiovascular disease

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5.1 Introduction

Over the past five decades, cardiovascular disease (CVD) incidence and mortality has declined, but the burden of disease associated with CVD has increased [192]. The age-standardised incidence of ischaemic heart disease (IHD), and age-standardised mortality due to stroke have both decreased globally [78, 123, 87]. On the other hand, age-standardised prevalence of heart failure, often a consequence of IHD, has increased since 1990 [78], and the absolute number of stroke survivors, disability life-years lost (DALYs) and deaths related to stroke have increased in absolute terms [123, 87]. The increasing burden of CVD has placed increasing pressure on health care services.

Current trends suggest that individuals with incident CVD will have several comorbidities that will affect their wellbeing, preferences and treatment options as a consequence of the ageing population, increased life-expectancy and higher survival rates [3]. Despite the importance and high prevalence of comorbidity, no previous study has investigated the patterns and temporal trends in comorbidity among incident CVD patients. The largest study in the area was conducted on 36,000 patients with stroke in Scotland, and demonstrated a 94% prevalence of comorbidity based on a list of 39 conditions [88]. Other reports on the presence of comorbidities among prevalent CVD patients have been typically confined to investigation of a few chronic conditions [193, 194] limited to specific sub-groups [195, 7, 196] or based on information from hospital admissions that may miss reports on important outpatient diagnoses [142, 137, 197, 198].

A summary of the major literature examining comorbidity or multimorbidity in CVD is provided in Table 5.1.

Table 5.1: Multimorbidity and CVD literature summary

Author year	Study aim	Population	Sample size	Main relevant results	Strengths	Limitations
McManus 2012	to examine the overall and changing (1990–2007) frequency and impact on 30–day and 1–year death rates from multiple cardiovascular comorbidities in adults from a large central New England metropolitan area hospitalized with acute myocardial infarction (AMI)	hospitalized with AMI at all 11 medical centers in the metropolitan area of Worcester, MA, during 10 annual periods between 1990 and 2007. The comorbidities examined included atrial fibrillation, diabetes, heart failure, hypertension, and stroke	9,581 patients	Thirty-five percent of participants had a single diagnosed cardiovascular comorbidity, 25% had two, 12% had three, and 5% had four or more comorbidities. Between 1990 and 2007, the proportion of patients without any of these comorbidities decreased significantly, while the proportion of patients with multiple comorbidities increased significantly during the years under study	Longitudinal (annual trends 1990–2007)	Small sample size; Limited number of comorbidities (cardiovascular only); population not generalisable (hospitalised, with AMI)

Author year	Study aim	Population	Sample size	Main relevant results	Strengths	Limitations
Chen 2013	to describe the prevalence of cardiac and noncardiac comorbidities in a community-based population of patients hospitalized with acute myocardial infarction (AMI) at all medical centers in central Massachusetts, and to examine whether multiple comorbidities were associated with in-hospital death rates and hospital length of stay	hospitalized with AMI, at all eleven greater Worcester medical centers in central Massachusetts during the three study years of 2003, 2005, and 2007	2,972 patients	Hypertension (75%) was the most common cardiac condition identified in patients hospitalized with AMI whereas renal disease (22%) was the most common noncardiac comorbidity diagnosed in this study population. Approximately one in every four hospitalized patients had any four or more of the seven cardiac conditions examined, while one in 13 had any three or more of the five noncardiac conditions studied		Small sample size; Limited number of comorbidities

Author year	Study aim	Population	Sample size	Main relevant results	Strengths	Limitations
Gallacher 2014	examined the prevalence of multimorbidity and polypharmacy in a large, nationally representative population of primary care patients with and without stroke, adjusting for age, sex and deprivation	aged 18 years and over, from 314 primary care practices in Scotland that were known to be demographically representative of the Scottish adult population. Data included information on the presence of stroke and another 39 long-term conditions, plus prescriptions for regular medications	35,690 people with stroke (from 1,424,378 participants)	In total, 35,690 people (2.5%) had a diagnosis of stroke. Of the 39 comorbidities examined, 35 were significantly more common in people with stroke. Of the people with a stroke, the proportion that had one or more additional morbidities present (94.2%) was almost twice that in the control group (48%) (odds ratio (OR) adjusted for age, sex and socioeconomic deprivation 5.18; 95% confidence interval (CI) 4.95 to 5.43)	large sample size (largest known in this area); large number of comorbidities (39 comorbidities)	

Author year	Study aim	Population	Sample size	Main relevant results	Strengths	Limitations
Boyd 2011	To describe the prevalence of co-existing conditions that affect clinical decision-making among adults with coronary heart disease (CHD)	NHANES, 1999–2004 aged - 45	1,259 with CHD (from 8654 people)	The prevalence of comorbid chronic diseases among subjects with CHD was: arthritis (56.7%), chronic lower respiratory tract disease (25.5%), diabetes (24.8%), stroke (13.8%), and congestive heart failure (29.0%)		Small sample size; cross-sectional; limited age group (not representative of general population)

Author year	Study aim	Population	Sample size	Main relevant results	Strengths	Limitations
Schmidt 2014	To examine 18–year trends in short-term and long-term stroke mortality and the prognostic influence of comorbidity	Danish National registry of patients covering all Danish hospitals aged ≤15 years old with a first time hospitalisation for stroke 1994–2011	219,354 patients with stroke	before the stroke diagnosis, 57.2% had no comorbidity, 18.5% had moderate comorbidity, 13.2% had severe comorbidity, and 11.0% had very severe comorbidity. From the first to the last calendar period, the proportion of patients without any comorbidity decreased 6.5 percentage points for ischemic stroke (from 59.5% to 53.0%) and 12.7 percentage points for intracerebral hemorrhage (from 68.0% to 55.3%), while the proportion of patients with very severe comorbidity increased 6.3 percentage points (from 8.5% to 14.8%) for ischemic stroke and 7.8 percentage points (from 6.3% to 14.1%) for intracerebral hemorrhage. The most prevalent comorbidities at the time of stroke diagnosis were atrial fibrillation or flutter (11.0%), cancer (10.9%), diabetes (9.0%), congestive heart failure (8.1%), chronic pulmonary disease (8.1%)	Large sample size	population not representative (hospitalization for stroke only)

Author year	Study aim	Population	Sample size	Main relevant results	Strengths	Limitations
Johansen 2006	To estimate the incidence of hospitalization for stroke and describe the impact of age, sex and comorbidity on in-hospital mortality, length of stay and readmission rates.	Health insurance numbers were used to link acute care hospitalizations across Canada in 1999/2000 for stroke patients with no discharges for a stroke within the preceding five years.	men (15,367) women (16,740)	Among these stroke patients, hypertension was codiagnosed in 35% diabetes in 17% arrhythmia in 15% ischemic heart disease in 13.6% and congestive heart failure in 5%	relatively small sample size	

The heterogeneity of research questions and methodology have made it difficult to compare the literature and draw overall conclusions about the burden and trends of comorbidity in people with CVD. A key series of work in the area of CVD and comorbidities is the US Department of Health and Human Services Multiple Chronic Conditions Research initiative examining comorbidities. One paper reports that among US Medicare beneficiaries, those with stroke or IHD have a prevalence of multimorbidity (defined as 3 or more conditions) of 70% and 61% respectively [6]. Another reports that in a Medicare population of people aged 65 years or more with at least one of four index cardiovascular conditions (IHD, heart failure, atrial fibrillation, stroke), the most common comorbid conditions included arthritis, diabetes mellitus, chronic kidney disease, cognitive impairment, and depression [195]. The American College of Cardiology/American Heart Association (ACC/AHA) report on medicare beneficiaries with CVDs including IHD, heart failure and atrial fibrillation showed that the most common comorbidities were hypertension (81-86%) and hyperlipidaemia (64-69%) across the three conditions [195]. It is challenging to draw conclusions from current literature to inform practice and policy for CVD patients because of the inconsistency of selected populations and comorbidities. Furthermore, previous literature are mostly cross-sectional studies and do not provide temporal trends.

To address the current knowledge gaps in the literature, I used a large longitudinal database of linked electronic health records to investigate the burden of comorbidity in patients with non-fatal incident CVD, defined as a diagnosis of ischaemic heart disease (IHD), stroke, or transient ischaemic attack (TIA). Information was extracted from 56 major comorbid chronic conditions in these patients and I investigated how their prevalence changed over the past 15 years, and how it varied by age, sex and, socioeconomic status (SES). Crude and age-standardised prevalences were compared in order to gain a better understanding of how any observed differences in comorbidity patterns might be due to population ageing versus other factors.

Parts of this chapter have been published in *PLOS Medicine* at `https://journals.plos.org/plosmedicine/article?id=10.1371/journal.pmed.1002513` [8].

Added value of this study:

- large representative study
- longitudinal data examining trends
- large number and types of comorbidities
- examines differences by age, sex and SES

5.2 Aim

To investigate the prevalence of comorbidities in patients with incident CVD, how it changed between 2000 and 2014, and how it varied by age, sex, and socioeconomic status (SES).

5.3 Methods

5.3.1 Data source

The study was conducted using linked EHR from the CPRD (refer to chapter 4)

5.3.2 Study population

In addition to the general selection criteria for patients aged over 16 years old, linked to HES and with quality data (refer to subsection 4.2.1), all patients selected for this study had an incident diagnosis of non-fatal CVD, defined as any reports of IHD, including any acute coronary syndrome (ACS) event such as myocardial infarction, or stroke or TIA recorded between 1st January 2000 to 31st December 2014. This excluded patients with a diagnosis of CVD outside each patient's capture period or the study period. Events were restricted to non-fatal events to focus on the

comorbidity burden of patients who continue to live after their incident CVD event. Note that the CVD subtype refers to the incident diagnosis of CVD, and is not mutually exclusive of the other subtype. For example, a patient classified as IHD subtype had an incident CVD event of IHD and may have developed stroke/TIA after incident IHD diagnosis (but conversely, would not have had a stroke before IHD diagnosis, otherwise would be classified as stroke/TIA subtype).

5.3.3 Study design

This was a longitudinal open cohort study capturing patients with data between 2000 and 2014. Repeated cross-sectional analysis was used for temporal trends.

5.3.4 Selection and definition of comorbidities

56 comorbidities that were considered clinically significant and prevalent in the UK were selected based on three representative and reputable sources: 1) the Quality and Outcomes Framework (QOF), a pay-for-performance incentive scheme for general practitioners in the UK, [172] 2) the Charlson comorbidity index, a classification system to help predict inpatient hospital mortality, [119] 3) the multiple chronic conditions list for the US Department of Health and Human Services Intiative [199] (refer to chapter 3 for further details).

Diagnosis of a prevalent comorbidity was defined as the recording of a diagnostic code for that comorbidity if it was diagnosed before the date of diagnosis of CVD. The look-back period to capture prevalent comorbidity diagnoses included all CPRD data, extending back to the inception of CPRD on 1stJan 1985. For each comorbidity, a list of diagnostic codes from ICD-10 (hospital) and Read codes (primary care) were compiled from online code repositories, previous work completed at The George Institute for Global Health, and medical dictionary keyword searches (refer to chapter 3 for further details). A brief definition of each of the 56 comorbidities is outlined in Table 5.2 (refer to subsection 4.2.5 and section A.6 for final code lists).

Table 5.2: Comorbidities selected

Group	Comorbidity	Included conditions
Cardiometabolic	Cardiac arrhythmia	Cardiac arrhythmias and dysrhythmias, including atrial fibrillation and flutter, paroxysmal tachycardia, atrioventricular blocks, and other conduction disorders
	Chronic kidney disease	Chronic kidney disease stage 3 or more, or dependence on transplant or dialysis
	Diabetes mellitus	Includes type I and II, and diabetes-specific sequelae
	Heart failure	
	Hyperlipidaemia	
	Hypertension	Includes hypertensive-specific sequelae
	Obesity	
	Peripheral arterial disease	Includes aortic aneurysm and dissection, embolism and thrombosis, and unspecified peripheral vascular diseases
Mental health	Adjustment disorder	Includes pathological reactions to severe stress
	Affective disorder	Unspecified, persistent, or other affective disorders
	Anxiety	Anxiety and phobic disorders
	Bipolar disorder	
	Depression	Depression and depressive mood disorders
	Eating disorder	Eating disorders, including bulimia and anorexia nervosa
	Psychoses	Psychotic and delusional disorders
	Schizophrenia	
	Substance abuse	Mental and behavioural disorders due to substances including alcohol, opioids, and cannabinoids
Respiratory	Asthma	
	Chronic obstructive pulmonary disease	
	Lung cancer	
	Other respiratory cancer	Respiratory organ cancer excluding lung cancer, e.g., laryngeal cancer, pleural cancer, and tracheal cancer

Group	Comorbidity	Included conditions
Musculoskeletal	Arthritis	Chronic arthritis, including osteoarthritis, secondary arthritides (e.g., arthropathy in Crohn disease and psoriatic arthritis), and other unspecified arthritides and sequelae; excluding acute arthritis (e.g., septic arthritis) and arthritides covered elsewhere: gout, rheumatoid arthritis, and connective-tissue-related arthritis
	Gout	
	Osteoporosis	
	Rheumatoid arthritis	
Neurological	Dementia	Includes Alzheimer disease, vascular dementia, and unspecified dementia
	Epilepsy	
	Hemiplegia	
	Learning disability	Disorders of psychological development, mental retardation, and childhood autism
Cancers	Bladder cancer	
	Breast cancer	
	Cervical cancer	
	Colon cancer	
	Ear, nose, and throat cancer	
	Leukaemia	
	Liver cancer	
	Lymphoma	
	Metastatic cancer	
	Oesophageal cancer	
	Ovarian cancer	
	Pancreatic cancer	
	Prostate cancer	
	Rectal cancer	

Group	Comorbidity	Included conditions
	Renal cancer	
	Skin cancer	
	Stomach cancer	
	Other female reproductive cancer	Female reproductive organ cancer excluding breast, ovarian, and cervical cancer, e.g., endometrial cancer, uterine cancer, and cancer of the vagina
	Other gastrointestinal cancer	Gastrointestinal cancer excluding oesophageal, stomach/gastric, colon, rectal, pancreatic, and liver cancer, e.g., cancer of the bile ducts, anal cancer, and peritoneal cancer
	Other male reproductive cancer	Male reproductive organ cancer excluding prostate cancer, e.g., testicular cancer
	Other urological cancer	Urological organ cancer excluding renal/kidney and bladder cancer, e.g., cancer of the ureter and cancer of the urethra
	Unspecified cancer	Cancer with unspecified anatomical region or origin
	Other cancer	Cancer not otherwise covered by all other cancers covered in the list of 56 comorbidities, e.g., brain cancer, cancer of the eye, and cancer of the endocrine glands
Other	Connective tissue disease	Systemic connective tissue disorders including systemic lupus erythematosus, systemic sclerosis, and polymyositis
	HIV/AIDS	
	Liver disease	Includes cirrhosis, portal hypertension, and hepatic failure; excludes liver cancer
	Peptic ulcer disease	Includes gastric and duodenal ulcers

5.3.5 Descriptive statistical analysis

Baseline characteristics (systolic and diastolic blood pressure (SBP and DBP), smoking status, body mass index [BMI]) for patients with incident CVD were taken as the most recent measurements within two years before diagnosis of CVD. If there were no measurements during this capture period, the measurement was classified as missing. BMI was stratified into "underweight" (<18.5 kg/m^2), "normal" (18.5-24.9 kg/m^2), "overweight" (25-29.9 kg/m^2), and "obese" ($\geq$0 kg/m^2), as defined by the World Health Organisation (WHO). Data on age, sex, SES (refer to below) and ethnicity was also extracted, with the assumption that sex, SES and ethnicity did not change. Age was derived from the "year of birth (yob)" variable in the CPRD and calculated by subtracting this from the year of incident diagnosis of CVD. Sex and ethnicity were variables provided in the CPRD. SES used linked data to the Index of Multiple Deprivation (IMD) 2015 and was split into even quintiles. IMD is widely used in the UK in health care research [171, 14, 200] that uses small area boundaries covering approximately 1500 people to calculate a deprivation score that covers seven broad dimensions of deprivation: income, employment, education, health, crime, housing and living environment [170]. In this thesis, the label SES1 to represents the “least deprived” and SES5 the “most deprived”. For baseline characteristics, results were presented as frequencies and percentages for categorical data, and standard deviations (SDs) for normal continuous data, stratified by sex, SES (using fifths for index of multiple deprivation (IMD)) and incident CVD diagnosis subtype (IHD or stroke/TIA) for all CVD patients.

Annual incidence rates for IHD, stroke/TIA and overall CVD were calculated by dividing the number of incident cases by the number of patient-years at risk in the cohort for the year of interest. Time-at-risk for each patient was restricted to start from the latest of: the start of the year, date of current registration with the practice, the practice’s up-to-standard date; and specified to finish at the earliest of: the end of the year, date of death, transfer out of practice date or the practice’s last date of collection. Age and sex-standardised incidences were computed by applying direct age-standardisation to the 2013 European Standard Population

[201] using 10-year age bands from ≤20 to ≥90 years old, and then averaging the sex-specific age-standardised incidences.

Prevalence for each comorbidity or number of comorbidities was calculated by dividing the number of cases by all patients diagnosed with CVD meeting the study inclusion criteria. Annual prevalence included all cases and CVD patients with a diagnosis recorded by the 1st of July of the year of interest. The number of comorbidities was reported in categories of 0, 1, 2, 3, 4 and ≥5. Additionally, patients were classified as multimorbid versus not by defining multimorbidity as the presence of one or more comorbidities (in addition to incident CVD) [108, 202]. Age and sex-standardised prevalences were computed by applying direct age-standardisation to the 2013 European Standard Population [201] using 10-year age bands from ≤20 up to ≥90 years old, and averaging the sex-specific age-standardised prevalences. Age, sex and SES specific prevalence was calculated by stratification into age groups (10 year age-bands: ≤20, 20-29, 30-39, 40-49, 50-59, 60-69, 70-79, 80-89, ≥90), sex and SES (IMD fifth) and year. Annual prevalences were plotted and fitted using locally-weighted non-parametric smoothing if necessary [203].

Confidence intervals (CIs) for crude prevalence were calculated using the Wilson-score method for binomial proportions (e.g. multimorbid or not) and Sison and Glaz method for multinomial proportions (e.g. 0, 1, 2, 3, 4 and ≥5 conditions) [204, 205, 206]. Wilson-score method was used in order to make reliable comparisons between different groups, as stratification may give small numbers of events in some categories, therefore normal approximation method of calculating CIs may give unusual CIs in lower or upper bounds (such as negative values) [207]. Chi-square test was used to test for association between two proportions for categorical variables and t-test was used to test for difference between means for categorical variables. The estimated prevalences were presented as percentages with 95% confidence intervals (95% CI) in brackets. All analyses were prospectively specified in the study protocol (Supporting Information S1 available at https://journals.plos.org/plosmedicine/article?id=10.1371/journal.pmed.1002513) and all statistical analyses were performed using R version 3.3.2 [208]. Reporting of

this study for publication was done in accordance with the REporting of studies Conduction using Observational Routinely collected Data (RECORD) guidelines [209, 191, 210].

5.3.6 Sensitivity analyses and additional analyses

Sensitivity analyses were performed to address some of the limitations associated with routinely-collected electronic health records. To assess the impact of the introduction of the QOF [172], the temporal trends in prevalence of selected common QOF conditions were compared with non-QOF conditions. There was an assumption that QOF conditions were better recorded in primary care, and could account for the increase in the number of condition diagnoses after 2004, when QOF was introduced. The effect of increasing number of diagnoses from accumulation over time was also assessed. The concern was that patients who were diagnosed with CVD in more recent years had a longer look-back period for diagnoses (since 1st Jan 1985), and hence would have higher numbers of diagnoses that would artificially create a trend of increasing diagnoses. The average and median look-back time was examined, and the number of diagnoses for unrestricted look-back time was compared to a restricted look-back time of 10 years.

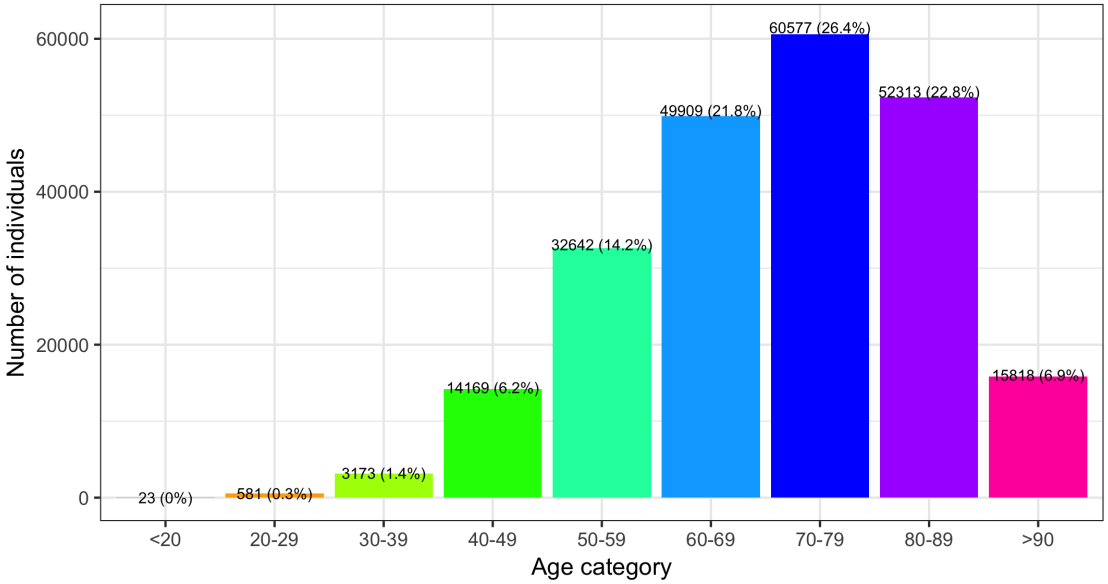
5.4 Results

5.4.1 Baseline characteristics

From a cohort of 4,198,039 patients with 29,110,997 person-years at risk, 229,205 patients with incident non-fatal CVD were identified. The mean age at the diagnosis was 71 years (range 16 to 113 years), with the majority of patients aged between 50-89 years (Figure 5.1).

Baseline characteristics of patients overall and by sex and CVD subtype are presented in Table 5.3. 48% of patients with incident non-fatal CVD were women and they were 6 years older than men (74, SD 14 vs 68, SD 13, $p<0.001$). Women were less likely to be current smokers (19.2% vs 25.0%, $p<0.001$) and less likely to be overweight (31.8% vs 40.9%, $p<0.001$) compared to men. Compared with the

Figure 5.1: Frequency of patients with incident CVD between 2000 to 2014 by age group (years)



least deprived patient group, patients in the most deprived group, were more likely to be obese (34.3% vs 25.5%, p<0.001) and to be current smokers (34.0% vs 14.8%, p<0.001). Mean blood pressure was 140/80 mmHg, and this was similar between sexes and SES categories. There were 140,828 patients (61.4%) with incident diagnosis of IHD, and 88,377 (38.6%) patients with incident diagnosis of stroke/TIA. Patients with incident stroke/TIA were older than those with incident IHD (mean age 73.8, SD 13.6 vs 68.7, SD 14.0), and more likely to be women (55.5% vs 43.8%).

Table 5.3: Baseline characteristics of cardiovascular disease patients

		CVD subtype		Sex		SES	
Characteristic	**All CVD** (n=229,205)	Ischaemic heart disease (n=140,828)	Cerebro-vascular disease (n=88,377)	Women (n=110,803)	Men (n=118,402)	Least deprived fifth (n=48,801)	Most deprived fifth (n=37,964)
Age (years), mean (SD)	70.6 (13.8)	68.7 (13.4)	73.7 (14.0)	73.8 (13.6)	67.6 (13.3)	71.5 (13.3)	68.4 (14.5)
Women, percent (n)	48.3 (110,803)	43.8 (61,733)	55.5 (43,428)	100 (110,803)	—	46.8 (22,854)	49.8 (18,906)
White ethnicity, percent (n)	97.0 (113,840)	96.7 (70,412)	97.5 (43,428)	97.3 (54,507)	96.7 (59,333)	97.8 (24,071)	95.5 (19,834)
	[111,833]	[67,990]	[43,843]	[54,803]	[57,030]	[24,194]	[17,198]
Fifths of deprivation index, percent (n)							
Q1: least deprived	21.3 (48,801)	21.0 (29,504)	21.8 (19,297)	20.6 (22,852)	21.9 (25,949)	100 (48,801)	—
Q2	22.2 (50,786)	22.0 (31,044)	22.3 (19,742)	21.9 (24,278)	22.4 (26,508)	—	—
Q3	21.2 (48,647)	21.1 (29,648)	21.5 (18,999)	21.3 (23,570)	21.2 (25,077)	—	—
Q4	18.6 (42,672)	18.8 (26,491)	18.3 (16,181)	19.0 (21,034)	18.3 (21,638)	—	—

		CVD subtype		Sex		SES	
	All CVD	Ischaemic heart disease	Cerebro-vascular disease	Women	Men	Least deprived fifth	Most deprived fifth
Q5: most deprived	16.6 (37,964)	17.0 (23,949)	15.9 (14,015)	17.1 (18,906)	16.1 (19,058)	—	100 (37,964)
SBP (mm Hg), mean (SD)	140.7 (22)	139.8 (21.4)	142.2 (22.8)	141.6 (22.9)	139.9 (21.2)	141.2 (20.9)	139.8 (22.8)
	[7,189]	[4,097]	[3,092]	[2,912]	[4,270]	[1,257]	[1,498]
DBP (mm Hg), mean (SD)	79.6 (12.2)	79.4 (12.1)	79.9 (12.4)	79.0 (12.1)	80.2 (12.3)	79.8 (12.1)	79.4 (12.8)
	[7,141]	[4,068]	[3,073]	[2,890]	[4,251]	[1,252]	[1,482]
Body mass index (kg/m^2), percent (n)							
Underweight	3.4 (3,756)	2.6 (1,847)	4.9 (1,909)	5.1 (2,702)	1.8 (1,054)	3.2 (717)	3.8 (747)
Normal	30.4 (33, 834)	27.1 (19,542)	36.5 (14,292)	33.1 (17,670)	27.9 (16,164)	32.8 (7,382)	28.6 (5,643)
Overweight	36.6 (40,667)	37.6 (27,058)	34.7 (13,609)	31.8 (16,976)	40.9 (23,691)	38.6 (8,687)	33.3 (6,575)
Obese	29.6 (32,957)	32.7 (23,574)	23.9 (9,383)	30.0 (15,989)	29.3 (16,968)	25.5 (5,741)	34.3 (6,781)
	[117,991]	[68,807]	[49,184]	[57,466]	[60,525]	[26,274]	[18,218]

		CVD subtype		Sex		SES	
	All CVD	Ischaemic heart disease	Cerebro-vascular disease	Women	Men	Least deprived fifth	Most deprived fifth
Current smokers, percent (n)	22.3 (33,246)	22.7 (21,394)	21.6 (11,852)	19.2 (13,459)	25.0 (19,787)	14.8 (4,583)	34.0 (8,745)
	[80,051]	[46,458]	[33,593]	[40,743]	[39,308]	[17,808]	[12,251]

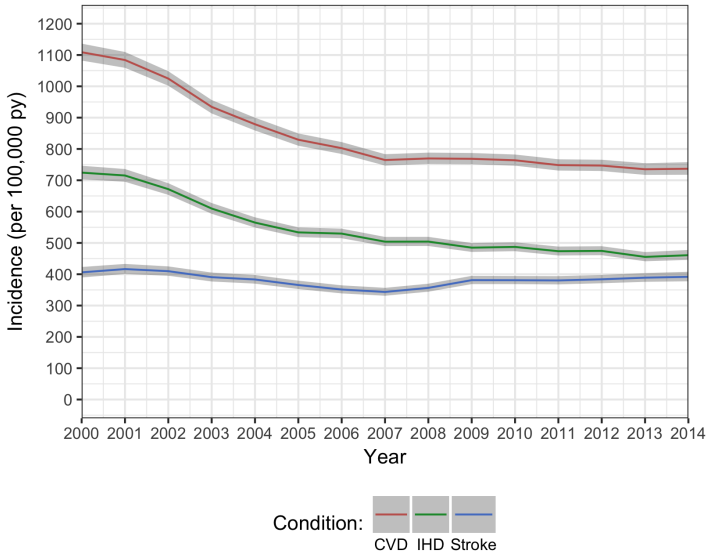
The category percentages refers to complete cases. Numbers in square brackets refer to the number of patients with missing data for the relevant characteristic. SES refers to the Index of Multiple Deprivation 2015 cut by quintiles, where Q1 is the least deprived fifth and Q5 is the most deprived fifth of the population. BMI categories are 'underweight' (<18.5 kg/m^2), 'normal' (18.5–24.9 kg/m^2), 'overweight' (25–29.9 kg/m^2), and 'obese' ($\geq$30 kg/m^2). CVD=cardiovascular disease; DBP=diastolic blood pressure; SES=socioeconomic status; SBP=systolic blood pressure.

5.4.2 Temporal trends in incidence of cardiovascular disease

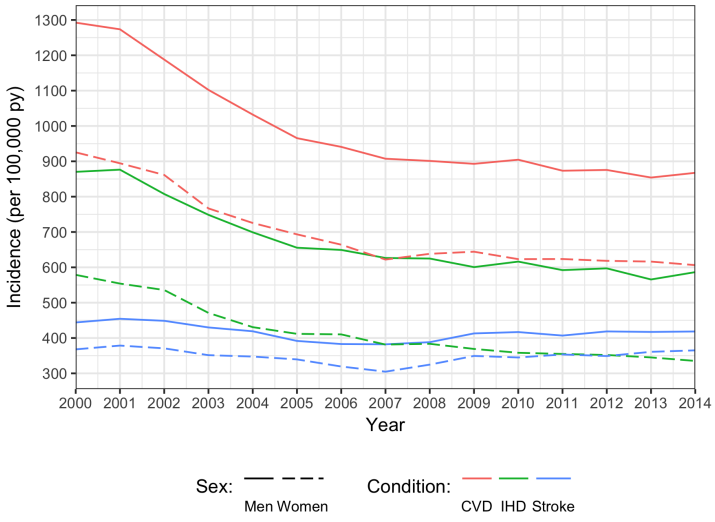
From 2000 to 2014, age/sex-standardised incidence of non-fatal CVD decreased by 34%; from 1,109 (95% CI 1,082-1,136) to 737 (718-754) per 100,000 person years (py). IHD decreased steadily by 36% (724 [703-746] to 455 [441-471] per 100,000 py) and stroke/TIA decreased overall (406 [390-423] to 391 [378-408] per 100,000 py) (Figure 5.2). Men had a higher incidence of CVD (and IHD, stroke/TIA) than women, and the sex difference remained relatively constant over time (Figure 5.2b). Mean age at diagnosis of non-fatal CVD remained stable between 70-71 years between 2000 and 2014 (70.7 years in 2000, 70.5 years in 2014), and the 6 year age difference between men and women was maintained (Table 5.4).

Figure 5.2: Annual age/sex-standardised incidence of CVD, IHD, and stroke/TIA

(a) all participants



(b) stratified by sex



Incidence is age-standardised to the European standard population 2013. CVD=cardiovascular disease (overall), IHD=ischaemic heart disease (including acute myocardial infarction, angina), Stroke/TIA=stroke or transient ischaemic attack

Table 5.4: Age of CVD patients at time of diagnosis each calendar year in women and men

Year	Women	Men
2000	73.6	67.7
2001	73.6	67.6
2002	73.6	67.5
2003	73.8	67.5
2004	73.8	67.4
2005	73.9	67.6
2006	73.7	67.3
2007	73.8	67.2
2008	74.0	67.6
2009	74.3	67.6
2010	73.9	67.6
2011	73.9	67.6
2012	74.1	67.8
2013	73.7	67.8
2014	73.9	67.6

5.4.3 Prevalence of multimorbidity and number of comorbidities

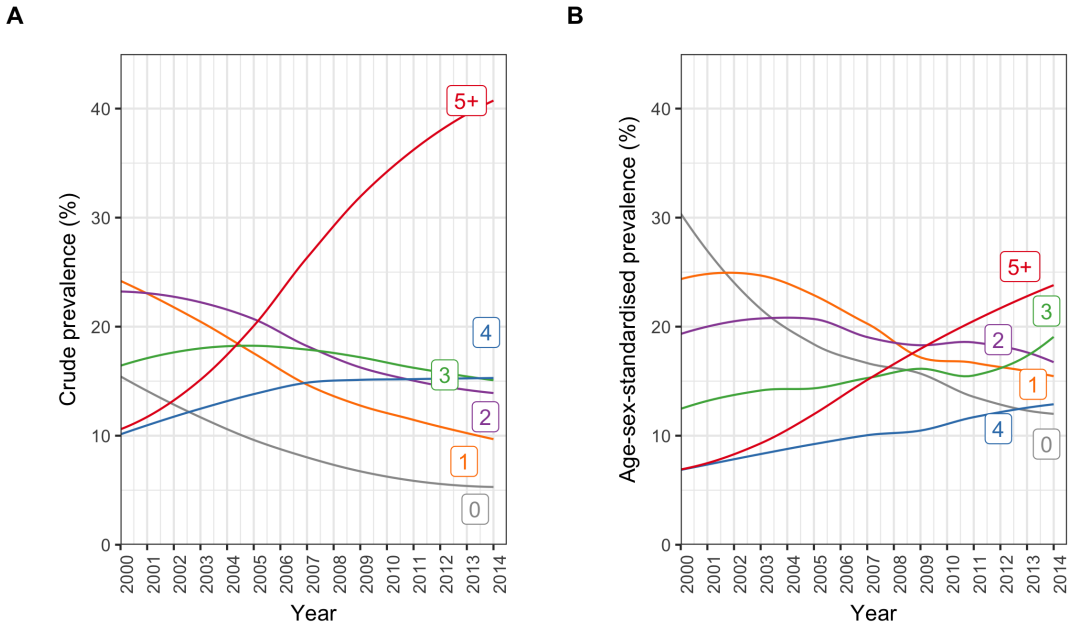
In all patients diagnosed with incident non-fatal CVD between 2000-2014 in the UK, the crude and age/sex-standardised prevalence of multimorbidity (defined as 1 or more comorbidities in addition to index condition CVD) were 91.0% (90.9%-91.1%) and 81.1% (78.7%-83.8%), respectively. For 5 or more conditions, the crude and age/sex-standardised prevalence were 25.3% (25.1%-25.5%) and 15.0% (14.3%-16.1%), respectively (Table 5.5).

Table 5.5: Prevalence of number of conditions from 2000 to 2014

Condition count	Cases	Crude rate (95% CI)	Age/sex-standardised rate (95% CI)
0	20678	0.09 (0.09-0.09)	0.19 (0.17-0.21)
1	36819	0.16 (0.16-0.16)	0.21 (0.20-0.23)
2	42859	0.19 (0.19-0.19)	0.20 (0.19-0.21)
3	39209	0.17 (0.17-0.17)	0.16 (0.14-0.18)
4	31620	0.14 (0.14-0.14)	0.10 (0.09-0.11)
$\geq$5	58020	0.25 (0.25-0.26)	0.15 (0.14-0.16)

There was a general trend of increasing numbers of comorbidities in incident CVD patients over time between 2000 to 2014 (Table 5.6, Figure 5.3). Crude prevalence of 5 or more comorbidities increased by 2.9 times from 10.6% (9.7%-11.4%) in 2000 to 40.9% (39.9%-41.8%) in 2014. Even in age/sex-standardised analysis, this increase was 2.8 times from 6.3% (5.6%-17.0%) in 2000 to 24.3% (22.1%-34.8%) in 2014, suggesting that the ageing population only partially explains the rapid increase in number of comorbidities. Crude and age/sex-standardised prevalence of actual number of comorbidities for those with 5 or more comorbidities, up to the maximum observed of 17 comorbidities, have all increased over time.

Figure 5.3: Annual crude and age/sex-standardised prevalence of number of comorbidities in incident cardiovascular disease patients



(A) Crude prevalence. (B) Age/sex-standardised prevalence. Number labels for each line refer to the number of comorbidities.

Table 5.6: Prevalence of number of conditions each year

Condition count	Year	Cases	Persons	Crude rate (95% CI)	Age/sex-standardised rate (95% CI)
0	2000	2,193	14,504	0.15(0.14-0.16)	0.32(0.23-0.48)
1	2000	3,515	14,504	0.24(0.23-0.25)	0.24(0.21-0.35)
2	2000	3,418	14,504	0.24(0.23-0.24)	0.19(0.17-0.29)
3	2000	2,388	14,504	0.16(0.16-0.17)	0.12(0.1-0.22)
4	2000	1,457	14,504	0.1(0.09-0.11)	0.07(0.06-0.18)
≥5	2000	1,533	14,504	0.11(0.1-0.11)	0.06(0.06-0.17)
0	2001	2,326	15,905	0.15(0.14-0.15)	0.24(0.19-0.34)
1	2001	3,628	15,905	0.23(0.22-0.24)	0.24(0.22-0.32)
2	2001	3,585	15,905	0.23(0.22-0.23)	0.22(0.18-0.31)
3	2001	2,690	15,905	0.17(0.16-0.18)	0.13(0.12-0.21)
4	2001	1,779	15,905	0.11(0.1-0.12)	0.07(0.06-0.14)
≥5	2001	1,897	15,905	0.12(0.11-0.13)	0.09(0.05-0.18)
0	2002	2,188	16,883	0.13(0.12-0.14)	0.23(0.18-0.3)
1	2002	3,706	16,883	0.22(0.21-0.23)	0.27(0.22-0.35)
2	2002	3,823	16,883	0.23(0.22-0.23)	0.19(0.17-0.25)
3	2002	3,011	16,883	0.18(0.17-0.19)	0.15(0.12-0.22)
4	2002	1,959	16,883	0.12(0.11-0.12)	0.08(0.07-0.14)
≥5	2002	2,196	16,883	0.13(0.12-0.14)	0.08(0.07-0.13)
0	2003	1,857	16,356	0.11(0.11-0.12)	0.26(0.17-0.42)
1	2003	3,376	16,356	0.21(0.2-0.21)	0.25(0.22-0.36)
2	2003	3,675	16,356	0.22(0.22-0.23)	0.19(0.17-0.3)
3	2003	2,958	16,356	0.18(0.17-0.19)	0.13(0.12-0.24)
4	2003	2,037	16,356	0.12(0.12-0.13)	0.08(0.07-0.18)
≥5	2003	2,453	16,356	0.15(0.14-0.16)	0.09(0.08-0.19)
0	2004	1,700	16,059	0.11(0.1-0.11)	0.17(0.15-0.38)
1	2004	3,111	16,059	0.19(0.19-0.2)	0.22(0.2-0.43)
2	2004	3,471	16,059	0.22(0.21-0.22)	0.21(0.18-0.42)
3	2004	2,921	16,059	0.18(0.17-0.19)	0.15(0.13-0.36)
4	2004	2,070	16,059	0.13(0.12-0.14)	0.09(0.08-0.3)
≥5	2004	2,785	16,059	0.17(0.17-0.18)	0.1(0.09-0.32)
0	2005	1,522	15,682	0.1(0.09-0.1)	0.2(0.13-0.33)
1	2005	2,721	15,682	0.17(0.17-0.18)	0.22(0.18-0.33)
2	2005	3,289	15,682	0.21(0.2-0.22)	0.23(0.17-0.37)
3	2005	2,848	15,682	0.18(0.17-0.19)	0.13(0.12-0.24)
4	2005	2,196	15,682	0.14(0.13-0.15)	0.1(0.08-0.21)
≥5	2005	3,106	15,682	0.2(0.19-0.21)	0.12(0.11-0.23)
0	2006	1,368	15,672	0.09(0.08-0.1)	0.16(0.14-0.37)
1	2006	2,532	15,672	0.16(0.15-0.17)	0.27(0.15-0.54)
2	2006	3,033	15,672	0.19(0.19-0.2)	0.19(0.17-0.4)
3	2006	2,845	15,672	0.18(0.17-0.19)	0.15(0.14-0.37)
4	2006	2,251	15,672	0.14(0.14-0.15)	0.09(0.08-0.31)

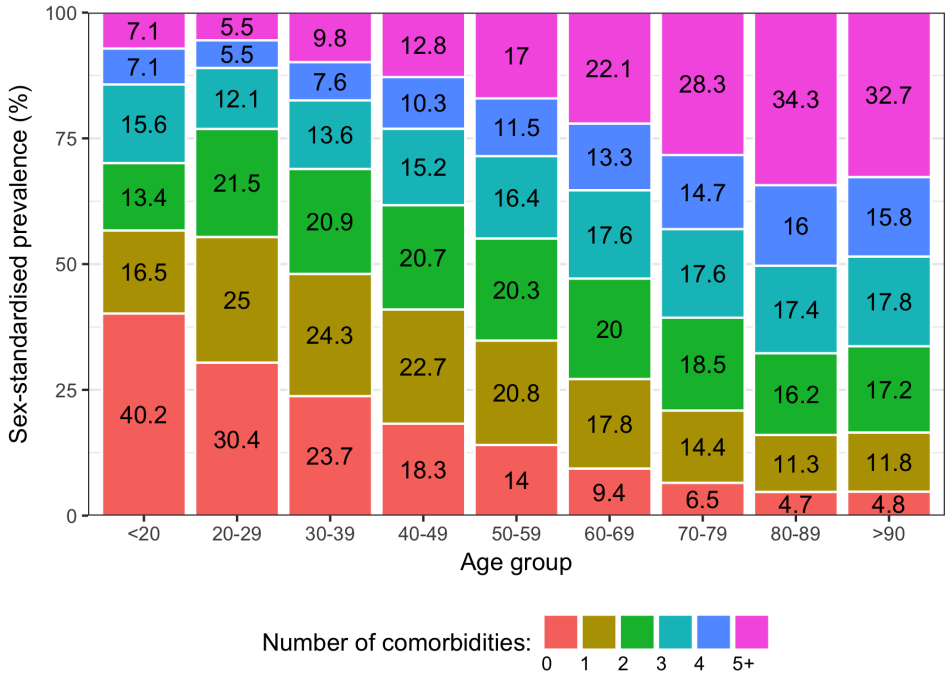
Condition count	Year	Cases	Persons	Crude rate (95% CI)	Age/sex-standardised rate (95% CI)
≥5	2006	3,643	15,672	0.23(0.22-0.24)	0.14(0.13-0.36)
0	2007	1,261	15,412	0.08(0.07-0.09)	0.18(0.15-0.39)
1	2007	2,217	15,412	0.14(0.14-0.15)	0.17(0.15-0.38)
2	2007	2,791	15,412	0.18(0.17-0.19)	0.19(0.16-0.4)
3	2007	2,772	15,412	0.18(0.17-0.19)	0.15(0.14-0.37)
4	2007	2,311	15,412	0.15(0.14-0.16)	0.1(0.09-0.32)
≥5	2007	4,059	15,412	0.26(0.26-0.27)	0.14(0.13-0.36)
0	2008	1,138	15,828	0.07(0.06-0.08)	0.14(0.12-0.35)
1	2008	2,166	15,828	0.14(0.13-0.14)	0.19(0.16-0.4)
2	2008	2,715	15,828	0.17(0.16-0.18)	0.19(0.17-0.4)
3	2008	2,796	15,828	0.18(0.17-0.18)	0.15(0.13-0.36)
4	2008	2,361	15,828	0.15(0.14-0.16)	0.1(0.09-0.32)
≥5	2008	4,651	15,828	0.29(0.29-0.3)	0.17(0.15-0.38)
0	2009	1,066	16,007	0.07(0.06-0.07)	0.19(0.13-0.33)
1	2009	2,064	16,007	0.13(0.12-0.14)	0.18(0.16-0.29)
2	2009	2,579	16,007	0.16(0.15-0.17)	0.17(0.15-0.27)
3	2009	2,687	16,007	0.17(0.16-0.18)	0.18(0.12-0.31)
4	2009	2,462	16,007	0.15(0.15-0.16)	0.11(0.1-0.21)
≥5	2009	5,149	16,007	0.32(0.31-0.33)	0.17(0.16-0.28)
0	2010	998	15,807	0.06(0.06-0.07)	0.12(0.1-0.34)
1	2010	1,881	15,807	0.12(0.11-0.13)	0.17(0.14-0.38)
2	2010	2,468	15,807	0.16(0.15-0.16)	0.18(0.16-0.4)
3	2010	2,726	15,807	0.17(0.16-0.18)	0.15(0.13-0.36)
4	2010	2,360	15,807	0.15(0.14-0.16)	0.11(0.1-0.33)
≥5	2010	5,373	15,807	0.34(0.33-0.35)	0.2(0.18-0.41)
0	2011	899	15,052	0.06(0.05-0.07)	0.15(0.1-0.24)
1	2011	1,748	15,052	0.12(0.11-0.12)	0.17(0.15-0.25)
2	2011	2,300	15,052	0.15(0.14-0.16)	0.21(0.16-0.3)
3	2011	2,400	15,052	0.16(0.15-0.17)	0.16(0.12-0.25)
4	2011	2,273	15,052	0.15(0.14-0.16)	0.1(0.09-0.17)
≥5	2011	5,432	15,052	0.36(0.35-0.37)	0.2(0.19-0.27)
0	2012	816	14,821	0.06(0.05-0.06)	0.12(0.09-0.33)
1	2012	1,654	14,821	0.11(0.1-0.12)	0.16(0.13-0.37)
2	2012	2,173	14,821	0.15(0.14-0.15)	0.17(0.15-0.39)
3	2012	2,297	14,821	0.15(0.15-0.16)	0.14(0.13-0.36)
4	2012	2,223	14,821	0.15(0.14-0.16)	0.12(0.1-0.34)
≥5	2012	5,657	14,821	0.38(0.37-0.39)	0.22(0.21-0.43)
0	2013	722	13,507	0.05(0.04-0.06)	0.1(0.08-0.21)
1	2013	1,383	13,507	0.1(0.09-0.11)	0.2(0.13-0.33)
2	2013	1,918	13,507	0.14(0.13-0.15)	0.19(0.17-0.3)
3	2013	2,088	13,507	0.15(0.15-0.16)	0.14(0.12-0.24)
4	2013	2,097	13,507	0.16(0.15-0.16)	0.15(0.09-0.29)
≥5	2013	5,299	13,507	0.39(0.38-0.4)	0.22(0.2-0.32)

Condition count	Year	Cases	Persons	Crude rate (95% CI)	Age/sex-standardised rate (95% CI)
0	2014	624	11,715	0.05(0.04-0.06)	0.14(0.11-0.25)
1	2014	1,117	11,715	0.1(0.09-0.1)	0.13(0.11-0.24)
2	2014	1,621	11,715	0.14(0.13-0.15)	0.16(0.13-0.26)
3	2014	1,782	11,715	0.15(0.14-0.16)	0.22(0.14-0.38)
4	2014	1,784	11,715	0.15(0.14-0.16)	0.11(0.1-0.22)
≥5	2014	4,787	11,715	0.41(0.4-0.42)	0.24(0.22-0.35)

In incident CVD patients, there was a general pattern of increasing prevalence of higher numbers of comorbidities with increasing age (Figure 5.4). In people who were ≥90 years, the sex-standardised prevalence of 5 or more comorbidities was 6.9 times that of no comorbidities (32.7% [31.7%-34.0%] and 4.8% [3.6%-5.9%], respectively), whilst this pattern was reversed in people who were ≤20 years where the sex-standardised prevalence of no comorbidities was 5.6 times that of 5 or more comorbidities (40.2% [13.0%-75.3%] and 7.1% [0.0%-40.5%], respectively). Patterns in crude prevalence were similar to sex-standardised (Figure 5.4b).

