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Epidemiology of multimorbidity and polypharmacy in ageing: a complementary analysis of mental and brain health in three datasets

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Doctor of Philosophy

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Declaration

I declare that the work in this thesis presented for the degree of PhD is my own, except where work which has formed part of jointly authored publications has been included. I confirm that appropriate credit has been given within this thesis where reference has been made to the work of others.

The work presented in Chapter 2 was previously published in *The BMJ* as "Measuring multimorbidity beyond counting diseases: systematic review of community and population studies and guide to index choice" by Lucy E Stirland (candidate), Laura González-Saavedra, Donncha S Mullin, Craig W Ritchie (PhD supervisor), Graciela Muniz-Terrera (primary PhD supervisor) and Tom C Russ (PhD supervisor). My contribution is clearly explained in Chapter 2.

The work presented in Chapter 5 was previously published in the *Journal of Alzheimer's Disease* as "Associations Between Multimorbidity and Cerebrospinal Fluid Amyloid: A Cross-Sectional Analysis of the European Prevention of Alzheimer's Dementia (EPAD) V500.0 Cohort" by Lucy E Stirland, Tom C Russ, Craig W Ritchie, Graciela Muniz-Terrera and the EPAD Consortium. My contribution is clearly explained in Chapter 5.

I declare that this thesis has not been submitted, in whole or in part, in any previous application for a degree.

Edinburgh, June 2020

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Abstract

Multimorbidity, the co-existence of two or more chronic conditions, is common and increasing in prevalence. It is associated with poor outcomes for patients and increased costs for healthcare providers, so is attracting attention both from policymakers and researchers. The use of multiple simultaneous medications (polypharmacy) frequently co-occurs with multimorbidity. Multimorbidity including physical and mental illnesses has been recognised as important and under-studied. It not only poses challenges for patient management but also provides opportunities for interventions which could prevent overall clinical decline.

This thesis separates physical and mental illnesses to explore associations between multimorbidity and polypharmacy with mental health outcomes and brain health biomarkers in ageing cohorts.

Although there are standard published definitions of multimorbidity, understanding the concept is difficult due to the numerous ways to measure it. This thesis opens with a systematic review of multimorbidity indices. Among 5 560 unique titles identified in a literature search, 35 full-text papers were relevant, and are described and evaluated in detail.

Data analysis took place in three datasets focused on ageing, with complementary designs. These are the PREVENT Dementia and European Prevention of Alzheimer's Dementia (EPAD) study cohorts, and routinely collected data from the National Health Service (NHS) Scotland's Information Services Division (ISD).

In PREVENT Dementia, participants aged 40-59 years are deeply phenotyped, allowing exploration of the epidemiological associations between increasing chronic conditions and medication use with various clinical and biological outcomes. These include self-reported depression, cognitive test results and markers of neurodegeneration on magnetic resonance imaging (MRI). From regression analysis of 210 participants' data, each additional condition was associated with increased

odds of self-reported depression (adjusted OR=1.41, 95% CI 1.11 to 1.80) and anxiety disorder (OR=1.71, 95% CI 1.35 to 2.21). Increasing medication use was associated with self-reported depression (adjusted OR per additional medication=1.36, 95% CI 1.07 to 1.73) but not anxiety disorder (OR=1.24, 95% CI 1.00 to 1.53). There were no meaningful associations between multimorbidity or polypharmacy with MRI or cognitive test outcomes.

The EPAD cohort permitted a more focused approach in people aged over 50 years, specifically examining associations between increasing chronic conditions and cerebrospinal fluid (CSF) amyloid-β. In 447 participants, each additional comorbid condition carried a decreased likelihood of amyloid positivity (multiply-adjusted OR=0.82, 95% CI 0.68 to 0.97). This informs the debate that amyloid may not play a part in the pathway between multimorbidity and the development of dementia.

Analyses of NHS data used routinely collected information on prescriptions, psychiatric hospital admissions and death certificate diagnoses from 1.23 million people aged over 50 years in Scotland. Adjusted hazard ratios for each additional drug were 1.03 (95% CI 1.03 to 1.04) for death with any psychiatric cause and 1.04 (95% CI 1.04 to 1.05) for admission to psychiatric hospital over 8.5 years of follow-up. In this and the analyses in PREVENT Dementia, the use of antidepressant or psychotropic medication attenuated the associations.

The importance of patient and public involvement in research is also discussed, including perspectives on this work from a Lay Contributor.

This thesis explores the measurement of multimorbidity in detail and provides further evidence that physical multimorbidity and polypharmacy are associated with poor mental health. However, the links with biological markers of brain disease such as MRI findings and amyloid are less convincing. This leads to a discussion of possible mechanisms, clinical implications, and proposed future work.

Lay summary

It is becoming more common to have many health conditions at once. This is called multimorbidity. People with multiple conditions usually take several medicines too, known as polypharmacy. Both multimorbidity and polypharmacy increase as people get older. Previous research has found that having multiple conditions is difficult for patients and costly for health services. It may also be bad for mental health and linked to dementia.

This thesis explores patterns in data to find links between multimorbidity, polypharmacy and mental or brain health.

The first part of the thesis focuses on how researchers measure multimorbidity. Some choose to count a person's number of diagnoses or medicines, whereas others use tools that assign more importance to some conditions than others. I did a detailed search and found 35 such tools, then summarised and appraised them.