Figure 5.4: Prevalence of number of conditions in patients with incident cardiovascular disease by age group (years)

(a) sex-standardised prevalence



(b) crude prevalence

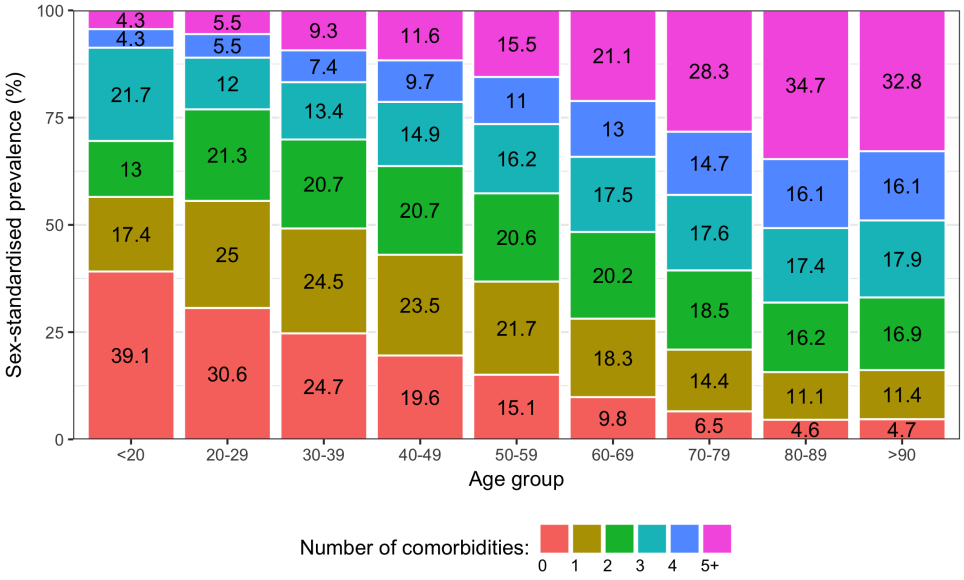
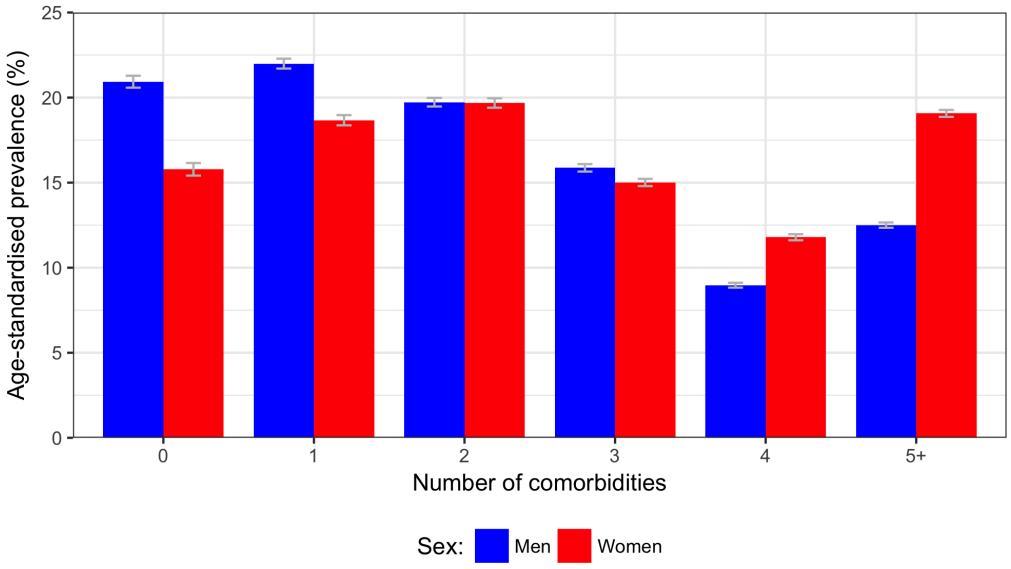


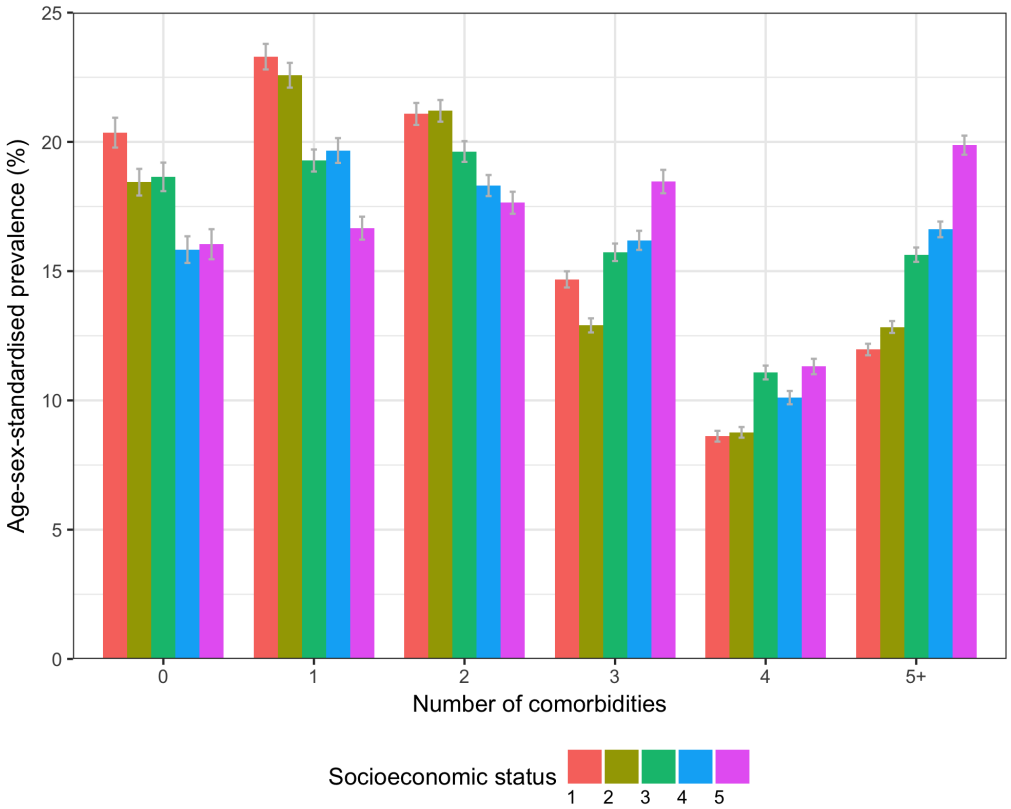
Figure 5.5: Age/sex-standardised prevalence of number of comorbidities in patients with incident cardiovascular disease by sex



Women had higher age-standardised prevalence of higher numbers of comorbidities (4 and 5 or more) compared to men (Figure 5.5), suggesting that the older age of women only partially explains the higher burden of comorbidity. The age-standardised prevalence of 5 or more comorbidities was 19.1% (17.2%-22.7%) in women and 12.5% (12.0%-13.9%) in men.

Figure 5.6 shows age/sex-standardised prevalences of numbers of comorbidities stratified by SES, with 1 indicating the least deprived and 5 the most deprived fifth. There was a general pattern of increasing prevalence of higher numbers of comorbidities with increasing deprivation. Those who were more deprived had a higher prevalence of higher numbers of comorbidities, with the sex-standardised prevalence of 5 or more conditions increasing from 12.0% (10.7%-19.1%) in SES1 to 19.9% (18.7%-40.8%) in SES5.

Figure 5.6: Age/sex-standardised prevalence of number of comorbidities in patients with incident cardiovascular disease by socioeconomic status



Socioeconomic status is split by quintiles of the Index of Multiple Deprivation for 2015, where 1 = the least deprived fifth, and 5 = the most deprived fifth

5.4.4 Prevalence of specific comorbidities

The most prevalent types of comorbidities in all incident CVD patients between 2000 to 2014 were cardiometabolic conditions, mental illness and arthritis. The most prevalent conditions by age/sex-standardised models were hypertension (28.9% [27.7%-31.4%]), depression (23.0%, [21.3%-26.0%]), arthritis (20.9% [19.5%-23.5%]), asthma (17.7% [15.8%-20.8%]) and anxiety (15.0% [13.7%-17.6%]) (Table 5.7).

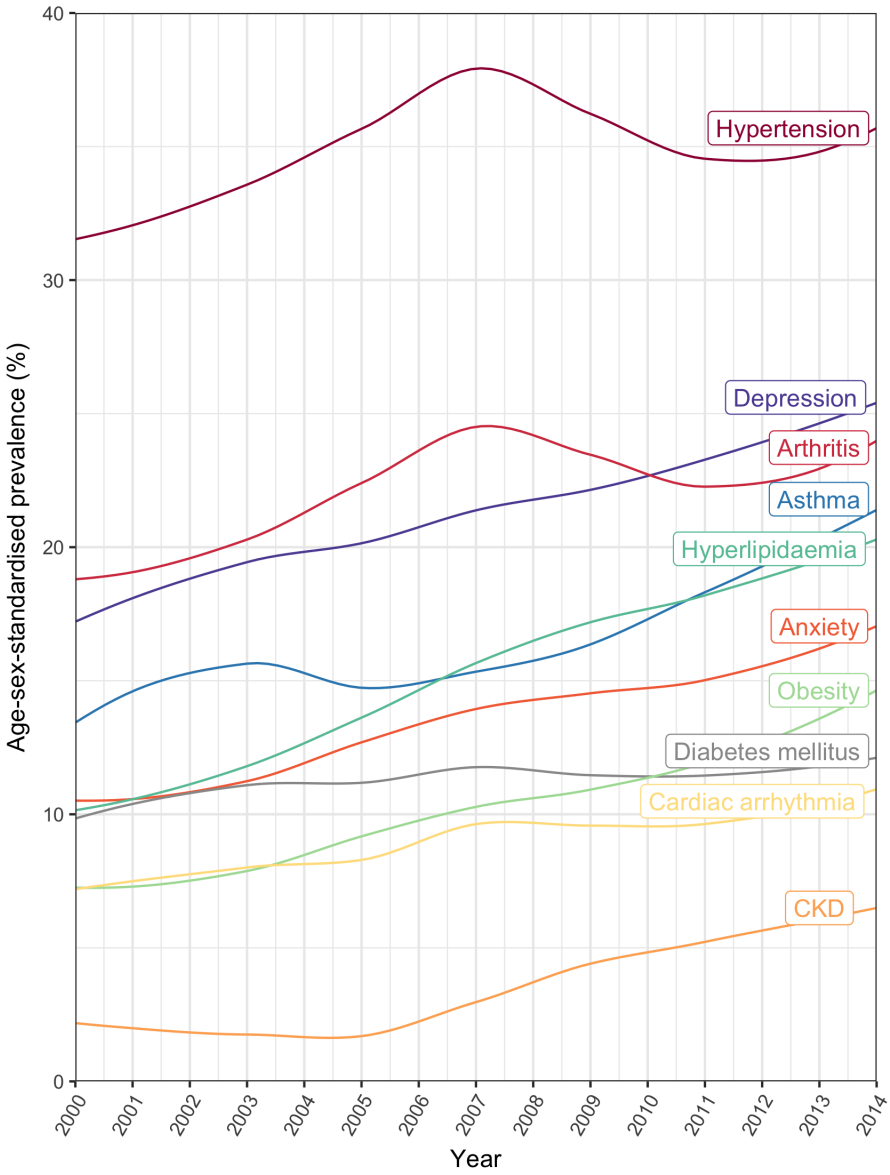
Table 5.7: Prevalence of comorbidities from 2000 to 2014

Condition	Cases	Crude rate (95% CI)	Age-sex-standardised rate (95% CI)
Hypertension	109,365	0.48(0.48-0.48)	0.29(0.28-0.31)
Depression	42,973	0.19(0.19-0.19)	0.23(0.21-0.26)
Arthritis	85,527	0.37(0.37-0.38)	0.21(0.19-0.24)
Asthma	31,103	0.14(0.13-0.14)	0.18(0.16-0.21)
Anxiety	30,255	0.13(0.13-0.13)	0.15(0.14-0.18)
Hyperlipidaemia	35,304	0.15(0.15-0.16)	0.11(0.11-0.14)
Diabetes mellitus	33,307	0.15(0.14-0.15)	0.11(0.1-0.14)
Obesity	22,315	0.1(0.1-0.1)	0.11(0.1-0.13)
Cardiac arrhythmia	27,695	0.12(0.12-0.12)	0.07(0.06-0.1)
Chronic kidney disease	24,314	0.11(0.1-0.11)	0.05(0.05-0.07)
Substance abuse	6,768	0.03(0.03-0.03)	0.05(0.05-0.07)
Chronic obstructive pulmonary disease	20,363	0.09(0.09-0.09)	0.04(0.04-0.07)
Adjustment disorder	5,077	0.02(0.02-0.02)	0.04(0.03-0.07)
Heart failure	19,090	0.08(0.08-0.08)	0.04(0.04-0.06)
Peripheral arterial disease	16,522	0.07(0.07-0.07)	0.04(0.04-0.06)
Epilepsy	5,057	0.02(0.02-0.02)	0.04(0.03-0.06)
Gout	14,255	0.06(0.06-0.06)	0.03(0.03-0.06)
Peptic ulcer disease	13,249	0.06(0.06-0.06)	0.03(0.03-0.06)
Other female reproductive cancer	2,346	0.02(0.02-0.02)	0.03(0.02-0.07)
Osteoporosis	15,655	0.07(0.07-0.07)	0.03(0.02-0.05)

The top 20 comorbidities ranked by age/sex-standardised prevalence are shown. Total population denominator was 229,205 for all conditions except 'other female reproductive cancer' where female population denominator was 110,803

Annual age/sex-standardised prevalence increased over time for most comorbidities (Figure 5.7). Many of the highly prevalent comorbidities increased from 2000 to 2014 in age/sex-standardised models, including hypertension, increasing by 11.9% from 32.0% (26.9%-45.9%) in 2000 to 35.8% (34.4%-40.1%) in 2014, and depression, increasing by 47.1% from 16.6% (13.8%-30.2%) in 2000 to 24.5% (22.7%-29.0%) in 2014. From the top 10 comorbidities ranked by age/sex-standardised prevalence, the largest increase between 2000 to 2014 was seen in chronic kidney disease (321.0% increase, 1.6% [0.5%-15.5%] to 6.6% [5.8%-10.6%]), followed by hyperlipidaemia (97.3% increase, 10.5% [8.4%-23.6%] to 20.6% [19.4%-24.6%]) and

Figure 5.7: Annual prevalence of the 10 most common comorbidities in patients with incident cardiovascular disease between 2000 and 2014



CKD=chronic kidney disease

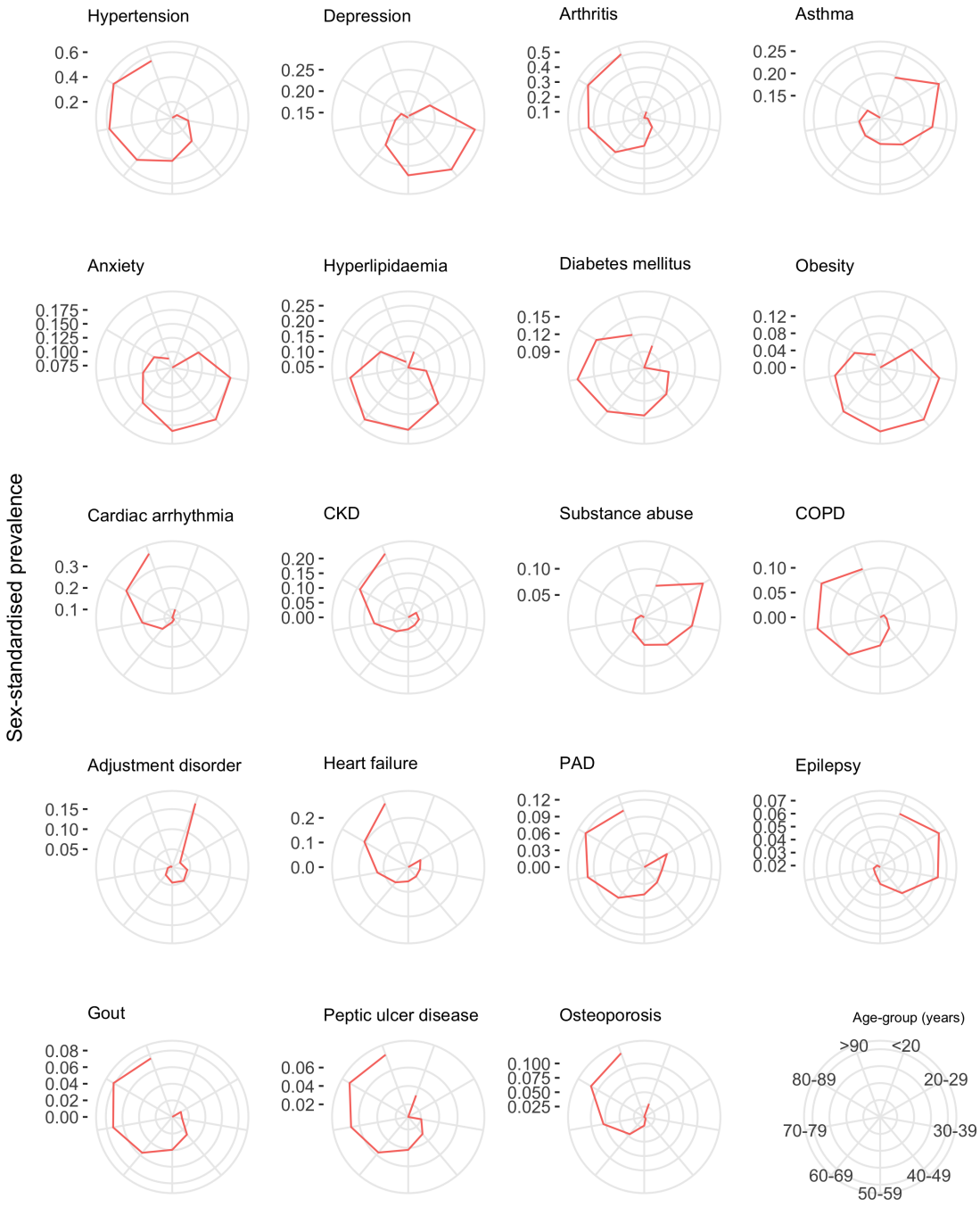
obesity (94.6% increase, 7.6% [5.8%-21.1%] to 14.9% [13.4%-19.2%]). There was a peak in prevalence of some conditions in 2007, namely hypertension and arthritis.

The age-specific prevalence of comorbidities stratified by 10-year age groups is shown in Figure 5.8. There was an age-specific pattern of comorbidities, with

a high prevalence of cardiometabolic conditions and arthritis in older age groups, and a high prevalence of mental illness in middle-aged to younger age groups. Hypertension had the highest prevalence in 80-89 year olds (62.7% [62.3%-63.1%]) and mental illnesses had highest prevalence in 30-39 years for depression (27.6% [26.1%-29.2%]) and 40-49 years for anxiety (17.3% [16.7%-17.9%]).

Table 5.9 shows the top 10 most prevalent comorbidities by sex-standardised prevalence in each age group. Cardiometabolic conditions are highly prevalent in all age groups, more so among older age groups. Hypertension was the most prevalent comorbidity in patients ≥40 years and increased with age; the prevalence in 40-49 years (31.5% [30.8%-32.3%]) was half that of 80-89 years (62.7% [62.3%-63.1%]). Arthritis also increased in prevalence and was ranked higher in older age groups, rising from 9th in 30-39 years (8.0% [7.1%-9.0%]) to the 2nd most prevalent comorbidity by 60-69 years 34.8% [34.4%-35.2%] and maintaining 2nd place until ≥90 years (53.5% [52.7%-54.2%]). Mental illnesses were highly ranked in younger age groups, with depression being the most prevalent comorbidity in 30-39 years (27.6% [26.1%-29.2%]), and reducing in prevalence to rank 8th by ≥90 years (15.1% [14.6%-15.7%]).

Figure 5.8: Sex-standardised prevalence of comorbidities in patients with incident cardiovascular disease by age group (years)



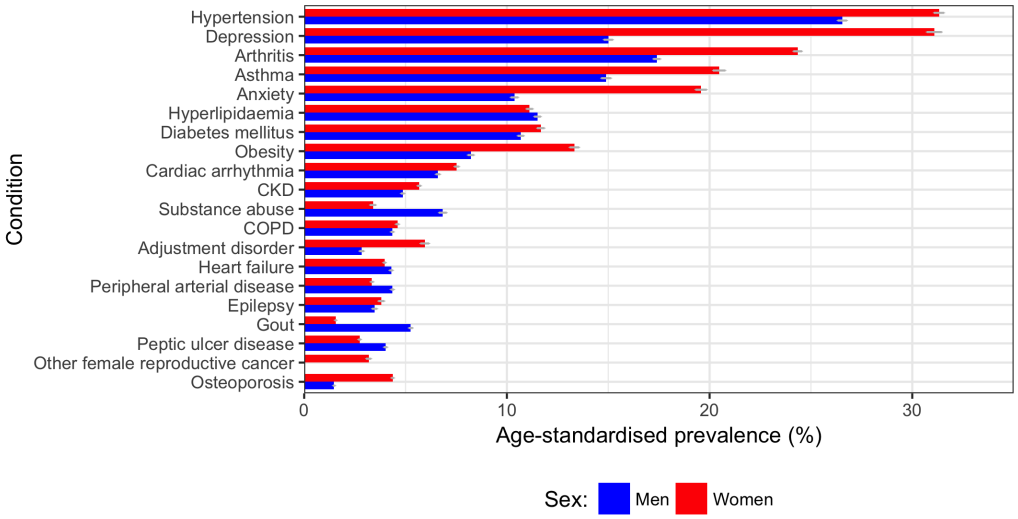
The spokes of each radial plot represent increasingly older age groups going clockwise from the first spoke after 12 o'clock (legend represented in bottom right of figure). The diameter axes show sex-standardised prevalence, and axis ticks/scale are specifically labelled for each plot. The most prevalent non-sex-specific conditions are shown.

Table 5.9: Age-specific ranking of the top 10 most prevalent comorbidities

Ranking	Age group (years)																	
	<20		20–29		30–39		40–49		50–59		60–69		70–79		80–89		≥90	
1	Asthma	21.7	Asthma	25.1	Depression	27.6	Hypertension	31.5	Hypertension	41.4	Hypertension	50.9	Hypertension	58.6	Hypertension	62.7	Hypertension	58.3
2	Learning disability	17.4	Depression	19.1	Asthma	20.8	Depression	26.5	Hyperlipidaemia	25.4	Arthritis	34.8	Arthritis	43.8	Arthritis	50.7	Arthritis	53.5
3	Adjustment disorder	13.0	Substance abuse	14.5	Hypertension	20.3	Hyperlipidaemia	21.0	Depression	24.3	Hyperlipidaemia	26.8	Hyperlipidaemia	24.0	Cardiac arrhythmia	30.5	Cardiac arrhythmia	36.9
4	Cardiac arrhythmia	8.7	Anxiety	12.4	Anxiety	17.0	Anxiety	17.3	Arthritis	23.1	Depression	20.5	Cardiac arrhythmia	20.4	Heart failure	20.4	Heart failure	27.4
5	Diabetes mellitus	8.7	Hypertension	11.4	Obesity	13.3	Asthma	16.3	Anxiety	16.7	Diabetes mellitus	16.3	Diabetes mellitus	17.9	Chronic kidney disease	18.9	Chronic kidney disease	22.2
6	Arthritis	8.7	Obesity	8.3	Hyperlipidaemia	11.5	Obesity	14.6	Diabetes mellitus	14.5	Asthma	14.5	Depression	16.8	Depression	16.7	Dementia	18.6
7	Hemiplegia	8.7	Epilepsy	7.1	Substance abuse	10.8	Arthritis	13.2	Asthma	14.4	Anxiety	14.3	Asthma	14.8	Hyperlipidaemia	15.5	Osteoporosis	15.9
8	Epilepsy	8.7	Cardiac arrhythmia	6.5	Diabetes mellitus	10.3	Diabetes mellitus	12.1	Obesity	13.9	Cardiac arrhythmia	13.5	COPD	12.9	Diabetes mellitus	15.4	Depression	15.1
9	Depression	8.7	Diabetes mellitus	6.2	Arthritis	8.0	Substance abuse	8.1	Cardiac arrhythmia	8.7	Obesity	12.8	Heart failure	12.7	Asthma	13.3	Diabetes mellitus	11.4
10	Hyperlipidaemia	8.7	Heart failure	5.9	Cardiac arrhythmia	6.4	Cardiac arrhythmia	7.6	Substance abuse	6.4	COPD	9.7	Anxiety	12.4	COPD	13.0	Anxiety	10.1

Sex-standardised prevalence (%) is listed to the right of each condition listed. Shading is as follows: cardiometabolic conditions, red; respiratory conditions, green; mental health conditions, yellow; neurological conditions, blue; and musculoskeletal conditions, purple. COPD=chronic obstructive pulmonary disease

Figure 5.9: Age-standardised prevalence of comorbidities in men and women

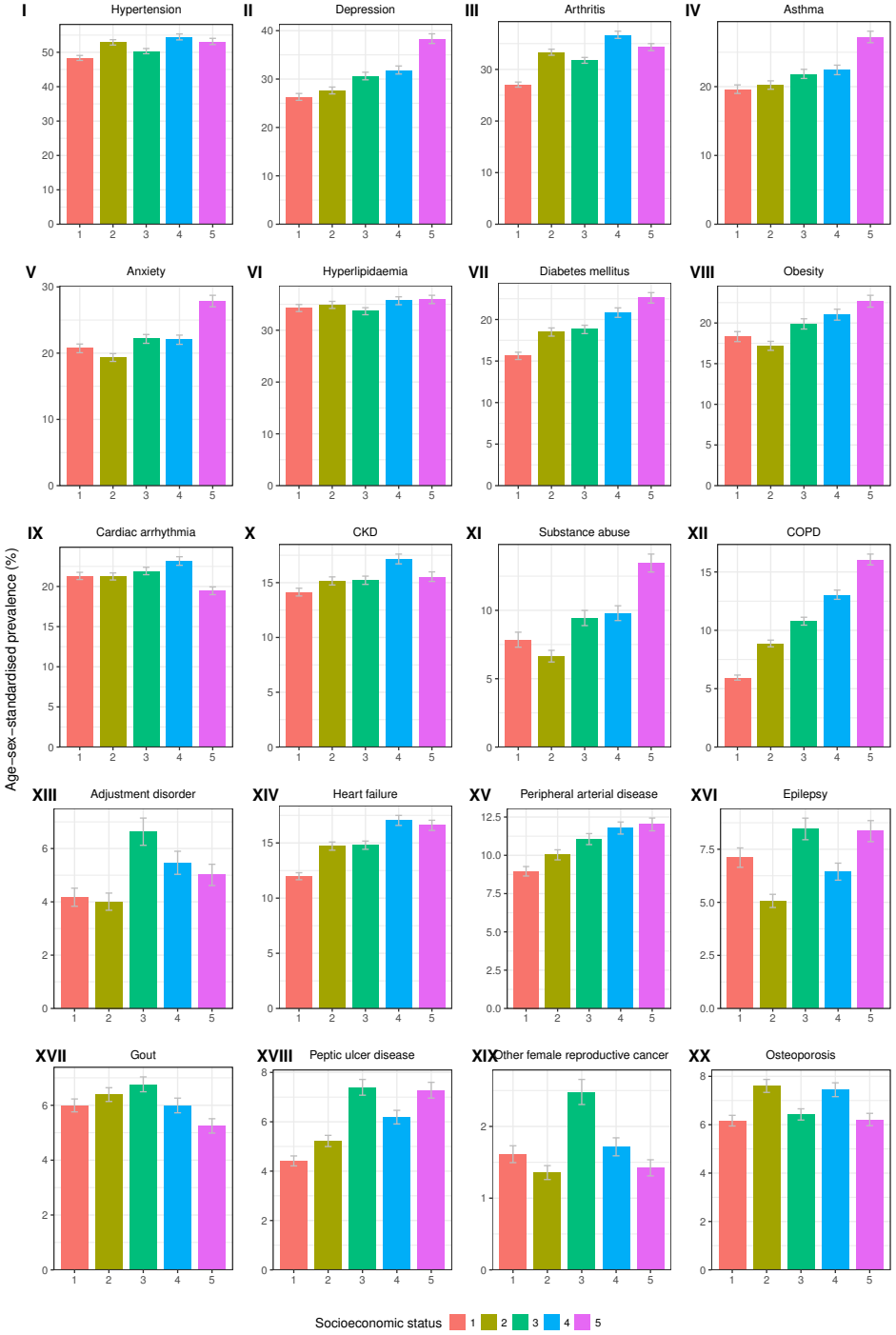


The top 20 comorbidities ranked by sex-specific age-standardised prevalence between 2000 and 2014 are shown for men (blue) and women (red). CKD=chronic kidney disease; COPD=chronic obstructive pulmonary disease; PAD=peripheral arterial disease

Sex-specific age-standardised prevalences are shown in Figure 5.9. Women had higher age-standardised prevalence of most comorbidities compared to men. The top 5 conditions in women by age-standardised prevalence were: hypertension (31.3% [29.4%-35.0%]), depression (31.1% [28.3%-35.5%]), arthritis (24.3% [22.5%-28.0%]), asthma (20.5% [18.4%-24.3%] and anxiety (19.6% [17.6%-23.3%]). In men, the top 5 conditions included hyperlipidaemia instead of anxiety, and by age-standardised prevalence were: hypertension (26.5% [26.1%-27.9%]), arthritis (17.4% [16.5%-19.0%]), depression (15.0% [14.3%-16.5%]), asthma (14.9% [13.1%-17.3%]) and hyperlipidaemia (11.5% [10.7%-13.1%]). Out of the top 10 most prevalent comorbidities, ranked by overall age/sex-standardised prevalence 2000-2014, the largest sex difference was for depression and anxiety, where women's age-standardised prevalence was 2.1 times men for depression (31.1% [28.3%-35.5%] vs 15.0% [14.3%-16.5%]) and 1.9 times for anxiety (19.6% [17.6%-23.3%] vs 10.4% [95%CI 9.8%-11.8%]).

For all comorbidities in the top 10, SES5 (most deprived fifth) had a higher prevalence compared to SES1 (least deprived fifth) (Figure 5.10). The largest difference between deprivation fifths in age/sex-standardised models for the top 10 comorbidities was for depression, with a prevalence 46% higher in SES5 compared to SES1 (38.4% [31.2%-62%] vs 26.3% [23.1%-34.5%]) followed by diabetes which was 45% higher in SES5 compared to SES1 (22.6% [21.2%-43.4%] vs 15.6% [14.3%-22.7%]). The ranking of the most common comorbidities across each fifth was similar; hypertension, hyperlipidaemia, arthritis, depression, cardiac arrhythmias and anxiety made up the top 5 comorbidities across each fifth.

Figure 5.10: Age/sex-standardised prevalence of comorbidities by SES

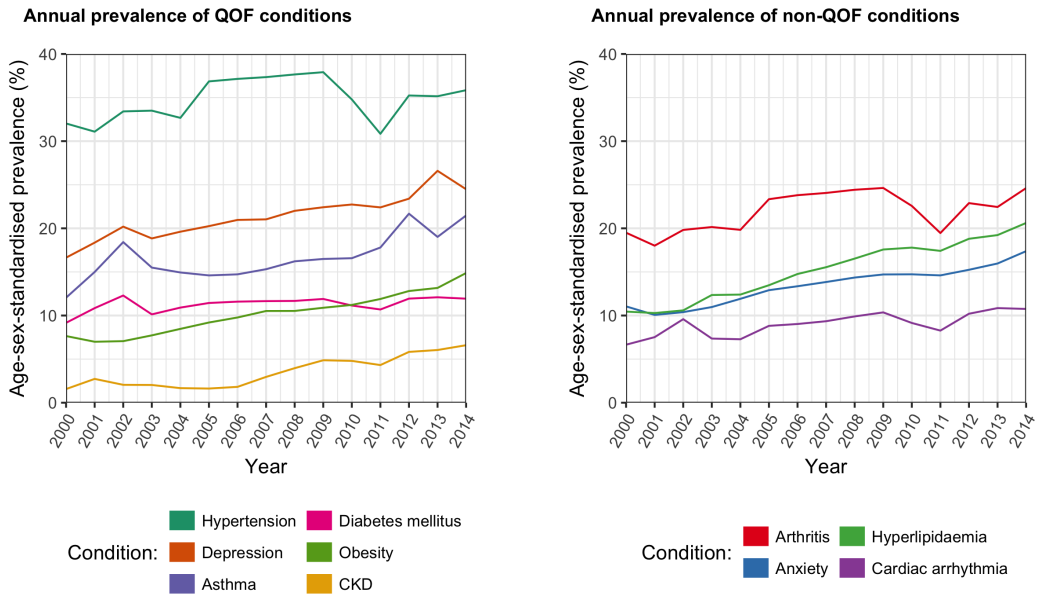


SES based on the Index of Multiple Deprivation for 2015 (IMD) split by fifths with 1= least deprived and 5= most deprived. I to XX represent the top 20 most prevalent comorbidities by overall age/sex-standardised prevalence. All plots share common axes; x-axis: SES fifth (same for all), y-axis: age/sex-standardised prevalence (%). N.B. not all plots are on the same scale on the y-axis.

5.4.5 Sensitivity and additional analyses

To assess the impact of the QOF on the trends in prevalence, QOF and non-QOF conditions were compared. Figure 5.11 shows the trends in the top 10 conditions separated into QOF and non-QOF conditions without locally weighted smoothing. Both groups of conditions demonstrated a trend of increasing prevalence over time. Hypertension (QOF) and arthritis (non-QOF) showed similar trends in prevalence over time, with a sharp rise from 2004 to 2005, followed by a steady increase until 2009, a drop in prevalence until 2011 and then a rise again. There were no appreciable differences that distinguished QOF and non-QOF conditions.

Figure 5.11: Trend in QOF vs non-QOF conditions

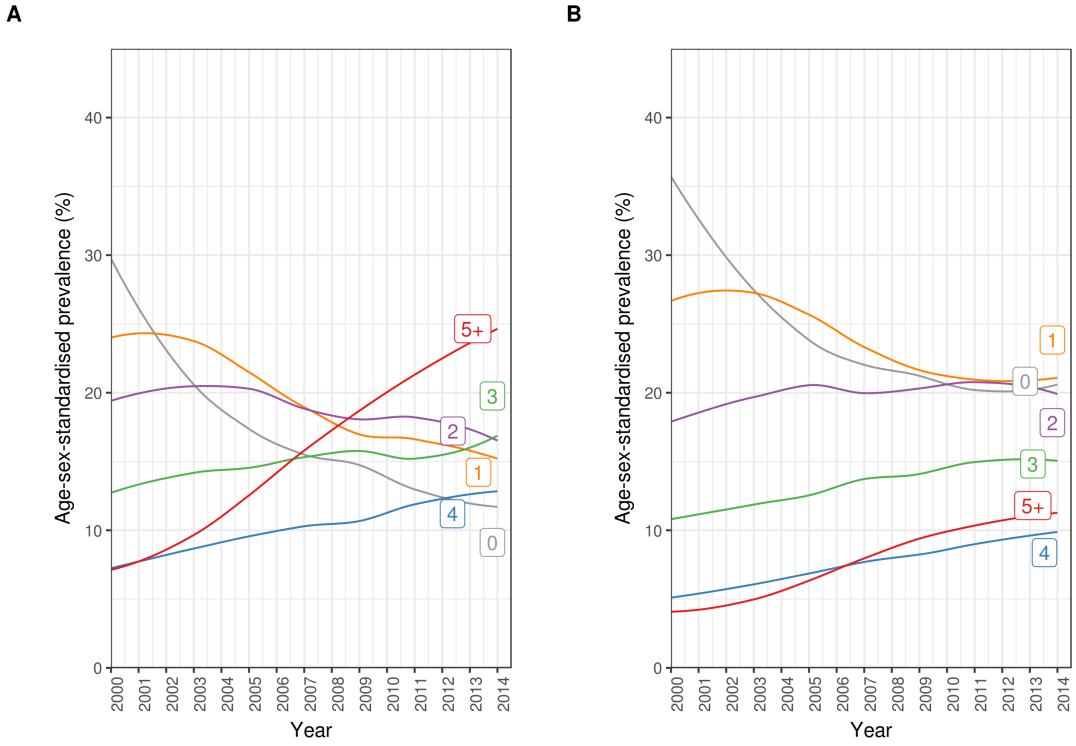


The 10 most common comorbidities by annual prevalence in patients with incident CVD between 2000-2014, stratified into QOF and non-QOF conditions. QOF= Quality and Outcomes Framework (GP contract in the UK), CKD=Chronic kidney disease

To assess the impact of look-back time and its contribution to the increase in number of conditions over time, results with restricted look-back time were compared to unrestricted look-back time. This was done to specifically test the hypothesis that the increase in prevalence of patients with higher numbers of conditions was due to a longer look-back time. If this hypothesis were true, patients diagnosed in more recent years (with a longer average look-back time since CPRD inception in 1985), would have more conditions diagnosed. If the prevalence of higher numbers of comorbidities in CVD patients had truly been increasing over time, this trend should still be present with restricted look-back time.

With unrestricted look-back time, median was 12.2 years with a range of 0 to 98.7 years. Restricted look-back time was limited to 10 years. Figure 5.12 shows the trend in number of conditions with comorbidity diagnosis restricted and unrestricted for look-back time. Overall, compared to unrestricted look-back time, the analysis using restricted look-back time had higher proportions of people with lower numbers of conditions, and lower proportions of people with higher numbers of conditions. For unrestricted look-back time, the increasing trend for higher numbers of conditions was slightly steeper than for restricted look-back time, but the trend for higher numbers of conditions increasing over time, and lower numbers of conditions decreasing over time, was still present with a restricted look-back time. For example, for unrestricted look-back, the prevalence of patients with 5 or more conditions increased 3.75 times from 2000 (6.7%) to 2014 (25.1%), whereas for the same patients in restricted look-back, prevalence increased 3.25 times from 2000 (3.6%) to 2014 (11.7%). Overall, restricted look-back time still demonstrated an increase in prevalence of higher numbers of conditions over time, and disproves the hypothesis that this increase was due to longer look-back time in more recent years.

Figure 5.12: Trend in number of conditions with unrestricted vs restricted look-back time



Unrestricted look-back time incorporated all diagnoses in the CPRD before the incident date of diagnosis of CVD. Restricted look-back time restricted the look-back time to 10 years before incident diagnosis of CVD.

5.5 Discussion

5.5.1 Summary of main findings

In a representative population of 4.2 million UK adults, 229,205 incident cases of non-fatal CVD were identified, and the prevalence of 56 major comorbidities prior to CVD diagnosis were measured. The age/sex-standardised incidence of non-fatal CVD has decreased by a third between 2000-2014, but the burden of multimorbidity and comorbidity has increased four times. Overall, 91% of non-fatal CVD patients were multimorbid at the time of diagnosis. Although part of the increase was accounted for by an ageing population, even in age/sex-standardised analysis, the prevalence of those with 5 or more comorbidities increased four times from 6.3% to 24.3% between 2000 and 2014. The patterns of comorbidities differed

substantially by age, sex and socioeconomic status. On average, older patients, women and socioeconomically-deprived groups had higher numbers of comorbidities, but the type of comorbidities differed by age and sex. Cardiometabolic comorbidities contributed substantially to the burden of comorbidities but 4 out of 10 major comorbidities were non-cardiometabolic.

5.5.2 Comparison with previous literature

This study shows that although CVD incidence is decreasing over time, the number of comorbidities in CVD patients is increasing over time even when increased look-back time in routinely-collected records is accounted for. The absence of previous reports on the burden of comorbidities in patients with incident CVD and trends over time, precludes a direct comparison of this study's findings with the literature. Two large-scale studies investigated comorbidity or multimorbidity in patients with prevalent CVD. In one study of US Medicare beneficiaries aged 65 or more, 56% of patients with prevalent stroke and 36% of patients with prevalent IHD were found to have 5 or more comorbidities [195]. In another cross-sectional study of patients with prevalent stroke in Scotland, 55% had 4 or more comorbidities [88]. The crude prevalence of 5 or more conditions had a range between 21.1% and 32.8% in CVD patients >60 years, and a crude prevalence of 4 or more conditions ranging from 8.7% to 50.7% in all CVD patients. The relatively higher prevalences in previous studies could be attributed to their selection of a prevalent CVD population, thus including comorbidity diagnoses after CVD diagnosis that were precipitated by increased contact with medical services for CVD care.

In this study, the prevalence of most individual comorbidities increased over time. Most of the increasing burden of comorbidity in CVD is in cardiometabolic comorbidities such as hypertension, diabetes and obesity, which is consistent with what has been reported previously with combinations of hypertension and IHD and stroke/TIA being the most prevalent combinations of comorbidities in the general population [211], and additionally between 80-90% of US Medicare beneficiaries diagnosed with IHD or stroke have hypertension [195]. There is convincing evidence

to suggest that concordant cardiometabolic conditions significantly reduce life expectancy and increase long-term mortality risk, based on the Emerging Risk Factors Collaboration study examining the combination of stroke, myocardial infarction and diabetes, where a combination of all three conditions multiplicatively increased mortality risk over and above what was expected in the additive risk of each individual condition [45].

However, there was also a large burden of comorbidities that were discordant with CVD care, such as arthritis, asthma and mental illness (depression and anxiety), which were not perceived to share a pathophysiological origin [93]. The high prevalence of comorbidities such as arthritis could be due to co-occurrence of diseases that are common in older populations; this study's reported prevalence of arthritis, which includes osteoarthritis and unspecified arthritis (likely to be osteoarthritis) is between 23% to 54% in those aged 40 or more, and is higher than that reported by Arthritis UK (now known as Versus Arthritis after merging with Arthritis Care) for the general population: 27% to 46% in those aged $\geq$45 years old [212]. Co-occurrence in old age does not explain the high prevalence of mental illnesses, where in younger patients aged between 40 and 59, depression is ranked 2nd and 3rd and affects about a quarter of these patients. These prevalences are higher than in the general UK population; reported prevalence of common mental disorders (anxiety and depression) is 17% in the UK according to the Adult Psychiatric Morbidity Survey [213]. The higher prevalence of discordant comorbidities could suggest that co-occurrence of arthritis and mental illness is not purely due to chance. The co-occurrence could be due to common aetiologies, such as social stress and inflammation playing a role in developing multimorbidity and shaping specific comorbidity patterns in those with CVD [14, 82]. Nonetheless, there is some evidence to suggest that the number and severity of discordant (and not concordant) comorbidities is associated with future cardiovascular risk and mortality [20], and discordant combinations significantly increases cost of care, especially in combination with depression [214]. The high prevalence of mental illness comorbidity is concerning, as comorbid depression with physical conditions

has been shown to associate with higher mortality rates and poorer quality of life [215]. The problem is also not isolated to CVD; studies have shown that 25% of patients with a chronic medical condition have comorbid depression, and about double the prevalence or odds of depression compared to those without any conditions [216]. Comorbidities need to be integrated into management of single chronic conditions, and CVD is no exception.

This study also shows the relationship between age and higher prevalence of multimorbidity, which has been reported previously [14]. In particular, CVD patients have a very high prevalence of cardiometabolic comorbidity, with the majority of the top 10 comorbidities in all age groups being cardiometabolic conditions, a pattern that was also shown in the US Medicare population [195]. The variation in comorbidity pattern in different age groups is indicative that age-specific comorbidity management in CVD needs to be considered, especially with mental illness in those aged between 30-59 years where about one quarter of CVD patients are affected.

Women with CVD have higher age-standardised prevalence of higher numbers of comorbidities, and most individual comorbidities. The sex-difference was maintained in most cardiometabolic conditions, despite the higher prevalence of cardiovascular risk factors in men at the time of diagnosis of CVD. There were particularly noticeable sex differences for depression and anxiety, where women had a prevalence of about 1.5 times that of men. The sex-difference in the prevalence of multimorbidity and physical-mental comorbidity has been identified in the general population [217]. The persistence of this sex-difference in CVD patients emphasises that although men are more likely to develop CVD, women have a higher burden of comorbidities, including discordant comorbidities, that complicate CVD management.

This study reinforces that CVD patients who are more socially deprived have a higher prevalence of more comorbidities. One fifth of patients in the most deprived fifth have 5 or more comorbidities, compared to the same percentage of people in the least deprived 80% of the population having one comorbidity. The comorbidity pattern did not vary much between categories of deprivation for the most common comorbidities, suggesting that those who are more deprived are

diagnosed with more of the most common comorbidities including hypertension, depression and arthritis. The socioeconomic gradient of multimorbidity has been extensively reported previously, including in a nationally representative primary care population in Scotland of 1.7 million [14], but to my knowledge, the socioeconomic gradient with multimorbidity has not been explicitly examined in a CVD population.

5.5.3 Strengths and limitations

One strength of this study is the use of a large representative cohort across primary and secondary care in the UK that provides sufficient power to analyse overall prevalence of multimorbidity and individual comorbidities, as well as sub-populations by age, sex and SES. This means that this study's results are generalisable not only to the UK general population, but also to developed nations such as North America and other European countries that have a similar profile of CVD incidence. This study's trends in CVD incidence are consistent with previous literature, showing a one third reduction in CVD over a similar period [218, 219]. The longitudinal nature of this study's data has also allowed analysis of temporal trends, which has not been investigated previously for multimorbidity and comorbidity in CVD patients in the general population [6, 88]. A population with incident diagnosis of CVD was selected, which allowed examination of prevalent diagnoses of comorbidities before CVD diagnosis, and reduced the effect of potential diagnosis-time-dependent differences between CVD patients, such as survival time and severity of disease, allowing direct comparisons of similar patients at different time points to inform trends over time.

A limitation of using electronic health records is the dependence on recorded diagnoses, and hence lack of inclusion of undiagnosed cases or those with no contact with healthcare services. Under-diagnosis is also likely to vary across conditions. For example, conditions like hypertension and depression may be diagnosed less than conditions that require health system contact like cancer. Other factors that could lead to under-diagnosis include age, sex and SES. Some of the patterns seen over time could be an artefact of recording bias, incentives and changes to clinical guidelines. However, the diagnosis of a comorbidity in EHR is more certain

than other data sources such as self-report questionnaires. There has been much investigation into the validity of diagnoses recorded by general practitioners in CPRD for a range of comorbidities, and the average positive predictive value is 89% with 92% completeness when compared to national registries [124]. Furthermore, QOF and non-QOF conditions were compared and there was no appreciable difference between the groups that could be attributed to the introduction of QOF in 2004. However, there was evidence that the introduction of QOF may have contributed to the increase in diagnoses after 2004, whereby the trend in prevalence of diagnoses increased after 2004 to a plateau, suggesting existing undiagnosed cases were recorded (and counted) shortly after the introduction of QOF.

A further discussion of the strengths and limitations of using the CPRD is provided in section 8.3.

Another limitation is the heterogeneity of approaches to measuring multimorbidity [108, 109], which meant that this study did not have a standardised approach to implement. This study used three different sources to collate a list of clinically-relevant and common chronic conditions (discussed in chapter 3). This list included the CVD risk factors hypertension, hyperlipidaemia and obesity, which a large number of CVD patients develop before incident CVD, and could contribute to the inflation of the increase in multimorbidity over time. The temporal trends in this study show that the increasing multimorbidity burden is unlikely to be attributable to these three conditions alone; the proportion of people who have 5 or more comorbidities has tripled between 2000-2014 and hypertension has only increased by 11.9% between 2000-2014, which was one of the lower percentage increases amongst the top 10 most prevalent comorbidities.

5.5.4 Clinical implications

The current paradigm in CVD practice and policy is single-disease focused. Although this may work well with CVD risk factors, sequelae and related conditions, such as hypertension, heart failure, and diabetes, this approach does not account for

discordant comorbidities. This study shows that there is a large burden of non-cardiometabolic comorbidity in CVD patients, including depression, arthritis, asthma, and anxiety, which were all in the top 10 comorbidities by crude and age/sex-standardised prevalence out of the 56 comorbidities studied. The burden of multimoridity is increasing in CVD, and practice and policy must change to meet this demand in CVD care, as well as management of other chronic medical conditions.

5.5.5 Future research

The high prevalence of multimorbidity, and particularly discordant comorbidity, has wide implications for future research. Future randomised-controlled trials involving patients with CVD should consider including, rather then excluding, patients with comorbidities and actively report the prevalences of these comorbidities and/or investigate the impact of comorbidities on the study outcome(s). Although only the prevalence of comorbidities in CVD was investigated, it is likely that a similar pattern and trend would exist for other conditions such as chronic obstructive pulmonary disease (COPD) and chronic kidney disease (CKD), and further work is required using different index conditions to define the full impact of comorbidities. Moreover, the pattern and trends of comorbidity may be different for stroke/TIA and IHD, and stratified analyses were beyond the scope of this study. Furthermore, lower and middle-income countries that face a different set of population health challenges such as the double burden of infectious and non-communicable diseases, may have a different pattern of comorbidity that requires characterisation. For instance, it is has been suggested that HIV increases the risk of CVD by up to 50% [220]. Finally, this is a descriptive study that provides insight into comorbidities in CVD, and further analytical studies to examine the impact of comorbidities on clinical outcomes and quality of care are required to further inform health service planning and clinical guidelines. Indeed, this is an interesting area for further investigation with great potential to provide novel insights that influence policy and practice.

5.5.6 Conclusions

The burden of multimorbidity and comorbidity in incident non-fatal CVD has increased over time. On average, older patients, women and socially-deprived groups had higher numbers of comorbidities, but the type of comorbidities varied by age and sex. Cardiometabolic conditions contributed substantially to the burden but 4 out of the 10 major comorbidities were non-cardiometabolic. The current single-disease paradigm in CVD management needs to broaden and incorporate the large and increasing burden of multimorbidity and comorbidity.

6

Multimorbidity and blood pressure

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6.1 Introduction

Hypertension affects over 20% of individuals and is a leading cause of mortality and morbidity worldwide [69].

It is rarely present in isolation. Up to two thirds of patients with hypertension have at least one comorbidity [70] and there is growing evidence that multimorbidity is increasing over time [8, 3]. Hypertensive patients with comorbidities are likely to be at higher risk of cardiovascular events, and are hence more likely to benefit from blood pressure (BP) lowering compared to those without comorbidities [221, 69]. However, these patients also have competing and/or conflicting treatment recommendations leading to higher risk of receiving poorer quality care, including less intensive antihypertensive therapy [222]. Some experts have advised cautious antihypertensive therapy in multimorbid patients [223] in response to concerns to the perception that higher treatment burden decreases adherence and increases the chance of adverse drug-drug interactions [224].

There is overwhelming evidence that BP lowering has benefits on mortality [225] and morbidity [103]. Evidence suggests that the effects of BP lowering are broadly consistent across patient subgroups, including by comorbidity status [226, 77].

Despite this, hypertension is poorly treated and controlled [227, 228]. A study of the Health Survey for England reported control rates of 61% for females and 63% for males [229]. Numerous studies have investigated the determinants of hypertension treatment and control, which can be divided into health system factors and patient factors. A major health systems factor is availability and affordability of antihypertensives, which has been shown to improve blood pressure (BP) control [230]. A major patient factor is adherence - patients who are highly adherent to antihypertensive therapy have been shown to have a lower risk of cardiovascular events [231]. It has also been suggested that the presence of patient comorbidity and its effects on health care provision, could also contribute to poor treatment and control of hypertension. With the expected rise in the burden of multimorbidity [8]

and hypertension [232], it is important to understand the impact of comorbidities on BP and its treatment to inform future practice, policy and research.

It has been shown that comorbidities are associated with usage of different hypertensive classes, as recommended by clinical guidelines [233]. However, prior literature provides conflicting evidence on control of BP. Some studies have shown that the number of cardiovascular comorbidities is associated with better BP control [234, 235]. It has also been shown that patients with more discordant comorbidities (for example, hypertension and depression, refer to subsection 3.4.3 for further explanation) are less likely to have their uncontrolled hypertension addressed with intensification of treatment [236], but it has also been shown that patients with more comorbidities, especially discordant comorbidities, have higher odds of receiving high quality of care for their hypertension [237]. Looking deeper at specific comorbidities, Sarkar et al have reported that mean SBP is lower in patients with higher numbers of comorbidities, irrespective of the type of comorbidity [238] yet Paulsen et al have reported that the association between SBP and comorbidities differs by the type of comorbidity [22]. It is not possible to make a conclusion about the impact of comorbidity on BP treatment and control based on the conflicting evidence. The main evidence is not only conflicting, but have methodological limitations that restrict the ability to draw valid conclusions. The studies to date are mostly cross-sectional, meaning that patterns cannot be assessed over time, and it is difficult to address reverse causation to determine the direction of the association. This is compounded by the selection of *prevalent* hypertensive populations at different points of their disease trajectory, meaning that the cases are not being compared like for like e.g. a patient newly diagnosed with hypertension is compared to a patient who has had hypertension for 30 years. Most previous studies have also only examined a limited number of comorbidites, often not investigating non-cardiovascular comorbidities, which are highly prevalent in patients with cardiovascular disease [8].

To address limitations in the previous literature, I explored how comorbidity affected BP management by using a large contemporary cohort, based on linked

electronic health records, with a high prevalent use of antihypertensives and regular routine clinical BP measurements.

Added value of this study:

- large representative study
- longitudinal data over the course of the hypertension disease trajectory
- comprehensive data on antihyertensive therapy and clinical BP measurements
- large number and types of comorbidities

6.2 Aims

In patients with incident hypertension, investigate the association of

1. Number and type of comorbidities with systolic BP
2. Number and type of comorbidities with antihypertensive prescription

6.3 Methods

6.3.1 Data source

The study was conducted using linked EHR from the CPRD (refer to chapter 4)

6.3.2 Study population

In addition to the general selection criteria for patients aged over 16 years old subsection 4.2.1), all patients selected for this study had at least one valid BP measurement in their primary care record. The population selected were patients with an incident diagnosis of hypertension, defined as the first recording of any diagnostic code of incident hypertension (Table 6.1) that was recorded during the capture period of quality data for each patient. Diagnoses were also restricted to those in the study dates between 1st January 2000 and 31st December 2014.

This excluded patients with a diagnosis of hypertension outside each patient's capture period or the total study period.

Table 6.1: Diagnostic codes for hypertension

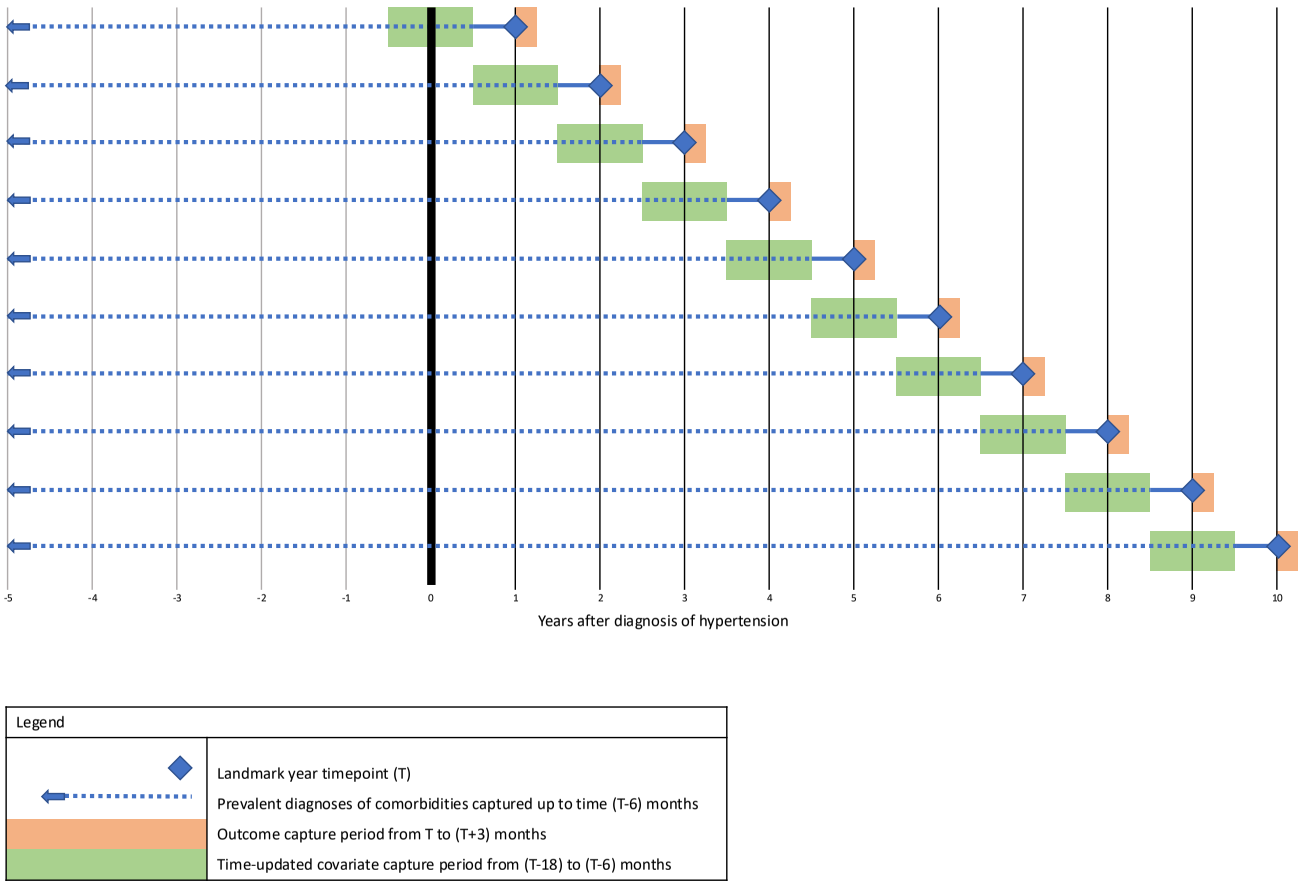
Medcode	Description
204	Hypertensive disease
799	Essential hypertension
1894	Benign essential hypertension
3712	Hypertension NOS
3979	Hypertensive encephalopathy
4372	Systolic hypertension
4668	Hypertensive renal disease
6702	Hypertensive retinopathy
7057	Hypertensive disease NOS
7329	Secondary hypertension
8732	BP - hypertensive disease
8857	Cardiomegaly - hypertensive
10818	Essential hypertension NOS
15106	Hypertensive renal disease NOS
15377	Malignant essential hypertension
16059	Secondary hypertension NOS
16173	Hypertensive heart disease NOS
16292	Hypertensive heart disease
18057	Antihypertensive therapy
18765	Other specified hypertensive disease
21826	Hypertension treatm. started
21837	Hypertensive heart&renal dis wth (congestive) heart failure
25371	Secondary benign renovascular hypertension
28684	Hypertensive heart and renal disease with renal failure
29310	Renal hypertension
31341	Hypertension secondary to drug
31387	Secondary renovascular hypertension NOS
31464	Hypertensive heart disease NOS
31755	Secondary malignant hypertension
31816	Hypertensive crisis
32423	Hypertensive renal disease with renal failure
34744	Hypertension secondary to endocrine disorders
37086	Blind hypertensive eye
39649	Malignant hypertensive renal disease
42229	Secondary hypertension NOS
43935	Benign hypertensive renal disease
50157	Malignant hypertensive heart disease
51635	Secondary benign hypertension NOS
52127	Benign hypertensive heart disease with CCF
52427	Benign hypertensive heart disease

Medcode	Description
57288	Secondary benign hypertension
57987	Hyperten heart&renal dis+both(congestv)heart and renal fail
61166	Hypertensive heart disease NOS without CCF
61660	Benign hypertensive heart disease without CCF
62718	Hypertensive heart disease NOS with CCF
63000	Benign hypertensive heart and renal disease
63466	Hypertensive heart and renal disease
67232	Malignant hypertensive heart and renal disease
68659	Hypertensive heart and renal disease NOS
69753	[X]Hypertensive diseases
72668	Malignant hypertensive heart disease with CCF
73293	Secondary malignant hypertension NOS
83473	Diastolic hypertension
95334	Malignant hypertensive heart disease without CCF
97533	[X]Hypertension secondary to other renal disorders

6.3.3 Study design

The study design was a landmark cohort design, which incorporates capture of time-updated information for continuous and categorical outcomes (Figure 6.1). Analyses were performed at every landmark with updated data on exposures, covariates and outcome. Cox regression, which can incorporate time-varying covariates, was not appropriate for this study as the outcomes were non-binary. Landmark time-points were set yearly up to 10 years after and up to 5 years before, the baseline date of hypertension diagnosis. The landmark time-point was the time of outcome measurement. For each landmark time-point, a sub-cohort of the population was selected who had a valid record in the year preceding the landmark time-point. Data was extracted at baseline and up to one year before the landmark time-point for covariates and exposures. This study design was used for both primary and secondary analyses.

Figure 6.1: Study design schema



Schematic diagram showing landmark time approach for each cohort analysed. Time-updated covariates were number of prescribed antihypertensive classes and cumulative BP. Age was also time-updated at time T-12 months. Covariates that were static or did not have adequate time-varying data, were not updated with each landmark: sex, Index of Multiple Deprivation (IMD), gender, ethnicity, body mass index (BMI), cholesterol, smoking status and year of hypertension diagnosis; these covariates were measured from up to 12 months before time of hypertension diagnosis

6.3.4 Study outcomes

At the landmark time-point, outcomes were captured over a time window of 0 to 3 months after the landmark time-point, to ensure that a representative value was assessed for each patient in each landmark cohort.

Primary outcome: systolic blood pressure

The outcome for the primary analysis was SBP, measured in mmHg during routine GP consultations. SBP was analysed as a continuous variable to detect changes in SBP, as well as compare to existing literature using the binary classification of BP success of treatment [234, 235]. For BP, there were three possible scenarios using the landmark window capture method (described above): 1) one reading, 2) multiple readings, 3) no readings. If there was one value, this was taken as the representative BP outcome measure for that landmark time-point. For multiple BP readings, the mean reading was calculated. In case of no BP readings, nearest neighbour imputation was used with univariate time-series modelling, which assumed auto-correlation between non-equidistant time intervals. BP readings that fell outside a reasonable range ($50 \leq$ SBP≤ 300, $10 \leq$ DBP≤ 200) were assumed to be erroneous and were dropped.

Secondary outcome: antihypertensive classes

The secondary outcome was number of classes of antihypertensive medications (range 0 to 5). This was used as a proxy measure for treatment intensity. Other measures, such as dosage and frequency of doses, were not used due to high degree of missingness. Antihypertensive classes were defined using the CPRD product codes mapped to the British National Formulary (BNF) (Table 6.2), categorised into 5 classes. Drugs that were listed under an antihypertensive class with a clear indication unrelated to hypertension (e.g. Tamsulosin, sildenafil) were excluded.

Table 6.2: Antihypertensive prescription medications: BNF codes and drug classes

BNF code	Description	Class				
		A	**B**	**C**	**D**	**O**
2020100	Thiazides and related diuretics				✓	
2020200	Loop diuretics				✓	
2020300	Potassium sparing diuretics & aldosterone antagonists				✓	
2020400	Potassium sparing diuretics & compounds				✓	
2020800	Diuretics with potassium				✓	
2040000	Beta-adrenoceptor blocking drugs		✓			
2040100	Beta-adrenoceptor blocking drugs with diuretic		✓		✓	
2050000	Hypertension and heart failure		✓			
2050100	Vasodilator antihypertensive drugs					✓
2050200	Centrally-acting antihypertensive drugs					✓
2050300	Adrenergic neurone blocking drugs					✓
2050400	Alpha-adrenoceptor blocking drugs					✓
2050500	Renin-angiotensin system drugs					
2050501	Angiotensin-converting enzyme inhibitors	✓				
2050502	Angiotensin-ii receptor antagonists	✓				
2050503	Renin inhibitors					
2050504	Angiotensin-ii receptor antagonists with diuretic	✓			✓	
2050800	Other adrenergic neurone blocking drugs					✓
2060200	Calcium-channel blockers			✓		
2050500*	Renin-angiotensin system drugs					

Classes were defined as: A) Angiontensin-converting enzyme inihibitors and angiotensin II receptor blockers, B) beta-blockers, C) calcium-channel blockers, D) diuretics, O) other (including alpha-blockers, vasodilators, centrally-acting antihypertensives); *Not all drugs under this code were in one class, so each drug in this BNF code was individually categorised into each of the five classes.

6.3.5 Study exposures and covariates

The main exposure was comorbidity status, classified in two ways: 1) number of comorbidities (hypertension alone as the reference group), 2) specific type of comorbidity or comorbidity group (no comorbidity or group as the reference group). Comorbidity status was defined using 22 conditions that have been shown to be highly prevalent and clinically significant, based on three representative and reputable sources: 1) the Quality and Outcomes Framework (QOF), a pay-for-

performance incentive scheme for general practitioners in the UK, [172] 2) the Charlson comorbidity index, a classification system to help predict inpatient hospital mortality, [119] 3) the multiple chronic conditions list for the US Department of Health and Human Services Initiative [199] (more details on how conditions selected in chapter 3. Each of the 22 conditions were identified using a list of diagnostic codes from ICD-10 (hospital) and Read codes (primary care), compiled from online code repositories, previous work completed at The George Institute for Global Health, and medical dictionary keyword searches. Refer to subsection 4.2.4 for further details. Diagnosis of a prevalent comorbidity was defined as the recording of a diagnostic code for that comorbidity if it was diagnosed before the date of diagnosis of hypertension. The look-back period to capture prevalent comorbidity diagnoses included all CPRD data, extending back to the inception of CPRD on 1stJan 1985.

For each landmark analysis, comorbidity status was time-updated using all recorded diagnoses from CPRD inception up until 6 months before the landmark time-point. This time-gap before landmark outcome measurement was used to prevent reverse causality. Specifically, the time-updated variables were: number of classes of prescribed antihypertensive (for the primary analysis), cumulative BP in the prior year (calculated as detailed in section A.3 for the secondary analysis), age (measured at landmark time-point) and comorbidity status. The remaining covariates were measured at baseline and not time-updated with each landmark. The capture period for baseline measurements was from 2 years before to baseline time-point. (Figure 6.1)

6.3.6 Statistical analyses

All models were adjusted for age, sex, socioeconomic status (SES) (based on fifths of the Index of Multiple Deprivation [IMD]), ethnicity, smoking status and body mass index (BMI, stratified into 'underweight' (<18.5 kg/m2), 'normal' (18.5–24.9 kg/m2), 'overweight' (25–29.9 kg/m2), and 'obese' (≥30 kg/m2)) and year of diagnosis of hypertension (to account for cohort effects). Age, comorbidities, number of prescribed antihypertensive classes and BP were time-updated for each

landmark cohort (Figure 6.1). Missing covariates for smoking, cholesterol and BMI were imputed using multiple imputation by expectation-maximisation with bootstrapping with five imputations datasets [239]. For each model, tests for collinearity, model fit and interactions with age and sex were performed.

Primary analyses

In primary analyses with BP as the outcome, linear regression was used to model differences in mean SBP by comorbidity status, and the calculated values were used to derive mean SBP using classical maximum likelihood models with asymptotic normal approximation to the log-likelihood and one thousand simulations [240]. Time-updated number of prescribed antihypertensives was included as a covariate in the models to assess the associations between comorbidity status and BP independent of differences in antihypertensive use.

Secondary analyses

In the secondary analysis with number of antihypertensive drugs as the outcome, the associations were assessed using Poisson regression. Time-updated BP was included as a covariate in the models to assess differences independent of BP differences. This BP was calculated as a mean for each participant at each landmark (-18 to -6 months before landmark timepoint) and then used the standardised area under the BP curve for the year as a covariate in the Poisson regression analyses (refer to section A.3 for further details)[241].

6.3.7 Sensitivity and additional analyses

In sensitivity analyses, the association of comorbidity status with SBP was examined by 1) removing adjustment for antihypertensive medications to assess the contribution of BP treatment on the observed BP differences, 2) additionally adjusting models for health exposure, using as a proxy, the number of BP readings in the time interval from 5 years before to time of diagnosis of hypertension, 3) adopting alternative methods for handling missing information about BP by using

a complete case analysis and last observation carried forward imputation. DBP was also assessed as an outcome.

Analysis was performed using a pre-determined analysis plan (section A.6). All analyses were performed using R version 3.3.2 [208]. Reporting of the study for publication was done in accordance with the REporting of studies Conduction using Observational Routinely collected Data (RECORD) guidelines [209, 191, 210].

6.4 Results

6.4.1 Baseline characteristics of participants

Between 1st January 2000 and 31st December 2014, there were 295,487 patients (51% women) with incident hypertension and mean age of 61.6 (SD 13.1) years. In this patient cohort, 63.9% had at least one other comorbidity. The baseline characteristics of incident hypertensive patients stratified by number of comorbidities is shown in Table 6.3.

Table 6.3: Baseline characteristics of incident hypertensive patients

Characteristic	All patients	Number of comorbidities					
		0	1	2	3	4	≥5
	(n=295,487)	(n=106,801)	(n=86,691)	(n=52,432)	(n=27,185)	(n=12,824)	(n=9,554)
Age [years], mean (SD)	61.5 (13.1)	58.9 (12.7)	61.3 (13.0)	63.0 (13.0)	64.9 (12.8)	66.5 (12.6)	69.7 (12.0)
<65, % (n)	60.7 (179,239)	69.8 (74,502)	61.4 (53,229)	55.8 (29,240)	49 (13,334)	44.2 (5,667)	34.2 (3,267)
≥65, % (n)	39.3 (116,248)	30.2 (32,299)	38.6 (33,462)	44.2 (23,192)	51.0 (13,851)	55.8 (7,157)	65.8 (6,287)
Women, % (n)	50.7 (149,787)	43.5 (46,415)	50.5 (43,807)	56.2 (29,480)	59.7 (16,228)	61.9 (7,935)	62.0 (5,922)
White ethnicity, % (n)	96.1 (116,574) [174,197]	95.8 (36,963) [68,198]	96.1 (34,115) [51,200]	96.4 (22,600) [28,998]	96.2 (12,192) [14,517]	96.6 (6,005) [6,609]	96.3 (4,699) [4,675]
Fifths of deprivation index, % (n)							
Q1 (least deprived)	23.3 (68,902)	25.6 (27,347)	23.8 (20,607)	21.8 (11,441)	20.7 (5,615)	18.1 (2,319)	16.5 (1,573)
Q2	22.6 (66,699)	23.6 (25,214)	22.8 (19,745)	21.9 (11,457)	21.4 (5,807)	20.4 (2,622)	19.4 (1,854)
Q3	21.0 (62,142)	20.8 (22,245)	21.3 (18,430)	21.3 (11,143)	20.8 (5,664)	20.8 (2,661)	20.9 (1,999)
Q4	18.2 (53,722)	17.4 (18,558)	17.9 (15,551)	18.8 (9,853)	19.2 (5,222)	20.2 (2,589)	20.4 (1,949)

Characteristic	All patients	Number of comorbidities					
		0	1	2	3	4	≥5
Q5 (most deprived)	14.8 (43,718)	12.5 (13,323)	14.1 (12,259)	16.2 (8,490)	17.8 (4,852)	20.5 (2,623)	22.7 (2,171)
Mean SBP (SD), mmHg	159.1 (21.1)	161.0 (21.4)	159.2 (20.8)	158.2 (20.6)	156.6 (20.8)	155.7 (21.0)	152.9 (21.4)
Mean DBP (SD), mmHg	91.0 (12.5)	93.4 (12.2)	91.3 (12.1)	89.8 (12.1)	88.0 (12.3)	86.6 (12.6)	83.4 (12.8)
Body mass index kg/m², % (n)							
Underweight	0.9 (1,552)	0.8 (412)	0.8 (415)	0.9 (285)	1.1 (207)	1.2 (112)	1.6 (121)
Normal	22.0 (37,849)	23.5 (12,843)	21.8 (10,811)	21.3 (6,987)	20.5 (3,772)	20.3 (1,879)	20.7 (1,557)
Overweight	38.6 (66,484)	41.8 (22,872)	39.1 (19,362)	37.0 (12,156)	35.2 (6,475)	33.4 (3,094)	33.6 (2,525)
Obese	38.5 (66,403) [123,199]	34.0 (18,621) [52,053]	38.3 (18,971) [37,132]	40.8 (13,384) [19,620]	43.2 (7,957) [8,774]	45.0 (4,166) [3,573]	44.0 (3,304) [2,047]
Smoking status, % (n)							
Current	20.1 (44,376)	20.8 (15,826)	19.7 (12,589)	20.2 (8,134)	19.2 (4,153)	20.0 (2,119)	18.8 (1,555)
Never	47.7 (105,304)	50.8 (38,608)	48.9 (31,208)	46.0 (18,511)	44.2 (9,555)	40.2 (4,261)	38.1 (3,161)
Ex-smoker	32.1 (70,871) [74,936]	28.4 (21,552) [30,815]	31.4 (20,015) [22,879]	33.8 (13,583) [12,204]	36.6 (7,919) [5,558]	39.9 (4,232) [2,212]	43.1 (3,570) [1,268]

Characteristic	All patients	Number of comorbidities					
		0	1	2	3	4	≥5
Mean total cholesterol (SD), mmol/L	5.5 (1.2)	5.7 (1.1)	5.6 (1.1)	5.5 (1.2)	5.3 (1.2)	5.1 (1.2)	4.9 (1.2)
	[104,581]	[44,923]	[31,425]	[16,844]	[7,104]	[2,864]	[1,421]
Year of hypertension diagnosis, % (n)							
2000	5.0 (14,822)	5.8 (6,195)	5.2 (4,477)	4.5 (2,383)	3.8 (1,038)	3.8 (490)	2.5 (239)
2014	3.4 (10,129)	2.8 (2,985)	3.2 (2,786)	3.7 (1,951)	4.4 (1,185)	4.8 (613)	6.4 (609)
Number of antihypertensive classes prescribed, % (n)							
1	13.9 (41,137)	9.0 (9,641)	13.3 (11,508)	17.0 (8,900)	20.3 (5,522)	23.5 (3,011)	26.7 (2,555)
2	6.5 (19,267)	4.0 (4,238)	5.3 (4,636)	7.4 (3,875)	10.4 (2,819)	13.7 (1,751)	20.4 (1,948)
≥3	2.7 (8,058)	1.4 (1,461)	1.9 (1,611)	3.0 (1,560)	4.7 (1,283)	6.8 (871)	13.3 (1,272)

The category percentages refers to complete cases. Numbers in square brackets refer to the number of patients with missing data for the relevant characteristic. Fifths of deprivation index refers to the Index of Multiple Deprivation 2015 cut by quintiles, where Q1 is the least deprived fifth and Q5 is the most deprived fifth of the population. BMI categories are 'underweight' (<18.5 kg/m^2), 'normal' (18.5–24.9 kg/m^2), 'overweight' (25–29.9 kg/m^2), and 'obese' (≥30 kg/m^2). DBP=diastolic blood pressure; SBP=systolic blood pressure.

Patients with 5 or more comorbidities, compared to those with hypertension alone, were more likely to be female, ex-smokers and in the most deprived fifth of the population. In these cross-sectional analyses, patients with more comorbidities had lower mean SBP, and were prescribed more classes of antihypertensives compared to patients with hypertension alone. The number of comorbidities increased over time after diagnosis (Table 6.4). The proportion of patients with five or more comorbidities increased from 3.2% in the year of hypertension diagnosis to 18.6% 10 years later.

Table 6.4: Characteristics of landmark cohorts over time

Characteristic	Time after diagnosis of hypertension (years)					
	-5 (n=145,964)	-1 (n=273,493)	0 (n=295,487)	1 (n=260,823)	5 (n=158,573)	10 (n=52,393)
Age [years], mean (SD)	56.6 (12.7)	60.5 (13.1)	61.5 (13.1)	62.6 (12.9)	66.2 (12.4)	70 (11.5)
<65, % (n)	74.4 (108,551)	63.7 (174,146)	60.7 (179,239)	57.8 (150,784)	47.6 (75,421)	35.2 (18,424)
≥65, % (n)	25.6 (37,413)	36.3 (99,347)	39.3 (116,248)	42.2 (110,039)	52.4 (83,152)	64.8 (33,969)
Women, % (n)	49.0 (71,482)	50.3 (137,700)	50.7 (149,787)	51.0 (133,098)	51.9 (82,375)	53.9 (28,247)
Number of comorbidities						
0	47.9 (69,856)	39.3 (107,551)	36.1 (106,801)	27.6 (72,090)	17.6 (27,979)	10.7 (5,594)
1	29.3 (42,719)	29.5 (80,549)	29.3 (86,691)	29.7 (77,399)	25.2 (39,945)	19.3 (10,107)
2	14.0 (20,397)	16.8 (46,059)	17.7 (52,432)	20.6 (53,744)	22.1 (35,100)	21.1 (11,066)
3	5.7 (8,272)	8.2 (22,365)	9.2 (27,185)	11.6 (30,358)	15.5 (24,653)	17.6 (9,195)
4	2.1 (3,119)	3.7 (10,090)	4.3 (12,824)	5.9 (15,287)	9.4 (14,901)	12.7 (6,663)
≥5	1.1 (1,601)	2.5 (6,879)	3.2 (9,554)	4.6 (11,945)	10.1 (15,995)	18.6 (9,768)

6.4.2 Association between comorbidity status and blood pressure

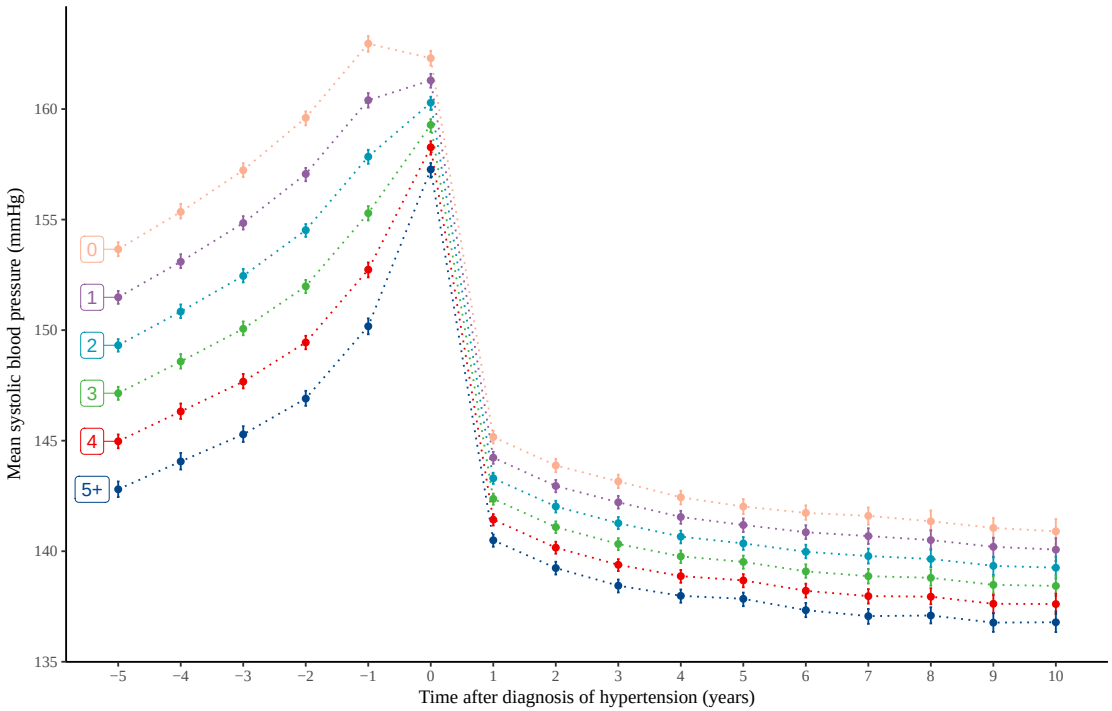
Figure 6.2 shows the adjusted mean SBP at -5 to 10 years after diagnosis of hypertension by number of comorbidities in longitudinal analyses. At time of diagnosis, patients with higher numbers of time-updated comorbidities had a lower adjusted mean SBP. Those with hypertension alone had an adjusted mean SBP of 162.3 mmHg (95% CI 162.0, 162.6) compared to 157.3 mmHg (95% CI 156.9, 157.6) in those with five or more comorbidities.

In each year after diagnosis of hypertension, patients with higher numbers of comorbidities had a lower SBP during follow-up. Mean SBP generally decreased with time after diagnosis of hypertension. For instance, those with hypertension alone had an adjusted mean SBP of 162.3 mmHg (95% CI 162.0, 162.6) at one year after diagnosis and 140.9 mmHg (95% CI 140.3, 141.5) at 10 years after diagnosis. In those with 5 or more comorbidities mean adjusted SBPs were 157.3 mmHg (95% CI 156.9, 157.6) and 136.8 mmHg (95% CI 136.3, 137.3), respectively.

Extended analyses to 5 years before the diagnosis of hypertension showed that the differences by comorbidity status in adjusted mean SBP were also present and even more pronounced in years preceding the diagnosis of hypertension than years after hypertension diagnosis Figure 6.2. For example, the difference in mean adjusted SBP between those with five or more comorbidities versus those with hypertension alone was 9.0 mmHg (95% CI 8.3, 9.7) at five years before diagnosis and the corresponding difference at 5 years after diagnosis was 4.4 mmHg (95% CI 4.1, 4.7).

Analysis by type of comorbidity showed that adjusted mean SBP was lower across all groups of comorbidities. However, the magnitude of difference varied by comorbidity group and individual comorbidities within each condition group (Figure 6.3). The largest difference in adjusted SBP was seen in patients with cardiometabolic comorbidities compared to those with no such comorbidities; at one year after diagnosis of hypertension, patients with any cardiometabolic condition had a 2.4 mmHg lower SBP (141.4 mmHg (95% CI 141.1; 141.7)) than those without

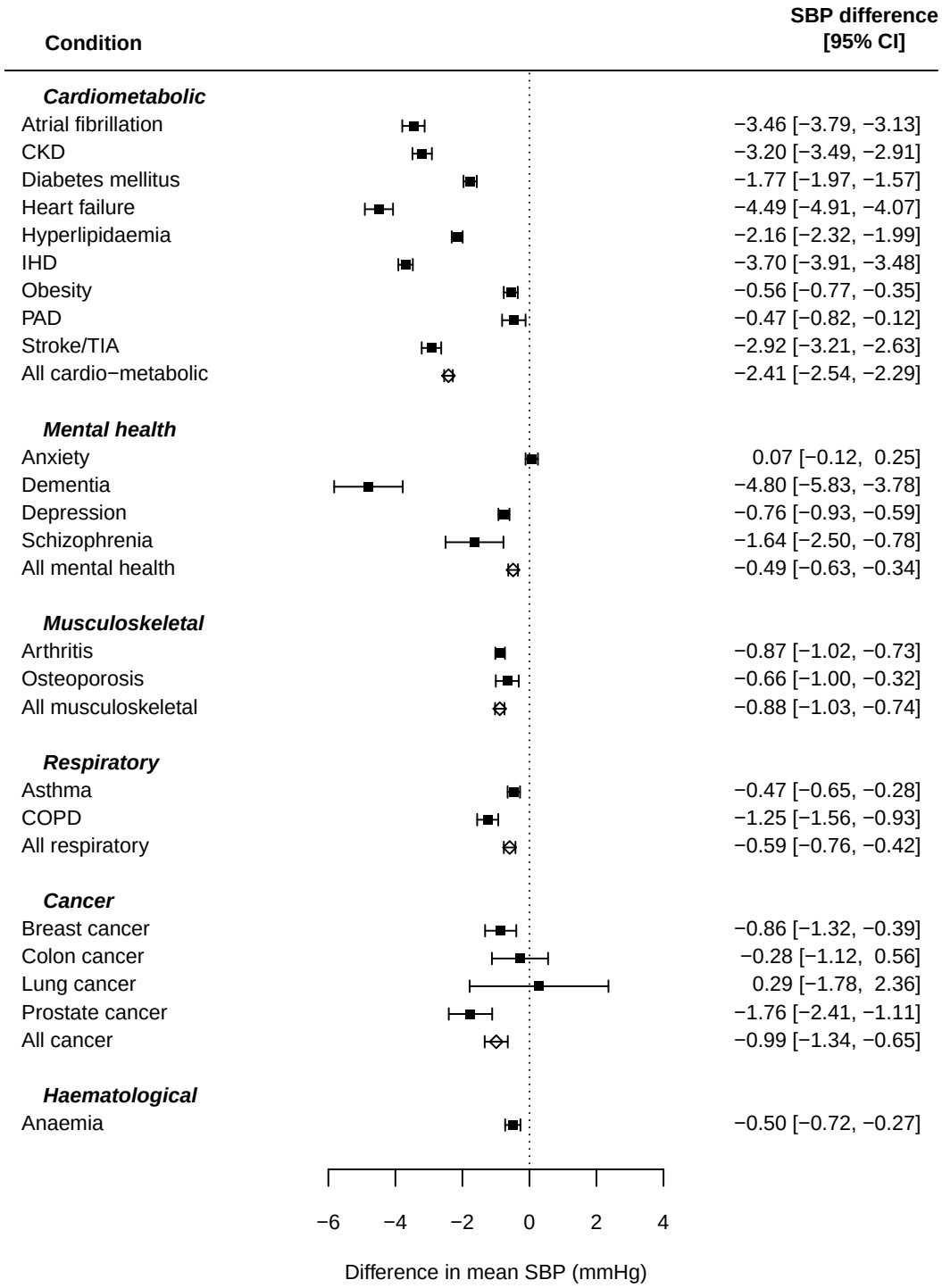
Figure 6.2: Adjusted mean systolic blood pressure over time stratified by number of comorbidities



Systolic blood pressure was calculated from linear regression models for each landmark cohort. All models were adjusted for age, sex, IMD, ethnicity, cholesterol, BMI, smoking status, number of classes of prescribed antihypertensive medications and year of diagnosis of hypertension.

any cardiometabolic conditions (143.8 (95% CI 143.6-144.1)) (Figure 6.3). Patterns were similar in years before hypertension diagnosis (Figure 6.4).