I also looked for links between multimorbidity, polypharmacy and mental or brain health in three sources. The PREVENT Dementia study included 210 participants aged 40-59 years. The European Prevention of Alzheimer's Dementia (EPAD) study had 447 volunteers aged 50 years and over. The third source was routinely collected National Health Service (NHS) data from 1.23 million people aged 50 years and over in Scotland.

In the PREVENT Dementia study, I found that having more physical conditions or taking more medicines increased the risk of depression and anxiety. In the NHS data, there were some links between taking more medicines and being admitted to psychiatric hospital or having a mental illness recorded at death. However, in both PREVENT Dementia and the NHS data, taking a psychiatric medicine (that is, already having a psychiatric diagnosis), seemed to explain this link.

Participants in PREVENT Dementia and EPAD did not have dementia. They had magnetic resonance imaging (MRI) scans and spinal fluid tests that can help predict dementia or Alzheimer's disease. I found that having more conditions was not linked with results suggesting a higher risk of dementia. This differs from previous research which showed that people with dementia usually have at least two other conditions.

All my results are observations. I cannot suggest that multimorbidity or polypharmacy cause mental illness, only that they co-exist.

The final chapter of this thesis includes my reflections on involving a Lay Contributor throughout my PhD.

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List of abbreviations

Aβ	Amyloid-β (Amyloid-β_{42})
ADL	Activities of Daily Living
APMS	Adult Psychiatric Morbidity Survey
APOE	Apolipoprotein E
ATC	Anatomic Therapeutic Chemical
BNF	British National Formulary
CAIDE	Cardiovascular Risk Factors, Aging, and Incidence of Dementia
CES-D	Center for Epidemiologic Studies Depression scale
CHI	Community Health Index
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
CSF	Cerebrospinal fluid
DBMA	Disease Burden Morbidity Assessment
eDRIS	electronic Data Research and Innovation Service
EPAD	European Prevention of Alzheimer's Dementia [Consortium]
EQ-5D	EuroQol five-dimension measure of health status
fMRI	Functional Magnetic Resonance Imaging
GP	General practitioner
GWAS	Genome-Wide Association Studies
HR	Hazard ratio
ICD-10	International Statistical Classification of Diseases and Related Health Problems 10th Revision
ISD	Information Services Division
LMIC	Low- and middle-income country
MeSH	Medical Subject Heading
MRI	Magnetic Resonance Imaging
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NRS	National Records of Scotland

NSS	NHS National Services Scotland
OR	Odds ratio
PBPP	Public Benefit and Privacy Panel for Health and Social Care
PIS	Prescribing Information System
PPI	Patient and public involvement
PREVENT	PREVention of dementia by ENvironmental intervention and Therapy [full name no longer used]
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
SD	Standard deviation
SF	Short Form health survey
SHARE	The Survey of Health, Ageing and Retirement in Europe
SIMD	Scottish Index of Multiple Deprivation
SMR	Scottish Morbidity Records
STAI	Spielberger State-Trait Anxiety Inventory
WHO	World Health Organization

Contents

Chapter 1 Introduction

1.1 INTRODUCTION

There is a saying, *"old age doesn't come alone"* – as people age, the number of challenges they face increases. Problems can occur in many domains, with health being a particularly demanding aspect. When several chronic health conditions co-exist, the term commonly used is multimorbidity. This thesis explores the associations between multimorbidity and polypharmacy (the simultaneous use of several medications) with markers of mental disorders and brain health, using an epidemiological approach, in three complementary datasets.

1.2 HISTORY AND DEFINITIONS

1.2.1 Multimorbidity

Multimorbidity is usually defined as the co-existence of multiple chronic diseases, where one is not necessarily more central than the others, within one person.[1] The similar concept of comorbidity refers to the co-existence of one or more diseases alongside one particular disease, known as an index disease.[2,3] The term 'comorbidity' was first used by Alvan Feinstein in the late 1960s and its use for the next thirty years often subsumed what is now called multimorbidity.[2,4] The German word *Multimorbidität* emerged in 1976 and between then and 1990, there were 77 published articles including this term or 'multimorbidity', of which 92% were written in German.[5] In 1997 a paper reviewing the use of the terms comorbidity and multimorbidity recommended that multimorbidity be used when there was no reference to an index disease, and this practice is now usually followed.[2]

Multimorbidity can be understood using the concepts of concordance and discordance.[6] In concordant multimorbidity, the co-existing conditions share common aetiology and therefore mutually benefit from treatments. For example, hypertension increases the risk of both cerebrovascular disease and coronary artery disease, and management of hypertension can improve outcomes in both conditions. This is also known as causal comorbidity.[2] Discordant multimorbidity (or associative comorbidity) describes co-existing conditions that apparently have separate aetiology and require different treatments.[2,6,7] These concepts may depend on assumptions

about causality and direction of comorbidity, but can be useful when considering combinations of diseases within an individual patient.

Two prominent bodies have proposed definitions of multimorbidity that refer to more than a dichotomous measure of whether or not an individual has two or more chronic diseases. The USA's National Quality Forum defines 'multiple chronic conditions' (its preferred term over multimorbidity) as:

> *"having two or more concurrent chronic conditions that collectively have an adverse effect on health status, function, or quality of life and that require complex healthcare management, decision-making, or coordination."* [8]

Their definition of 'condition' includes entities that may be considered risk factors elsewhere, such as obesity and harmful use of alcohol. The European General Practice Research Network published a comprehensive definition of multimorbidity in 2013, summarised by the following phrase:

> *"Multimorbidity is defined as any combination of chronic disease with at least one other disease (acute or chronic) or bio-psychosocial factor (associated or not) or somatic risk factor."* [5]

Including risk factors as conditions introduces heterogeneity within this definition of multimorbidity because there is no clear distinction of what constitutes a bio-psychosocial factor or somatic risk factor. However, risk factors such as smoking status are included in some multimorbidity indices.[9,10]

In this thesis, I have focused on chronic conditions, both with continuous counts and dichotomous markers of multimorbidity. This is discussed in detail in Chapter 3 (section 3.5.2).

1.2.2 Chronic conditions

Although acute conditions can have major impacts on patients' lives and illness burden, multimorbidity definitions usually specify that conditions must be chronic

because of their associated long-term consequences.[11] Defining chronicity can be challenging. A 2017 article reviewing the overlap between multimorbidity and frailty says:

> *"a condition is classified as chronic if it is permanent, it is caused by non-reversible pathologic alterations or requires rehabilitation or a long period of care".*[12]

Given the lack of consensus, when selecting conditions to include in analyses, I opted for a definition that captures both duration and impact. I used a combination of definitions from the International Classification of Primary Care, version 2,[13] and from NHS Scotland Information Services Division [14] to generate the following definition:

> Conditions should:
>
> - last at least six months
> - have an impact on quality of life (either directly or through sequelae)
> - clearly meet diagnostic criteria, and
> - have a pattern of recurrence or deterioration.

Describing what is meant by 'conditions' or 'disease' is also problematic as there is no universally accepted definition. The term disease may refer to either a recognisable set of symptoms and signs, or phenomena arising from a specific disorder or other cause.[15] For some conditions, such as type I diabetes, there is a clear pathological abnormality, physiological consequences and treatment. Other conditions or states such as deafness, obesity and addictions may be more contentious, even where standard definitions exist. Lay people and doctors differ in their judgement of whether these constitute disease.[16] Prevalence of diseases or conditions can also change depending on how they are defined, such as cut-offs in 'normal' blood pressure or using a certain threshold of serum troponin to diagnose myocardial infarction.[17] In addition, there is a question of whether a state counts as disease in its own right or solely increases the risk of another condition. Hypertension and hypercholesterolaemia fall into this category, and emerging labels such as pre-diabetes further complicate this picture.[17–19]

I restricted my definition of chronic conditions to include diagnosable diseases rather than symptoms (such as pain) or risk factors (such as hypercholesterolaemia). Using existing data means that in many situations, the decision on what counts as a disease has already been taken. This could be by the study designers who generated a set list of conditions to ask participants about, participants' own doctors who have diagnosed a condition and participants themselves, who declare these conditions when asked about their medical history. Throughout this thesis, I use pragmatic approaches to this issue, tailored to each dataset, as there is no single accepted list of conditions from which to measure multimorbidity.

1.2.3 Terminology

The concept of multimorbidity suggests a holistic approach to individuals, not starting with a particular diagnosis or body system, and this is often most relevant in primary care.[20] Some researchers have rejected the term, however, mostly due to its unpopularity with patients, and prefer to say 'multiple chronic conditions',[8,21] 'multiple health conditions'[22] or 'complex needs'.[23] Although I acknowledge that people with multimorbidity have challenging lives including social and environmental factors which influence outcomes, my focus in this thesis is on quantifying multiple chronic conditions. Therefore, throughout this thesis I use the term multimorbidity. It is widely used and understood in the literature, for example gaining its own Medical Subject Heading (MeSH) term for indexing in PubMed in January 2018.[24] When I use a count of chronic conditions or medicines, I refer to them accordingly, to avoid conflating this continuous measure with the implied dichotomy of multimorbidity or polypharmacy. Multimorbidity can include any condition, whether classified as physical or mental. This thesis explores mental and brain health outcomes so in most analyses I separate physical and mental diagnoses in order to examine their interplay.

1.2.4 Polypharmacy

Polypharmacy is defined as the concurrent prescription of multiple medications.[25] Because medication is the primary treatment for most chronic medical conditions, polypharmacy commonly co-exists with, or is a direct result of multimorbidity,[26,27]

although this association is relatively under-studied.[28,29] As it is usually clear how many medications a person is receiving, either from self-report or prescribing records, polypharmacy is most often measured by count alone. This does not always reflect the number of medications the person actually takes.[30] Unlike for multimorbidity where most definitions agree on a cut-off of two or more conditions, there is no established number of medications that counts as polypharmacy. The Scottish Government, which publishes comprehensive guidance on polypharmacy, defines it as two or more medications, in keeping with the word's Greek origin where poly means 'more than one'.[27,31] However, their reports focus more on situations where the use of multiple medications is hazardous and potentially avoidable (known as inappropriate polypharmacy) and are less concerned with overall counts.

A 2017 systematic review of polypharmacy definitions found 110 articles, of which 90 (81.8%) used a numerical distinction, with the remainder using or adding information about treatment duration.[32] Of those with a numerical cut-off, the most commonly used was five or more drugs (51 studies). Another systematic review of the association between polypharmacy and mortality highlighted that many studies compare groups using categorical variables, for example 0-4, 5-9 and ≥10 medications.[33] There has been a recent call to clarify terminology around drug prescribing and a proposal of the terms 'index drug' and 'codrug', but polypharmacy is widely used and understood in the literature and is the term I will use in this thesis.[34] Some studies use other terms, such as excessive polypharmacy or hyperpolypharmacy, to mean polypharmacy including ≥10 drugs.[35,36] These terms may imply that this polypharmacy is inappropriate which cannot be proven by count alone; I use numerical definitions instead in this thesis.