Figure 6.3: Adjusted mean systolic blood pressure by comorbidity type at 1 year after diagnosis



Difference in mean systolic blood pressure (SBP) was calculated using linear regression models on landmark cohorts for each timepoint. All models were adjusted for age, sex, IMD, ethnicity, cholesterol, BMI, smoking status, number of classes of prescribed antihypertensive medications and year of diagnosis of hypertension. Reference group for each point estimate was patients without that particular comorbidity; CKD=chronic kidney disease, IHD=ischaemic heart disease, PAD=peripheral arterial disease, TIA=transient ischaemic attack, COPD=chronic obstructive pulmonary disease

Figure 6.4: Adjusted mean systolic blood pressure by comorbidity type before hypertension diagnosis before and at hypertension diagnosis

(a) One year before hypertension diagnosis

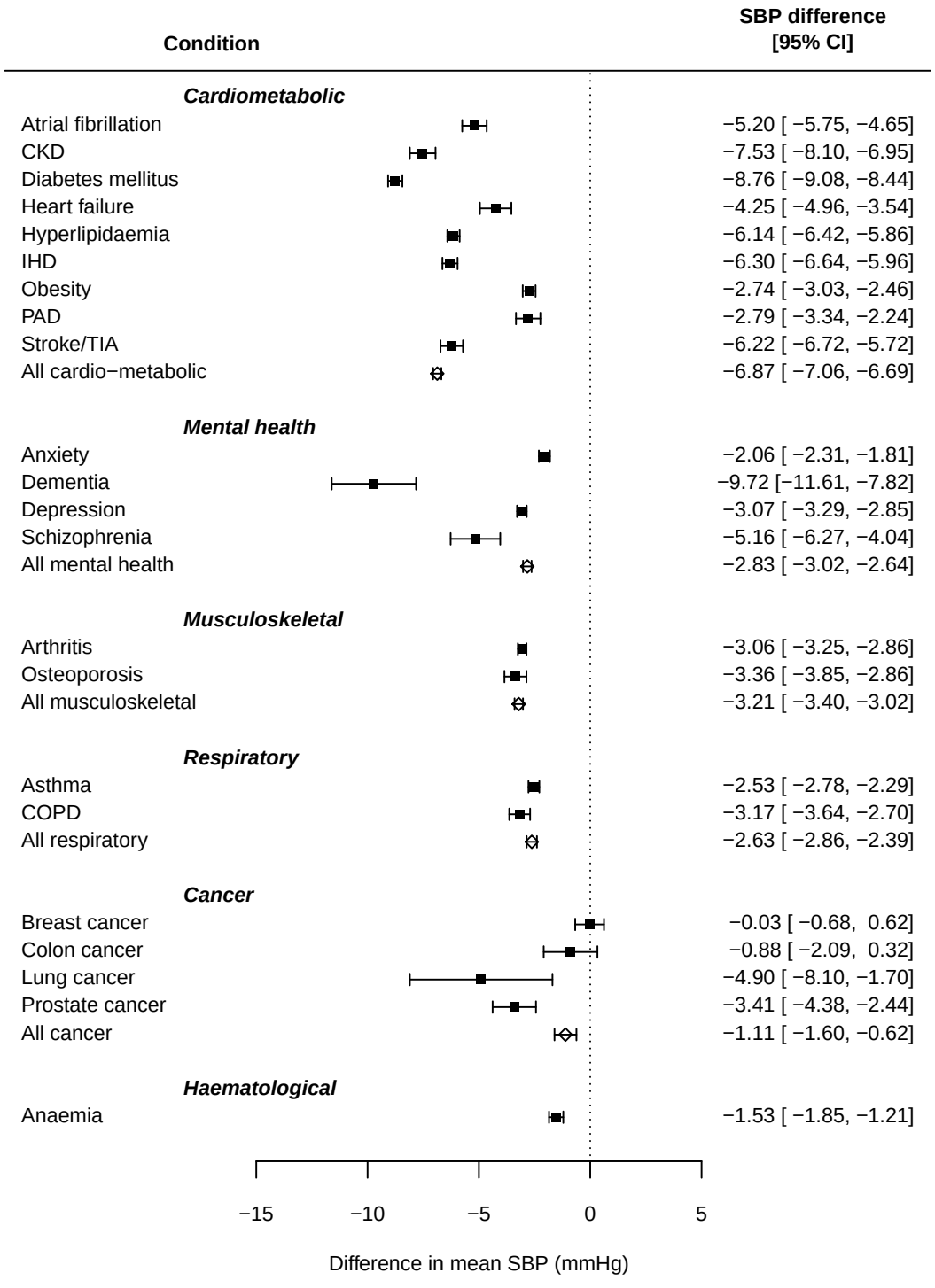
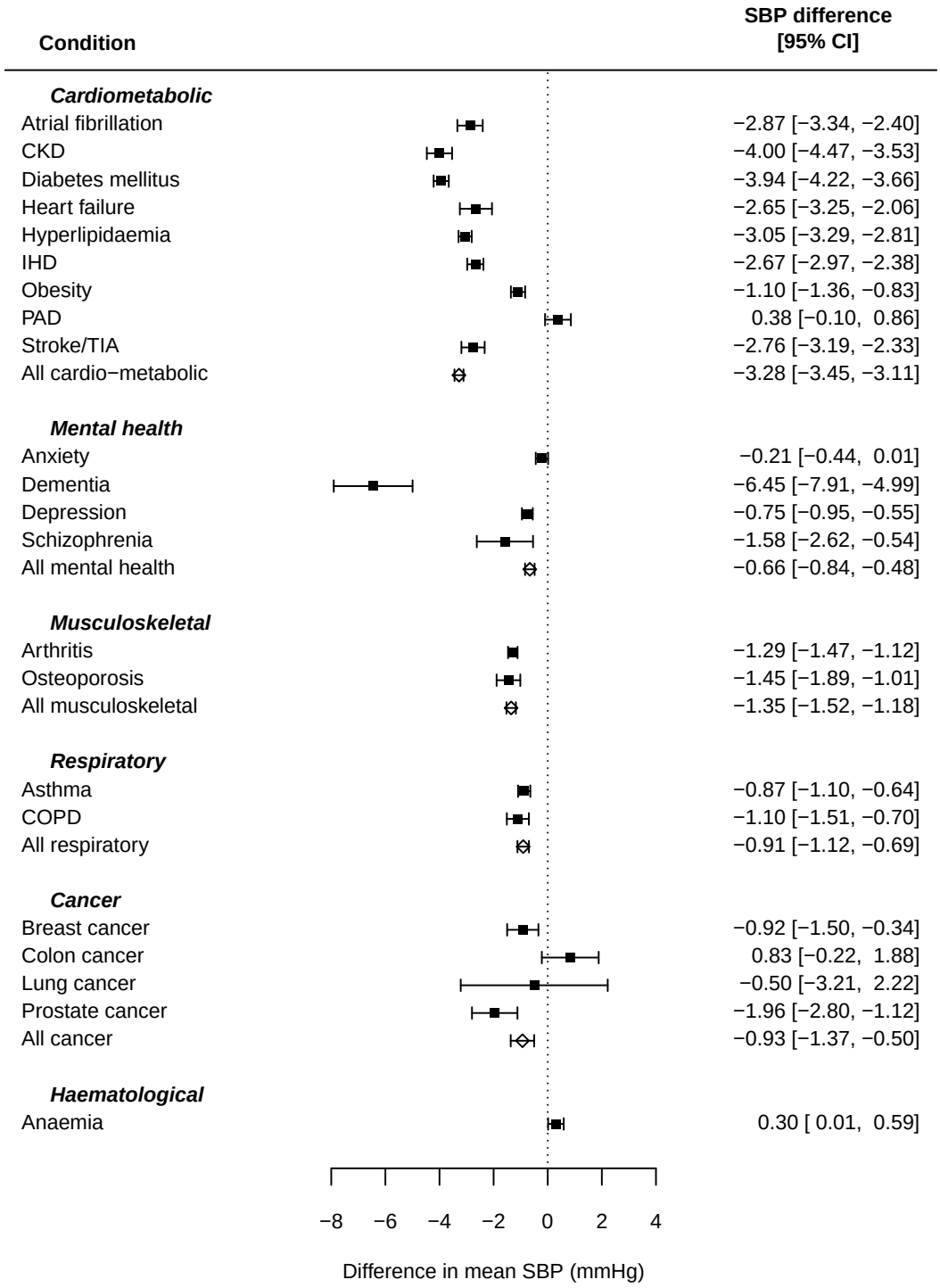


Figure 6.4: continued...

(b) At hypertension diagnosis

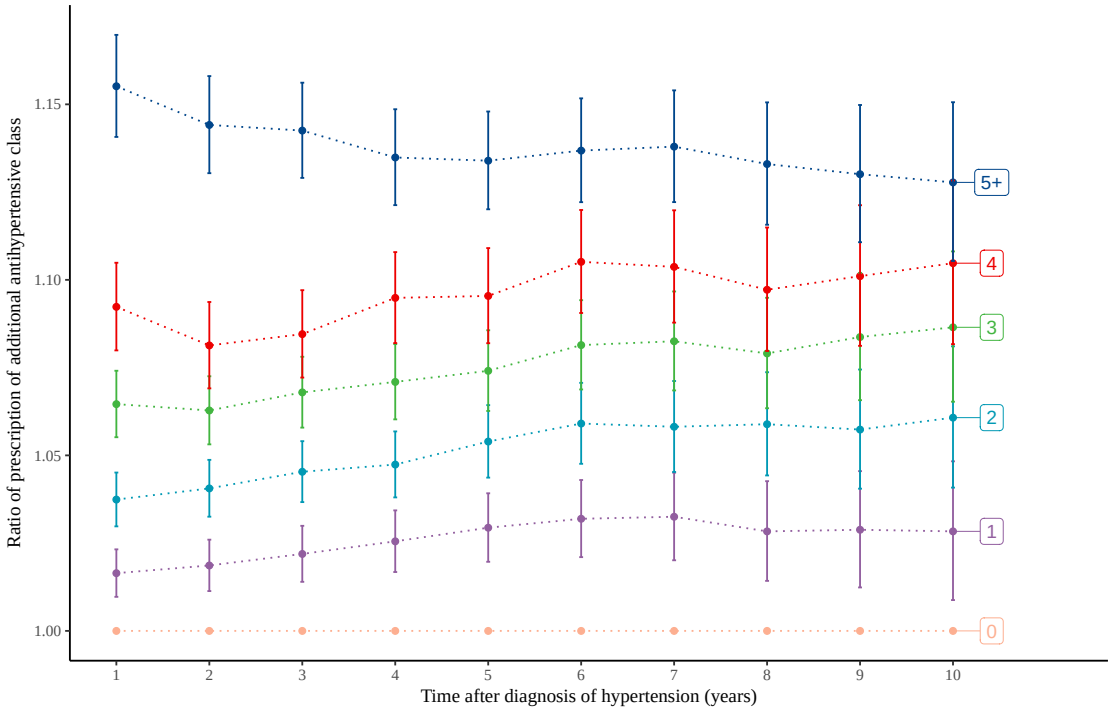


Difference in mean systolic blood pressure (SBP) difference was calculated as for Figure 6.3. Reference group for each point estimate was patients without that particular comorbidity CKD=chronic kidney disease, IHD=ischaemic heart disease, PAD=peripheral arterial disease, TIA=transient ischaemic attack, COPD=chronic obstructive pulmonary disease

6.4.3 Association between comorbidity status and prescription of antihypertensive

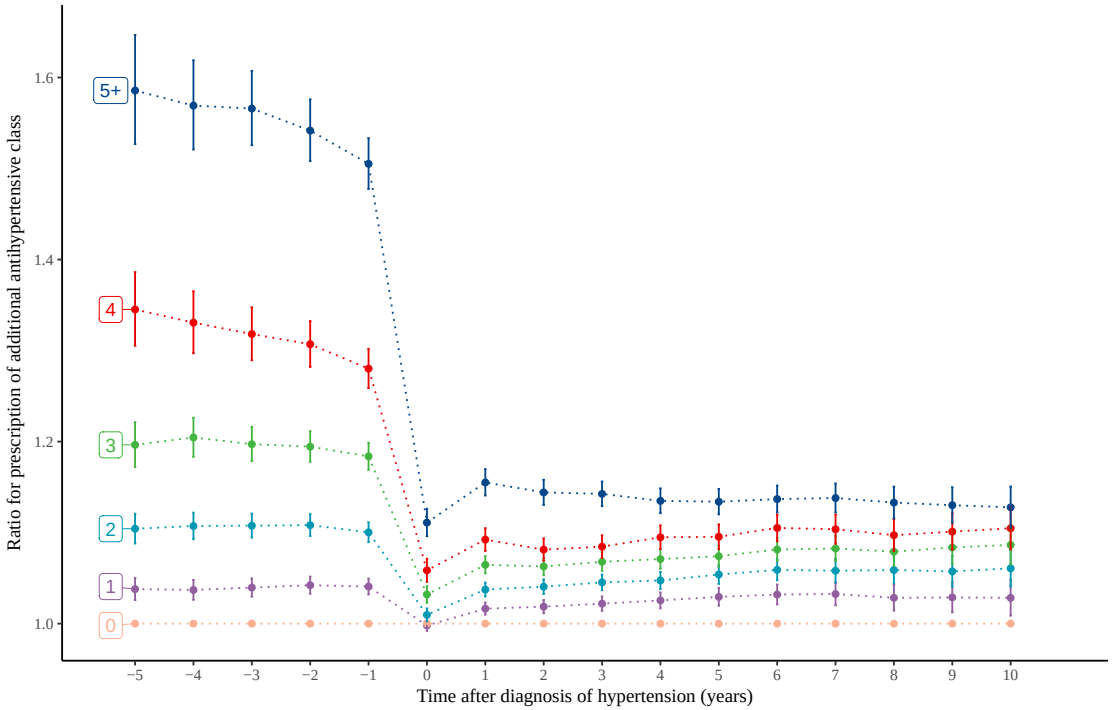
A positive relationship between the number of comorbidities and number of antihypertensive classes that patients were prescribed during follow-up was observed (Figure 6.5). For instance in the first year after diagnosis, patients with five or more comorbidities were 1.16 times (95% CI 1.14, 1.17) more likely than patients with hypertension alone to be prescribed an additional class of antihypertensive. Extension of analyses to 5 years before hypertension diagnosis showed that the higher rate of antihypertensive prescription among those with multiple comorbidities preceded the diagnosis of hypertension. Indeed, differences by number of comorbidities were larger in years prior to diagnosis than in years after diagnosis (Figure 6.6). Analysis stratified by types of comorbidity revealed that the observed differences both before and after diagnosis of hypertension were largely attributable to the group of cardiometabolic conditions (Figure 6.7, Figure 6.8b). By contrast, there was no material difference in number of prescribed classes of antihypertensives when patients with other condition groups were compared to those without such conditions (Figure 6.7).

Figure 6.5: Number of comorbidities and likelihood of prescription of an additional antihypertensive by years after hypertension diagnosis



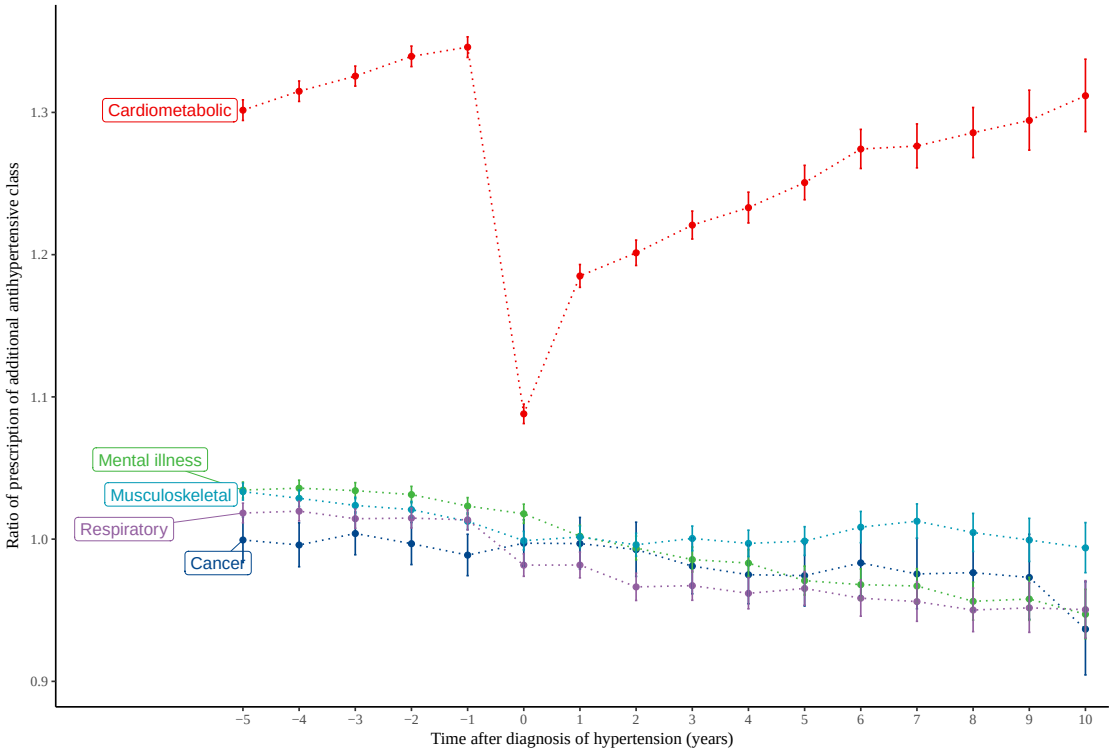
Likelihood per unit increase in prescription of antihypertensive class was calculated using Poisson regression models on a landmark dataset for each timepoint. All models were adjusted for age, sex, IMD, ethnicity, cholesterol, BMI, smoking status, cumulative blood pressure and year of diagnosis of hypertension. Reference group for each point estimate was patients with hypertension alone (i.e. 0 comorbidities).

Figure 6.6: Likelihood of prescription of an additional antihypertensive class stratified by number of comorbidities by years from diagnosis of hypertension



Likelihood per unit increase in prescription of antihypertensive class was calculated using Poisson regression models on a landmark dataset for each timepoint. All models were adjusted for age, sex, IMD, ethnicity, cholesterol, BMI, smoking status, cumulative blood pressure and year of diagnosis of hypertension. Reference group for each point estimate was patients with hypertension alone (i.e. 0 comorbidities). Negative time indicates time period before diagnosis of hypertension.

Figure 6.7: Likelihood of prescription of an additional antihypertensive class stratified by comorbidity condition group by years from diagnosis of hypertension



Likelihood per unit increase in prescription of antihypertensive class was calculated using Poisson regression models on a landmark dataset for each timepoint. All models were adjusted for age, sex, IMD, ethnicity, cholesterol, BMI, smoking status, cumulative blood pressure and year of diagnosis of hypertension. Reference group for each point estimate was patients without that particular comorbidity group e.g. at time of diagnosis (time=0), patients with cardiometabolic conditions were 1.09 times more likely to be prescribed an additional antihypertensive class, compared to those without any cardiometabolic conditions. Negative time indicates time period before diagnosis of hypertension.

Figure 6.8: Likelihood of prescription of an additional hypertensive class stratified by comorbidity at 1 year before, 1 year after and at time of hypertension diagnosis

(a) One year before hypertension diagnosis

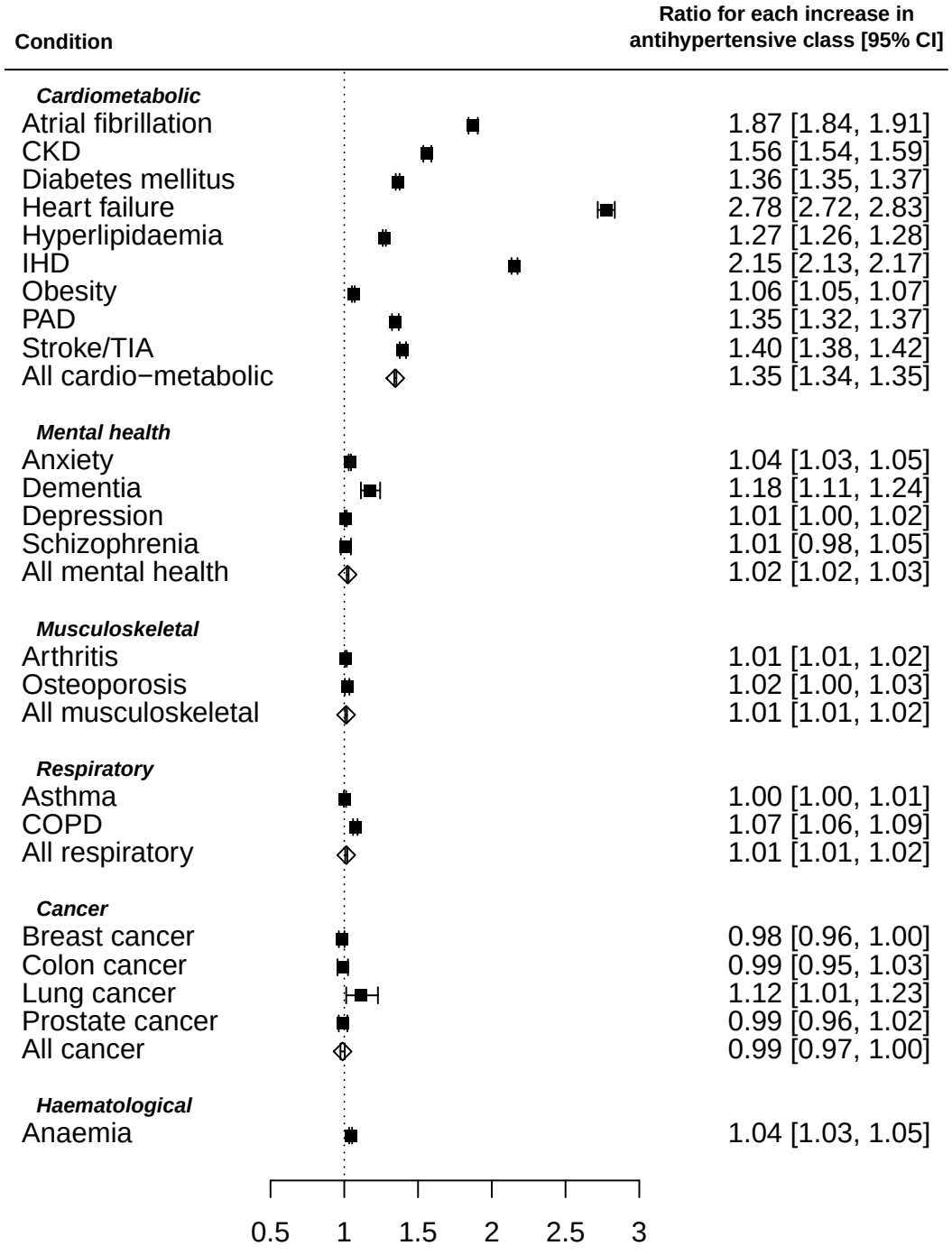


Figure 6.8: continued...

(b) At hypertension diagnosis

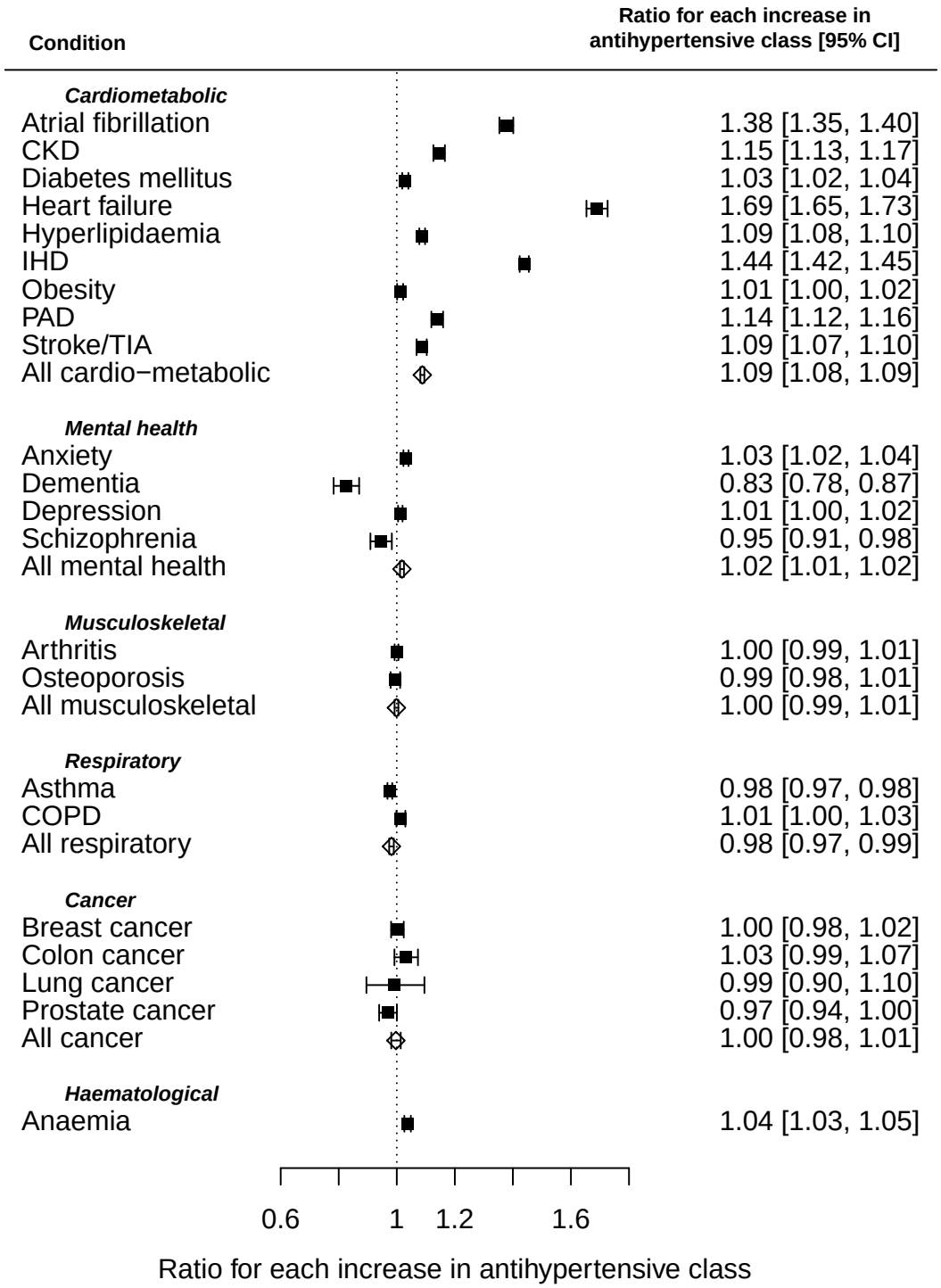
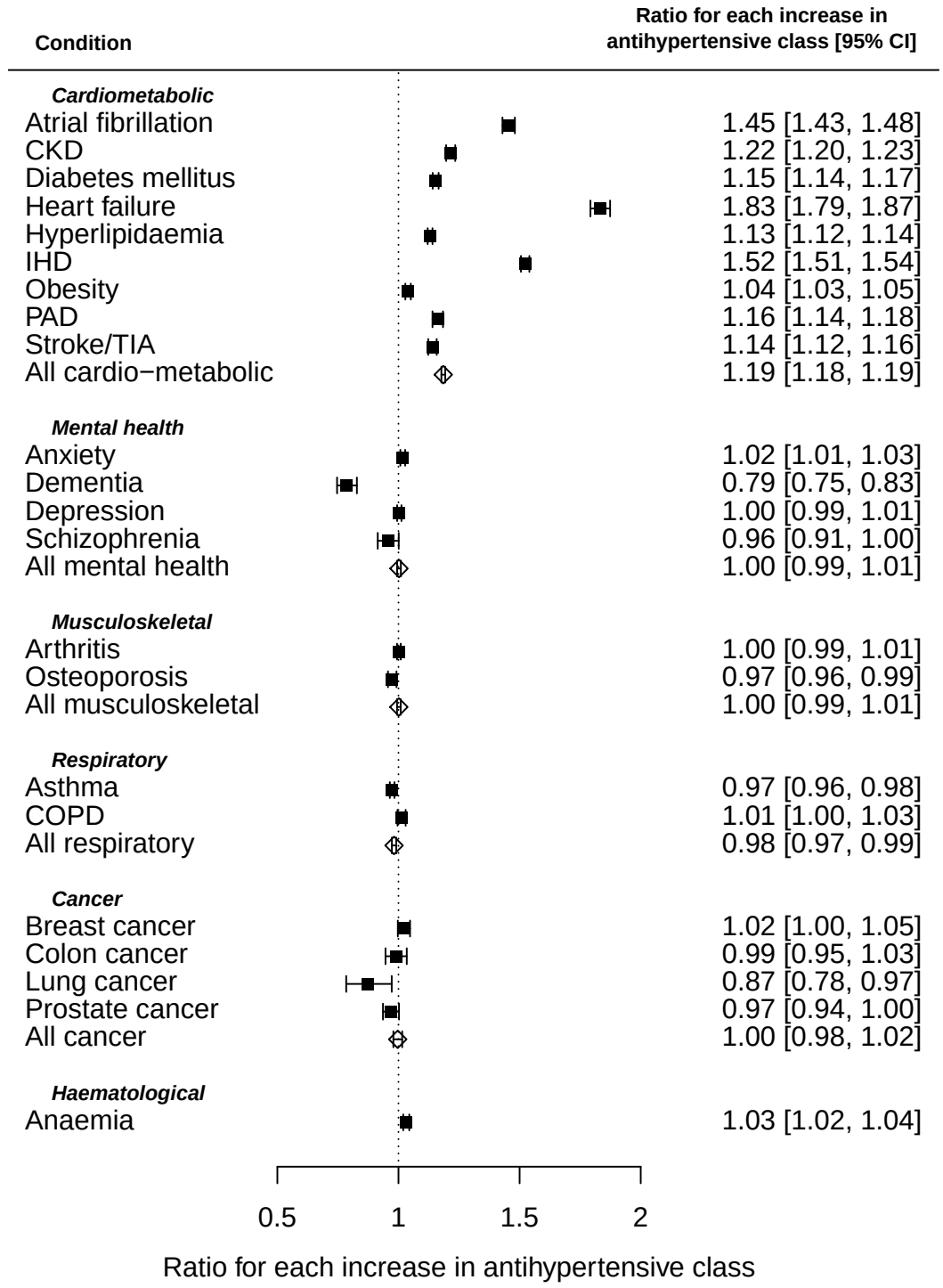


Figure 6.8: continued...

(c) One year after hypertension diagnosis



Likelihood per unit increase in prescription of antihypertensive class was calculated using Poisson regression models on a landmark dataset for each timepoint. All models were adjusted for age, sex, IMD, ethnicity, cholesterol, BMI, smoking status, cumulative blood pressure and year of diagnosis of hypertension. Reference group for each point estimate was patients without that particular comorbidity e.g. patients with atrial fibrillation are 1.16 times more likely to be prescribed an additional antihypertensive class compared to those without atrial fibrillation; CKD: chronic kidney disease, IHD: ischaemic heart disease, PAD: peripheral arterial disease, TIA: transient ischaemic attack, COPD: chronic obstructive pulmonary disease.

6.4.4 Effect of exposure to health services on the relationship between comorbidity status and blood pressure

To further explore the extent to which differences in BP by comorbidity status might be due to differences in frequency of interactions of patients with health services ('informed presence bias'), frequency of BP recording at 5 years before and 5 years after hypertension diagnosis was measured, shown in Table 6.5. Those with higher numbers of comorbidities had a substantially higher frequency of BP measurements before the diagnosis of hypertension, compared to those with lower numbers of comorbidities. On average, patients with 5 or more comorbidities had 13.7 (SD 9.0) previous BP readings in the 5 years before hypertension diagnosis vs 6.3 (SD 5.4) previous BP readings in those with hypertension alone and these differences attenuated over time. A comparison was also made between the mean number of classes of antihypertensive medication in the year before vs after diagnosis of hypertension (Table 6.5). Patients with higher numbers of comorbidities were prescribed more classes of antihypertensives compared to those with lower numbers of comorbidities both before and after diagnosis of hypertension. Similar to number of BP readings, these differences attenuated over time; as there was a ten fold difference in mean number number antihypertensive classes in patients with 0 vs 5 comorbidities before hypertension diagnosis, compared to a a 1.27 fold difference after diagnosis. The crude mean of number of antihypertensive classes one year after diagnosis of hypertension is similar for all comorbidity groups (range 1.5 to 2.0), whereas there was a significant difference between groups with adjustment (Figure 6.6).

However, additional adjustment of the models for these markers of health service use had minimal impact on the inverse association between number of comorbidities and SBP (Figure 6.9). At one year after diagnosis of hypertension, early diagnosis and treatment contributed to lower average SBP in those with 4 and 5 or more comorbidities – average SBP is 141.4 (141.2-131.7) and 140.5 (140.2-140.8) without adjustment, and 141.7 (141.5-142.0) and 141.0 (140.8-141.3) with adjustment respectively.

Table 6.5: Descriptive statistics of blood pressure management before and after diagnosis of hypertension

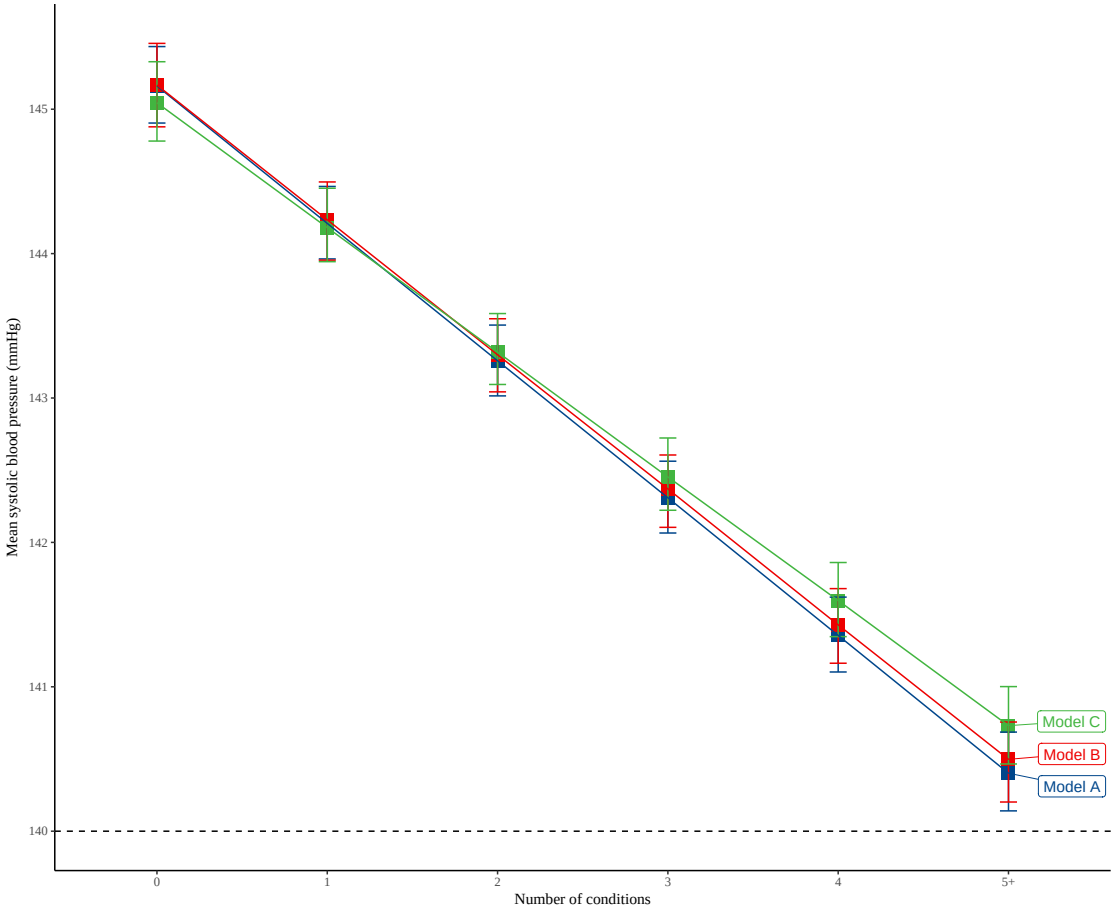
	Mean number of BP readings (SD)*		**Mean number of antihypertensive classes prescribed (SD)#**	
Number of comorbidities	Before diagnosis	After diagnosis	Before diagnosis	After diagnosis
Total	8.0 (6.6)	15.5 (10.0)	0.3 (0.7)	1.5 (0.9)
0	6.3 (5.4)	15.1 (9.7)	0.1 (0.5)	1.5 (0.9)
1	7.7 (6.1)	15.6 (10.0)	0.2 (0.6)	1.5 (0.8)
2	9.0 (6.8)	15.7 (10.2)	0.3 (0.7)	1.5 (0.9)
3	10.2 (7.4)	15.9 (10.6)	0.5 (0.8)	1.6 (0.9)
4	11.3 (7.9)	16.0 (11.0)	0.6 (0.9)	1.7 (0.9)
$\geq$ 5	13.7 (9.0)	16.0 (11.8)	1.0 (1.1)	1.9 (1.0)

*Capture period was 5 years from diagnosis of hypertension i.e. mean number of blood pressure readings were counted from 5 years before diagnosis to time of diagnosis, and from time of diagnosis to 5 years after diagnosis. #Capture period was 1 year from time of diagnosis of hypertension i.e. mean number of antihypertensive classes prescribed were counted from 1 year before diagnosis to time of diagnosis, and from time of diagnosis to 1 year after diagnosis. All differences between groups statistically significant ($p<0.01$) using ANOVA. BP=blood pressure, SD=standard deviation

6.4.5 Stratified results and sensitivity analyses

Stratified subgroup analyses demonstrated similar results between men and women, and age-groups. Sensitivity analyses demonstrated similar results using models with comorbidity status at baseline (not time-updated) and different methods of univariate time series imputation of BP as an outcome. Results for DBP were also similar to those demonstrated by SBP. Stratified results and sensitivity analyses are shown in section A.4.

Figure 6.9: Systolic blood pressure (SBP) vs number of conditions - comparing models adjusted and unadjusted for markers of exposure to health services



Model A=SBP ~comorbidity status + age + sex + IMD + ethnicity + smoking status + BMI + year of diagnosis of hypertension; Model B: Model A + adjustment for number of prescribed antihypertensive classes; Model C: Model B + additional adjustment for number of BP readings before hypertension diagnosis. All models are based on the landmark analysis at 12 months after diagnosis of hypertension

6.5 Discussion

6.5.1 Summary of main findings

In this large-scale representative population-based study of incident hypertensive patients, 64% of 295,487 patients had at least one comorbidity. The trajectory of BP, was driven by BP at diagnosis. At hypertension diagnosis, patients with higher numbers of comorbidities had lower SBP: those with five or more comorbidities had

mean adjusted SBP of 157.3mmHg (95% CI 156.9, 157.6), compared to 162.3mmHg (95% CI 162.0, 162.6) in those with no comorbidities. Mean SBP decreased with time after diagnosis across all patient groups, but patients with higher numbers of comorbidities consistently maintained lower SBP. The differences in SBP by number of comorbidities was even more pronounced in years preceding hypertension diagnosis. The association between higher number of comorbidities and lower SBP changed minimally when treatment intensity and prior health service exposure were accounted for. After adjustments, each comorbidity was associated with approximately 1 mmHg lower SBP during follow-up. Analysis by type of comorbidity showed that adjusted mean SBP was lower across all groups of comorbidities. The magnitude varied by comorbidity type, with the largest difference seen in patients with any cardiometabolic condition, who had a 2.4 mmHg (95% CI 2.3,2.5) lower SBP than those without cardiometabolic conditions. There was also a positive relationship between the number of comorbidities and number of antihypertensive classes prescribed during follow-up. Patients with five or more comorbidities were 1.16 times (95% CI 1.14, 1.17) more likely than patients with hypertension alone to be prescribed an additional class of antihypertensive 1 year after diagnosis, and this likelihood persisted over time.

Examining specific conditions, patients with comorbid cardiometabolic conditions were 7% more likely to be prescribed an additional antihypertensive and had a 4.5 mmHg lower systolic BP, which was expected as antihypertensive medications are indicated as guideline recommended treatment (e.g. beta-blockers for heart failure) or secondary prevention (e.g. ACE-inhibitors for ischaemic heart disease). Patients with comorbid dementia had a BP that was on average 4.8mmHg lower despite being 10% less likely to be prescribed an additional antihypertensive compared to patients with hypertension alone. There is some evidence suggesting that dementia lowers BP, but the underlying pathophysiolocal process is unknown [242]. However, overall, the observed differences in BP by comorbidity status were not due to differential treatment after diagnosis.

6.5.2 Comparison with previous literature

There are conflicting views in previous literature about whether or not multimorbid patients should receive guideline-indicated care, based on the perception that multimorbid patients are complex. In a UK cohort study of patients with AMI, patients with more conditions had a lower chance of receiving pharmacological therapies, but also increased risk of death and decreased life expectancy [243] suggesting that under-treatment in multimorbid patients leads to morbidity and mortality. On the other hand, the ACOVE study showed that multimorbid older patients received better quality care based on a range of medical and geriatric care indicators [244]. It is not clear whether hypertensive patients with multimorbidity are appropriately treated, and how this affects their long-term BP[22, 238]. This large-scale longitudinal study specifically examines hypertension treatment, and provides evidence that multimorbid patients receive more intensive BP treatment, which partly explains the lower long-term BP.

This study takes these earlier findings further by showing no evidence of poorer BP management in patients with comorbidity over time. To the contrary, BP levels were lower and remained lower in patients with more comorbidities for years after diagnosis; a finding that was not confined to particular groups of comorbidities. These observed differences in BP cannot be simply attributed to more intensive treatment or biological disease interactions leading to a BP decline – as often assumed in cross-sectional studies. Rather, differences are partly related to provider behaviour that tend to diagnose patients at a BP level that is nearer the recommended threshold for hypertension definition when comorbidities are present. Thus, research that compares BP "control" rates within and between populations [228, 22] might come to misleading conclusions if BP differences at incident diagnosis are not considered as even small differences in diagnostic thresholds could have substantial and long-term effects on BP differences between and within populations.

This study also takes previous studies further by following patients back in time, to show that differences in BP were even more pronounced in years before hypertension diagnosis. Patients with more comorbidities were more likely to

be prescribed antihypertensives before hypertension diagnosis, mainly driven by cardiometabolic comorbidities such as heart failure, where medication with blood-pressure lowering properties is indicated by guidelines [245]. However, differences in prescription of antihypertensives had little effect on BP differences between groups, suggesting that the observed differences in BP were mostly determined by the initial BP level at diagnosis.

6.5.3 Strengths and limitations

This study using EHR has several strengths which make it a valuable addition to the current literature. A large representative sample of the UK population was used, and with longitudinal records, it has been possible to examine patterns over time and time-update variables using landmark datasets. Also, incident cases of hypertension were selected and separate capture periods for exposure and outcome were used to control for reverse causality. Another strength of the CPRD is the completeness of the prescription data, as the large majority prescriptions must go through the CPRD [9].

A limitation of using the CPRD is the dependence on recorded diagnoses, hence risking under-estimation of diagnoses due to a lack of inclusion of undiagnosed cases. However, there has been much investigation into the validity of diagnoses recorded by general practitioners in CPRD for a range of comorbidities, and the average positive predictive value is 89% with 92% completeness when compared to national registries [124]. In addition, from a policy perspective, diagnoses recorded in health records are likely to be of higher relevance than routine population screening because the former remains the basis for service planning and payment. Another limitation of this study is the missingness in BP measurements, which means this study's conclusions represent patients who are actively being monitored for their hypertension in primary care. Reliance on measured BP could also be subject to "digit preference" to fit in with incentives to improve hypertension control rates [246].

The QOF, introduced in 2004, impacts on recorded diagnoses and management of long-term conditions in routinely-collected electronic health records (EHR). This

study has accounted for cohort effects, such as the QOF, by adjusting for year of diagnosis of hypertension. Hypertension, as well as the majority of conditions included in this study are included in QOF. As seen in chapter 5, recorded diagnoses of hypertension increased after QOF introduction until 2007, suggesting accumulation of historical diagnoses being recorded. Overall, QOF most likely improves recorded diagnoses of conditions in this study. The effect on management is more unclear. The QOF indicators for hypertension and blood pressure encourages GPs to record BP, and improve recording in the hypertension register, but does not specifically target management of blood pressure. Indicators that encourage management of BP to a target threshold, or prescription of antihypertensives, are included under coronary heart disease and secondary prevention of CVD. This could partly explain the lower BP in multimorbid patients and more research is required investigate this further. Other limitations related to using recorded diagnoses, have been discussed in subsection 5.5.3.

A further discussion of the strengths and limitations of the CPRD can be found in section 8.3.

This study showed that antihypertensive prescription only partly explained the differences in BP by comorbidity group. This difference may be explained by differences in specific antihypertensive classed or dosages, which were not included in the scope of this study. Further studies examining with more detailed data and analysis of antihypertensives is needed to investigate the contribution of treatment to lower BP in multimorbid patients.

The reasons for the lower BP at diagnosis in patients with comorbidities could not be explained by this study. Patients with more comorbidities were more likely to have their BP monitored, but this only had a small effect on the observed associations. Thus, it is possible that more complex clinical decision-making processes than the frequency of BP measurement determine when to diagnose hypertension [247]. For instance, it is plausible that the perceived risk of future cardiovascular events or mortality [45] or the potential to benefit from antihypertensive treatment [221] could impact physician and patient preferences for diagnosis and management. Irrespective

of the underlying causes, the finding of differential thresholds at which hypertension was diagnosed and its impact on long-term BP trajectories has implications for future research and practice.

6.5.4 Clinical implications

Current guidelines around hypertension management are not designed for multimorbid patients, despite the fact that up to two thirds of hypertensive patients have a comorbidity. Guidelines are clear about drug therapy for specific comorbidities, such as chronic kidney disease, but there remains uncertainty about which agents to choose for multimorbid patients [70]. Furthermore, it has been reported that for patients with comorbidity, clinicians do not adhere to guidelines in initiating therapy, and their prescription pattern of antihypertensives changes over time [248]. This study shows that BP treatment and control, is better in patients with comorbidity, but is far from ideal. Part of the reason for the long-term lower BP associated with multimorbidity or comorbidity is more frequent monitoring of BP and earlier diagnosis and treatment. Hypertension treatment should be integrated into a chronic disease treatment model that prioritises early diagnosis and treatment.

This study demonstrated that the long-term trajectory of BP in hypertensive patients was driven largely by initial BP at diagnosis, whereby initial lower BP determined future lower BP. The diagnostic threshold for hypertension is a contentious issue, mainly due to the evidence of a log-linear relationship between blood pressure and risk of morbidity and mortality [249]. Hence, international and national guidelines vary in their advice about diagnostic and target treatment threshold for BP in hypertensive management [249]. Evidence is emerging that reduction of BP, regardless of diagnostic BP, is worthwhile, at least for stroke patients [249, 250]. However, the evidence for "lower is better" is not consistent: the SPRINT trial showed that a lower threshold below 130mmHg was beneficial [77], and this was also supported by the SPS3 trial in stroke patients [250], but on the other hand, the HOPE-3 trial demonstrated that the threshold of 140mmHg was sufficient for primary prevention of cardiovascular events [251]. Despite controversy about

the exact diagnostic threshold, it is clear from this analysis that a lower diagnostic threshold for hypertension would lead to lower BPs for all patient subgroups and whether this translates into reduced risk has not yet been established.

Another insight from this study is that beyond the first year after hypertension diagnosis, the decline in SBP was modest in all comorbidity groups. This long period of relative BP stability, in particular in patients with fewer comorbidities who maintain a high BP over years, suggests an opportunity to help reduce long-term BP by changing current routine care to more regular follow-up and re-assessment of treatment options in those with recorded hypertension diagnosis.