Although medication use is somewhat useful as a marker for chronic conditions, polypharmacy is an issue in its own right, due to the potential adverse effects of each drug and interactions between them.[37] Therefore, multimorbidity and polypharmacy should be considered separately. In order to capture the full range of medication use, in most analyses I use the count of medications as a continuous variable, rather than a categorical definition of polypharmacy.

1.2.5 Definitions of mental and brain health outcomes

The exploration of mental health outcomes in this thesis is three-fold, including clinical or symptomatic manifestations of mental disorders, cognitive test scores and biomarkers of neurodegenerative disease. These outcomes are used depending on the specific questions asked and the availability of data. The co-existence of mental and physical components within multimorbidity is prevalent, with mild and moderate depression particularly important in mid-life and comorbidities with dementia prominent in older people.[38,39]

There is current research interest in identifying modifiable risk factors for neurodegenerative diseases such as dementia, with the aim of preventing or delaying the onset of disease and reducing incidence.[40–42]. Depression and anxiety in mid-life have been identified as risk factors for dementia,[43–45] although the direction of the association remains uncertain.[46] Multimorbidity and polypharmacy also co-exist with dementia and cognitive impairment.[39,47,48] If all of these factors were managed, theoretically the risk of neurodegenerative diseases could be reduced. In addition, if multimorbidity and polypharmacy are risk factors for anxiety, depression and other mental disorders, their identification and management (and possibly prevention) could have personal benefits to the health of individuals.

I use the term mental disorders to include clinically diagnosed diseases including depression, anxiety, and dementia, as the term ‘mental illness’ is not always understood to capture dementia. To reflect the diversity of manifestations of mental disorders: clinical, pre-clinical and sub-clinical, I explore a variety of outcomes across three datasets, as follows:

1. Mental disorders
    a. Depression and anxiety disorder
        i. Self-reported diagnoses
        ii. Scores on symptom scales
    b. Mental or behavioural disorders recorded on death certificates

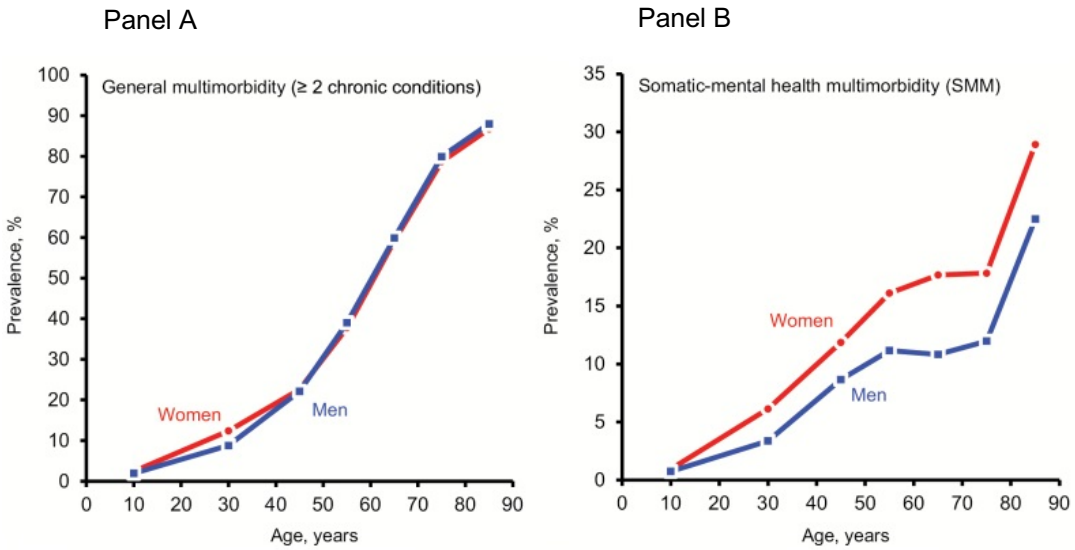
    c. Admission to psychiatric hospital
2. Cognitive test results
3. Biomarkers of neurodegenerative disease
    a. Structural magnetic resonance imaging (MRI) measures
    b. Cerebrospinal fluid (CSF) amyloid-β_{42}

1.2.6 Understanding multimorbidity in ageing

Although multimorbidity is common in older people and has been called in one review *"the ultimate geriatric syndrome*",[49] there are more people with multiple chronic conditions in mid-life due to population demographics.[39] Exploration of multimorbidity in mid-life is additionally important given its likely contribution to later brain health.

A population study of 138 858 people in Minnesota explored multimorbidity using a list of 19 possible conditions, of which five were mental disorders (including dementia).[50] The authors separated multimorbidity into general multimorbidity, which they defined as two or more of any of the conditions, and somatic-mental multimorbidity, where at least one of the conditions was a mental disorder. They found that somatic-mental multimorbidity was more common in women and plateaued at around 55-75 years, but with a sharp increase after 80 years, as shown in Figure 1-1, Panel B. This increase was more marked in participants with somatic-mental multimorbidity compared to general multimorbidity (Panel A). This suggests that multimorbidity including both physical and mental illness in mid-life and later life may not represent the same clinical presentation and may be best examined separately.

Figure 1-1: Prevalence of general multimorbidity and somatic (physical)-mental health multimorbidity, from Bobo et al., 2016 [50] *(note different y-axis limits)*[1]



In this thesis I therefore analyse data from people in a mid-life cohort aged 40-59 years (PREVENT Dementia, Chapter 4)[42,51]. There is also value in analysing the physical and brain health of older people where multimorbidity is almost ubiquitous, so the other two analytic chapters include people aged over 50 years. Chapter 5 features the European Prevention of Alzheimer's Dementia (EPAD) cohort study, comprising volunteers aged over 50 years where the mean age was 66 years (standard deviation [SD]=6.6 years).[52] The sample in Chapter 6 includes all members of the Scottish population aged 50 years and over at baseline (mean age 67.4 years, SD=10.8).[53] In all analyses, I pay careful attention to age, both including it as a covariate and testing for interactions or stratifying analyses where appropriate.

1.2.7 Frailty

Multimorbidity is distinct from frailty, a related and similarly pertinent topic in the care of older people. Frailty is a dynamic clinical state of decreased resilience which manifests as an increased risk of adverse health outcomes or death after a stressor.[12,54] There are three main approaches to measuring frailty. Firstly, the

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phenotypic approach is concerned with symptoms or biomarkers, including weakness or weight loss.[55] Secondly, it is possible to measure the accumulation of deficits, such as slow gait and poor grip strength.[56] Frailty can also be considered in terms of dimensions, including physical, cognitive and social or quality of life.[57]

Frailty may co-exist with, or be a consequence of, multimorbidity. A systematic review and meta-analysis of studies examining this co-occurrence found that the prevalence of multimorbidity in people with frailty was 72% (95% CI 63% to 81%) and the prevalence of frailty in people with multimorbidity was 16% (95% CI 12% to 21%).[58] This highlights the difference between these two states, and perhaps suggests that frailty captures more of the clinical functional state compared to multimorbidity's focus on diagnoses.

1.3 IMPORTANCE

1.3.1 Epidemiology of multimorbidity

Multimorbidity and polypharmacy are acknowledged as widespread and common, but estimates of their prevalence vary. A systematic review of papers published between 1961 and 2013 found 39 studies on multimorbidity prevalence, with varying age ranges and numbers of conditions considered.[59] Most studies were cross-sectional, and estimates of multimorbidity (two or more conditions) ranged from 13% when the minimum age was 18 years to 95% in those aged 65 years and over. All studies found a positive association between increasing age and multimorbidity, with the majority of older people having multimorbidity. Socioeconomic deprivation was also universally associated with multimorbidity. Another systematic review including only people aged over 65 years in high-income countries found 52 articles, of which the majority reported prevalence of more than 50% for having two or more concurrent conditions.[60] The authors also reported an overall pooled prevalence of 66.1% but their methods for pooling such diverse data were not explained. There are fewer studies that track rates of multimorbidity longitudinally.[7]

The global population is ageing, but evidence from the most recent Global Burden of Disease study shows that an increase in life expectancy is not equivalent to adding healthy years to life.[61] Therefore, it is assumed that rates of chronic diseases and multimorbidity will increase due to population ageing.[62] A study of over 350 000 patients from GP practices in the Netherlands (using a list of 28 conditions and defining multimorbidity as ≥2 conditions) found that rates of multimorbidity increased from 12.7% in 2004 to 16.2% in 2011.[63] Standardising for age still gave an increase of 2.7%, suggesting that rates are increasing regardless of the ageing population. Danish data have been published stating that the number of patients attending multiple outpatient clinics increased from 4.0% in 2004 to 7.7% in 2014.[64] This repeated cross-sectional study suggests that multimorbidity may increase over time but did not adjust for age; this increase may be explained by population ageing. In addition, repeated cross-sectional data from around 70 000 participants of the Survey of Health, Ageing and Retirement in Europe (SHARE) across ten countries found that, using a list of 14 potential conditions, multimorbidity increased from 38.2% in 2006-7 to 41.5% in 2015 (multiply-adjusted prevalence ratio 1.05).[65] Multimorbidity is therefore common and increasing in prevalence.

In this thesis, I use data from Scotland, England and across Europe. A widely cited 2012 paper by Barnett and colleagues reported multimorbidity rates from one-third of the Scottish population of all ages in 2007, counting from a list of 40 conditions.[39] Their overall reported rate of multimorbidity was 23.2%, and among people with at least one condition, 54.9% had two or more. A more recent study by Cassell et al. used a similar list of 36 conditions in over 400 000 general practice patients aged ≥18 years in England in 2012.[38] This found that the rate of multimorbidity was 27.2%. The difference in patient ages and potential conditions counted between these studies means that the prevalence estimates cannot be meaningfully compared. Researchers analysing data from SHARE counted multimorbidity from a list of 12 conditions.[66] In the 2013 data collection, the overall prevalence of multimorbidity, adjusted for age and gender, was 31.4% (95% CI 30.7% to 32.2%). Rates varied by country, with lower prevalence in northern Europe and the highest rates in Eastern and Central Europe.