6.5.5 Future research

This study demonstrates novel findings in the UK primary care population and more studies are required to validate the findings in other populations. A potential starting point would be another longitudinal UK population, such as the UK Biobank. It is likely that these findings are generalisable to other high-income countries with government-funded access to prescriptions, but the situation may be different in countries such as the United States (US), where not everyone may have the financial means or access to appropriate antihypertensive prescriptions. Furthermore, SES is associated with multimorbidity, which is linked to poor access to health care; this may ameliorate the association between multimorbidity and lower BP found in this study in countries such as the US. Lower and middle-income countries also have different considerations to account for, and more research is required to investigate whether the associations observed in this study are also present in these contexts, which would suggest a biological reason for the BP trajectory rather than a health-system-related factor.

No other study has examined BP trajectories longitudinally after diagnosis of hypertension and pinpointed the diagnostic threshold as a driver of disease trajectory. The fact that BP values several years after diagnosis of hypertension are still sensitive to initial BP at diagnosis suggests that researchers might be over-interpreting the impact of treatment for diseases diagnosed by a binary classification

of a continuous variable, which is then also used to determine success of treatment. A recent study has found that BP trajectory preceding hypertension diagnosis follows a sigmoidal shape with relatively stable BP maintained up to 120-125mmHg, followed by rapid elevation in BP towards diagnostic thresholds [252], supporting the idea that the diagnostic threshold for hypertension could prove more useful if lowered below the standard threshold of 140/90 (or the newly introduced 130/80 [75]). The novel findings in this study have wide implications in interpreting results for research, and calls for the consideration of the impact of diagnostic measurements in future research, for example, inclusion of diagnostic HbA1c levels as a confounder when assessing efficacy of anti-diabetic medications. There is great potential for investigating the effect of diagnostic thresholds and comorbidity on management of other index conditions. The evidence generated by this study could also serve as starting point for trials in people with multimorbidity and moderate BP to further investigate the impact of multimorbidity on BP, in relatively healthy (not hypertensive) populations.

In this context, it is interesting to reflect on other conditions that have a diagnostic and therapeutic target based on the same scale, such as anaemia and diabetes. Anaemia has been previously defined by studying a 'healthy population' and determining normal values that lie within the two standard deviations of the reference population (i.e. excluding the lowest and highest 2.5%) and these have varied between guidelines based on the different populations that have been studied [253]. A study that identified whether this was clinically relevant examined 17,000 people and found that the risk of mortality was lowest if haemoglobin concentration was between 13-15g/dl for women and 14-17g/dl for men [254]. Diabetes thresholds have similarly been determined by the threshold at which risk can be prevented [253]. It would be interesting to take this further and perform an analysis similar to the analysis on BP in hypertensive patients in this thesis, to determine whether the actual diagnostic thresholds determine long-term disease trajectory.

Future research could also examine the impact of medication adherence on BP. Data on medication adherence was not available for this study, but previous work

has shown that medication adherence is higher in those with more morbidities [148]. Further work is required to assess the impact of medication adherence and characterise what factors drive medication adherence to contribute to better antihypertensive prescription and control in multimorbid patients to further inform integrated chronic disease management. Furthermore, Mendelian randomisation studies could help understand the causal association between antihypertensives and BP in subgroups of comorbidity. Moreover, differences in BP in comorbidity subgroups could be assessed using using genome wide association studies to investigate possible biological pathways.

6.6 Conclusion

The widely held assumptions that multimorbid patients receive poorer quality health care, and are less likely to achieve clinical targets, are not supported by the findings of this large-scale, high-resolution study of BP management. Patients with comorbidity and multimorbidity are generally more likely to have lower BP. This is partly accounted for by more intense treatment, more frequent monitoring, earlier diagnosis at a lower BP and earlier treatment. These findings demonstrate the heterogeneity of BP management by comorbidity status and emphasise the need to diagnose and treat early to successfully lower BP for all subgroups.

7

Multimorbidity and mortality risk

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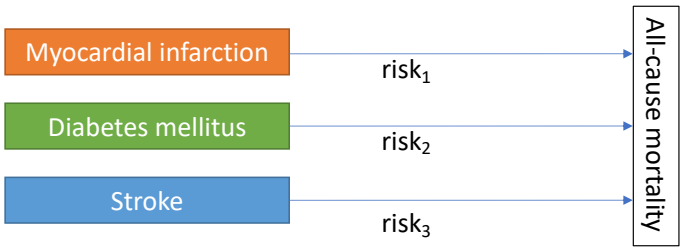
7.1 Introduction

Multimorbidity is associated with an increased risk of all-cause mortality. Patients with multimorbidity have a 44% increased mortality risk compared to those without multimorbidity, and it has also been shown that each condition is associated with a 20% increased risk of mortality [44].

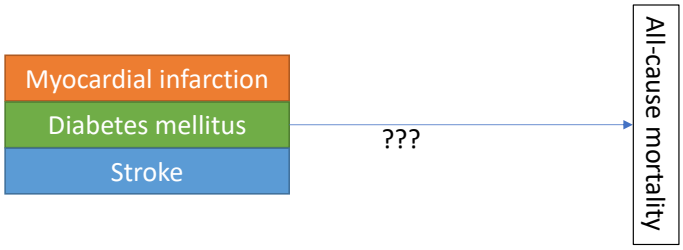
Although there is considerable evidence on the mortality risk associated with individual conditions, the evidence of mortality risk in concomitant conditions is sparse [45]. The higher mortality risk in patients with multimorbidity could be explained by several different models. Each condition in a multimorbid patient has an associated relative risk individually. The additive model of risk results in a combined risk that is proportionate to the addition of risk associated with each individual condition. A risk that is more than additive is where the combined risk of conditions is more than the additive model. One example of this is a multiplicative model, where if a patient had three conditions, each with a relative risk of 2, the multiplicative risk would be 2x2x2=8, which is more than the additive risk of 2+2+2=6. A risk that is less than additive is where the combined risk of conditions is less than the additive model. This could occur if mortality were more closely related to shared risk factors, pathophysiological pathways or management, leading to overlapping risk [255]. For example, patients with concordant conditions have been shown to receive better quality care [244, 93], that could lead to risk that is less than additive. In multimorbid patients, it is unclear whether the relative risk of conditions in combination result in a risk that is more or less than additive (Figure 7.1, Figure 7.2). This has clinical relevance for service provision as well as individual mortality risk evaluation, providing direction on effective strategies to manage multimorbidity that involve shared risk factors or common management paths.

Figure 7.1: Risk of mortality in multimorbidity: individual vs combination

(a) Individual conditions



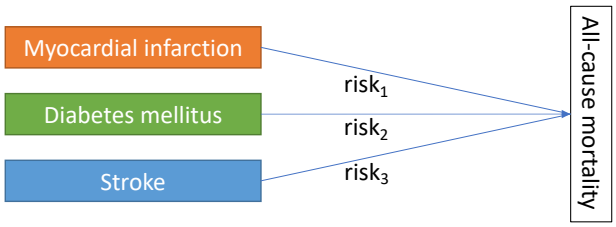
(b) Combination of conditions



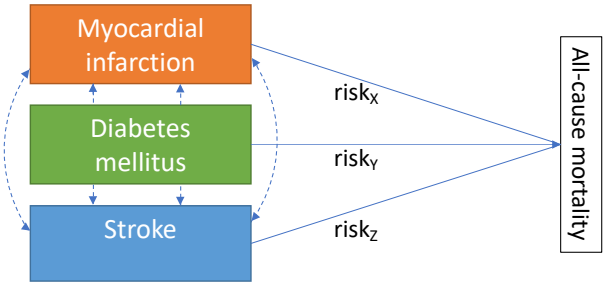
Risk of mortality for (a) single conditions, could be different to, (b) conditions in combination, due to disease-disease, disease-treatment and other interactions

Figure 7.2: Risk of mortality in multimorbidity: models of risk

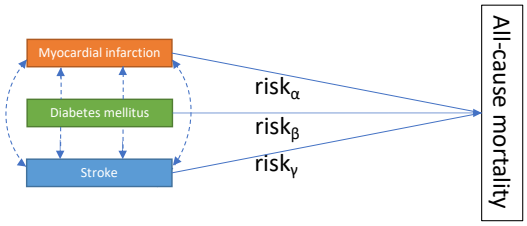
(a) Additive



(b) More than additive



(c) Less than additive



(a) Mortality risk for combination conditions is additive: $risk_1+risk_2+risk_3$; (b) Mortality risk is more than additive, as diseases interact to increase risk of each other. $risk_X+risk_Y+risk_Z > risk_1+risk_2+risk_3$; (c) Mortality risk is less than additive. This could be due to shared risk factors or other confounders. $risk_\alpha+risk_\beta+risk_\gamma < risk_1+risk_2+risk_3$; size of boxes are representative of magnitude of risk. Only disease-disease interactions are shown. Other interactions such as disease-treatment or disease-environment interactions could interact with conditions to increase or decrease relative risk

The literature investigating the interaction of concomitant conditions, and the association with mortality risk is sparse. Research investigating the effects of concomitant cardiometabolic conditions requires large sample sizes and availability of data on comorbidities [45]. Furthermore, extensive data have not been available to examine changing diagnoses of additional comorbidities over time, and its effects on mortality risk.

One key study investigating cardiometabolic multimorbidity and mortality risk was conducted by the Emerging Risk Factors Collaboration (ERFC). The ERFC is the only study so far, to my knowledge, that has quantified the interactions between comorbid conditions. The study examined the comorbid conditions myocardial infarction (MI), stroke and diabetes mellitus (DM), and demonstrated that the mortality risk associated with these conditions was multiplicative [45]. It is unclear why these concordant conditions were associated with a disproportionately higher risk for all-cause mortality compared to an additive risk for combined conditions. One explanation for the disproportionately higher risk is that patients with more cardiometabolic conditions are also more likely to have other comorbidities that contribute to their all-cause mortality risk. Patients with all three cardiometabolic conditions in the ERFC are possibly more likely to have more serious and higher numbers of comorbidities than those without all three cardiometabolic conditions, as a result of common ageing mechanisms that result in accumulation of conditions [256]. The hypothesis for the analyses in this chapter was that incomplete adjustment for additional comorbidities partly explains the increased relative risk of all-cause mortality for concomitant cardiometabolic conditions. A secondary hypothesis for this study was that due to unadjusted confounding by additional comorbidities, the relative risk of mortality in patients with concomitant cardiometabolic conditions is less than the additive risk of the individual conditions.

To address the gap in the literature and test these hypotheses, this study used a large longitudinal database of linked electronic health records (EHR) to investigate all-cause mortality risk in patients with cardiometabolic comorbidity, and the contribution of additional comorbidities.

Added value of this study:

- mortality risk in patients with cardiometabolic conditions is adjusted for confounding by a wide range of additional comorbidities
- large study population with the power to detect differences in mortality risk in sub-groups with different combinations of cardiometabolic conditions
- longitudinal analysis with information about onset of conditions to enable time-updating variables: comorbidity and cardiometabolic status

7.2 Aim

To investigate the effect of comorbidity on risk of mortality in patients with cardiometabolic conditions (myocardial infarction (MI), stroke and diabetes mellitus (DM)).

Hypotheses

1. Incomplete adjustment for additional comorbidities partly explains the increased relative risk of all-cause mortality for multiple concomitant cardiometabolic conditions
2. Mortality risk for patients with multiple concomitant cardiometabolic conditions is less than the additive risk of the individual conditions

7.3 Methods

7.3.1 Data source: the CPRD

Please refer to chapter 4

7.3.2 Study population

In addition to the population described in subsection 4.2.1, all patients had an active valid record on the 1st of January 2005 to ensure quality data for the cohort.

7.3.3 Study design

The study design was a retrospective cohort study.

7.3.4 Population categories

Population categories were chosen to replicate the ERFC study and test the hypothesis generated from the study that the all-cause mortality risk of concomitant cardiometabolic conditions is multiplicative. The study population was classified into the following mutually exclusive groups of cardiometabolic conditions, herein referred to as *cardiometabolic status*:

- Reference group: no MI, stroke or DM
- MI only
- Stroke only
- DM only
- MI and stroke (no DM)
- MI and DM only (no stroke)
- DM and stroke (no MI)
- MI, DM and stroke

Prevalent diagnosis of a cardiometabolic condition(s) were captured in the CPRD using all available data up until the 1stof January 2005.

7.3.5 Selection and definition of comorbidities

The additional conditions that were used to adjust for the mortality risk are described in Table 7.1. These conditions will herein be referred to as *additional comorbidities*. These conditions were selected as they were highly prevalent and clinically significant, based on three representative and reputable sources: 1) the Quality and Outcomes Framework (QOF), a pay-for-performance incentive scheme for general practitioners

in the UK, [172] 2) the Charlson comorbidity index, a classification system to help predict inpatient hospital mortality, [119] 3) the multiple chronic conditions list for the US Department of Health and Human Services Intiative [199] (refer to chapter 3 for details about how these conditions were selected). Each of the 53 conditions were identified using a list of diagnostic codes from ICD-10 (hospital) and Read codes (primary care), compiled from online code repositories, previous work completed at The George Institute for Global Health, and medical dictionary keyword searches (refer to subsection 4.2.4 for further details). Diagnosis of a prevalent comorbidity was defined as the recording of a diagnostic code for that comorbidity if it was diagnosed before the 1stof January 2005. The look-back period to capture prevalent comorbidity diagnoses included all CPRD data, dating back to the inception of CPRD on the 1stJan 1985.

Table 7.1: Additional comorbidities selected

Group	Comorbidity	Included conditions
Cardiometabolic	Cardiac arrhythmia	Cardiac arrhythmias and dysrhythmias, including atrial fibrillation and flutter, paroxysmal tachycardia, atrioventricular blocks, and other conduction disorders
	Chronic kidney disease	Chronic kidney disease stage 3 or more, or dependence on transplant or dialysis
	Heart failure	
	Peripheral arterial disease	Includes aortic aneurysm and dissection, embolism and thrombosis, and unspecified peripheral vascular diseases
Mental health	Adjustment disorder	Includes pathological reactions to severe stress
	Affective disorder	Unspecified, persistent, or other affective disorders
	Anxiety	Anxiety and phobic disorders
	Bipolar disorder	
	Depression	Depression and depressive mood disorders
	Eating disorder	Eating disorders, including bulimia and anorexia nervosa
	Psychoses	Psychotic and delusional disorders
	Schizophrenia	
	Substance abuse	Mental and behavioural disorders due to substances including alcohol, opioids, and cannabinoids
Respiratory	Asthma	
	Chronic obstructive pulmonary disease	
	Lung cancer	
	Other respiratory cancer	Respiratory organ cancer excluding lung cancer, e.g., laryngeal cancer, pleural cancer, and tracheal cancer

Group	Comorbidity	Included conditions
Musculoskeletal	Arthritis	Chronic arthritis, including osteoarthritis, secondary arthritides (e.g., arthropathy in Crohn disease and psoriatic arthritis), and other unspecified arthritides and sequelae; excluding acute arthritis (e.g., septic arthritis) and arthritides covered elsewhere: gout, rheumatoid arthritis, and connective-tissue-related arthritis
	Gout	
	Osteoporosis	
	Rheumatoid arthritis	
Neurological	Dementia	Includes Alzheimer disease, vascular dementia, and unspecified dementia
	Epilepsy	
	Hemiplegia	
	Learning disability	Disorders of psychological development, mental retardation, and childhood autism
Cancers	Bladder cancer	
	Breast cancer	
	Cervical cancer	
	Colon cancer	
	Ear, nose, and throat cancer	
	Leukaemia	
	Liver cancer	
	Lymphoma	
	Metastatic cancer	
	Oesophageal cancer	
	Ovarian cancer	
	Pancreatic cancer	
	Prostate cancer	
	Rectal cancer	

Group	Comorbidity	Included conditions
	Renal cancer	
	Skin cancer	
	Stomach cancer	
	Other female reproductive cancer	Female reproductive organ cancer excluding breast, ovarian, and cervical cancer, e.g., endometrial cancer, uterine cancer, and cancer of the vagina
	Other gastrointestinal cancer	Gastrointestinal cancer excluding oesophageal, stomach/gastric, colon, rectal, pancreatic, and liver cancer, e.g., cancer of the bile ducts, anal cancer, and peritoneal cancer
	Other male reproductive cancer	Male reproductive organ cancer excluding prostate cancer, e.g., testicular cancer
	Other urological cancer	Urological organ cancer excluding renal/kidney and bladder cancer, e.g., cancer of the ureter and cancer of the urethra
	Unspecified cancer	Cancer with unspecified anatomical region or origin
	Other cancer	Cancer not otherwise covered by all other cancers covered in the list of 53 comorbidities, e.g., brain cancer, cancer of the eye, and cancer of the endocrine glands
Other	Connective tissue disease	Systemic connective tissue disorders including systemic lupus erythematosus, systemic sclerosis, and polymyositis
	HIV/AIDS	
	Liver disease	Includes cirrhosis, portal hypertension, and hepatic failure; excludes liver cancer
	Peptic ulcer disease	Includes gastric and duodenal ulcers
	Anaemia	

7.3.6 Other covariates

Age, sex and socio-economic status (by Index of Multiple Deprivation (IMD) quintile) was extracted (refer to chapter 4 for more details) and adjusted for in every model.

7.3.7 Outcome

All-cause mortality and date of death was extracted from linked records from the death registry (Office of National Statistics (ONS)) (chapter 4). A patient was assumed to be living for the entirety of their active record if there was no recording of death in ONS. All-cause mortality was selected as the primary outcome to maximise power of the study. Mortality risk will herein be used to refer to all-cause mortality risk.

7.3.8 Statistical analyses

There were five models that were used. In all analyses, Cox proportional hazards regression was used with adjustment for age, sex and SES. The start of the study was the 1stof January 2005, and patients were censored at the earliest of: time of outcome (date of death), transfer out of practice date, last collection date of quality data for their practice, or end of the study on the 31stDecember 2014. For each model, the hazards ratios (HRs) for mortality were generated for each category of cardiometabolic status, where the reference group was patients with none of the conditions MI, stroke or DM. In the first model, the aim was to replicate the analyses in the ERFC study, and no further adjustments were made. In the second model, the study population was restricted to people who did not have a diagnosis of any of the additional comorbidities in order to investigate all-cause mortality risk by cardiometabolic status, without the effect of additional comorbidities. In the third model, every additional comorbidity was adjusted for in the model to directly test the first hypothesis that the disproportionately higher all-cause mortality risk in patients with concomitant multiple cardiometabolic conditions was partly explained by additional comorbidities. In the fourth model, additional comorbidities were time-updated so that incident diagnosis of disease during patient

follow-up was accounted for and in the fifth model, the cardiometabolic status strata were also time-updated with incident diagnosis of MI, stroke or DM during follow-up i.e. patients would move into a cardiometabolic status category with more conditions with each incident diagnosis of either MI, stroke or DM. Time-updating was performed to test whether time-updated information further explained all-cause mortality. Violation of the proportional hazards assumption was tested by examining unadjusted Kaplan-Meier survival curves and Schoenfeld residuals [257]. Statistical models were also compared to estimated HRs for an additive model by comparing the difference between mean HRs calculated from Cox models to those calculated in an additive risk model. Ratio of change of HR with each additional cardiometabolic condition was also calculated to compare the magnitude of adding an additional cardiometabolic condition to all-cause mortality.

7.3.9 Sensitivity analyses

In sensitivity analyses, the population was restricted to those who were aged 85 years old or less to select a more comparable population to that studied in previous literature (the ERFC study [45]). Due to the large differences in mean age between study groups and concerns regarding inadequate adjustment for these age differences between exposure groups, Cox proportional hazards regression was also performed using age as the time-scale for follow-up (instead of follow-up time from study entry) as confounding by age was a concern [258].

7.4 Results

7.4.1 Baseline characteristics

There were 2,099,224 patients with an active record on the 1stof January 2005 with 8.4 years median follow-up time (14,750,438 years total), mean age of 51.4 years (SD 17.5), and 51.1% women. 92.7% of patients did not have any of the three cardiometabolic conditions MI, stroke or diabetes. There were relatively lower proportions of women with MI (30.1%), diabetes (47.1%), or any combination of two or three cardiometabolic conditions, compared to those with no conditions (51.7%).

There was also a lower proportion of patients with diabetes who were of white ethnicity: 94.0% compared to 96.3% in patients with no conditions (Table 7.2).

In general, patients with any of the cardiometabolic conditions had a higher mean blood pressure (BP), were more likely to be overweight or obese and were more likely to be ex-smokers compared to those with none of the three cardiometabolic conditions. Those with all three of MI, stroke and diabetes had a mean BP of 148/84 mmHg compared to 129/78 mmHg for those who did not have any of the three conditions. Of the patient groups with cardiometabolic conditions, those with MI (142/83 mmHg), diabetes (144/84 mmHg) or MI & diabetes (145/84 mmHg) had lower mean BP, compared to any of strata who had stroke e.g. those with only stroke had a BP of 147/84 mmHg. Patients with only stroke had the highest proportion of normal BMI (40.7%) of patients with any of the three cardiometabolic conditions, whereas any of the patient groups with diabetes had a relatively higher proportion of obesity, with 41.6% of patients with only diabetes being obese. There was a relatively high proportion of patients with only diabetes who had never smoked (52.3%), and a relatively high proportion of those with MI in any combination who were ex-smokers (MI only 39.3%, MI & stroke 38.5%, MI & diabetes 43.8%, MI, stroke & diabetes 41.3%) (Table 7.2).

Table 7.2 also shows follow-up characteristics of all patients stratified by cardiometabolic status. Overall, patients had a mean age of 51.4 years at study entry and 58.4 years at study exit. Patients with any combination of cardiometabolic conditions were generally older at study entry and exit, with a shorter follow-up time, compared to those with none of the three cardiometabolic conditions. For patients with no conditions compared to patients with all three conditions respectively, mean study entry age was 48 years old vs 76 years old, mean study exit age was 57.1 years old vs 79.5 years old, and median follow-up time was 8.5 years vs 3.8 years. There were 270,036 events in total. Crude death rate was generally higher in patients with more cardiometabolic conditions, for example, 48% [95%CI 47.5-48.5] of patients with MI only had a fatal event during the study, compared with 78.3% [95%CI 75.5-80.8] of patients with all three of MI, stroke and diabetes. Mean age

of death was 82 years old and ranged from 78.7 to 83.9 years old for all groups of patients stratified by cardiometabolic status.

Table 7.2: Baseline and follow-up characteristics of participants

Characteristics	All patients	Cardiometabolic status at baseline							
		None	MI	Stroke	Diabetes	MI and stroke	MI and diabetes	Stroke and diabetes	MI, stroke, diabetes
Number of participants	2,009,224	1,863,009	33,657	25,234	71,471	2,920	7,223	4,771	939
Age, mean (SD), years	51.4 (17.5)	50.0 (17.0)	71.4 (11.7)	73.7 (13.5)	64.5 (14.3)	76.8 (10.2)	71.3 (10.5)	73.8 (10.6)	75.1 (9.1)
Women % (n)	51.1 (1,026,209)	51.7 (963,256)	30.1 (10,132)	53.1 (13,405)	47.1 (33,671)	36.1(1,055)	30.4 (2,199)	45.7 (2,178)	33.3 (313)
White ethnicity % (n)	96.3 (641,878) [665,615]	96.3 (579,995) [593,789]	98.1 (15,883) [16,119]	98.3 (11,590) [12,288]	94.0 (27,541) [35,033]	98.7 (1,423) [1,419]	95.3 (3,013) [3,904]	95.4 (2,014) [2,568]	96.5 (419) [495]
Fifths of IMD, % (n)									
Q1: least deprived	24.4 (490,428)	24.8 (461,371)	21.1 (7,105)	20.3 (5,131)	19.5 (13,948)	20.4 (596)	18.1 (1,308)	17.1 (816)	16.3 (153)
Q2	22.3 (449,057)	22.4 (417,426)	22.3 (7,519)	21.6 (5,459)	21.6 (15,432)	20.3 (594)	20.6 (1,491)	19.9 (948)	20.0 (188)
Q3	20.9 (420,806)	20.9 (389,755)	20.9 (7,034)	21.2 (5,359)	21.4 (15,300)	20.4 (595)	21.2 (1,533)	21.8 (1,038)	20.4 (192)

Characteristics	All patients	Cardiometabolic status at baseline							
		None	MI	Stroke	Diabetes	MI and stroke	MI and diabetes	Stroke and diabetes	MI, stroke, diabetes
Q4	17.9 (359,930)	17.8 (331,360)	18.7 (6,293)	19.4 (4,887)	19.8 (14,127)	20.4 (596)	20.4 (1,476)	20.7 (988)	21.6 (203)
Q5: most deprived	14.2 (284,488)	13.9 (258,849)	16.7 (5,624)	17.2 (4,347)	17.6 (12,552)	18.3 (534)	19.5 (1,405)	20.4 (974)	21.6 (203)
Mean SBP (SD), mmHg	130.4 (21.0) [125,945]	129.3 (20.5) [125,301]	141.5 (22.2) [145]	146.7 (24.1) [223]	144.2 (22.7) [229]	146.3 (23.7) [14]	145.3 (22.5) [7]	150.7 (23.2) [21]	148.2 (23.1) [5]
Mean DBP (SD), mmHg	78.8 (11.7) [125,945]	78.3 (11.5) [125,301]	82.6 (11.7) [145]	84.2 (12.4) [223]	84.4 (12.1) [229]	83.7 (12.2) [14]	83.7 (12.0) [7]	85.3 (12.5) [21]	84.2 (12.4) [5]
Body mass index kg/m_2, % (n)									
Underweight	2.6 (34,803)	2.7 (33,312)	1.5 (399)	2.6 (474)	0.8 (483)	2.2 (50)	0.6 (38)	1.1 (42)	0.6 (5)
Normal	46.2 (627,549)	48.1 (595,174)	34.4 (9,460)	40.7 (7,322)	20.3 (12,551)	37.1 (837)	17.9 (1,150)	22.9 (898)	19.2 (157)
Overweight	34.0 (460,881)	33.4 (413,036)	44.3 (12,158)	39.1 (7,022)	37.3 (23,028)	43.3 (976)	42.4 (2,724)	39.9 (1,564)	45.5 (373)

Characteristics	All patients	Cardiometabolic status at baseline							
		None	MI	Stroke	Diabetes	MI and stroke	MI and diabetes	Stroke and diabetes	MI, stroke, diabetes
Obese	17.2 (233,929) [652,062]	15.8 (195,032) [626,455]	19.9 (5,457) [6,183]	17.6 (3,160) [7,256]	41.6 (25,668) [9,741]	17.4 (393) [664]	39.1 (2,516) [795]	36.2 (1,419) [848]	34.7 (284) [120]
Smoking status, % (n)									
Current	27.2 (401,396)	27.8 (375,286)	22.7 (6,645)	23.4 (4,679)	19.9 (12,285)	20.1 (491)	17.3 (1,123)	18.3 (744)	17.1 (143)
Never	55.9 (825,284)	56.7 (766,096)	37.4 (10,979)	50.5 (10,071)	52.3 (32,270)	41.4 (1,014)	38.9 (2,526)	48.7 (1,980)	41.6 (348)
Ex-smoker	16.9 (250,083) [532,461]	15.6 (210,490) [511,137]	39.9 (11,703) [4,330]	26.1 (5,212) [5,272]	27.9 (17,205) [9,711]	38.5 (943) [472]	43.8 (2,840) [734]	33.0 (1,344) [703]	41.3 (346) [102]
Follow-up characteristics									
Number of participants	2,009,224	1,863,009	33,657	25,234	71,471	2,920	7,223	4,771	939
Number of events, n (%)	270,036	204,445	16,153	14,824	24,261	2,152	4,209	3,257	735

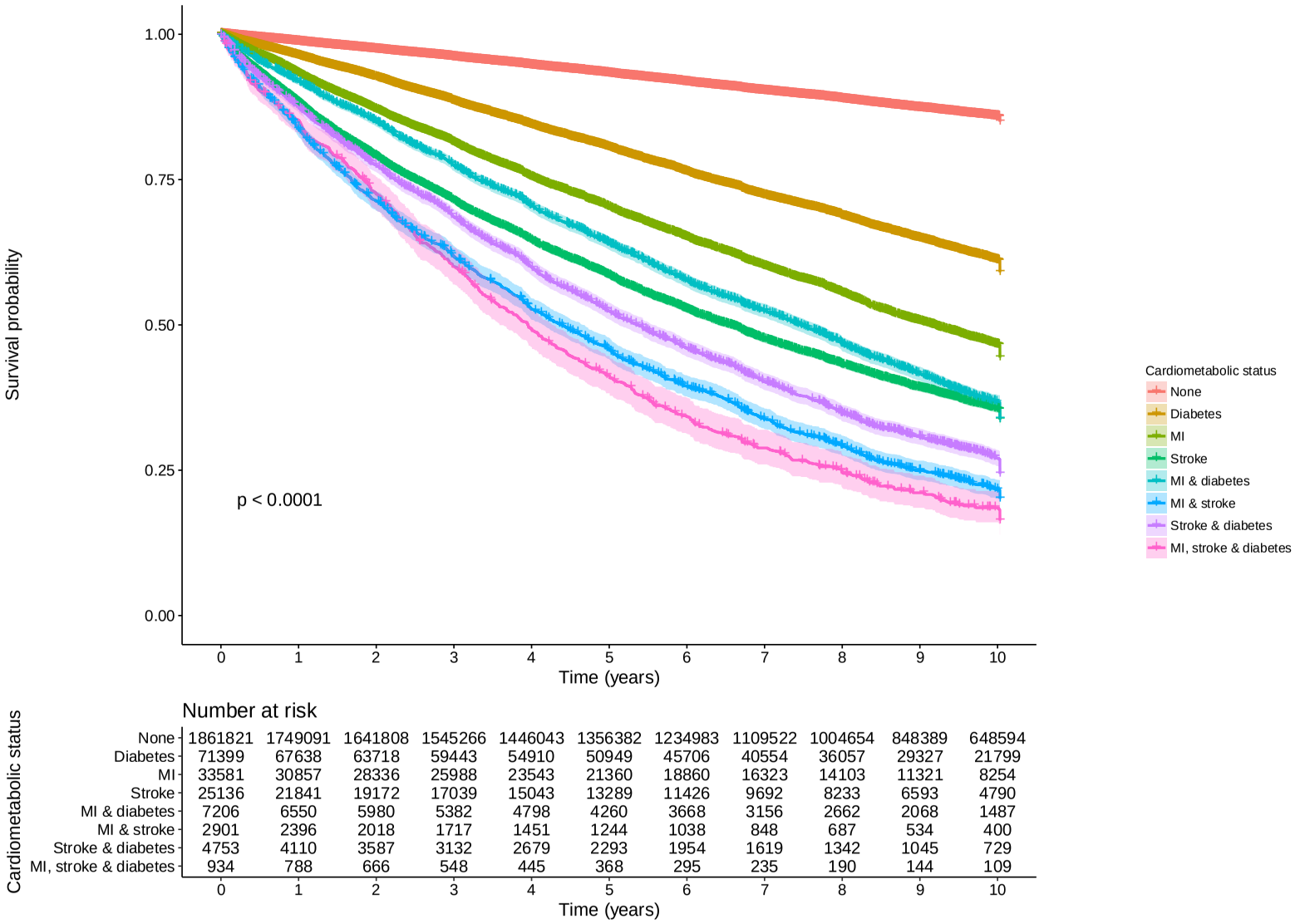
Characteristics	All patients	Cardiometabolic status at baseline							
		None	MI	Stroke	Diabetes	MI and stroke	MI and diabetes	Stroke and diabetes	MI, stroke, diabetes
Death rate, % (95% CI)	13.4 (13.4-13.5)	11.0 (10.9-11.0)	48.0 (47.5-48.5)	58.7 (58.1-59.4)	33.9. (33.6-34.3)	73.7 (72.1-75.3)	58.3 (57.1-59.4)	68.3 (66.9-69.6)	78.3 (75.5-80.8)
Follow-up time, median (IQR), years	8.4 (4.5-10)	8.5 (4.6-10)	6.8 (3.3-9.9)	5.4 (2.1-9.2)	8.1 4.4-10.0)	4.0 (1.6-7.8)	6.1 (3.0-9.5)	4.8 (2.0-8.5)	3.8 (1.8-7.1)
Study entry age, mean (SD), years	51.4 (17.5)	48.0 (17.0)	72.0 (11.6)	76.0 (13.5)	66.0 (14.3)	78.0 (10.2)	72.0 (10.5)	75.0 (10.6)	76.0 (9.1)
Study exit age, mean (SD), years	58.4 (17.7)	57.1 (17.4)	77.7 (11.0)	79.1 (12.6)	71.4 (13.9)	81.4 (9.4)	77.2 (9.9)	79.0 (9.9)	79.5 (8.5)
Age at death, mean (SD), years	82.0 (12.9)	78.7 (13.6)	83.9 (9.3)	81.0 (9.0)	79.3 (11.0)	79.7 (9.1)	82.2 (9.3)	83.0 (8.5)	80.2 (8.1)

The category percentages refers to complete cases. Numbers in square brackets refer to the number of patients with missing data for the relevant characteristic. Fifths of IMD refers to the Index of Multiple Deprivation 2015 cut by quintiles, where Q1 is the least deprived fifth and Q5 is the most deprived fifth of the population. BMI categories are 'underweight' (<18.5 kg/m^2), 'normal' (18.5–24.9 kg/m^2), 'overweight' (25–29.9 kg/m^2), and 'obese' (≥30 kg/m^2). DBP=diastolic blood pressure; SBP=systolic blood pressure, IMD=Index of Multiple Deprivation, SD=standard deviation, IQR=interquartile range

7.4.2 Survival in patients with cardiometabolic comorbidities

Figure 7.3 shows the unadjusted survival probability of patients stratified by cardiometabolic status. In general, there was lower survival probability for patients with more conditions. Patients with no comorbidities had the highest survival probability and patients with all three conditions had the lowest survival probability. The exception to this was that patients with stroke had a lower probability of survival compared to patients with MI and diabetes. The difference in survival between groups was significant ($p<0.001$).

Figure 7.3: Kaplan-Meier curves for probability of survival by cardiometabolic status

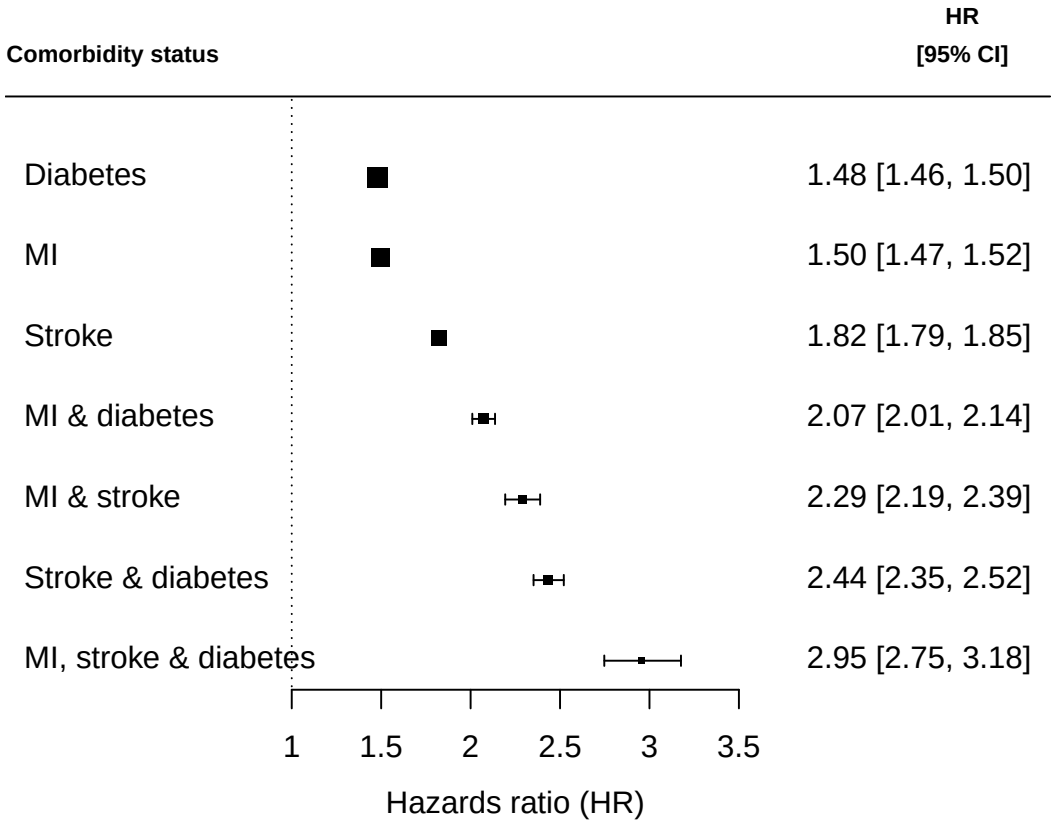


p-value refers to log-rank test comparing the survival distributions of population by cardiometabolic status

7.4.3 All-cause mortality in patients with cardiometabolic comorbidities

Figure 7.4 shows the HRs of patients by cardiometabolic status, compared to those with none of the three cardiometabolic conditions. The HRs for any combination of conditions were increased compared to having none of the conditions, and generally increased with more conditions. Patients with MI or diabetes had a HR that was approximately 1.5 (1.50 [95%CI 1.47-1.52], 1.48 [1.46-1.50] respectively), and patients with stroke had a HR of 1.82 [95%CI 1.79-1.85]. Combinations of two conditions increased HRs to between 2 to 2.5. Patients with all three conditions had an even higher HR of 2.95 [95%CI 2.75-3.18].

Figure 7.4: Relative mortality risk by cardiometabolic comorbidity status

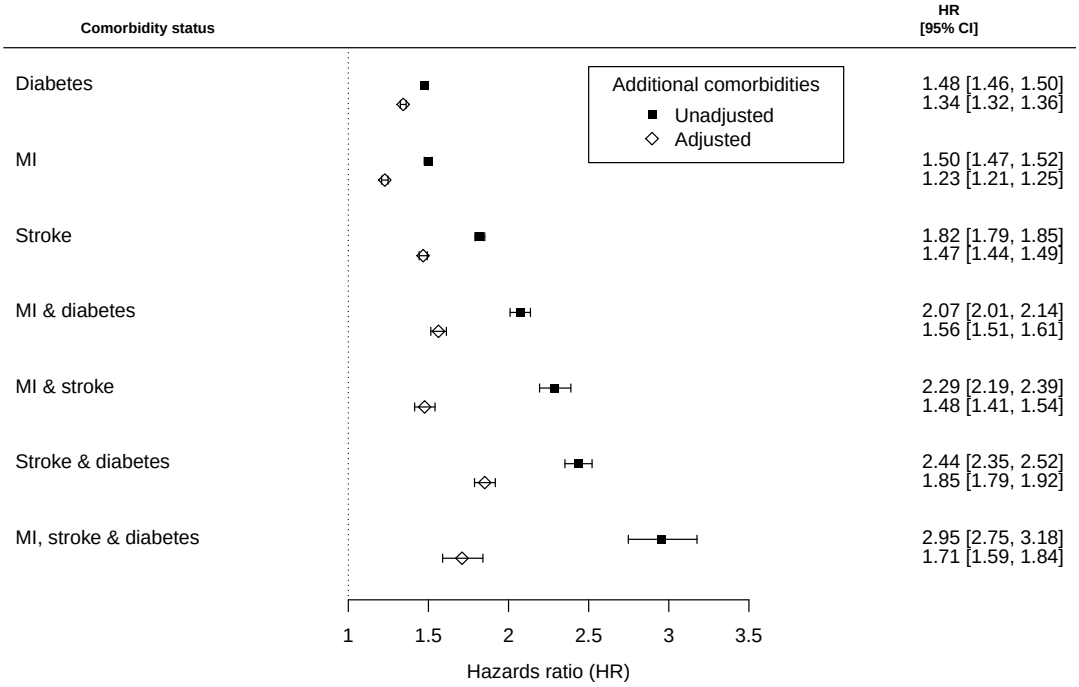


Hazards ratios (HRs) were calculated from Cox proportional hazards regression. All models were adjusted for age, sex and IMD.

7.4.4 Effect of adjustment for additional comorbidities on all-cause mortality

Figure 7.5 shows the HRs of patients by cardiometabolic status, comparing models unadjusted and adjusted for additional comorbidities at baseline. In all patient subgroups, adjustment for additional comorbidities reduced the HR. For example, the HR in patients with MI was 1.50 [95%CI 1.47-1.52] without adjustment, which decreased to 1.23 [95% CI 1.21-1.25] with adjustment for an additional 53 conditions; in patients with MI, stroke and diabetes, HR reduced from 2.95 [95% CI 2.75-3.16] to 1.71 [95%CI 1.59-1.84].

Figure 7.5: Relative mortality risk by cardiometabolic comorbidity status adjusted vs unadjusted for additional comorbidities



Hazards ratios (HRs) were calculated from Cox proportional hazards regression. All models were adjusted for age, sex and IMD. Black squares were unadjusted for additional comorbidities; open diamonds were adjusted for additional comorbidities.

The ratio of change in HR from one to two, and from two to three cardiometabolic conditions was used to compare the magnitude of effect of each extra cardiometabolic condition on relative risk of mortality. Table 7.3 shows the average HRs and the ratio of change in the HR with each additional cardiometabolic condition, comparing

the base model with step-wise adjustment for additional comorbidities, and then time-updated additional comorbidities. For example, ratio of change of 1.42 from one to two diseases indicates that the relative risk of mortality from two diseases was 0.42 more than the risk of mortality from one disease. Overall, with progressive adjustment, the ratio of change for each extra cardiometabolic condition was reduced, i.e. the relative risk of mortality attributed to each cardiometabolic condition was accounted for by additional comorbidities. For instance, without adjustment for additional comorbidities, having three diseases increased relative risk of mortality by a ratio change of 0.30, and with adjustment for additional comorbidities, this increased relative risk was reduced by a ratio change of 0.05. Moreover, further adjustment with time-updated additional comorbidities actually reduced the ratio change of relative risk of mortality by 0.05. Furthermore, in models adjusted for time-updated additional comorbidity status, the relative risk of mortality with one, two or three diseases, was approximately the same, at an average HR of 1.20.

Table 7.3: Ratio of change in HRs for multiple cardiometabolic conditions

	Mean HR			**Ratio of change**	
	Number of diseases			Change in diseases	
Model	1	2	3	1 to 2	2 to 3
Adjusted for age, sex, SES	1.60	2.27	2.95	1.42	1.30
Adjusted for age, sex, SES +adjusting for baseline additional comorbidities	1.35	1.63	1.71	1.21	1.05
Adjusted for age, sex, SES +adjusting for *time-updated* additional comorbidities	1.18	1.24	1.18	1.05	0.95

HR=hazards ratio. Mean HRs are calculated from estimates derived from Cox proportional hazards regression. For example, mean HR for 1 disease in the model adjusted for age, sex and SES is the mean of HR for diabetes (1.48), MI (1.50) and stroke (1.82) i.e. 1.60. Ratio of change is calculated by dividing the HR for the higher number of diseases by the HR for the lower number of diseases. For example, ratio of change for 1 to 2 in the model adjusted for age, sex and SES is 2.27/1.60

7.4.5 Assessing the magnitude of effect of cardiometabolic conditions on mortality

The effect of cardiometabolic status on mortality risk and whether this effect was additive or otherwise, was determined and compared between different models.

Additive HRs were calculated and compared to actual HRs derived from Cox regression models (Table 7.4). In the models adjusted only for age, sex and SES, actual HRs were higher than what a purely additive interaction would be (0.07 and 0.16 for two and three diseases respectively). With adjustment for baseline additional comorbidities, actual HRs were less than additive, and this divergence from the additive model increased with further adjustment for time-updated additional comorbidities, which had HRs 0.12 and 0.36 lower than the additive models for two and three diseases respectively.

Table 7.4: Mean estimated HRs vs additive HRs for cardiometabolic conditions

	Two diseases			**Three diseases**		
Model	mean HR	additive HR	difference	mean HR	additive HR	difference
Adjusted for age, sex, SES	2.27	2.20	0.07	2.95	2.80	0.16
Adjusted for age, sex, SES +adjusting for baseline additional comorbidities	1.63	1.69	-0.06	1.71	2.04	-0.33
Adjusted for age, sex, SES +adjusting for *time-updated* additional comorbidities	1.24	1.36	-0.12	1.18	1.54	-0.36

HR=hazards ratio, Additive HR is calculated by adding the risk over 1 of average HR for one disease. Difference in HR= mean HR - additive HR

7.4.6 Mortality associated with comorbidity type

The mortality risk in patients varies by the type of comorbidity. Table 7.5 shows the HRs for each additional comorbidity in models with time-updated additional comorbidities adjusted for time-updated cardiometabolic status. Most chronic conditions were associated with a significantly increased HR. Cancers, especially metastatic cancer (HR 5.28 [95%CI 5.14-5.43]), pancreatic cancer (HR 4.42 [95%CI 4.01-4.87]) and oesophageal cancer (HR 3.37 [95%CI 3.10-3.67]) had the highest HR. Dementia (HR 2.94 [95%CI 2.89-3.00]), learning disability (HR 2.15 [95%CI 1.99-2.33]), substance abuse (HR 2.13 [95%CI 2.05-2.20]) and liver disease (HR 2.43 [95%CI 2.05-2.90]), were the highest ranking non-cancer conditions and made up 4 out of the top 10 conditions ranked by HR. The top cardio-metabolic conditions, other than those included in the cardiometabolic status, were within the top 30: heart failure (1.82 [95%CI 1.79-1.86]), cardiac arrhythmias (1.41 [95%CI 1.39-1.43]) and peripheral arterial disease (1.36 [95%CI 1.34-1.39]). Five conditions also had a significantly lower HR compared to those who did not have the condition: asthma (0.93 [95%CI 0.92-0.95]), adjustment disorder (0.93 [95%CI 0.90-0.96]), gout (0.93 [95%CI 0.91-0.95], skin cancer (0.91 [95%CI 0.89-0.93] and arthritis (0.89 [95%CI 0.88-0.90]). As there were concerns about the residual confounding of age, these analyses were also conducted using age (as opposed to time after start of study) as the time-scale. For the five conditions with a lower HR in the previous model, the HRs in the age time-scale model were: asthma (0.99 [95%CI 0.99-1.00]), adjustment disorder (0.95 [95%CI 0.94-0.96]), gout (0.98 [95%CI 0.98-0.99], skin cancer (0.76 [95%CI 0.76-0.77] and arthritis (0.82 [95%CI 0.82-0.83]) (results not shown).