Identifying people with multimorbidity can inform care planning that includes the person as a whole. For example, this might mean awareness of patients at risk of an acute admission in order to prevent one, mobilising community supports rather than approaching acute medical care in a health crisis, or even recognising when a palliative approach might be the most appropriate action.[67,68]

1.3.2 Adverse consequences of multimorbidity

By definition, multimorbidity suggests that patients are unwell or experience a greater burden of disease than comparable patients without multimorbidity. It is thought that conditions are synergistic, with multimorbidity affecting overall health more than the addition of each condition separately.[69] Therefore, some outcomes such as higher mortality are to be expected. A systematic review of prospective primary care cohort studies in multimorbidity reviewed six published papers, finding associations between multimorbidity and increased health service use and costs, mortality rates and reduced physical function.[70] Another systematic review with a broader focus studied 41 papers and found that multimorbidity was associated with disability, functional decline, high healthcare costs and poor quality of life.[71] It found that some, but not all studies showed an association between multimorbidity and an increased risk of mortality. However, a further systematic review focusing only on multimorbidity and mortality included 26 studies.[72] On meta-analysis, results showed that each additional condition had a hazard ratio (HR) for mortality of 1.20 (95% CI 1.10 to 1.30), and having two or more conditions compared to zero or one carried a HR of 1.73 (1.41 to 2.13). However, in all systematic reviews and meta-analyses in this field, it must be remembered that the original papers are often heterogeneous, especially when they count conditions from lists of different lengths.

Multimorbidity is costly to healthcare services and to individuals. A systematic review of cost-of-illness studies in multimorbidity found 26 articles published between 2000 and 2016, the majority of which were from countries with private healthcare systems.[73] The original studies measured multimorbidity in diverse ways, precluding meta-analysis, but there was consistent evidence that multimorbidity was associated with higher healthcare costs. Cassell and colleagues' more recent study of NHS primary care in England found that people with two or more of a possible list

of 36 chronic conditions had 2.58 (95% CI 2.48 to 2.69) times as many hospital admissions in four years as patients without multimorbidity, and a similarly increased rate of GP visits (2.56, 95% CI 2.48 to 2.64).[38] There is additional evidence from a systematic review of 14 studies, that primarily took place in countries without universal healthcare, that out-of-pocket expenditure on medicines increases with patients' number of conditions.[74]

Quality of life is also adversely affected for people with multimorbidity. A systematic review searched the literature in September 2018 and found 74 studies of multimorbidity and quality of life.[75] The majority of included studies used disease counts, and on meta-analysis of 19 studies that used the same outcome, the EQ-5D scale, each added disease carried an overall decline in health-related quality of life of 3.9% (95% CI -5.4% to -2.4%). Fifteen studies used the Short Form (SF) instrument and meta-analysis showed a steeper decline in its physical health (-3.3% with each additional condition) than mental health functioning components (-1.6% per condition). In addition, people with multimorbidity have been shown to be excluded from clinical trials for single diseases, and are therefore discriminated against in the development of new treatments.[76,77]

In summary, multimorbidity is attracting increasing research attention as it is linked with outcomes relevant to healthcare services such as costs and mortality, and those important to patients such as quality of life.

1.3.3 Epidemiology of polypharmacy

Polypharmacy is also common, especially among older adults. A Scottish Government report using prescribing data from 2014 stated that 13.3% of the whole population aged 50 years or over and 26% of those aged over 80 years were prescribed ten or more medications simultaneously.[25] A recent Swedish population study of over 1.7 million people aged ≥65 years found that 44.0% were taking ≥5 drugs and 11.7% took ≥10 drugs.[78] This study also quantified the association between multimorbidity and polypharmacy, reporting an increase of 0.95 medications

(95% CI 0.94 to 0.96) per additional chronic disease. On four-year follow-up of over 400 000 general practice patients in England, the yearly rate ratio for number of prescriptions was 5.91 (95% CI 5.71 to 6.12) for people with multimorbidity (two or more conditions) compared to those without.[38] Adverse outcomes associated with polypharmacy are explored further in section 6.1.

1.3.4 Epidemiology of mental disorders

The wide scope of what is meant by mental disorders means that overall, these are highly prevalent at population level, particularly in milder states. The majority of psychological symptoms are experienced in the community by people who may never seek medical attention. Of those who do, most are managed by GPs, a smaller number will reach the attention of a community psychiatrist, and fewer still will be admitted to psychiatric hospital.

The Adult Psychiatric Morbidity Survey (APMS) is a repeated cross-sectional survey of a representative sample of the population in England aged 16 years or over.[79] The latest survey wave, conducted in 2014, found that 15.7% (95% CI 14.7% to 16.7%) of this population had symptoms of mental disorder that would warrant clinical attention. This proportion has increased since the 1993 survey when rates using the same measure were 14.1%.[80] The rate of self-reported mental disorders in 2014 was slightly higher than that detected by symptom questionnaires, at 17.0% (16.0% to 18.1%). Among people aged over 65 years, rates were lower than in the rest of the population: 10.2% of 65 to 74 year olds and 8.1% of those aged 75 years and over had symptoms of common mental disorders, excluding cognitive impairment. The MentDis_ICF65+ study surveyed older adults across five European countries and Israel.[81] Among 3 142 adults with a mean age of 73.7 years, the total point prevalence of any mental disorder, according to diagnostic interview, was 23.3% (adjusted for age and gender, 95% CI 19.9% to 26.7%). This disparity compared to the English data may be explained by MentDis_ICF65+ including cognitive impairment. Mental disorders are therefore prevalent in the general population and among older people.

1.3.5 Importance of physical-mental multimorbidity

The 2012 Scottish population study by Barnett et al. found that among people with at least one condition, 19.8% had multimorbidity including both mental and physical conditions.[39] Among all people aged 65-84 years, 17.5% had both physical and mental health diagnoses, with this figure rising to 30.8% in those aged over 85 years. Cassell and colleagues' study in England found that 9.5% of all patients had mental and physical comorbidity and that this was present in 33.8% of people who had multimorbidity.[38][2] In the previously discussed cross-sectional study of 138 858 patients in Minnesota, the authors emphasised that in terms of absolute numbers, 71% of people with physical-mental multimorbidity were aged under 65 years.[50]

In a cohort study of over 252 000 survey participants across the USA, multimorbidity (the highest compared to lowest quartile score on a weighted index) was associated with a three-fold increased risk of death by suicide on 24-year follow-up.[82] This association remained when adjusting for baseline health-related quality of life. Measuring factors associated with suicide is difficult due to its low incidence, but a study of suicidal ideation among 7 403 participants of the 2007 APMS in England found that suicidal thoughts were common in people with physical-mental multimorbidity.[83] However, the increased odds were not elevated beyond those expected with either having physical conditions or common mental disorders alone. Further analyses of a Scottish cohort study by the same group of researchers found that having multimorbidity increased the risk of suicidal thoughts and suicide attempts, but not any more than having mental illness.[84]

Co-existing physical and mental multimorbidity can increase costs for health services. A King's Fund report into this issue found that having a comorbid mental health condition in addition to physical illness increased costs to the healthcare system for that individual by at least 45%.[62] It also concluded that these people's clinical outcomes are worse and their ability to manage their own physical symptoms is impaired. A study of over 180 000 patients from GP practices in Scotland found that

[2] I use the term 'patients' throughout this thesis where the people in question are under study because of their use of healthcare, and 'participants' where they are volunteers in a cohort study

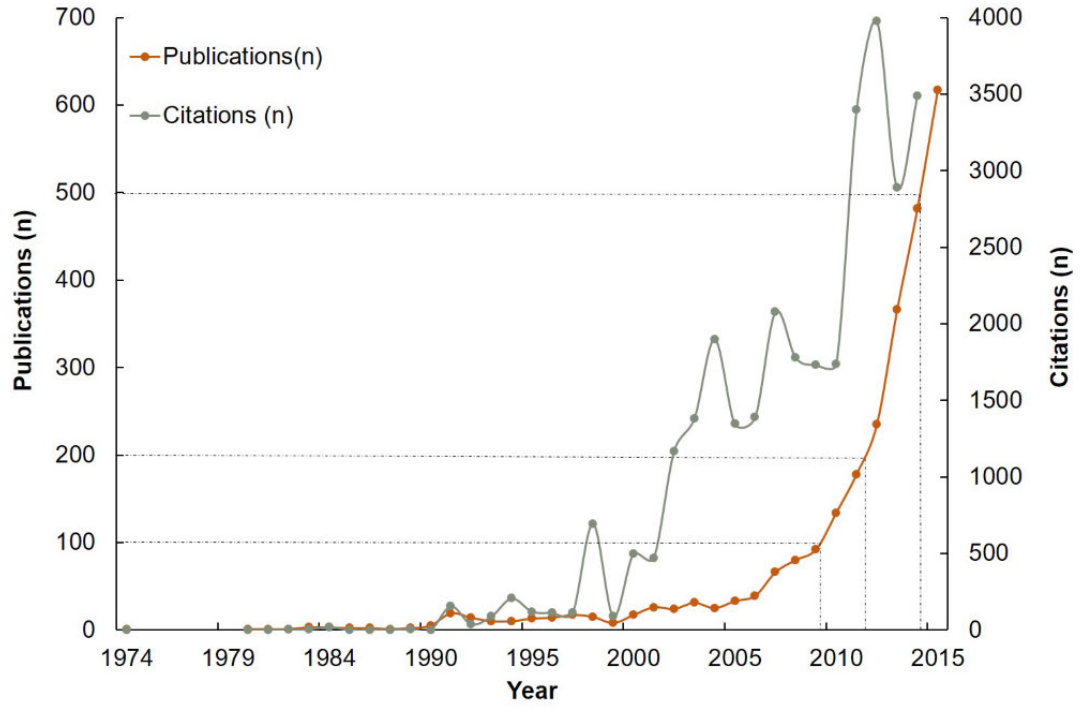
while multimorbidity increased the risk of unplanned hospital admissions within the following year, the risk was exacerbated by having a co-existing mental disorder.[85] The co-existence of physical and mental conditions with multimorbidity is therefore prevalent, costly and associated with poor outcomes.

The co-existence of physical and mental illnesses within multimorbidity may be due to shared biological aetiology, socioeconomic risk factors and other psychosocial factors such as health and illness behaviour.

1.4 AREAS OF RESEARCH NEED

A systematic review reporting a literature search carried out in June 2016 found 2 864 publications on multimorbidity (and its synonyms) in Web of Science since 1900.[86] The number rose steeply between 2010-16, as shown in Figure 1-2. This study only searched one database, so the total quantity of research in this area may be even higher.