Table 7.5: Relative mortality risk of 53 additional comorbidities

	Condition	Hazards ratio	Lower CI	Upper CI	p value
1	Metastatic cancer	5.28	5.14	5.43	<0.01
2	Pancreatic cancer	4.42	4.01	4.87	<0.01
3	Oesophageal cancer	3.37	3.10	3.67	<0.01
4	Lung cancer	2.99	2.83	3.16	<0.01
5	Dementia	2.94	2.89	3.00	<0.01
6	Liver cancer	2.43	2.05	2.90	<0.01
7	Ovarian cancer	2.27	2.13	2.43	<0.01
8	Learning disability	2.15	1.99	2.33	<0.01
9	Substance abuse	2.13	2.05	2.20	<0.01
10	Liver disease	2.12	2.04	2.21	<0.01
11	Leukaemia	2.11	2.02	2.21	<0.01
12	Heart failure	1.82	1.79	1.86	<0.01
13	Lymphoma	1.81	1.70	1.92	<0.01
14	Cervical cancer	1.74	1.56	1.93	<0.01
15	Schizophrenia	1.68	1.57	1.79	<0.01
16	Stomach cancer	1.67	1.54	1.82	<0.01
17	Chronic obstructive pulmonary disease	1.61	1.58	1.64	<0.01
18	Other cancer	1.54	1.50	1.58	<0.01
19	Other respiratory cancer	1.53	1.42	1.64	<0.01
20	Hemiplegia	1.51	1.41	1.62	<0.01
21	Epilepsy	1.43	1.38	1.48	<0.01
22	Cardiac arrhythmia	1.41	1.39	1.43	<0.01
23	Eating disorder	1.39	1.25	1.55	<0.01
24	Renal cancer	1.39	1.23	1.57	<0.01
25	Anaemia	1.38	1.36	1.40	<0.01
26	Peripheral arterial disease	1.36	1.34	1.39	<0.01
27	Other gastrointestinal cancer	1.35	1.22	1.49	<0.01
28	ENT cancer	1.34	1.24	1.45	<0.01
29	Other urological cancer	1.30	1.17	1.45	<0.01
30	Rheumatoid arthritis	1.30	1.25	1.35	<0.01
31	Bipolar disorder	1.30	1.20	1.40	<0.01
32	Rectal cancer	1.25	1.18	1.32	<0.01
33	Bladder cancer	1.13	1.08	1.18	<0.01
34	Depression	1.13	1.11	1.14	<0.01
35	Osteoporosis	1.11	1.09	1.13	<0.01
36	Other female reproductive cancer	1.10	1.05	1.15	<0.01
37	HIV/AIDS	1.09	1.04	1.13	<0.01
38	Prostate cancer	1.08	1.04	1.13	<0.01
39	Peptic ulcer disease	1.07	1.05	1.10	<0.01

	Condition	Hazards ratio	Lower CI	Upper CI	p value
40	Connective tissue disease	1.07	1.04	1.10	<0.01
41	Psychoses	1.07	1.00	1.14	0.06
42	Unspecified cancer	1.06	1.02	1.11	<0.01
43	Affective disorder	1.05	0.97	1.14	0.23
44	Breast cancer	1.05	1.01	1.08	<0.01
45	Anxiety	1.02	1.00	1.04	0.01
46	Chronic kidney disease	1.01	0.99	1.02	0.31
47	Other male reproductive cancer	0.98	0.81	1.20	0.88
48	Colon cancer	0.95	0.91	1.00	0.04
49	Asthma	0.93	0.92	0.95	<0.01
50	Adjustment disorder	0.93	0.90	0.96	<0.01
51	Gout	0.93	0.91	0.95	<0.01
52	Skin cancer	0.91	0.89	0.93	<0.01
53	Arthritis	0.89	0.88	0.90	<0.01

Hazards ratios were calculated from Cox proportional hazards regression. All models were adjusted for age, sex and index of multiple deprivation, and time-updated cardiometabolic status. All additional comorbidities listed were time-updated during follow-up. ENT=Ear, nose and throat; HIV/AIDS=Human immunodeficiency virus infection and acquired immune deficiency syndrome

7.4.7 Sensitivity analyses

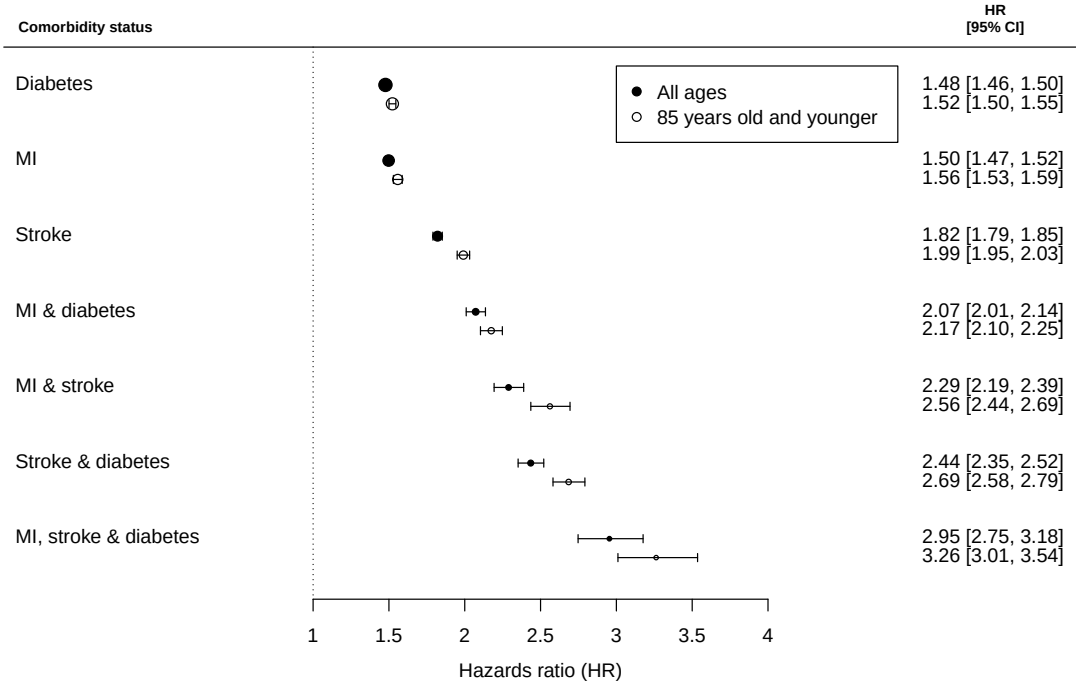
Comparing the general population and those ≤85

Sensitivity analyses using a sub-population restricted to those who were 85 years old and younger were performed to compare results with existing studies [45]. Generally, patients ≤85 years old had higher HRs compared to the whole population. The relative differences in HR comparing different cardiometabolic status strata were similar in both populations.

Comparing follow-up and age time-scale

Sensitivity analyses using age as the primary time scale were compared to using follow-up time since start of study as the primary time scale, to address concerns regarding inadequate adjustment for confounding by age [258]. The relative and absolute HRs using both time scales were similar, and no appreciable difference was observed. For example, patients with diabetes had a the same HR of 1.48 [95%CI

Figure 7.6: Mortality risk by cardiometabolic status comparing total population with ≤85



Hazards ratios (HRs) were calculated from Cox proportional hazards regression. All models were adjusted for age, sex and IMD. Note that no adjustment for additional comorbidities or time-updated comorbidities was included.

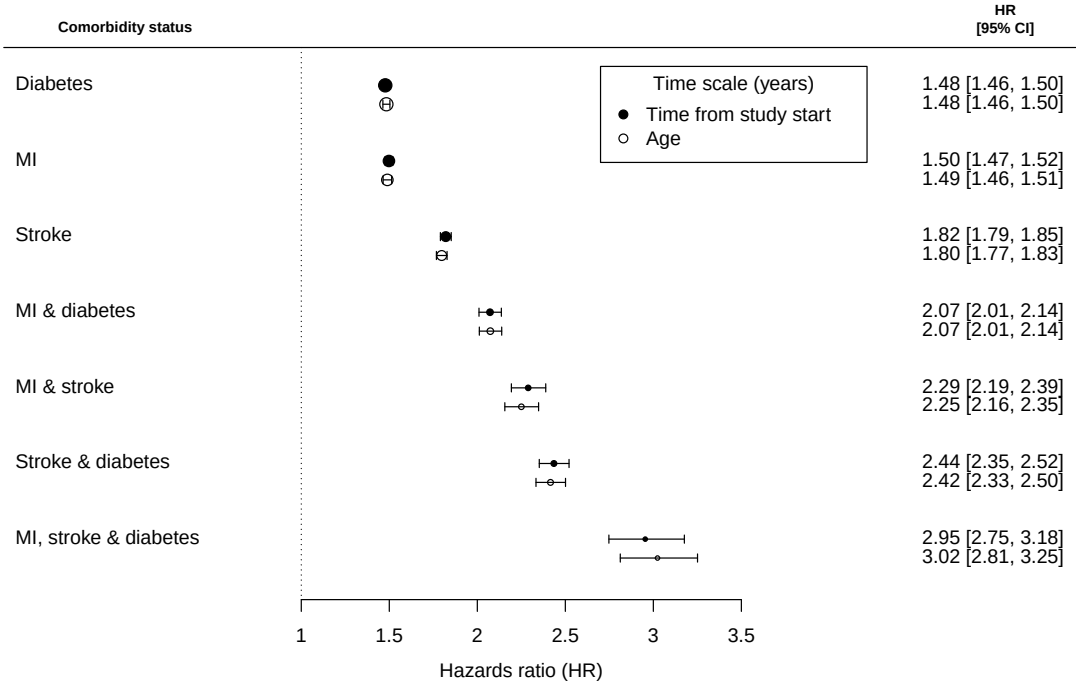
1.46-1.50] in follow-up time and age time scales. With the addition of MI, HRs were also the same at 2.07 [95%CI 2.01-2.14] (Figure 7.7).

7.5 Discussion

7.5.1 Summary of main findings

In this large-scale cohort study of over 2 million patients, the relative mortality risk in patients with cardiometabolic conditions was investigated with adjustment for an additional 53 comorbidities. Patients with cardiometabolic comorbidities MI, stroke and diabetes had higher HRs compared to those with none of these conditions. The HRs associated with each extra cardiometabolic condition was reduced with adjustment. Without taking into account additional comorbidities, HRs seemed to increase with higher numbers of cardiometabolic conditions following an approximately additive effect, with 1 condition conferring a HR of between 1.48-1.82, 2 conditions

Figure 7.7: Mortality risk by cardiometabolic status comparing timescales: time from study entry vs age



Hazards ratios (HRs) were calculated from Cox proportional hazards regression. All models were adjusted for age, sex and IMD. Note that no adjustment for additional comorbidities or time-updated comorbidities is included.

between 2-2.5 and three conditions almost 3. Taking additional comorbidities into account with adjustment, HRs decreased, suggesting that mortality risk in all patient groups can be partly explained by baseline additional comorbidities. In patients with MI, stroke and diabetes, HRs reduced from 2.95 [95% CI 2.75-3.16] to 1.71 [95%CI 1.59-1.84] with adjustment for baseline additional comorbidities. Further adjustment with time-updated additional comorbidities further decreased the HRs. Overall, the mortality risk associated with cardiometabolic conditions was less than additive and not multiplicative as previously reported. The HRs associated with each type of additional comorbidity varied by comorbidity type, with cancers making up the majority of conditions with the highest HRs.

7.5.2 Comparison with previous literature

Comparing these results with the ERFC study, the relative risk of concomitant cardiometabolic conditions is less than additive, rather than multiplicative. The

ERFC claims to have demonstrated a multiplicative effect of MI, stroke and DM with a HR of 6.9 for all three cardiometabolic conditions, and an average HR of 2 for one condition (multiplicative effect: 2x2x2=8, close to 6.9) [45]. On closer examination, this HR of 6.9 was only observed in the ERFC cohort, adjusted only for age at baseline. Further adjustment for age, sex and risk factors reduced the HR to 6, with average HR of 1.87 for one disease, which computes to an effect slightly less than multiplicative. In the same study, the UK biobank cohort was used to validate findings, and this cohort showed generally lower HRs and an effect that was less than multiplicative but still more than additive. In this thesis, the cohort study done by the ERFC is taken further by using routinely-collected electronic health records (EHR), and adjusting for age, sex, SES and additional comorbidities. The study in this thesis demonstrated a relative mortality risk that was less than additive with further adjustment, suggesting that the interaction of diseases does not lead to an excess relative mortality risk. Moving from research database of selected populations to routine data, it is expected that absolute risk would increase, but the HRs in this study were lower than those reported in the cohort of the ERFC study. The difference in this study's results compared to the ERFC might be explained by differences in study population. The general population used in the ERFC (UK biobank and ERFC) could have a much healthier reference group compared to the GP population of patients in the CPRD, which would magnify the relative mortality risk in patients with cardiometabolic conditions. The population in this study had a wider age range and a lower average age (e.g. average age in UK Biobank of population with no cardiometabolic comorbidities was 56.7 years old, compared to 50 years old in this study), and as seen in sensitivity analyses, restricting age in this cohort to mimic the ERFC, increased HRs, but not to the magnitude of HRs reported in the ERFC. Furthermore, using a time-scale of age, instead of time from study start in order to adequately adjust for confounding by age, showed little difference in absolute and relative HRs, suggesting that age was adequately adjusted for as an added covariate in this study. Additionally, the population in this cohort was relatively contemporary compared to the ERFC

cohort: the 91 cohorts in the ERFC were followed up from baseline year ranging from 1960 to 2007, and the cohort in this study had a baseline year of 2005. The impact of advances in medicine over this time, such as the widespread use of statins after its approval in 1987 [259], leading to reductions in mortality [260], is likely to explain some of the larger absolute differences in HRs between this study and the ERFC. This study was also conducted after the introduction of the Quality and Outcomes Framework (QOF), which is likely to have improved recording of diagnoses as well as management of chronic conditions, compared to pre-2004 before the introduction of QOF [172]. It is possible that the combination of strengths of this study provide a more accurate estimate of current relative mortality risk.

This study also builds on previous research in several ways. Most previous studies have reported an increased mortality risk with multiple conditions rather than the change in relative risk with multiple concomitant conditions [89, 261] with the EFRC study being an exception [45]. However, the ERFC study did not have access to a breadth of patient diagnoses nor diagnoses over time [45], whereas this study was able to extract data on 53 different chronic conditions and track them during follow-up. The large sample size also allowed detection of differences in sub-groups by cardiometabolic status. There have been few studies that have examined the longitudinal trajectory of comorbiditiy diagnoses on relative mortality risk [262]. Furthermore, most studies investigating comorbidity and mortality have focused on the Charlson Comorbidity index, and few studies have examined the impact of specific comorbidities on mortality risk [263, 264].

7.5.3 Strengths and limitations

The key strength of this study was in using the power and breadth of EHR. The CPRD is a large dataset from a single source, providing generalisable results to the UK population, broadly representative in age, sex and ethnicity [9], and similar to countries such as the US, Australia and Canada. Using longitudinal data, it has also been possible to follow-up patients over time and use time-updated cardiometabolic status and additional comorbidity diagnoses. The inclusion of 53

additional comorbidities in this analysis provides detailed insight and comparisons of specific conditions and relative mortality risk. Additionally, the completeness of death data in ONS adds to the strength of the study [169].

One limitation is the dependence on recorded diagnoses, which risks underestimating diagnoses due to a lack of inclusion of undiagnosed cases. Nonetheless, the reported average positive predictive value of diagnoses in the CPRD was 89% with 92% completeness when compared to national registries [177]. This is further improved for conditions covered under the UK's QOF [172], which includes the majority of the comorbidities used in this study, that benefit from high reliability of recorded diagnoses. In addition, from a policy perspective, diagnoses recorded in health records are likely to form the basis for service planning and payment.

There were some conditions, such as arthritis and adjustment disorder, that were associated with a lower relative risk of mortality (i.e. HR<1.0) compared to those without those conditions, as opposed to most other additional comorbidities where there was an associated higher relative risk compared to those without the condition. These lower associations were present even when residual confounding by age was addressed by using age as a time-scale. The reason behind the protective effect of these conditions could not be explained by this study. It has been shown that non-utilisation and poor quality of health care are major drivers of excess mortality [265]. It is possible that residual confounding from health system factors, such as higher consultation rates, longer consultations, and better coordination of care for patients with these conditions, could explain the apparent lower relative risk of mortality.

Risk factors (i.e. hypertension, obesity, hyperlipidaemia) were not included as additional comorbidities because the aim of the study was to examine comorbidities that could explain relative mortality risk in excess of the risk of individual cardiometabolic conditions. In the ERFC study, it has been shown that adjustment for risk factors further reduces the relative risk of all-cause mortality [45], and it would be expected that the HRs estimated in this study would similarly be reduced with additional adjustment for risk factors.

This study also only examined all-cause mortality as an outcome, which is only one of several important health outcomes for patients with multimorbidity. With increasing life expectancy, patients are expected to live longer, and quality of life measures have become an important part of multimorbidity research [3]. Examining these other outcomes was beyond the scope of this study, and the CPRD does not have reliable detailed data on quality of life measures.

A more general discussion of EHR and CPRD strengths and limitations is included in section 8.3

7.5.4 Implications

This study shows that additional comorbidities in patients with cardiometabolic conditions significantly contribute to relative mortality risk and emphasises the need for clinicians to assess additional comorbidities in determining long-term prognosis for patients. Although cardiovascular diseases are the largest burden of disease and leading cause of mortality worldwide [266], this study suggests the contribution of these conditions to cardiometabolic comorbidity leads to minimal interaction and does not increase risk above what is expected additively. This suggests that the relative mortality risk of cardiometabolic conditions is overlapping, and probably explained by common pathophysiology, risk factors and management. In fact, this study shows discordant conditions, especially cancer, have a higher relative mortality risk than any of the cardiometabolic conditions. Although end-stage cancers often dominate clinical encounters, other conditions, such as dementia and substance abuse, also have a higher relative mortality risk compared to other cardiometabolic conditions. A more holistic approach to managing long-term prognosis is needed to reduce the burden and relative mortality risk of multimorbidity.

7.5.5 Future research

Further investigation into the causal association between cardiometabolic conditions and overlapping relative mortality risk is needed. It is likely that shared pathophysiology or risk factors, such as smoking, hypertension and obesity, interact with

diseases to reduce the relative risk of mortality associated with each individual condition in multimorbid patients. A lack of adjustment for these shared risk factors likely contributes partly to relative mortality risk, and adjustment for them would made the HRs less strong. To explore this further, analyses could adjust for these risk factors. Previous research has shown that the accumulation of cardiovascular disease, stroke and diabetes is partly due to shared risk factors [255]. Another way of looking at this would be to look at cause-specific mortality (e.g. CVD), where one would expect to see stronger HRs but hopefully less increase in them with adjustments for additional comorbidities. This was not done for this study due to the lower number of expected events and the additional considerations required for this type of analysis e.g. competing risk models for cause-specific mortality analyses, which were beyond the scope of this study. Another direction of study could examine combinations of discordant condition combinations and their effect on relative mortality risk - if the hypothesis of shared risk factors driving overlapping relative mortality risk is true, discordant conditions would not demonstrate overlapping relative mortality risk. On the other hand, it may also be possible that chronic conditions share pathological mechanisms that lead to death, such as inflammation [82], which means that all combinations of conditions, regardless of whether or not they are concordant, would likely have an element of overlapping risk. The overlapping risk of mortality in cardiometabolic multimorbidity could also be due to shared management, and the disease-disease interactions for cardiometabolic conditions that we observed could also be extended to disease-treatment, disease-environment and other interactions for further adjustment.

Another interesting area of further research is the sequence and timing of accumulating cardiometabolic conditions. The order of developing conditions could be important in relative mortality risk, for example, patients who develop MI and then diabetes could have a higher relative mortality risk compared to patients who have diabetes and then MI, as diabetes is a "silent" disease and part of its management is targeted at reducing macrovascular events, including MI, that could lead to reduction in relative mortality risk [267]. There has also been some

evidence to suggest that the anti-diabetic drug metformin reduces the incidence of MI and mortality [268]. Furthermore, the time gap between diagnoses could also be important, as a rapid accumulation of conditions could be indicative of undiagnosed disease being uncovered with increased healthcare utilisation after an incident disease diagnosis, which could be important in determining relative mortality risk [269]. The timing and sequence in the trajectory of multimorbidity may also explain the apparent reduced relative risk of mortality for additional comorbidities e.g. asthma, arthritis, found in this study.

Future investigation could also directly compare models with additive and multiplicative hazard for cardiometabolic conditions. In this study, as the population sample size was large, and mutually exclusive populations with combinations of the three cardiometabolic conditions could be examined, the HRs for mortality could be calculated for each of these sub-groups. Another way of examining risk associated with each individual condition is to examine each condition in an additive model, and compare this model with a model including interaction terms. If interaction is shown to be significant and improve model fit, this would suggest that interaction between conditions is likely to significantly contribute to relative mortality risk and deviate from an additive model. The direction of the coefficient of interaction terms would indicate the positive or negative nature of the interaction. For example, a negative interaction term for MI and diabetes, would indicate that the relative mortality risk in MI is reduced from diabetes compared to those with no MI.

Future research could also focus on validating relative mortality risk in a range of contexts. Although the CPRD is generalisable to the UK, and likely to reflect patterns in similar well-developed countries such as US, Canada and Australia, whether these associations occur in lower and middle income countries is unknown. Furthermore, more than 90% of the population in this study was of white ethnicity, and further research is needed to determine whether the relative risks are higher or lower in other ethnic groups.

7.5.6 Conclusions

Additional comorbidities contribute significantly to relative mortality risk in patients with cardiometabolic conditions. The overall relative mortality risk in cardiometabolic patients is less than additive when adjusting for age, sex, SES and additional comorbidities. The treatment of multimorbid patients requires a holistic view of their chronic conditions to determine long-term prognosis. Further research is needed to understand the causal mechanism of comorbidities and overlapping risk in multimorbid patients.

8 Discussion

Contents

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8.1 Summary of main findings

This thesis consisted of two methods chapters and three results chapters on the topic of multimorbidity and cardiovascular disease (CVD) using the United Kingdom's (UK) Clinical Practice Research Datalinke (CPRD). This discussion chapter will discuss the overall results of this thesis; specific discussion points for each chapter

are provided in the respective discussion sections.

Chapter 3, as a methods chapter, outlined foundational work that determined the approach for measuring multimorbidity in the CPRD. It described the literature review process and results. There were two main outputs. Firstly, the operational definition of multimorbidity (2 or more conditions in the same individual) and identifying the utility of examining multimorbidity as a count of conditions and specific comorbidities. Secondly, the selection of 60 chronic conditions to consider in subsequent studies, which were chosen based on clinical importance and high prevalence in the UK population, to ensure relevance of results to clinical practice and policy.

Chapter 4, as the second major methods chapter, described the process of converting raw CPRD data into data for epidemiological analyses. The contents of this chapter provided enough detail for a reader to replicate use of the CPRD in subsequent analyses of this thesis. The majority of work in this chapter was subsection 4.2.4, phenotyping condition diagnoses, which involved synthesis of previous work and assessment of appropriateness for use in the CPRD, a highly manual process of checking every code against clinical expertise and knowledge of the CPRD.

Chapter 5, the first of three results chapters, laid out the context for the prevalence of comorbidities in a population with incident CVD. The strength of the analysis was in using age/sex-standardisation of prevalences, and measuring these prevalences in a population at the time of diagnosis of CVD (defined as stroke/TIA or IHD), which allowed comparison of like for like. This analysis found that the burden of multimorbidity has been increasing over time. On average, older patients, women and socially-deprived groups had higher numbers of comorbidities, but the type of comorbidities varied by age and sex. Additionally, 4 out of the 10 major comorbidities were non-cardiometabolic.

Chapter 6 examined patients with incident hypertension, the single biggest risk factor for CVD. In this analysis, patients were followed up 5 years before and 10 years after diagnosis, examining the outcomes of blood pressure and prescription of

anti-hypertensives using linear and Poisson regression in a landmark cohort design. The results showed that patients with multimorbidity, had lower BP and higher numbers of prescriptions, rather than high BP and lower number of prescriptions as a result of clinical complexity, which is the common perception. Furthermore, the association between higher numbers of comorbidities and lower BP were not fully explained by treatment differences. In fact, they were largely driven by the BP at time of diagnosis, suggesting that the diagnostic BP threshold for hypertension has an important role in determining long-term trajectories of BP.

Chapter 7 examined the association between cardiometabolic comorbidity (of MI, stroke and diabetes) and mortality risk. This study tested the hypothesis that cardiometaboic conditions interact to increase mortality risk in a multiplicative fashion, as shown in an Emerging Risk Factors Collaboration (ERCF) study [45]. The analysis used Cox proportional hazards regression with adjustment for an additional 53 comorbidities, and then further adjustment for time-updated comorbidities during follow-up. The study showed that in baseline models adjusted for age, sex and SES, mortality risk for the three cardiometabolic conditions was less than additive, rather than multiplicative, in nature. Adjustment for additional comorbidities reduced both the absolute HRs and the magnitude of effect of each cardiometabolic comorbidity, and this reduction was even greater for time-updated additional comorbidities.

A summary table of each chapter is provided below.

Table 8.1: Summary of main findings in this thesis

Chapter	Chapter type	Aim	Methods	Results	Implications
3: Multimorbidity framework	Methods	To identify an appropriate framework for researching multimorbidity in the CPRD	Literature review	Methods of measuring multimorbidity are highly heterogeneous and an approach to multimorbidity must be tailored to the specific research question. For this thesis, a list of 60 conditions (clinically significant and highly prevalent) were chosen to measure unweighted disease counts, specific comorbidities and comorbidity combinations.	The subsequent analyses in this thesis used the condition list and method of multimorbidity measurement derived from the results of this chapter.

Chapter	Chapter type	Aim	Methods	Results	Implications
4: Data source: The Clinical Practice Research Datalink	Methods	To describe the CPRD and conversion of raw data to data ready for epidemiological analyses, including phenotyping conditions	N/A	Algorithms for extracting and cleaning data	The methods described in this chapter can be used to replicate the analyses in this thesis

Chapter	Chapter type	Aim	Methods	Results	Implications
5: Multimorbidity in incident cardiovascular disease (CVD)	Analytical	To investigate the prevalence of comorbidities in patients with incident CVD, how it changed between 2000 and 2014, and how it varied by age, sex, and socioeconomic status (SES)	Descriptive study of patients with incident CVD (IHD or stroke). Age/sex-standardised prevalences were calculated for number of conditions and specific comorbidities based on 56 chronic conditions. Prevalences were also calculated, stratified by year of incident CVD diagnosis, age-group, sex and SES	The burden of multimorbidity and comorbidity in incident non-fatal CVD has increased over time. On average, older patients, women and socially-deprived groups had higher numbers of comorbidities, but the type of comorbidities varied by age and sex. Cardiometabolic conditions contributed substantially to the burden but 4 out of the 10 major comorbidities were non-cardiometabolic.	The current single-disease paradigm in CVD management needs to broaden and incorporate the large and increasing burden of multimorbidity and comorbidity.

Chapter	Chapter type	Aim	Methods	Results	Implications
6: Multimorbidity and blood pressure	Analytical	In patients with incident hypertension, investigate the association of number and type of comorbidity with systolic BP and anti-hypertensive prescription	Multiple landmark cohort study of patients with incident hypertension. Linear regression was used to examine the association between comorbidities and blood pressure, and Poisson regression was used to investigate the association between comorbidities and antihypertensive prescriptions.	The widely held assumptions that multimorbid patients receive poorer quality health care, and are less likely to achieve clinical targets, were not supported by the findings of this study. Patients with comorbidity and multimorbidity were generally more likely to have lower BP, driven largely by BP at diagnosis.	These findings demonstrate the heterogeneity of BP management by comorbidity status and emphasises the need to diagnose and treat at a lower diagnostic BP threshold to successfully lower BP for all subgroups.

Chapter	Chapter type	Aim	Methods	Results	Implications
7: Multimorbidity and mortality risk	Analytical	To investigate the effect of comorbidity on risk of mortality in patients with cardiometabolic conditions (myocardial infarction, stroke and diabetes)	Cohort study of patients from 1st Jan 2005 to 31st Dec 2014. Cox proportional hazards regression was used to investigate the hazard of death of patients by cardiometabolic status. Models were adjusted for additional comorbidities, and then also time-updated.	The relative mortality risk of multiple cardiometabolic comorbidities decreased with adjustment for additional comorbidities. This relative risk of mortality was less than the additive relative risk of the individual conditions.	Additional comorbidities partly explain the less than additive relative mortality risk in multiple cardiometabolic comorbidity, and should be taken into account in the management of multimorbidity.

8.2 Addition to previous literature

8.2.1 Longitudinal analysis of multimorbidity

The analyses in this thesis go beyond the cross-sectional studies of literature in the field of multimorbidity. There are very few longitudinal studies in multimorbidity; the large majority of previous studies are cross-sectional [269]. For example, the landmark study that first described the association between social deprivation and higher numbers of conditions was a cross-sectional study of 1.7 million Scottish primary care patients in 2007 [14]. The longitudinal approach in this thesis went beyond cross-sectional studies, and provided valuable information on temporal trends, as well as stronger evidence for causal associations, as the risk of reverse causality was reduced when time between exposure and outcome were accounted for in all three analytical chapters. Time was also tailored to each specific research question, which was possible because each study population was selected from an open cohort in the CPRD, with accurate data available on dates. The CPRD provided an opportunity to design clinically-relevant studies by examining time from different perspectives. In chapter 5, the population was followed up using calendar year of diagnosis of CVD; in chapter 6, time from diagnosis of hypertension was used; and in chapter 7, two time-scales: follow-up time from start of study, and age. Additionally, the availability of date data enabled this thesis to extend beyond other longitudinal studies, such as the ERFC, by using time-updated data on a range of variables, including 53 additional comorbidities (chapter 7)[45].

8.2.2 Focusing on CVD and multimorbidity

Multimorbidity is an important issue in CVD, which contributes to the largest burden of mortality and morbidity worldwide [266]. Furthermore, CVD increases the risk of multimorbidity or comorbidity [270]. Despite the rising burden of both multimorbidity and CVD, multimorbidity in CVD patients is an under-researched area. There have been a series of large-scale studies on US Medicare beneficiaries

that have examined comorbidities in CVD patients, but these have all been cross-sectional, and only include other cardiovascular conditions [6, 195]. This thesis strengthens the exisiting evidence by providing large-scale, longitudinal analyses of multimorbidity in range of issues related CVD and its management.

Most studies examining comorbidities and CVD have limited their investigation to cardiovascular-related comorbidities [6, 195, 270]. A systematic review has concluded that the rationale behind the measurement and selection of comorbidities in CVD research has generally been unsubstantiated [271]. In all three analyses in this thesis, I used an approach to measure multimorbidity and comorbidity based on a comprehensive literature, and also found that the contribution of non-cardiometabolic conditions to the burden, management and mortality risk in patients was significant (chapter 5). This is consistent with results from the few previous studies that have been conducted on large populations, such as a Dutch hospital register study examining patients admitted for CVD between 2000-2010, that found more than 40% of all CVD patients had at least one non-cardiovascular comorbidity [272]. It has also been shown that the presence of non-cardiovascular comorbidities, such as osteoarthritis, increased physical limitations associated with CVD [273], and severity of non-cardiovascular comorbidities increased mortality risk and hospitalisation [274]. The evidence presented in this thesis supports the case for future health planning in CVD to incorporate the prevention and management of comorbidities, both related and unrelated to cardiovascular disease.

8.2.3 Overlapping risk and management in multimorbidity

Although it is clear that multimorbidity cannot be considered simply as a sum of individual conditions, whether the sum is greater than the constituent parts is unclear.

Chapter 5 showed the co-occurrence of chronic conditions, whether concordant or discordant, is high. A large number of previous studies also support this finding and show that multimorbidity occurs more frequently than expected by chance [14, 26, 6, 275]. It is likely that shared risk factors, such as smoking, obesity, poor

diet and physical inactivity, and shared pathophysiological mechanisms, such as inflammation, contribute to the development of multimorbidity [3, 276].

Chapter 6 showed hypertensive patients with multimorbidity were more likely have lower BP and be prescribed more antihypertensive medications, independent of health service utilisation. There has not been much research in this area, and the study was unable to explain why multimorbidity was associated with lower BPs, compared to those with lower numbers of conditions, at all time points after hypertension diagnosis. This study challenges the assumption that multimorbid patients are complex and hence their care is compromised [94], but rather, emphasises an association between increasing numbers of comorbidities and lower BP as well as higher likelihood of antihypertensive prescription, partly attributed to diagnosis at a lower BP threshold.

Chapter 7 challenged the idea that multimorbid patients have worse outcomes, by examining the relative mortality risk of patients with single vs multiple conditions and demonstrating the relative mortality risk for multiple conditions was less than the additive relative risk of individual conditions. This is in opposition to what has been demonstrated in a large-scale cohort study conducted by the Emerging Risk Factors Collaboration, where they showed that the mortality risk of three cardiometabolic conditions was multiplicative [45]. In this thesis, the mortality risk analysis in chapter 7 adjusted for additional comorbidities, which were shown to significantly increase mortality risk and partly explain the mortality risk in patients with any of the three cardiometabolic conditions. From a pathophysiological viewpoint, multimorbid patients have conditions that have shared risk factors and lead to overlapping pathological mechanisms, and hence, it is logical that conditions share overlapping risks for mortality, rather than interact to increase mortality risk more than expected for each single condition. It is also plausible that the positive effect on management of higher numbers of conditions, described in chapter 6, also contributes to lower mortality risk.

This thesis views multimorbidity from multiple different angles using the same datasource, the CPRD, and confirms existing evidence that although chronic

conditions are more likely to co-occur due to their shared pathophysiolgy, the effect on management and health outcomes is more positive than the common assumption that multimorbid patients are complex, receive compromised care, and are hence worse off than those who have fewer conditions.

8.3 Strengths and limitations

The following table provides an overview of the strengths and limitations for the thesis overall, and for each analytical chapter.

Table 8.2: Strengths and limitations

Chapter	Strengths	Limitations	Explanation/Potential steps to address limitations
Overall	• The CPRD is a large, longitudinal dataset with a breadth of variables • The definition of multimorbidity and selection of conditions is evidence-based, comprehensive and pragmatic • The phenotyping of conditions is extensive, and tailored to each research question	• The CPRD has missing data e.g. interrupted time continuity, genetic data not available • the quality of data in the CPRD is subject to external factors outside the control analyses, such as consultation rates, policy changes, QOF* • replication of findings in contexts outside the UK is needed to strengthen the findings in this thesis	• replication of studies using other datasets

Chapter	Strengths	Limitations	Explanation/Potential steps to address limitations
Chapter 5: Multimorbidity in incident cardiovascular disease	• Use of longitudinal data to examine temporal trends • Large, representative sample of incident CVD patients • Power to examine differences in prevalence by subgroups: age, sex and SES • Large number and range of comorbidities included • Incident population of CVD patients allowing valid comparisons	• Dependence on recorded diagnoses	• recorded diagnoses are representative of health service utilisation and changes in clinician behaviour, which is highly relevant to health policy and service planning

Chapter	Strengths	Limitations	Explanation/Potential steps to address limitations
Chapter 6: Multimorbidity and blood pressure	• Large, representative sample of incident CVD patients • Comprehensive data available on outcomes: BP clinical measurements and prescription of antihypertensives • Large number and range of comorbidities included • Incident population of hypertensive patients allowing valid comparisons	• Missingness of BP readings • Data not available on adherence to medications	• further studies required to explain the mechanism of higher numbers of conditions leading to lower BP e.g. using data on medication adherence

Chapter	Strengths	Limitations	Explanation/Potential steps to address limitations
Chapter 7: Multimorbidity and mortality risk	• Power to examine sub-groups of patients with combinations of cardiometabolic conditions • Comprehensive adjustment for confounders, including additional comorbidities • Longitudinal data available for time-updating variables	• Other areas of investigation outside the scope of the study e.g. adjusting for shared risk factors, examining discordant condition combinations	• Further studies required to explain the reason for a less than additive relative mortality risk of multiple conditions

*Quality and Outcomes Framework

The next two sections will discuss the strengths and limitations of the overall thesis in more detail.

8.3.1 Strengths

The CPRD

The CPRD is a dataset that provides linkage of primary care data with secondary care, disease registries and mortality data. It is beneficial to epidemiological research in the UK, and globally. The CPRD is a unique and powerful dataset. Given the paucity of data and linkage of EHR in other countries, it is difficult to replicate studies of this scale using data that is not the CPRD. The results from the analyses performed in this thesis have global implications as they provide a representation of what is likely to be occurring in other high-income countries such as Australia, Canada, the United States (US) and other European countries, but it is also likely to represent the future of lower and middle income countries, as the burden of multimorbidity from chronic non-communicable diseases rises over time [3]. This provides a great opportunity for the global scientific community to explore multimorbidity and curb the trajectory of the increasing burden in order to reduce strain on health care systems designed for treating individual conditions.

Validity of the CPRD

There have been several studies that have shown high concordance of results from the CPRD with results from studies using other data sources [277]. For example, the CPRD has shown that there was no correlation between the measles, mumps and rubella vaccine and risk of autism [278], supporting the results of a previous study using a case-series method [279]. Another example is the CPRD being used to confirm the association between increased risk of venous thromboembolism and hormone replacement therapy [280, 281]. The CPRD has also been used to validate the QAdmissions score for estimating emergency hospital admissions, with results in the CPRD similar to those conducted on a subset of the QResearch database that

was used to develop the risk prediction algorithm [282]. The CPRD is generally consistent with results using other methods or data sources.

There has also been much investigation into the validity of diagnoses recorded by GPs in CPRD for a range of comorbidities. The average positive predictive value (PPV) is 89% with 92% completeness when compared to national registries [124, 283]. It has also been shown that people with asthma or COPD can be accurately identified in the CPRD using Read codes, with a PPV of more than 80% when compared with clinician judgement, and the inclusion of additional variables such as spirometry and prescription of medications, does not improve accuracy of diagnoses [284, 285]. Furthermore, the use of multiple sources of linked EHR, as was used in this thesis, improves completeness and diagnostic validity of diagnoses [177]. Furthermore, the conditions covered under QOF, which were selected for use in this thesis, have been shown to have improved completeness of recording after 2004, when QOF was introduced [9]. The methods used to select conditions and identify diagnoses in this thesis have improved the reliability and validity of results presented.

The reliability and validity of results derived from the CPRD can be improved through appropriate data extraction for analysis. There is considerable scepticism in the research community regarding the reliability and validity of data from the CPRD, as the routinely-collected data are not collected specifically for research purposes. As the data are recorded by GPs during a consultation, data quality checks must be performed before analytical use [9]. These data quality checks were followed in this thesis, including selection of patients and practices with research-quality data, and exclusion of values outside a reasonable range (refer to chapter 4). All appropriate and pragmatic measures have been taken to ensure the validity and quality of data used in analyses for this thesis were optimised, and the specific limitations of using the CPRD are discussed further in section 8.3.2.

Large population size

The analyses in this thesis have benefited from the large population sizes available in the CPRD. Chapter 5 examined 229,205 patients with incident cardiovascular disease, chapter 6 analysed the trajectories of 295,487 patients with incident

hypertension and chapter 7 investigated mortality risk in 2,099,224 patients with an active record in 2005. These sample sizes are much larger than what would be available in traditional cohort or nested cohort studies, where similar studies in the same area have been limited to 1000s, and sometimes only 100s of people. Comparing this with other studies using the CPRD, 1.7 million Scottish patients have been used to investigate multimorbidity in a cross-sectional descriptive analysis [14], 7.7 million patients have been used to examine trends in diabetic retinopathy [286], and 5.24 million patients have been used to investigate the association between BMI and cancer [160]. The population selection criteria used in each analysis has meant that not all 7.6 million patients in the CPRD data cut available to the TGI have been included, but the pay-off is high quality data for a population specific to each research question.

The large sample sizes have several benefits. Firstly, it provides high-powered studies where the margin of error is small. Most of the results from this thesis had narrow confidence intervals and were statistically significant. Secondly, smaller effect sizes can be detected with larger sample sizes. This was particularly relevant to detect differences in effect sizes of sub-groups with or without a specific scomorbidity, where previous studies have not had the adequate power to detect such effects. For example, a previous study has found no difference in BP control by comorbidity type [238], which is challenged by the results in chapter 6. Finally, a large sample size also makes it possible to stratify and examine sub-groups with sufficient power to detect associations, which was particularly useful in Chapter 5 to examine prevalence of comorbidities stratified by age, sex and SES quintiles.

Longitudinal data

The availability of longitudinal data is an advantage, particularly compared to much of the current literature that has used cross-sectional data, and this has been beneficial for all analyses in this thesis, as discussed above in subsection 8.2.1. Firstly, temporal trends of incidence and prevalence could be calculated, as in chapter 5 where CVD incidence and prevalence of multimorbidity and specific conditions were examined over time. Secondly, cohort effects could be adjusted

for. For example, in chapter 5, the year of diagnosis of CVD, which reflect general management patterns for CVD cohorts, was adjusted for. Thirdly, the effects of reverse causation could be addressed by ensuring adequate time between exposure and outcome, as in chapter 6. Finally, Cox regression analyses could be performed, and time-varying variables could be updated, as shown in chapter 7.

Breadth of variables

The CPRD has a wide range of variables available that provide a range of demographic, clinical and social data points on each patient (described further in chapter 4). This has made it possible to examine a range of variables, such as clinical BP measurements, anti-hypertensive prescriptions and diagnosis of comorbidities, all in a single study (chapter 6). For this thesis, this has particularly been useful for identifying a large number and variety of comorbidities (up to 60), over and above what most studies in multimorbidity have been able to examine e.g. 40 conditions in a Scottish population [14].

Routinely-collected data

The CPRD is a representation of health in the community. CPRD patients have been shown to be broadly representative of the general UK population for age, sex and ethnicity [9, 287]. Therefore, the population is often more representative of the general population compared to other epidemiological studies, where issues like selection bias and the healthy-cohort effect can lead to over or under-estimation of results. Some of the differences in the magnitude of results in this thesis, such as the lower mortality risk in patients with cardiometabolic conditions compared to cohort studies in chapter 7, could be explained by differences in the populations represented by the datasets used [45]. As the CPRD reflects real health care utilisation, the results from this thesis have high relevance to health service planning and policy implementation.

Other benefits of EHR

Using EHR reduces the likelihood of some forms of bias. It reduces recall bias that is often associated with self-report data, as EHR provides specific timing

for variables such as doctor-diagnosed conditions, blood test results and clinical measurements [9]. This has been used to re-evaluate controversial topics, for example, a longitudinal study investigating the risk of autism associated with vaccinations [288]. It also reduces observer bias, as neither patient nor practitioner are aware of the future research questions that will be applied to the routinely-collected data [9]. Furthermore, the Hawthorne effect (change in a subject's behaviour due to knowledge of being observed) or social desirability bias is less likely to be an issue in EHR [96]. An additional benefit of CPRD, as a GP record, is the accuracy of event dates that are not prone to recall bias.

Definition of multimorbidity

Multimorbidity, a well-understood yet nebulous concept, does not have a standardised definition (chapter 4). This is problematic, as studies cannot be directly compared to each other. However, studies have different research questions, which require different definitions of multimorbidity [3]. In this thesis, a literature review was conducted to select the method of measurement and component conditions in the definition of multimorbidity used in subsequent analyses. This approach led to a broad range of conditions that were highly prevalent and clinically significant in the UK, which provided a strong rationale that went beyond the majority of studies in the field. Additionally, these conditions are highly relevant to other contexts around the world, including lower and middle-income countries, such as South Africa, where there is a high "double-burden" of disease with both non-communicable diseases and communicable disease such as HIV/AIDS, which are covered by the extensive condition list used in this thesis.

8.3.2 Limitations

The CPRD

Missing data

Missing data in the CPRD must be carefully considered by understanding the mechanism and pattern of missingness and applying appropriate techniques to

handle missing data [9]. Complete case analyses may bias results, as recording of patient data is dependent on GP visits. For example, patients with hypertension are more likely to have more frequent recordings of BP (chapter 6), and BMI may be more frequently recorded in patients with an ongoing serious health issue [9]. However, it has also been shown that historical measurements (e.g. baseline) of variables such as BP and BMI can be reliably used to predict later disease risk [289]. Furthermore, as is widely accepted practice using the CPRD data, absence of a diagnostic code is treated as absence of a disease [9]. This can be problematic, as absence of a code could be due to a patient not attending health care visits, GP not recording, or GP recording under a different field, such as free text. However, the validity of diagnoses in the CPRD has been well-established [124].

Interrupted time continuity of data

Although the EHR provides a holistic view of patients in the general population, one of the limitations is gaps in data recording in EHR. EHRs capture open cohorts of patients, where the investigator defines the period of observation of the patient [97, 96]. In this thesis, criteria were applied to ensure that individual patient observation periods coincided with periods of relative data quality. However, gaps in patient records still occur. A gap in a patient record could indicate that the patient left the practice, left the NHS, has been well enough to not to seek care, or may be so unwell that they have missed appointments [96]. This information cannot be ascertained from the raw EHR, and can lead to bias in calculating person-time relevant for incidence estimates or Cox regression analyses. Additionally, data may be left or right censored, as the data available for study is determined by when a patient seeks care, and not by follow-up points determined by a research protocol [96].

Data standardisation

Another limitation is that data are not collected in a standardised format. Not all patients will have the same data collected in the same way. Traditional epidemiological studies often use standardised questionnaires to collect data, whereas EHR may have data collected in different parts of the record, and recorded in different formats such as diagnostic codes, referrals, medication orders or unstructured free

text [290]. This makes it difficult to define algorithms for case ascertainment, which is why a robust phenotyping process for conditions and other clinical variables, as described in subsection 4.2.4 is important.

Mild conditions

The EHR is not strong for investigating conditions that are mild. This occurs because patients may not seek care, the condition is self-resolving e.g. sprains, or does not require frequent care e.g. mild asthma [96]. These conditions affect some of the conditions used in this thesis, such as asthma, and most chronic conditions in their early phase e.g. early diabetes (only lifestyle interventions recommended, patients do not have to seek care for repeat prescriptions or check-ups for end-organ damage). However, for the most part, conditions in thesis were chronic and required ongoing contact with care providers.

Data fields not available

There are several types of variables that are not available or frequently not recorded in the CPRD, which restricts the types of studies that are possible. Extensive data on social support, activities of daily living, over-the-counter medications and treatment adherence, are generally not available [9]. The CPRD also does not have genetic data, nor is it possible to link family members because of restrictions on data privacy [96].

The CPRD is also generally not a good source for data for the patient perspective. Data from prospective cohort studies demonstrates varying levels of disagreement between patient perceived illness and clinician-reported diagnoses [291], which can have implications in defining multimorbidity in patient cohorts. Self-report data, rather than routine records, is generally better for symptoms-based conditions [292].

The analyses in this thesis were also not able to assess the effectiveness of interventions, which is a growing area of interest in the field of multimorbidity. A key limitation is the lack of patient perspective data, discussed above, available in the CPRD. There has been an increase in literature exploring the importance of the patient perspective in effective care for multimorbidity. A convening in 2012

of experts in multimorbidity designed the Adriadne principles for guiding decision-making for multimorbid patients, which included an assessment of interactions between prioritisation of the patient's preferences and the patient's condition, treatments & context for personalised management [138]. A Cochrane collaboration on personalised care planning concluded that self-management efficacy, on top of physical and mental health status, was critical for successful personalised care planning, and was even greater with interventions that were intensive, comprehensive and well-integrated into routine care [293], which are variables that are generally not available for assessment in the CPRD.

External influences

Patient factors

The CPRD exclusively records data on patients who decide to use primary health care services. This results in a selection bias of people who are more likely to have high health literacy, and/or care about their health [9]. This means that patients who do not see a GP are not included, and these patients are more likely to be less healthy than the CPRD population, as a result of less preventative health interventions and check-ups, leading to a population selection bias towards the 'worried well' and 'worried unwell.' [96]. However, this bias is lower in magnitude than other epidemiological studies, where participants must actively opt in [294]. Additionally, certain sub-populations who do not access GP services are missing from the CPRD, such as homeless people, prisoners and private patients [9].

Consultation rates

There are many factors that determine GP consultation rates. It has been shown that smokers, females, older age groups, and practices with more GPs staffed, have increased consultation rates [295]. It has also been shown that being female and older, is associated with longer GP consultations [296]. The overall workload in primary care for England has increased by 16% and may have extended beyond the capacity of primary care to provide adequate quality clinical care to patients [297]. All of these factors can affect the frequency of recording of data in the CPRD

and hence skew results, and must be taken into account when interpreting results from the CPRD. For example, the relatively high prevalence of higher numbers of conditions in females is likely to be partly attributable to higher consultations rates and longer consultation times.

Clinician factors

There are many factors that can affect the accuracy of data recorded in the CPRD, and although the validity and reliability of CPRD has been established, there are still some patterns that are important to be aware of when interpreting results from the CPRD. It has been shown that the quality of guidelines for diagnostic tests is associated with clinician adherence, so changes to clinical guidelines may change diagnosis rates for disease [298]. There has also been a general trend in overdiagnosis over time, which has been shown for cancers, and may contribute to the increasing prevalence of higher numbers of conditions demonstrated by this thesis (chapter 5) [299]. There have also been reports of differences in recording by practice, which can also influence diagnosis rates and level of missingness in the data [124, 96].

8.4 Implications

8.4.1 Clinical care

Overall, the results of this thesis show that there is a large burden of comorbidities that need to be considered in clinical guidelines and practice. This thesis demonstrated that different subgroups were likely to have different numbers or combinations of conditions, and these conditions affected a patient's BP trajectory, likelihood of BP treatment, and relative mortality risk. A single-disease approach to CVD management is likely to miss the large burden of comorbidities, especially discordant conditions, in certain sub-groups. Some risk scores used for CVD diagnosis and management account for comorbidities. For example, the QRISK3 score incorporates the diagnosis of a range of comorbidities including chronic kidney disease, migraine and severe mental illness [300]. This highly focussed approach moves closer towards a holistic approach to multimorbidity. Clinicians must find

a balance between accounting for comorbidities to tailor clinical care vs applying broadly effective approaches to all patients. On the one hand, a shared decision-making approach to patient care that considers an individual's circumstances is needed to fully integrate the range and impact of a patient's comorbidity profile on clinical care and prognosis. On the other hand, all patient sub-groups seem to benefit from a lower diagnostic threshold for hypertension diagnosis. With the increasing burden of multimorbidity, it is increasingly important for clinicians to balance a patient-centred approach with evidence-based medicine.

Holistic approach to patient care

The large and increasing burden of multimorbidity supports a holistic approach to patient care that moves away from the single-disease paradigm. This is particularly true of discordant conditions. Four out of the top ten most prevalent comorbidities in incident CVD patients were non-cardiometabolic, and included arthritis, anxiety and asthma. These conditions have different risk factors as well as management, and prioritisation of managing these conditions should be a collaborative conversation between clinician and patient [11]. Different discordant conditions also differentially affect management and mortality risk, for example, dementia is associated with a lower BP in hypertensive patients compared to patients without dementia (chapter 6), and cancers are associated with the highest relative mortality risk out of 53 additional comorbidities (chapter 7). Clinicians need to consider the broad range of comorbidities and their wide-ranging impact to provide adequate care to multimorbid patients.

The importance of mental illness as a comorbidity provides strong evidence for the integration of care for mental and physical conditions. Mental illnesses were highly-prevalent (chapter 5), and were also associated with lower BP and higher relative mortality risk (chapter 6, chapter 7), showing a direction of association that was consistent with other physical conditions. Regardless of whether mental illness is a risk factor or consequence of other chronic conditions, mental illnesses

should be considered alongside physical conditions in the ongoing care of chronic conditions [301].

Outcomes associated with multimorbidity

The assumption that multimorbid patients receive poorer quality care and are at a much greater risk of mortality are challenged by the findings of this thesis [1]. Chapter 6 shows a higher number of conditions was associated with a lower, rather than higher, BP in patients with hypertension; Chapter 7 shows the relative mortality risk of concomitant cardiometabolic conditions was less than the additive risk of the individual conditions, and age of death does not largely differ from those without any conditions. Previous evidence has also shown that multimorbidity is associated with better quality of care in elderly adults [244]. Clinicians should carefully consider assumptions about multimorbid patients and treat patients with the knowledge that poorer health outcomes are not necessarily the norm in multimorbid patients.

Lower thresholds for diagnosis

Chapter 6 demonstrated that the trajectory of lower BP after hypertension diagnosis was partly driven by a lower BP at diagnosis. This evidence has broad implications for BP management, and also potential implications for conditions that use the same measurement criteria to diagnose and assess success of management, e.g. HbA1c$\geq$7mmol/L is the diagnostic threshold, as well as target, for management of diabetes mellitus [302]. This is particularly relevant to multimorbid patients, as the pattern of lower BP was evident in all comorbidity sub-groups. Given the complexity and burden of treatment associated with multimorbidity [303], approaches that are broadly effective for all sub-groups are an attractive opportunity to improve the care for all patients with multimorbidity, regardless of their comorbidity profile. More research is required to discover and investigate similar associations between multimorbidity and diagnostic thresholds.

The results of chapter 5, chapter 6 and chapter 7 are likely to be influenced by a lower threshold of diagnosis of concordant conditions to the index condition. For example in Chapter 5, "co-diagnosis" of hypertension with CVD is more likely than

with cancer. This may have exaggerated the reported prevalences of cardiometabolic comorbidities, relative to non-cardiometabolic comorbidities in an incident CVD population. Similarly for Chapter 6, co-diagnosis with cardiometabolic conditions in hypertensive patients would have led to higher populations in these subgroups compared to those with only discordant comorbidities. These effects are difficult to investigate using EHR and further studies using community data on under-diagnosis are required to explore this further.

8.4.2 Health care systems and policy

This thesis provides evidence for policy-makers to increase health systems support for multimorbid patients, as the burden of multimorbidity is large and has consequences for quality of care and prognosis. A health system tailored for multimorbid patients includes more integrated care with clear communication channels, a focus on generalism and primary care, and incentives for patient-centred approaches [2].

Integrated care

The large burden of discordant conditions suggests that patients with multimorbidity require an integrated approach to care. This includes greater coordination and communication between primary and secondary care, as well as a focus on generalist specialties, such as primary care and geriatrics, to adequately assess and monitor patients and the breadth of their medical issues [62, 56]. An integrated approach better addresses discordant conditions, such as depression and arthritis, which are associated with management outcomes and long-term mortality (chapter 6, chapter 7). This approach moves away from the single-disease paradigm, towards improving safety and quality of care by recognising the contribution of multiple interactions between conditions, therapy, and other environmental factors [11].

Electronic health records

EHR has great utility in providing valuable population health information on multimorbidity. This thesis uses the EHR to conduct retrospective analyses, ranging from descriptive analysis (chapter 5) to investigating associations between conditions

and blood pressure (chapter 6). Use of real-time EHR data could further support patients with multimorbidity. Better EHR support for team-based communication would help integrate patient care across specialties and care settings [11]. Integration of EHR with other data, such as physical activity data from wearables, or ambulatory blood pressure monitoring devices, may help coordination of care and a collaborative approach to disease monitoring between patients and clinicians [3]. It is likely that the ongoing advancement and standardisation of data in EHR will improve the accessibility and utility of EHR data [10].

Resource allocation

Broad approaches that cover multiple conditions are needed to provide adequate care for multimorbid patients. In this thesis, a lower diagnostic threshold for hypertension diagnosis was a key driver for a lower BP trajectory (chapter 6). The relative mortality risk of concomitant cardiometabolic conditions was also shown to be less than the additive risk, suggesting that there could be shared risk factors, or other interacting factors that contribute to the overlapping relative mortality risk in co-occurring conditions (chapter 7). Targeting broad approaches such as these are likely to improve multimorbid patient care beyond the single-disease approach.

There are many evidence gaps in the field of multimorbidity, and it is difficult to coordinate research efforts towards meaningful results to inform policy and practice. The Academy of Medical Sciences (AMS) working group on multimorbidity produced recommendations on future research directions for multimorbidity [3]. This report consolidated previous evidence to identify the cost-effective and urgent evidence gaps in multimorbidity. Among these recommendations, it was recognised that patients with comorbidities should be included in (rather than excluded from) research studies; existing data, such as independent patient data from existing studies, should be used in meta-analyses to examine subgroups of comorbidities for differences in effectiveness; and research analysis plans should include comparisons of those with and without comorbidities [3]. More efforts like the AMS multimorbidity working group, are required to focus resources to effectively improve multimorbidity research.

8.5 Future research

Multimorbidity is an increasingly important issue that is becoming increasingly more common. The quality of studies on multimorbidity has also increased with the demand for evidence to address health service planning and policy. Chapter 3 of this thesis informed the recommendation that studies investigating multimorbidity provide a clear rationale for the method of measuring multimorbidity [3]. Additionally, with the identification of the high burden of multimorbidity and the availability of data in EHR, as shown in Chapter 5, the importance of including multimorbid patients in traditional studies such as randomised controlled trials (RCTs) is being recognised. More than 75% of patients in RCTs assessing interventions for chronic conditions exclude patients with comorbidities [304]. Finally, this thesis provides evidence using EHR that challenges commonly accepted notions of multimorbidity (chapter 6, chapter 7).

An important step towards designing effective interventions for multimorbidity is understanding the development, progression and consequences of multimorbidity over time [11]. This thesis addresses these evidence gaps in relation to cardiovascular disease. Further research using longitudinal data is required to further improve the multimorbidity evidence base to inform policy, practice and research.

8.5.1 Replication of findings

The findings in this thesis have been conducted on the CPRD, and replication of findings using other data sources is needed to increase the strength of evidence. For example, replication using the UK Biobank would be useful to validate the results from this thesis. Furthermore, replication using data from other countries, such as South Africa and China, would be able to provide a comparison to analyse regional differences. For example, it would be expected that the burden of HIV/AIDS would be much higher in South Africa [3]. Indeed, it would be interesting to further these analyses in a lower or middle income country that is experiencing the "double-burden" of communicable and non-communicable disease.

8.5.2 Extending findings

Other index and combination conditions

The studies in this thesis have focused on CVD and it is not known whether the general patterns observed are also true in other index conditions. These analyses could be replicated for different conditions. For example, chapter 7 showed that the concordant cardiometabolic conditions MI, stroke and diabetes had overlapping increased mortality risk. Whether this association is true for discordant conditions, such as chronic kidney disease, chronic obstructive pulmonary disease and colon cancer, is yet unknown. As the permutations of condition combinations is large, machine learning approaches addressing the breadth of CPRD data could have great potential in extracting meaningful results.

Other outcomes

The analyses in this thesis were also not able to assess the patient perspective. This data is generally not available in the CPRD. Such data would allow examination of important outcomes for patient-centred care, such as quality of life and physical limitations [3]. Furthermore, this type of data from patients would be key in assessing effectiveness of interventions, where issues such as prioritisation, ability to self-manage and well-being are important to assess [47]. Further research is needed to examine the patient perspective.

Mechanisms

Another area of interest is the mechanism behind multimorbidity and how it changes care and prognosis. As described earlier in this discussion, this thesis suggests that concomitant conditions in multimorbidity affect management and relative mortality risk which may be due to the development of multimorbidity from shared risk factors such as lifestyle factors, inflammation or ageing-related mechanisms [256, 255]. Investigation into the mechanism of multimorbidity development may help understand how to prevent and further manage multimorbidity. Other interactyions

such as disease-disease interactions, disease-treatment interactions and disease-environment interactions could also play a significant role in the development and trajectory of multimorbidity. Additionally, it is likely that health service and patient factors, such as clinician assessment of risk, and patient adherence to medications, affects the quality of care and health outcomes of multimorbid patients. Further research into the health system factors that promote improved health outcomes in multimorbidity may help inform more coordinated and personalised care for multimorbid patients [1].

Time sequence

The sequence and timing of accumulating conditions could be an important factor in the trajectory of multimorbidity. For instance, the order of developing conditions could be important in relative mortality risk: patients who develop MI and then diabetes could have a higher relative mortality risk compared to patients who have diabetes and then MI, as diabetes is a "silent" disease and is concordant with MI [267]. Additionally, the time gap between diagnoses could also be important, as a rapid accumulation of conditions could be indicative of undiagnosed disease being uncovered with increased healthcare utilisation after an incident disease. These factors are difficult to examine using traditional epidemiological methods, where exposure and outcome are defined during a specific time window. Machine learning approaches that can model vectors of disease development could be useful in investigating the time sequence of multimorbidity development [305].

8.6 Conclusions

Overall, this thesis provides descriptive and analytical evidence for the increasing burden and impact of multimorbidity in CVD.

Two key methodological steps were described to lay the foundation for studying multimorbidity and CVD in the CPRD. Firstly, an evidence-based approach to measuring multimorbidity in the CPRD was established that was based on 60

chronic conditions. Secondly, the raw CPRD data was extracted and cleaned to provide quality, relevant data for further analyses.

Three main analyses provided evidence that there was a large and increasing burden of multimorbidity in CVD patients, blood pressure was lower in multimorbid patients and driven by initial diagnostic threshold, and mortality risk from concordant cardiometabolic conditions were partly explained by additional comorbidities and less than the additive relative mortality risk.

Multimorbidity is not simply "the sum of all its parts." Clinical practice, policy and research in CVD needs to move away from a single-disease paradigm and incorporate an integrated, coordinated approach to care for an increasingly multimorbid population.

Appendices

A

Supplementary material

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A.1 Summary of literature: multimorbidity framework

Table A.1: Multimorbidity literature summary

Author	Year	Title	Objective	Definition of multimorbidity	Condition list	Number of conditions	Definition of "condition"	Rationale
Afrin	2016	Multimorbidity predicts falls differentially according to the type of fall in postmenopausal women	To ascertain whether the risk of falls of different types is related to morbidity (number of chronic medical conditions) among postmenopausal women		hypertension, hypercholesterolemia, coronary heart disease, other heart disease, cerebrovascular disease, venous thrombosis in leg, pulmonary embolism, type 1 diabetes, chronic kidney disease, chronic liver disease, rheumatoid arthritis, epilepsy, asthma or chronic obstructive pulmonary disease, lactose intolerance, hyperthyroidism, hyperparathyroidism, alcoholism, chronic mental disease, osteoporosis and cancer	20	chronic medical conditions	available in baseline survey of cohort

Author	Year	Title	Objective	Definition of multimorbidity	Condition list	Number of conditions	Definition of "condition"	Rationale
Barnett	2012	Epidemiology of multimorbidity and implications for health care, research, and medical education: a cross-sectional study	We examined the distribution of multimorbidity,and of comorbidity of physical and mental health disorders, in relation to age and socioeconomic deprivation.	those with two or more chronic morbidities	hypertension, depression, painful condition, asthma, coronary heart disease, treated dyspepsia, diabetes, thyroid disorders, rheumatoid arthritis & other inflammatory polyarthropathies, & systematic connective tissue disorders, hearing loss, chronic obstructive pulmonary disease, anxiety & other neurotic stress related and somatoform disorders, irritable bowel syndrome, new diagnosis of cancer in last five years, alcohol problems, other psychoactive substance misuse, treated constipation, stroke & TIA, chronic kidney disease, diverticular disease of the intestine, atrial fibrillation, peripheral vascular disease, heart failure, prostate disorders, glaucoma, epilepsy, dementia, schizophrenia or bipolar disorder, psoriasis or eczema, inflammatory bowel disease, migraine, blindness, chronic sinusitis, learning disability, anorexia or bulimia, bronchiectasis, parkinson's disease, multiple sclerosis, viral hepatitis, chronic liver disease	40	morbidities	We specifically sought to include morbidities recommended as core for any multimorbidity measure by a systematic review,11 diseases in the quality and outcomes framework (QOF) of the UK general practice contract,18 disorders identified as important by NHS Scotland. We selected 40 such morbidities

Author	Year	Title	Objective	Definition of multimorbidity	Condition list	Number of conditions	Definition of "condition"	Rationale
Brilleman	2013	Comparing measures of multimorbidity to predict outcomes in primary care: a cross sectional study	Assess the predictive validity of commonly used measures of multimorbidity in rela- tion to a health outcome (mortality) and a measure of health service utilization (consultation rate)	six measures of multimorbidity: count of chronic diseases from the Quality and Outcomes Framework (QOF); Charlson index; count of prescribed drugs; three measures from the John Hopkins ACG software [Expanded Diagnosis Clusters count (EDCs), Adjusted Clinical Groups (ACGs), Resource Utilisation Bands (RUBs)].	QOF (17), Charlson (17), ACG case-mix system (114), Adjusted Clinical groups (68), RUBs (6)		range: chronic conditions, clinical dimen- sions/categories, categories of resource utilisation	previously specified
Cottrell	2015	Lived experiences of multimorbidity: An interpretative meta-synthesis of patients', general practitioners' and trainees' perceptions	(i) understand lived experiences of patients, general practitioners and trainees regarding multimorbidity, (ii) identify how similarities and differences in experiences should shape future solutions.	'the co-existence of two or more chronic conditions, where one is not necessarily more central than the others,				
Dhalwani	2016	Long terms trends of multimorbidity and association with physical activity in older English population	we aimed to assess the longitudinal trends of multimorbidity and the association between multimorbidity and physical activity	presence of two or more of these conditions	diabetes, hypertension, stroke, myocardial infarction, congestive heart failure, angina, lung disease, asthma, arthritis, osteoporosis, cancer, hearing problems, Parkinson's disease, Alzheimer's disease, dementia and eye conditions including macular degeneration and glaucoma	16	doctor diagnosed condition	

Author	Year	Title	Objective	Definition of multimorbidity	Condition list	Number of conditions	Definition of "condition"	Rationale
Dhalwani	2016	Association Between Lifestyle Factors and the Incidence of Multimorbidity in an Older English Population	whether these lifestyle factors individually or in combination predicted multimorbidity	defined multimorbidity as presence -2 of the above conditions.	recorded conditions in ELSA	5	chronic conditions	
Diederichs	2010	The Measurement of Multiple Chronic Diseases—A Systematic Review on Existing Multimorbidity Indices	to provide a comprehensive overview on existing instruments on the basis of a systematic literature review.	the coexistence of 2 or more chronic diseases				
Fabbri	2016	Association Between Accelerated Multimorbidity and Age-Related Cognitive Decline in Older Baltimore Longitudinal Study of Aging Participants without Dementia	To explore the association between rate of physical health deterioration, operationalized as rising multimorbidity overtime, and longitudinal decline in cogni- tive function in older adults without dementia.	the co-occurrence of multiple chronic diseases	hyperten- sion, diabetes mellitus, coronary artery disease, congestive heart failure, stroke, chronic obstructive pulmonary dis- ease, cancer, Parkinson's disease, history of hip fracture, lower extremity joint disease	13	chronic conditions:	13 candidate chronic conditions that could be reliably adjudicated based on the data avail- able and are known to have high prevalence and be associ- ated with high disability and mortality risk in older adults was selected a priori.
Fortin	2005	Multimorbidity is common to family practice Is it commonly researched?	to quantify the literature on multimorbidity (or comorbidity) and to compare the number of publications on it with the number of publications on three common chronic conditions (asthma, hypertension, and diabetes), and second, to describe the articles on multimorbidity.	several concurrent medical conditions within one person.				

Author	Year	Title	Objective	Definition of multimorbidity	Condition list	Number of conditions	Definition of "condition"	Rationale
Fortin	2005	Prevalence of Multimorbidity Among Adults Seen in Family Practice	to estimate its prevalence in family practice patients by counting the number of chronic medical conditions and using a measure that considers the severity of these conditions, the Cumula- tive Illness Rating Scale (CIRS).	the simultaneous occurrence of several medical conditions in the same person.			as defined by the Cumula- tive Illness Rating Scale (CIRS)	
France	2012	Multimorbidity in primary care: a systematic reviewof prospective cohort studies	This reviewidentifies prospective cohort studies of multimorbidity in primary care to determine: their nature, scope and key findings; themethodologies used; and gaps in knowledge.	the co-occurrence of two ormore long-termconditions within an individual , without a specific index condition being specified				
Friedman	2015	Inflammation Partially Mediates the Association of Multimorbidity and Functional Limitations in a National Sample of Middle-Aged and Older Adults: The MIDUS Study	examine the role of inflammation in mediating the relationship between multimorbidity and disability	the co-existence of two or more chronic medical conditions within the same individual			not specified	
Glynn	2008	Multimorbidity and risk among patients with established cardiovascular disease: a cohort study	To examine the effect of the presence of chronic kidney disease and diabetes on mortality and morbidity among patients with established cardiovascular disease.	the simultaneous coexistence in individuals ofmore than one disease state	coexisting cardiovascular disease and diabetes, and/or chronic kidney disease		coexisting cardiovascular disease and diabetes, and/or chronic kidney disease	cardiovascular multimorbidity
Gross	2006	Multimorbidity and Survival in Older Persons with Colorectal Cancer	To ascertain the effect of common chronic conditions on mortality in older persons with colorectal cancer.	the occurrence of multiple diseases in an individual person has been conceptualized as multimorbidity				Chronic conditions were selected based on prior published indices as well as clinical judgment.

Author	Year	Title	Objective	Definition of multimorbidity	Condition list	Number of conditions	Definition of "condition"	Rationale
Guthrie et al	2016	NICE guidelines	Guidelines for clinical practice	multimorbidity refers to the presence of 2 or more long-term health conditions			defined as physical and mental health conditions such as diabetes or schizophrenia ongoing conditions such as learning disability symptom complexes such as frailty or chronic pain sensory impairment such as sight or hearing loss alcohol and substance misuse.	
Hansen	2014	Agreement between self-reported and general practitioner-reported chronic conditions among multimorbid patients in primary care - results of the MultiCare Cohort Study	to analyze the agreement of self-reported and general practitioner-reported chronic conditions among multimorbid patients in primary care, and to discover which patient characteristics are associated with positive agreement.	the coexistence of at least three chronic conditions			from a list of 29 diseases	
Harrison	2016	The prevalence of complex multimorbidity in Australia	To measure prevalence of multimorbidity and complex multimorbidity in the Australian population from a nationally representative prospective study and to identify the most prevalent patterns of chronic conditions and body systems affected	Multimorbidity was defined as the “co-occurrence of two or more chronic conditions within one person without defining an index chronic condition” and ’complex multimorbidity’, defined as the “co-occurrence of three or more chronic conditions affecting three or more different body systems within one person, without defining an index chronic condition"			all chronic conditions	available through GP recordings

Author	Year	Title	Objective	Definition of multimorbidity	Condition list	Number of conditions	Definition of "condition"	Rationale
Held	2015	Association Rules Analysis of Comorbidity and Multimorbidity: The Concord Health and Aging in Men Project	use a novel analytic approach called Association Rules together with network analysis to evaluate multimorbidity (two or more disorders) and comorbidity in old age.	“multimorbidity” was used to describe the presence of two or more diseases in an individual without reference to any index disease	arthritis, chronic obstructive pulmo- nary disease/asthma, angina, heart failure, heart attack, Parkinson’s disease, stroke, peripheral arterial disease, diabetes mellitus, hearing impairment, depression, anxiety, visual impairment, back pain, obe- sity, osteoporosis, and cognitive impairment.	17	morbidities	they are common, usually chronic, symptomatic, and similar to the most commonly reported conditions in other studies except that disorders such as hypertension, hyperlipidemia, atrial fibrillation, and reduced creatinine clearance were excluded because they are largely asymptomatic risk factors rather than diseases and are often effectively treated.
Holden	2011	Patterns of multimorbidity in working Australians	This paper aims to identify nonrandom clusters of multimorbidity	two or more health conditions; when no reference condition is considered		23	conditions	available in the Health and Productivity Questionnaire from the WHO
Hopman	2015	Health care utilization of patients withmultiple chronic diseases in The Netherlands: Differences and underlying factors	To examine health care utilization of people with multiple chronic diseases in The Netherlands com- pared to people with one chronic disease, and to identify different subgroups of multimorbid patients based on differences in health care utilization.	the co-occurrence of multiple chronic diseases within a person		29	chronic diseases	a high prevalence and a chronic and severe character

Author	Year	Title	Objective	Definition of multimorbidity	Condition list	Number of conditions	Definition of "condition"	Rationale
Huntley	2012	Measures of Multimorbidity and Morbidity Burden for Use in Primary Care and Commu- nity Settings: A Systematic Review and Guide	identify measures of multimorbidity and morbidity burden suitable for use in research in primary care and commu- nity populations, and to investigate their validity in relation to anticipated asso- ciations with patient characteristics, process measures, and health outcomes.	the co-occurrence of multiple diseases or medical conditions within 1 person				
Kirchberger	2012	Patterns of Multimorbidity in the Aged Population. Results from the KORA-Age Study	to explore patterns of comorbidity and multimorbidity in an elderly population using different analytical approaches	coexistence of two or more chronic diseases in the same individual	myocardial infarction, hypertension, stroke, diabetes mellitus or a malignant disease and other self-reported conditions		self-reported conditions	
Krishnaswami	2015	Multimorbidity is strongly associated with long-termbut not short-term mortality after cardiac valve replacement	to determine the association of multimorbidity with mortality in patients undergoing cardiac valve replacement	defined as 2 or more chronic conditions			baseline comorbidities, not specified	not specified
Lappenschaar	2013	Multilevel temporal Bayesian networks can model longitudinal change in multimorbidity	multilevel temporal Bayesian networks were adopted to study the course of multimorbidity in the expectation that this would yield new clinical insight	co-occurrence of two or more medical, especially chronic, conditions within a person at the same time	obesity, hypertension, lipid disorder, diabetes mellitus, heart failure, stroke, ischemic heart disease, retinopathy, and nephropathy	6	chronic cardiovascular conditions	primarily interested in chronic cardiovascular diseases and related disorders
Laux	2008	Co- and multimorbidity patterns in primary care based on episodes of care: results from the German CONTENT project	to describe co- and multimorbidity as well as health care utilization based on episodes of care for the study population of the first participating general practices.	the co- occurrence of two or more chronic conditions as defined by van den Akker et al.			defined by van den Akker	defined by van den Akker

Author	Year	Title	Objective	Definition of multimorbidity	Condition list	Number of conditions	Definition of "condition"	Rationale
Lawson	2013	Double trouble: the impact of multimorbidity and deprivation on preference-weighted health related quality of life a cross sectional analysis of the Scottish Health Survey	To investigate the association between multimorbidity and Preference_Weighted Health Related Quality of Life (PW_HRQoL), a score that combines physical and mental functioning, and how this varies by socioeconomic deprivation and age.	2+ conditions		40	longstanding conditions	as recorded in Scottish Health Survey
Lee	2015	Impact of Noncommunicable Disease Multimorbidity on Healthcare Utilisation and Out-Of-Pocket Expenditures in Middle-Income Countries: Cross Sectional Analysis	assess the impact of NCD multimorbidity on healthcare utilisation and out-of-pocket expenditures in sixmiddle-income countries: China, Ghana, India, Mexico, Russia and South Africa	defined as persons with two or more co-existing chronic conditions	angina, arthritis, asthma, cataracts, diabetes, stroke, chronic lung disease, hypertension and depression		chronic conditions	NCDs asked about in the SAGE study
Lefevre	2014	What do we mean by multimorbidity? An analysis of the literature on multimorbidity measures, associated factors, and impact on health services organization	to define the spectrum of multimorbidity and to discuss current implications for the organization of care.	co-occurrence of at least two chronic conditions in the same person				
Lochner	2010	Prevalence of Multiple Chronic Conditions Among Medicare Beneficiaries, United States, 2010	to use the US Department of Health and Human Services Strategic Framework on multiple chronic conditions as a basis to examine the prevalence of multiple chronic conditions among Medicare beneficiaries.	having 2 or more chronic conditions		15	chronic conditions	

Author	Year	Title	Objective	Definition of multimorbidity	Condition list	Number of conditions	Definition of "condition"	Rationale
Maneman	2016	Multimorbidity in Heart Failure: Effect on Outcomes	To investigate the effect of the number and type of comorbid conditions on death and hospitalizations in individuals with incident heart failure (HF).	the co-occurrence of two or more chronic conditions		20	chronic conditions	U.S. Department of Health and Human Services recently identified 20 chronic conditions that are consid- ered a public health priority
Marengoni	2011	Aging with multimorbidity: A systematic review of the literature	to summarize the existing scientific evidence concerning occurrence, causes, and consequences of multimorbidity (the coexistence of multiple chronic diseases) in the elderly as well as models and quality of care of persons with multimorbidity	defined as any co-occurrence of diseases in the same person			chronic diseases	
Marengoni	2009	Patterns of Chronic Multimorbidity in the Elderly Population	To describe patterns of comorbidity and multimorbidity in elderly people	any co-occurrence of two or more chronic or acute diseases and medical conditions within one person, whether coincidental or not		30	chronic diseases; 30 detected	
McNamara	2016	Health professional perspectives on the management of multimorbidity and polypharmacy for older patients in Australia	to explore current approaches to multimorbidity management, and perceived barriers and enablers to deliver appropriate medications management for community-dwelling patients with multimorbidity and polypharmacy, from a broad range of healthcare professional (HCP) perspectives in Australia.	defined as experiencing two or more long-term health conditions			not specified	

Author	Year	Title	Objective	Definition of multimorbidity	Condition list	Number of conditions	Definition of "condition"	Rationale
Melis	2014	Incidence and Predictors of Multimorbidity in the Elderly: A Population-Based Longitudinal Study	to calculate 3-year incidence of multimorbidity, defined as the development of two or more chronic diseases in a population of older people free from multimorbidity at baseline and identify predictors of incident multimorbidity amongst life-style related indicators, medical conditions and biomarkers.	any co-occurrence of two or more chronic conditions in the same individual, whether coincidental or not			A disease was classified as chronic if it satisfied one of the following criteria: 1. being permanent, 2. caused by non-reversible pathological alteration, 3. requiring rehabilitation, or 4. requiring a long period of care.	
Min	2007	Multimorbidity is Associated With Better Quality of Care Among Vulnerable Elders	We sought to determine whether coexisting combinations of 8 common chronic conditions (hypertension, coronary artery disease, chronic obstructive pulmonary disease, osteoarthritis, diabetes mellitus, depression, osteoporosis, and having atrial fibrillation or congestive heart failure) are associated with overall quality of care among vulnerable older patients.	not specified	hypertension (HTN), coronary artery disease (CAD), chronic obstructive pulmonary disease (COPD), osteoarthritis (OA), diabetes mellitus (DM), depression, osteoporosis (OP), atrial fibrillation (AF), and congestive heart failure (CHF)	9	conditions	inclusion in previous literature; prevalence <5%

Author	Year	Title	Objective	Definition of multimorbidity	Condition list	Number of conditions	Definition of "condition"	Rationale
Muth	2014	Current guidelines poorly address multimorbidity: pilot of the interaction matrix method	To develop a framework to identify and classify interactions within and among treatments and conditions and to test this framework with guidelines on chronic heart failure and its frequent comorbidity	the co-occurrence of two or more acute or chronic condi- tions	asthma, benign prostatic hyperplasia, chronic back disorders (low back pain), chronic kidney dis- ease, COPD and bronchiectasis, dementia, depression, diabetes mellitus, hypercholesterolemia, hypertension, lower respiratory diseases (LRD, including lower respira- tory tract infection), ocular disorders (ocular hyperten- sion/glaucoma), osteoarthritis, osteoporosis, peripheral and visceral atherosclerosis, and thyroid disorders (hyper- and hypo-thyroidism)	18	non-cardiac conditions	prevalence over 5% reported

Author	Year	Title	Objective	Definition of multimorbidity	Condition list	Number of conditions	Definition of "condition"	Rationale
Nagel	2008	The impact of education on risk factors and the occurrence of multimorbidity in the EPIC-Heidelberg cohort	we investigated the association between educational attainment and multimorbidity in a prospective cohort study, taking also into account intermediate factors that could explain such associations.	>= 2 concurrent chronic diseases	Chronic diseases were regrouped into cancer (all except non-melanoma skin cancer), diabe- tes mellitus, thyroid disease, stroke, myocardial infarction (MI), heart diseases (except MI), lung diseases (asthma, chronic obstructive pulmonary disease), gastrointestinal diseases (reflux esophagitis, chronic gastritis, gastric ulcer, Crohn's disease, ulcerative colitis, chronic diverticulitis), liver/kidney diseases, pancreatitis, muscle/bone diseases (rheumatic disease, osteoporosis), diseases of the central nervous system (multiple sclerosis, Alzheimer disease, Parkinson's disease), hypertension, dyslipidemia, and hyperuricemia.		prevalent chronic diseases;	prevalent chronic conditions
Ornstein	2013	The Prevalence of Chronic Diseases and Multimorbidity in Primary Care Practice: A PPRNet Report	prevalence of 24 chronic illnesses and multimorbidity from primary care practices across the United States.	Multimorbidity was alternatively defined as the presence of >=2or >=3 chronic con- ditions.		24	chronic conditions;	common conditions
Palladino	2016	Associations between multimorbidity, healthcare utilisation and health status: evidence from 16 European countries	to investigate determinants of multimorbidity and its impact on healthcare utilisation and health status in Europe.	the presence of two or more of chronic diseases			chronic diseases, not specified	available in the Survey of Health, Ageing and Retirement in Europe

Author	Year	Title	Objective	Definition of multimorbidity	Condition list	Number of conditions	Definition of "condition"	Rationale
Pefoyo	2015	The increasing burden and complexity of multimorbidity	to estimate the population-based prevalence and trends of multimorbidity in Ontario, Canada and to examine patterns in the co-occurrence of chronic conditions	coexistence of two or more chronic conditions	arth- ritis (excluding rheumatoid arthritis), hypertension, asthma, depression, diabetes, cancer, chronic coronary syndrome (CCS), cardiac arrhythmia, osteoporosis, chronic obstructive pulmonary disease (COPD), congestive heart failure (CHF), renal failure, dementia, rheumatoid arthritis, stroke and acute myocardial infarction (AMI)	16	common chronic medical conditions	selected conditions based on their clinical relevance and burden, both in terms of cost and outcome (e.g. attributable deaths) as described in previous literature
Perruccio	2012	Health burden in chronic disease: Multimorbidity is associated with self-rated health more than medical comorbidity alone	To investigate the association between multimorbidity – a construct comprised of several health domains (medical comorbidity, musculoskeletal, physical and social functional status, mental health, geriatric problems) – and overall self-rated health, an important chronic disease health outcome. We investigate whether medical comorbidity effects are mediated through other health domains and whether these domains have independent effects on self-rated health.	The literature has identified a number of health domains that influence both short- and long- term health outcomes. We will refer to multimorbidity as the co-occurrence of states or situations related to these health domains and refer to the collective impact of multimorbidity as the 'aggregate health burden'.	stroke; cancer; heart attack; congestive heart failure; high blood pressure; diabetes; kidney disease; asthma, bronchitis, emphysema, or other lung disease; ulcer or stomach disease; anemia or other blood disease; rheumatoid arthritis		chronic diseases experienced in the last 10 years	
Riegel	2016	Effectiveness of Motivational Interviewing in Decreasing Hospital Readmission in Adults With Heart Failure and Multimorbidity	to test the effectiveness of motivational interviewing (MI) in decreasing hospital readmissions for heart failure	-2 comorbid conditions			not specified	

Author	Year	Title	Objective	Definition of multimorbidity	Condition list	Number of conditions	Definition of "condition"	Rationale
Rizza	2012	Age- and gender-related prevalence of multimorbidity in primary care: the swiss fire project	age- and gender-related prevalence of multimorbidity and compared these estimates to the prevalence estimates of other common specific diseases found in Swiss primary care	three different methods to define multimorbid- ity as present: 1) two or more chronic health conditions referring to different rubrics of the ICPC-2 classification system; 2) two or more chronic health conditions refer- ring to different chapters of the ICPC-2 classification system; 3) and two or more medical specialties involved in the care of chronic health conditions in one patient (i.e., stroke refers to the nervous system and not the cardiovascular system, and is managed by the neurolo- gist and not the cardiologist).	A total of 147 (21.4%) codes from the 686 ICPC-2 codes were identified		chronic conditions.	
Rocca	2014	The prevalence of multimorbidity in a geographically defined American population: patterns by age, sex, and ethnicity	To describe the prevalence of multimorbidity involving 20 selected chronic conditions in a geographically defined US population, emphasizing age, sex, and ethnic differences.	combinations of chronic conditions; 2 or more conditions		20	chronic conditions	proposed by the US DHHS
Ruel	2014	Understanding the Evolution of Multimorbidity: Evidences from the North West Adelaide Health Longitudinal Study (NWAHS)	to describe the evolution of multimorbidity	the presence of two or more medical conditions in an individual	asthma, cardiovascular disease and stroke (CVD), chronic obstructive pulmonary disease (COPD), diabetes, mood and anxiety disorders, any other mental disorders, hypercholesterol- emia and hypertension.	8	chronic diseases	not specified

Author	Year	Title	Objective	Definition of multimorbidity	Condition list	Number of conditions	Definition of "condition"	Rationale
Salisbury	2011	Epidemiology and impact of multimorbidity in primary care: a retrospective cohort study	To describe the epidemiology of multimorbidity and relationships between multimorbidity and primary care consultation rates and continuity of care.	Multimorbidity was operationalised in two ways. The primary approach was to define it as a patient who, on the index date, hadmore than one of 17 important chronic conditions for which care is incentivised under the QOF; As a secondary approach, the Johns Hopkins University Adjusted Clinical Groups (ACG® System17) Case-Mix was used to identify whether or not each patient had one or more of a much wider list		17	QOF or Johns Hopkins University Adjusted Clinical Groups (ACG) Case-Mix system	
Salive	2013	Multimorbidity in Older Adults	1) What is the prevalence of multimorbidity in older adults, particularly those living in the community? 2) How does multimorbidity affect health outcomes? 3) What are the implications of multimorbidity for public health and medicine?	the coexistence of 2 or more chronic conditions		15	15 prevalent chronic conditions	consistent with the US Department of Health and Human Services framework
Scafer	2009	The German MultiCare-study: Patterns of multimorbidity in primary health care – protocol of a prospective cohort study	Study protocol description	at least three different diagnoses out of a list of 29 illnesses and syndromes		29	illnesses and syndromes	In order to enrich the sample, we therefore decided to include only patients with at least three chronic conditions; In order to ensure a wide range of diseases and syndromes, those with a prevalence of more than 25% were not used for inclusion into the sample.

Author	Year	Title	Objective	Definition of multimorbidity	Condition list	Number of conditions	Definition of "condition"	Rationale
Schafer	2014	Reducing complexity: a visualisation of multimorbidity by combining disease clusters and triads	to depict which diseases were associated with each other on person-level within the clusters and which ones were responsible for overlapping multimorbidity clusters.	presence of multiple chronic conditions		46	defined diagnosis groups of chronic diseases	the most frequent conditions documented in GP surgeries as listed in a panel survey of the Central Research Institute of Statutory Ambulatory Health Care in Germany
Schafer	2012	The influence of age, gender and socio-economic status on multimorbidity patterns in primary care. first results from the multicare cohort study	The objective of this paper is to analyze the association of socio-demographic variables, and especially socio-economic status with multimorbidity in general and with each multimorbidity pattern.	at least three different diagnoses out of a list of 29 illnesses and syndromes		29	illnesses and syndromes	In order to enrich the sample, we therefore decided to include only patients with at least three chronic conditions; In order to ensure a wide range of diseases and syndromes, those with a prevalence of more than 25% were not used for inclusion into the sample.
Schafer	2010	Multimorbidity Patterns in the Elderly: A New Approach of Disease Clustering Identifies Complex Interrelations between Chronic Conditions	to increase the knowledge of specific processes of multimorbidity in an unselected elderly population by identifying patterns of statistically significantly associated comorbidity	not specified		46	conditions	
Sinnge	2013	The Prevalence of Disease Clusters in Older Adults with Multiple Chronic Diseases – A Systematic Literature Review	to describe the prevalence of disease combinations (i.e. disease clusters) in older patients with multimorbidity	co-occurrence of multiple (often chronic) diseases or medical conditions within one person				
Smith	2012	Cochrane review	To determine the effectiveness of interventions designed to improve outcomes in patients with multimorbidity in primary care and community settings.	Multimorbidity was defined as two or more chronic conditions in the same individual				

Author	Year	Title	Objective	Definition of multimorbidity	Condition list	Number of conditions	Definition of "condition"	Rationale
St Sauver	2014	Risk of developing multimorbidity across all ages in an historical cohort study: differences by sex and ethnicity	To study the incidence of de novo multimorbidity across all ages in a geographically defined population with an emphasis on sex and ethnic differences.	people living with -2 chronic conditions		20	chronic conditions	recommended by theUS-DHHS for studying multimorbidity.
Taylor	2010	Multimorbidity - not just an older person's issue. Results from an Australian biomedical study	This study used cross-sectional data from an existing Australian cohort study to examine characteristics of those with mul- tiple chronic conditions	the simultaneous occurrence of two or more chronic conditions	asthma, cardiovascu- lar disease (CVD), chronic obstructive pulmonary disease (COPD), diabetes, a current mental health condition, arthritis and osteoporosis		chronic conditions	
Uijen	2008	Multimorbidity in primary care: Prevalence and trend over the last 20 years	To determine the prevalence of multimorbidity in primary care, by age, sex, and socio-economic class, and to analyse the trend in multimorbidity over the last 20 years	defined as the co-existence of two or more chronic conditions			not specified	
van den Akker	2000	Marginal impact of psychosocial factors on multimorbidity: results of an explorative nested case-control study	examine differences between subjects with zero, one or two or more new diseases	two or more diseases			registered diseases	
van den Akker	1998	Multimorbidity in General Practice: Prevalence, Incidence, and Determinants of Co-Occurring Chronic and Recurrent Diseases	We studied the prevalence, incidence, and determinants of multimorbidity and the statistical clustering of chronic and recurrent diseases in a general practice setting.	any co-occurrence of diseases		335	diagnostic categories	

Author	Year	Title	Objective	Definition of multimorbidity	Condition list	Number of conditions	Definition of "condition"	Rationale
van Oostrom	2014	Multimorbidity of chronic diseases and health care utilization in general practice	to examine the relationship between multimorbidity (i.e. the number of diseases and specific combinations of diseases) and the use of general practice services in the Dutch population of 55 years and older.	the co-occurrence of two or more diseases		28	conditions	28 highly prevalent, chronic and severe diseases
Vassilaki	2015	Multimorbidity and Risk of Mild Cognitive Impairment	To determine the association between multiple chronic conditions and risk of incident mild cognitive impairment (MCI) and dementia.	the coexistence of two or more chronic conditions in an individual	autism spectrum disorder or human immunodeficiency virus, 17 chronic conditions (hyperlipidemia, hypertension, depression, diabetes mellitus, arthritis, cancer, cardiac arrhythmias, asthma, coronary artery disease, substance abuse disorders (drugs and alcohol), chronic obstructive pulmonary disease, osteoporosis, chronic kidney disease, stroke, congestive heart failure, schizophrenia, hepatitis)	19	chronic conditions	19 chronic conditions (excluding dementia) that the U.S. Department of Health and Human Services proposed in 2010 for studying multimorbidity
Violan	2014	Prevalence, Determinants and Patterns of Multimorbidity in Primary Care: A Systematic Review of Observational Studies	to systematically review studies of the prevalence, patterns and determinants of multimorbidity in primary care.	the presence of more than one health condition in an individual			not specified	

Author	Year	Title	Objective	Definition of multimorbidity	Condition list	Number of conditions	Definition of "condition"	Rationale
Violan	2013	Comparison of the information provided by electronic health records data and a population health survey to estimate prevalence of selected health conditions and multimorbidity	1) to measure and compare the prevalence and distribution of multimorbidity in HS and EHR data, and 2) to test specific hypotheses about potential differences between HS and EHR reporting of diseases with a symptoms-based diagnosis and those requiring diagnostic testing.	"the co-occurrence of multiple medi- cal conditions within one person without any reference to an index condition"			chronic health problems	there was Health Survey information.
Vos	2012	Finding potentially new multimorbidity patterns of psychiatric and somatic diseases: exploring the use of literature-based discovery in primary care research	To explore the usefulness of literature-based discovery in primary care research through the key-case of finding associations between psychiatric and somatic diseases relevant to general practice in a large biomedical literature database	the co-occurrence of two or more chronic medical conditions within a single individual			not specified	
Ward	2014	Multiple Chronic Conditions Among US Adults: A 2012 Update	update earlier estimates of prevalence rates of single chronic conditions and multiple (>2) chronic conditions (MCC) among the noninstitutionalized, civilian US adult population.	>2 chronic conditions	hypertension, coronary heart disease, stroke, diabetes, cancer, arthritis, hepatitis, weak or failing kidneys, current asthma, or chronic obstructive pulmonary disease [COPD]		chronic conditions	10 physical conditions from a list of 20 conditions identified by the US Department of Health and Human Services (HHS) to foster a more consistent and standardized approach to measuring the occurrence of chronic conditions in the United States

Author	Year	Title	Objective	Definition of multimorbidity	Condition list	Number of conditions	Definition of "condition"	Rationale
Weimann	2016	A cross-sectional and spatial analysis of the prevalence of multimorbidity and its association with socioeconomic disadvantage in South Africa: A comparison between 2008 and 2012	to investigate the cross-sectional and spatial distribution of multi-morbidity and the association with socioeconomic disadvantage in South Africa for 2008 and 2012.	the presence of two or more chronic health conditions existing simultaneously in an individual	? Hypertension, diabetes, tuberculosis, HIV (iteratively derived and not pre-specified)		chronic diseases	most likely to contribute to multimorbidity, most prevalent
Weiss	2007	Patterns of Prevalent Major Chronic Disease Among Older Adults in the United States	to estimate patterns of major chronic disease co-occurrence in older adults.	not specified	arthritis, cerebrovascular accident, chronic lower res- piratory tract disease, coronary heart disease, and diabe- tes mellitus	5	disease types	leading cause of death or morbidity
White	2015	Multimorbidity and the process of living with ongoing illness	to understand how people with multiple health conditions experience their illness.	two or more health conditions			not specified	
Wister	2016	Multimorbidity, health and aging in Canada and Australia: a tale of two countries	to examine selected health outcomes associated with multimorbidity across older age groups/cohorts and gender, comparing Canada and Australia	multiple chronic illness	arthritis/osteoporosis, asthma, blood pressure (hypertension), bron- chitis/emphysema, cancer, diabetes, and heart disease.	7	chronic conditions	conditions available in the HILDA data set
Wister	2016	A Lifecourse Model of Multimorbidity Resilience: Theoretical and Research Developments	to advance a Lifecourse Model of Multimorbidity Resilience	not specified			not specified	

Author	Year	Title	Objective	Definition of multimorbidity	Condition list	Number of conditions	Definition of "condition"	Rationale
Wong	2011	Longitudinal administrative data can be used to examine multimorbidity, provided false discoveries are controlled for	presents methods for using administrative data to study multimorbidity in hospitalized individuals and indicates how the findings can be used to gain a deeper understanding of hospital multimorbidity.	the simultaneous presence of more than one disease in an individual			138 groups of diseases in total	International Shortlist for Hospital Morbidity Tabulation (ISHMT) format
Yokota	2016	Impact of Chronic Conditions and Multimorbidity on the disability burden in the older population in Belgium	To assess the impact of chronic conditions and multimorbidity on the disability burden in the older population in Belgium.	co-occurrence of diseases within an individual	six chronic conditions/groups: chronic respiratory diseases (asthma, chronic bronchitis, and chronic pulmonary diseases), diabetes, cancer, depression, cardiovascular diseases (ischemic heart diseases or stroke), musculoskeletal conditions (low back pain, osteoporosis, rheumatoid arthritis, or osteoarthritis), and neurological diseases (epilepsy and Parkinson's disease)	14		These diseases were included in the analysis because they were available in the three HIS and showed an important contribution to the ADL and mobility limitation prevalence in Belgium
Zellweger	2014	Prevalence of chronic medical conditions in Switzerland: exploring estimates validity by comparing complementary data sources	estimate population-based prevalence rates of four common chronic medical conditions with high impact on cardiovascular health (diabetes mellitus, hypertension, dyslipidemia, obesity).	defined as more than one chronic medical condition in one individual			four common chronic medical conditions with high impact on cardiovascular health (diabetes mellitus, hypertension, dyslipidemia, obesity).	
		King's fund		3 or more chornic conditions				

A.2 Clinical practice research datalink: structural details

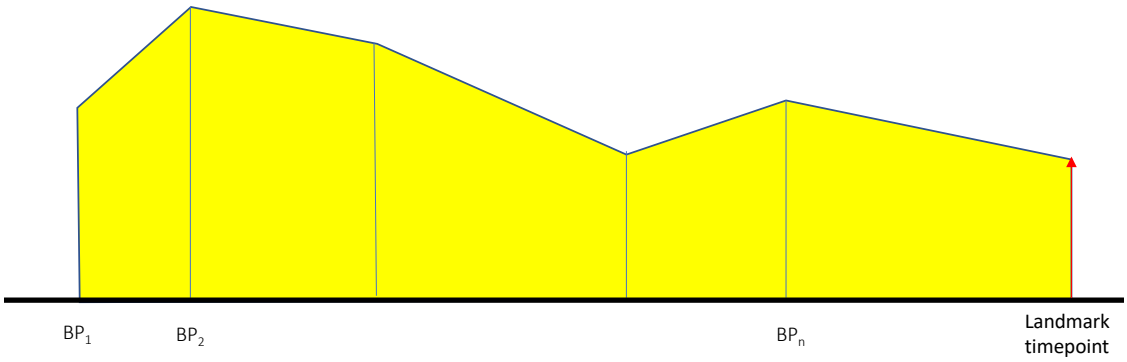
The CPRD is split into ten sets of files, each with a particular theme. In this thesis, the file sets used were: *Patient*, *Practice*, *Clinical*, *Additional Clinical* and *Therapy*. For each of these file sets, text files are provided for each practice that had agreed to provide data to the CPRD. Each file is named according to the de-identified practice number. For example, Patient_001 contains all the patients in Practice number 1. Within each file, rows represent an observation, for example in the Patient_XXX files, each row represents a patient. The columns are variables/data relevant to that particular theme, for example, Patient_XXX has columns "gender", "year of birth" and identifier column "patid," which is the unique identifier number for each anonymised patient in the CPRD. Data are linked between file sets by "patid" for most file sets, and "pracid" between the practice file set and other individual patient file sets. The last three digits of the "patid" are the "pracid" for that patient. The "patid" is also used to link CPRD files to linked databases [164].

The CPRD also uses codes to link to other additional information that a GP records during an encounter. "Entity" (also known as "enttype" codes) are used to provide additional clinical details. The "Entity.xls" file provides descriptions of each enttype and what the data in each column represents. Depending on the enttype, the *Additional Clinical* file columns provide a varying number of columns containing different data. For example, smoking status is identified through enttype=4, which can be found in the enttype column in both the *Clinical* and *Additional Clinical* file sets. The *Clinical* and *Additional Clinical* files are linked via the unique observation identifier in the "adid" and "patid" column in both files. Once combined, the *Clinical* file provides the date of recording of the smoking status, and the *Additional Clinical* file provides the smoking status category, number of cigarettes per day and start date and stop date of smoking. As another example, enttype=1 is blood pressure, and the *Additional Clinical* columns provides diastolic blood pressure (DBP), systolic blood pressure (SBP), Korotkoff sounds, laterality and posture. Data lookup codes are another way the CPRD provides details for

commonly-used categories or measurements. These are used in the *Additional Clinical* files, where the "dataX_lkup" column (where X represents the column number in the *Additional Clinical* file) in the "Entity.xls" file provides what look-up to search for in the "Lookups XXX.rtf" file. For example, the data look-up "YND" in the "dataX_lkup" column details smoke/drink status where 0=data not entered, 1=Yes, 2=No, 3=Ex; another example is the data look-up "SUM" details "Specimen unit of measure" with coding that includes 0=data not entered, and units of measurement such as 1=% and 98=mL.

A.3 Cumulative blood pressure

Figure A.1: Cumulative blood pressure schema



Cumulative blood pressure using area under the curve is calculated as described by Zemaitis et al [241]:

$$\text{AUB} = [(\text{BP1} + \text{BP2})/2 \times \text{time}_{1\text{-}2}] + \ldots + [(\text{BP}_{\text{n-1}} + \text{BP}_{\text{n}})/2 \times \text{time}_{(\text{n-1})\text{-n}}]$$

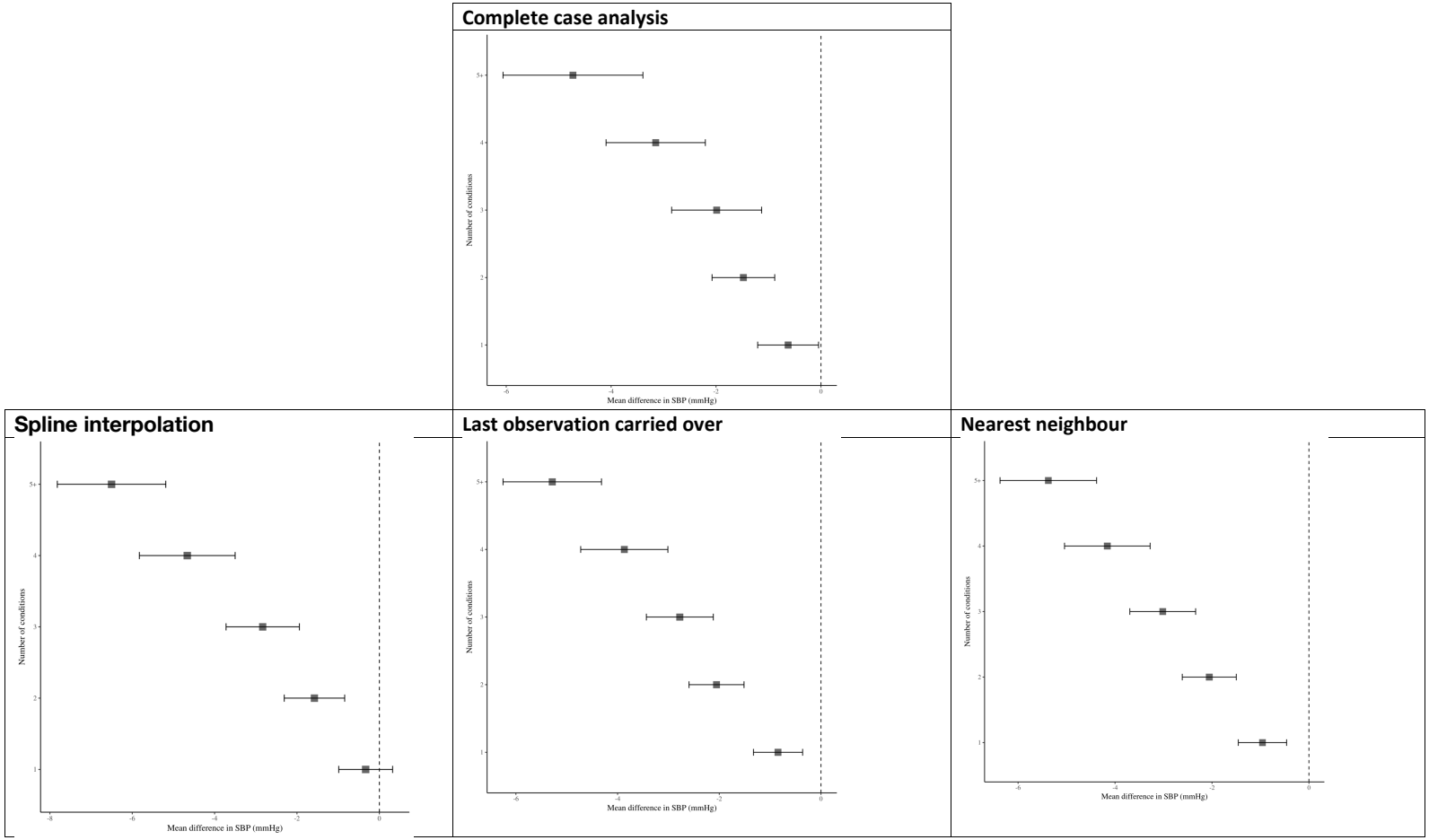
where BP_1, BP_2, ... and BP_n are measurements of BP recorded from the first, the second, and last medical examinations from the landmark timepoint backward (see figure below), and $\text{time}_{1\text{-}2}$ and $\text{time}_{(\text{n-1})\text{-n}}$ are the time intervals between the first and the second, and the (n-1)th and the nth BP measurements. AUP for SBP and

DBP are calculated similarly. Standardised cumulative BP (sAUB) is calculated as AUB/($\text{time}_{1\text{-}2} + \ldots + \text{time}_{(n\text{-}1)\text{-}n}$), including sAUB for SBP and DBP.

A.4 Multimorbidity and blood pressure management: stratified and sensitivity analyses

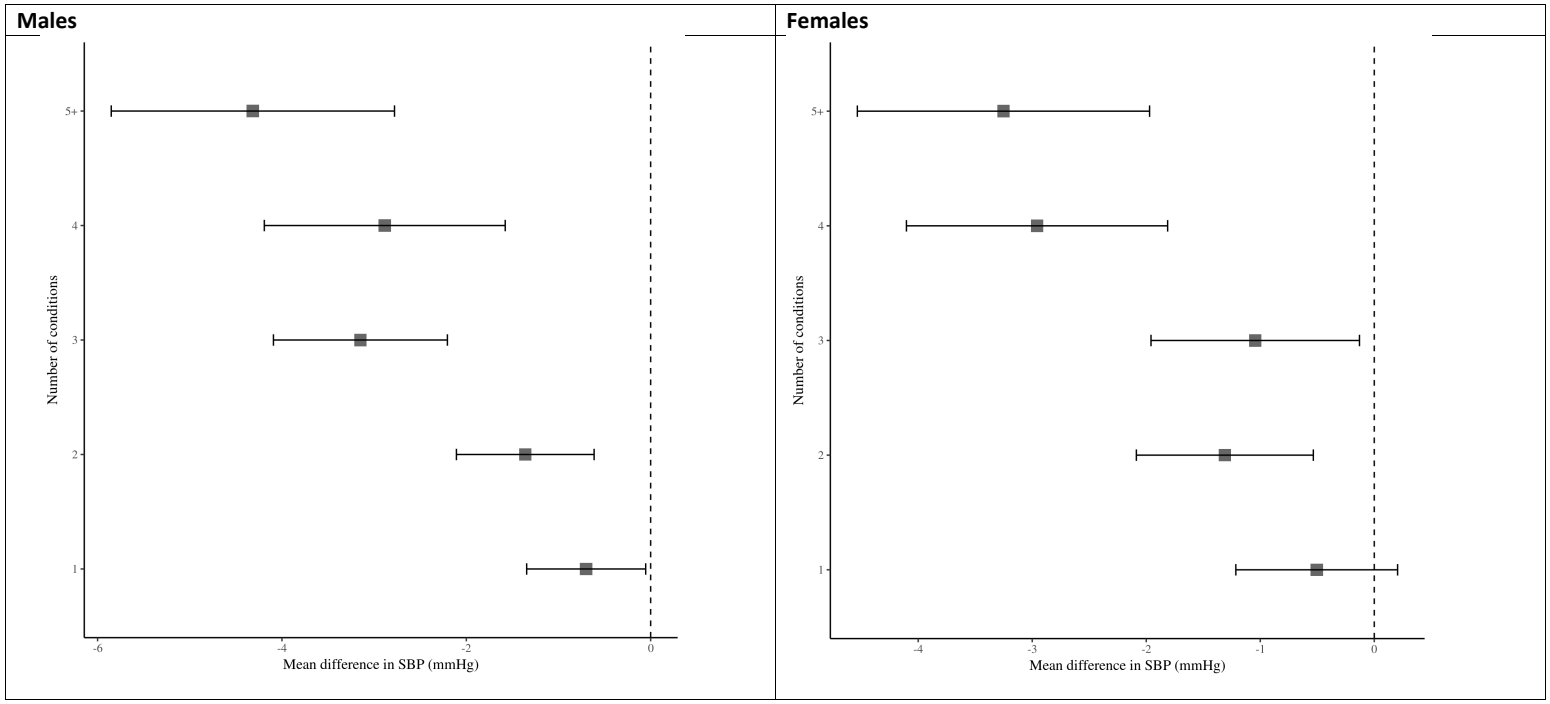
To inform final methods and analyses for chapter 6, stratified analyses and sensitivity analyses were performed on a 10% sample of the study population. Results were unremarkable for differences by sex, age-group and SBP vs DBP. Different imputation of time-series BP data also showed very similar results. Hence, in final analyses, stratified results, results by SBP and DBP, and different imputation methods were not shown in the main body of this thesis.

Imputation methods



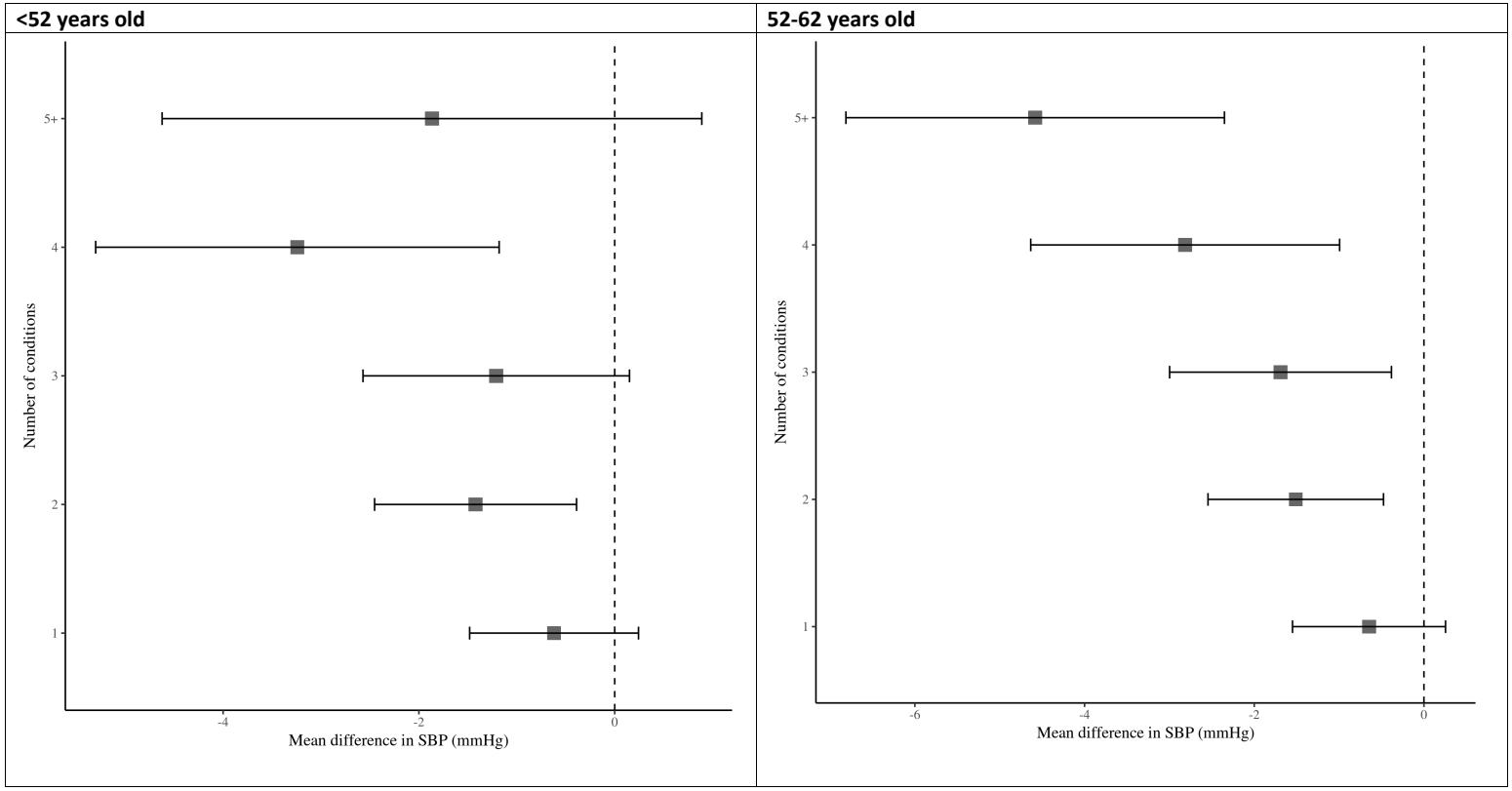
Time: 1 year after diagnosis of hypertension

Stratification by sex



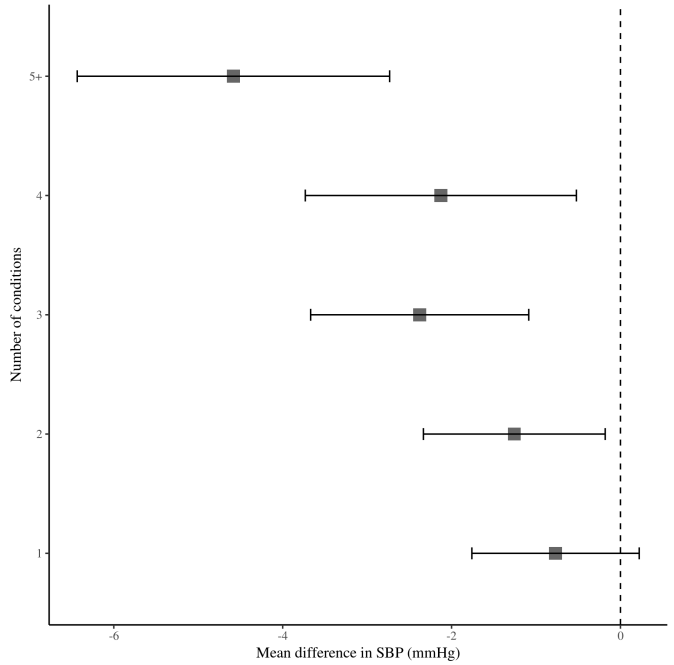
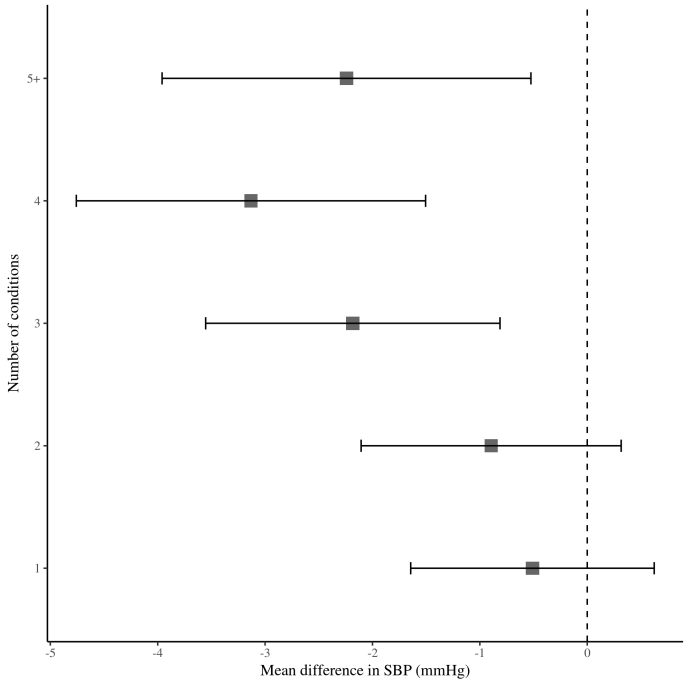
Time: 1 year after diagnosis of hypertension

Stratification by age-group



Time: 1 year after diagnosis of hypertension

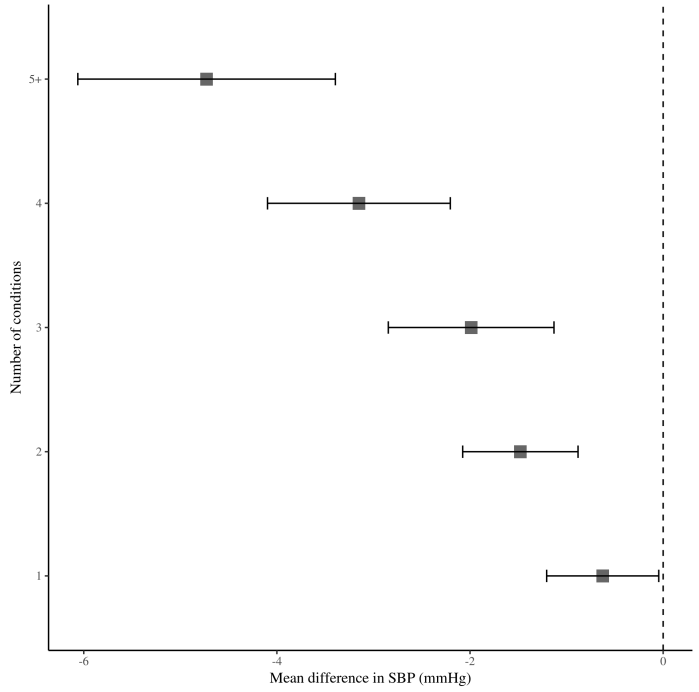
Stratification by age-group continued…

62-71 years old	>71 years old
	

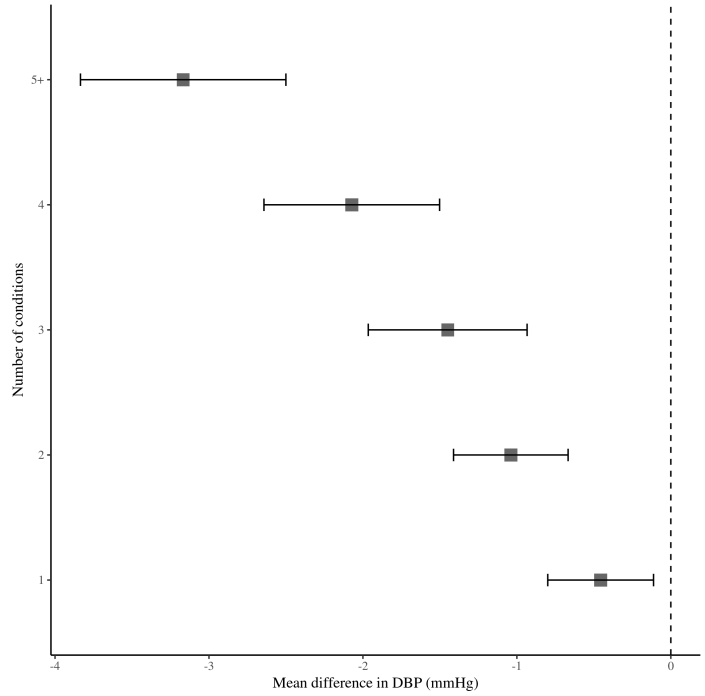
Time: 1 year after diagnosis of hypertension

SBP and DBP

SBP 1 year after diagnosis of hypertension

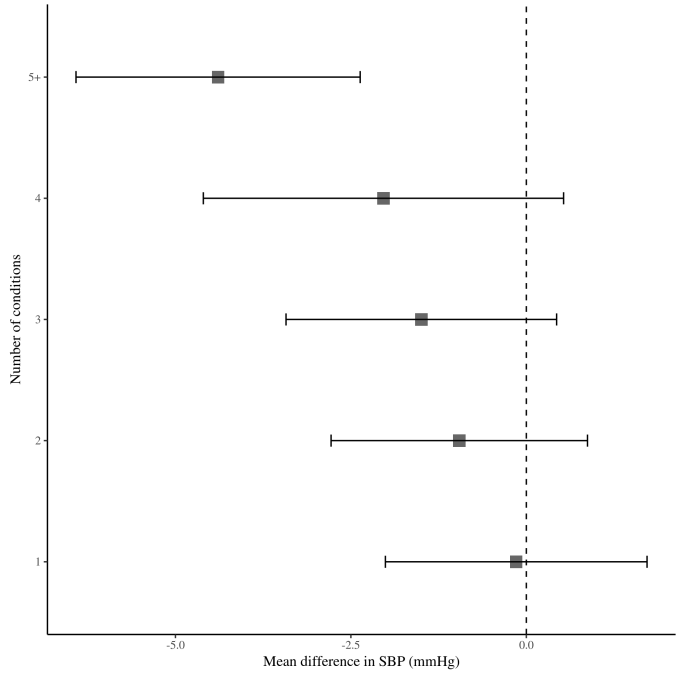


DBP 1 year after diagnosis of hypertension

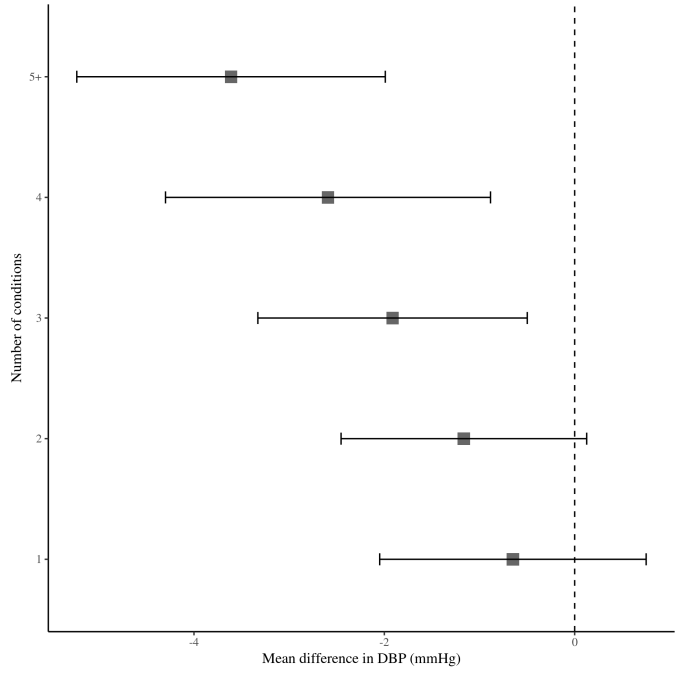


SBP and DBP continued...

SBP 10 years after diagnosis of hypertension



DBP 10 years after diagnosis of hypertension



A.5 Multimorbidity and mortality: additional analysis results

For chapter 7, additional analyses were performed as pre-specified in the analysis plan to inform the remaining analyses. This section summarises results from these analyses. Firstly, in a cohort excluding patients with additional comorbidities, showing that patients without any additional comorbidities had a lower HR compared to analysis using the whole population. Secondly, time-updating additional comorbidities and cardiometabolic status during follow-up had varying effects on the HR.

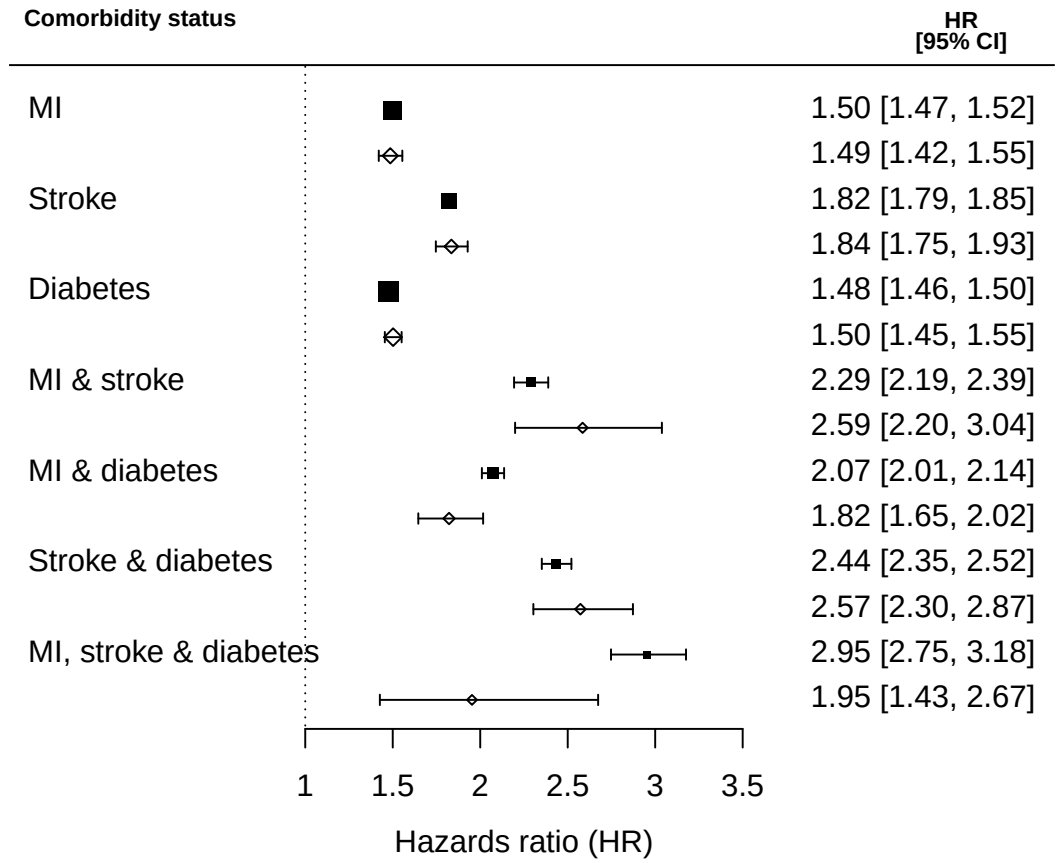
A.5.1 Exclusion of additional comorbidities reduces mortality risk

Figure A.2 compared the HRs of the base model with analysis of a population that excludes all patients with any of the additional comorbidities. Exclusion of additional comorbidities from the population led to minimal change or reduction in HR. For example in patients with MI, there was minimal change: HR was 1.50 [95%CI 1.47-1.52] without exclusion and 1.49 [95%CI 1.42-1.55]. However in patients with all three cardiometabolic conditions, a reduction in HR was observed: HR was 2.95 [95%CI 2.75-3.18] without exclusions and 1.95 [95%CI 1.43-2.67] with exclusion.

A.5.2 Cumulative risk of comorbidities over time

Further adjustment for time-updated additional comorbidities changed HRs further compared to adjusting only for baseline additional comorbidities. Figure A.3 shows a comparison of hazard of death by cardiometabolic status comparing models with adjustment for additional comorbidities at baseline only, to models with additional comorbidities updated throughout follow-up. In general, adjustment for time-updated comorbidities had a lower HR compared to baseline only although not all HRs were statistically significant. For example, risk of death in patients with stroke was 1.47 [95%CI 1,44-1.49] when adjusted for baseline additional comorbidities, and 1.32 [95%CI 1.29-1.36] when adjusted for time-updated additional

Figure A.2: Mortality risk by cardiometabolic comorbidity status comparing total population vs population excluding patients with additional comorbidities

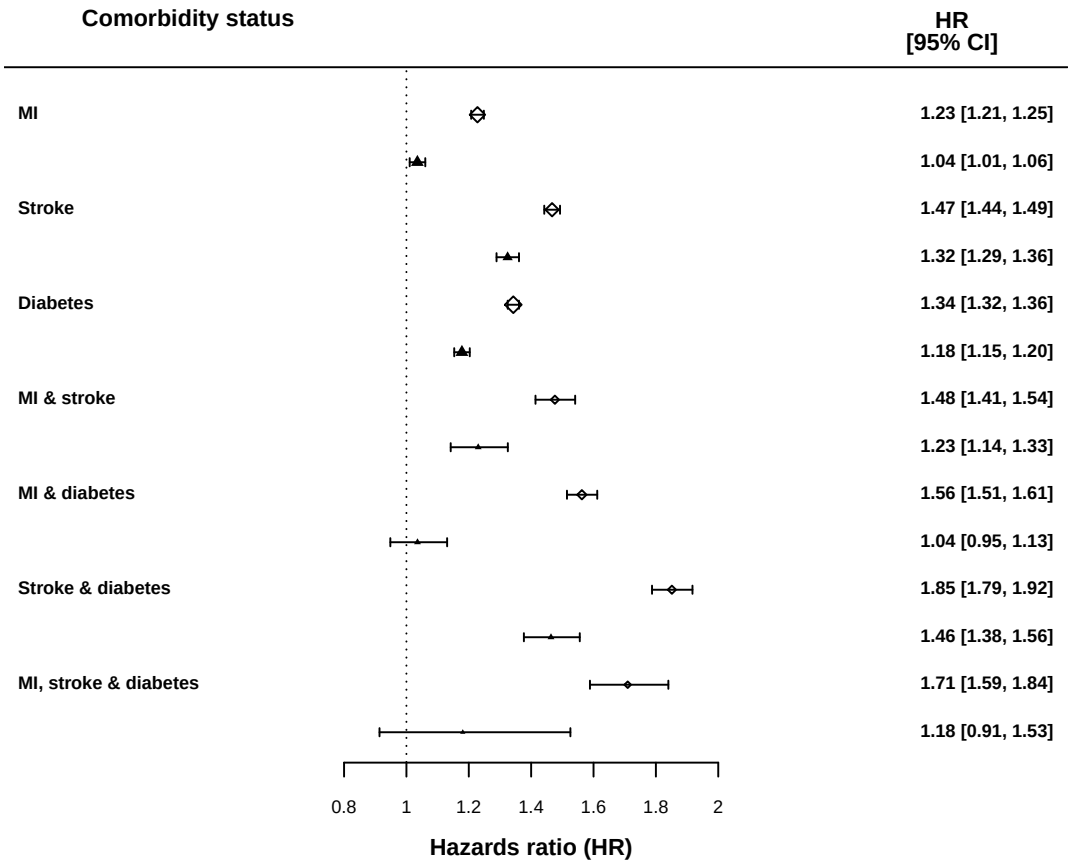


Hazards ratios were calculated from Cox proportional hazards regression. All models were adjusted for age, sex and index of multiple deprivation. Black squares are unadjusted for additional comorbidities; open diamonds are analyses on a population without additional comorbidities.

comorbidities; and for patients with all three conditions 1.71 [95%CI 1.59-1.84] and 1.18 [95%CI 0.91-1.53] respectively.

Figure A.4 shows mortality risk comparing adjustment for baseline additional comorbidities with time-updated adjustment for both additional comorbidities and cardiometabolic status. There was heterogeneity in the direction of change in HR with adjustment for time-updated comorbidities and cardiometabolic status. Patients with any combination of MI or stroke had a comparatively higher HR with adjustment for time-updated additional comorbidities and comorbidity status. Patients with MI had a 1.35 [95%CI 1.32-1.38] risk of death compared to 1.23

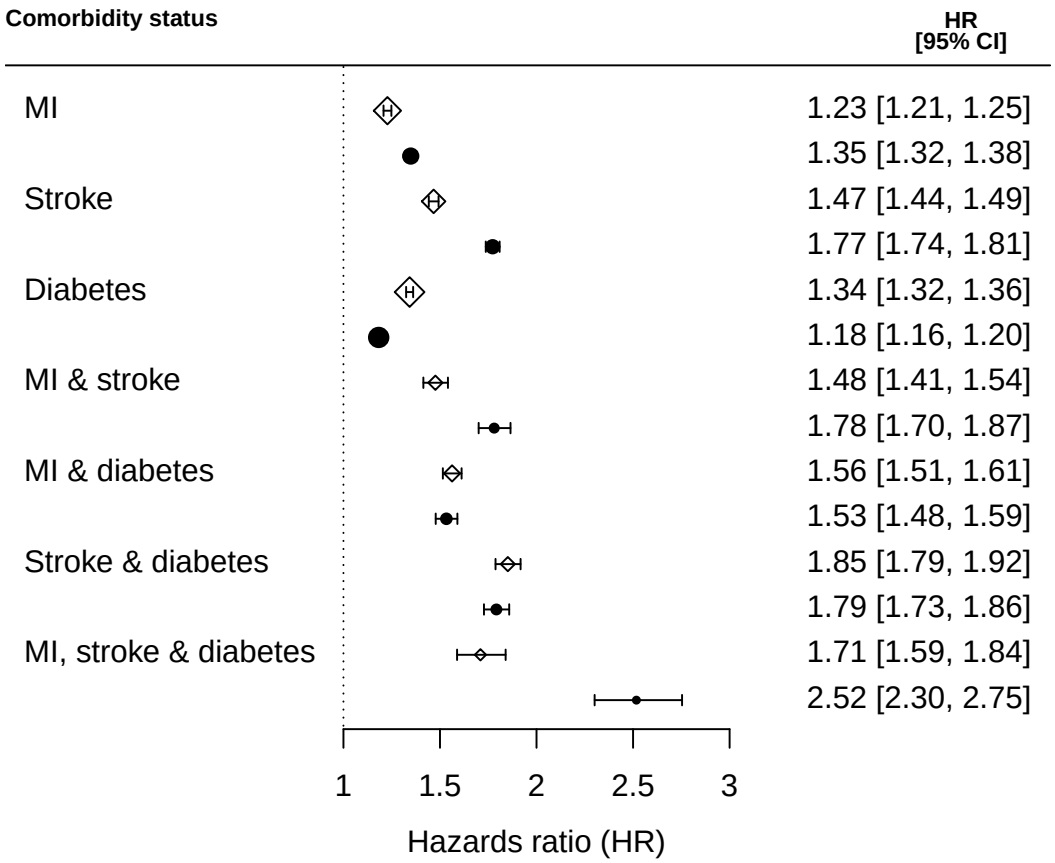
Figure A.3: Mortality risk by cardiometabolic comorbidity status comparing adjustment for baseline additional comorbidities vs adjustment for time-updated additional comorbidities



Hazards ratios (HRs) were calculated from Cox proportional hazards regression. All models were adjusted for age, sex and index of multiple deprivation. Open diamonds are adjusted for additional comorbidities without time-updating; black triangles are adjusted for comorbidities with time-updating.

[95%CI 1.21-1.25] when only adjusted for baseline comorbidities; similarly with stroke: 1.47 [95%CI 1.44-1.49] with baseline adjustment, and 1.77 [95%CI 1.74-1.81] with time-updated adjustment. With MI & stroke, the HR also increased from 1.48 [95%CI 1.41-1.54] to 1.78 [95%CI 1.70-1.87] with time-updated adjustment, and likewise with MI, stroke & diabetes: 1.71 [95%CI 1.59-1.84] to 2.52 [95%CI 2.30-2.75]. On the other hand, these additional time-updated adjustments for diabetes decreased mortality risk: HR was 1.34 [95%CI 1.32-1.36] with baseline adjustment vs HR 1.18 [95%CI 1.16-1.20] with time-updated adjustment; a reduction was also apparent when diabetes was combined with MI or stroke.

Figure A.4: Mortality risk by cardiometabolic comorbidity status comparing adjustment for baseline additional comorbidities vs adjustment for time-updated additional comorbidities and time-updated comorbidity status



HRs were calculated from Cox proportional hazards regression. All models were adjusted for age, sex and index of multiple deprivation. Open diamonds are adjusted for additional comorbidities at baseline; black circles are adjusted for time-updated additional comorbidities and cardiometabolic comorbidity status.

A.6 Other supplementary material - online

Other supplementary material relevant to this thesis can be found at

`https://www.researchgate.net/profile/Jenny_Tran20`, including:

- final code lists for each condition
- ISAC protocol approved for the CPRD data cut used
- pre-analysis study protocols for chapter 5, chapter 6 and chapter 7

These are not included in the supplementary appendix due to the large size of all codes (more than 1000 pages), and also for other researchers to download and use the codes in a computer-ready format.S

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