Figure 1-2: Annual number of publications and citations on multimorbidity worldwide, from Xu et al., 2017 [86][3]



A similar study, also searching Web of Science in 2016, included 'comorbidity' in its search terms and found 85 994 papers, of which 76 350 were original research and 9 644 review articles.[87] This review showed the same rate of increase between 2010 and 2016, and also noted the prominence of papers on psychiatric comorbidity. A further review searched PubMed between 1985 and 2014 with less robust search criteria on multimorbidity and comorbidity and found 3 054 papers.[88] The author remarked that although all numbers of citations across PubMed had consistently increased during that period, the growth in multimorbidity citations was much higher than that in the rest of the medical literature.

Despite this striking expansion in multimorbidity research in the last ten years, the limited research focus on multimorbidity is still out of proportion with its large prevalence, compared to that on single diseases.[86] Multimorbidity is a topical area,

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with policy and research interest highlighted by two recent reports from the Academy of Medical Sciences.[7,89] The reports have identified areas of research need, including further exploration of the consequences of polypharmacy.[89] Other research priorities in this area have been established by the James Lind Alliance and National Institute for Health and Care Excellence (NICE).[90,91] The James Lind Alliance has patient-focused priorities, two of which relate to the psychological wellbeing of patients and carers and the specific questions raised would be best answered by trials. NICE recommended research into stopping unnecessary medicines and predicting life expectancy, along with improvements to general practice structure and management.

1.4.1 Physical-mental multimorbidity

The need to consider physical and mental health together is currently pertinent. Evidence from the APMS in England suggests that common mental disorders frequently co-exist with long-term conditions, but when they do, 71.2% of common mental disorders are untreated.[92] Recent reports from the Royal College of Psychiatrists and Academy of Medical Royal Colleges highlight the importance of managing physical health in people with mental disorders,[93,94] but there is comparatively little research into the mental health of people with physical multimorbidity. For example, research into specific mental health measures such as symptom scales in people with polypharmacy is scarce.[95] The authors of a systematic review of primary care multimorbidity studies highlighted that mental illness in people with multimorbidity was not covered in the papers they reviewed and was an important gap.[70] A consensus paper published in 2018 reported a Delphi process among 26 expert panellists developing a Core Outcome Set for multimorbidity research.[96] Mental health was among the top three highest-rated outcomes and was deemed essential.

The World Health Organization (WHO) also ascribes importance to the interactions between physical and brain health. In its recent guidelines on preventing cognitive decline and dementia, it recommended optimising specific physical conditions.[97] There is a small amount of research into associations between multimorbidity and specific biomarkers, such as hippocampal volume and cortical thickness.[98,99]

There is potential that better understanding of these associations could inform strategies to delay or prevent dementia. This is therefore an area where further work could provide an impact in advancing the field.

Mental disorders are prevalent, and physical-mental multimorbidity is increasingly recognised as important. There is also scope for better understanding of the impact of multimorbidity on biomarkers of brain health.

1.5 HYPOTHESES EXPLORED IN THIS THESIS

In this thesis, I explore mental health outcomes and brain health biomarkers in people with multimorbidity, comparing them to those without. Owing to the continued paucity of knowledge on broad issues in physical-mental multimorbidity, I use epidemiological methods to explore these associations.

1.5.1 Multimorbidity with depression, anxiety and cognitive impairment

Depressive and anxiety disorders are the commonest mental disorders in adulthood, particularly in middle age when multimorbidity is most prevalent.[79] They may reflect the everyday burden of psychological distress that has many financial and personal costs but does not reach psychiatric attention. As depression and anxiety disorders are often included in lists of conditions in multimorbidity studies, it can be difficult to extract them to address the overall questions about physical-mental multimorbidity. There may be common aetiological factors between multimorbidity and depression or anxiety, including biological (for example, vascular) mechanisms and psychosocial predispositions.

Cognitive impairment is a manifestation of neurodegenerative disease that can emerge early in the disease course, for example in mid-life. Detecting it at this stage can improve prospects for possible disease modification or slowing of progression.[41] It is therefore of interest when exploring brain health within multimorbidity, relating to likely common aetiological factors.

1.5.1.1 Hypothesis 1

Physical multimorbidity (or having a larger number of chronic conditions), will be associated with an increased risk of mental disorders. The greater the burden of multimorbidity, the higher the individual's risk of developing a mental disorder. These include:

a. Depression
b. Anxiety
c. Cognitive impairment (specific deficits on cognitive testing)

1.5.2 Polypharmacy with depression, anxiety and broader psychiatric outcomes

Polypharmacy commonly co-exists with, but is distinct from, multimorbidity. Its relationship to mental health may be explained by biological or psychosocial factors. Biologically, psychiatric adverse effects of specific medicines are common and well-recognised. These can be immediate and short-term such as anxiety when using beta-$_2$ agonists,[100] medium-term including depression with beta-blockers or proton pump inhibitors,[101] or more chronic such as cognitive impairment with benzodiazepines [102] or anticholinergic drugs.[103] The burden of taking multiple medications may also be associated with self-reported feelings of stress, anxiety or low mood.[104]

Specific quantitative outcomes can be difficult to measure in large scale studies using routinely collected data. Broader outcomes such as evidence of psychiatric hospital admission or mental disorder on the death certificate provide good specificity but limited sensitivity.

1.5.2.1 Hypothesis 2

Polypharmacy, or using larger numbers of medications (accounting for antidepressant or psychotropic drugs), will be associated with poorer mental health, and the greater the burden of polypharmacy, the higher a person's risk of developing a mental disorder, including

a. Depression, anxiety, cognitive impairment
b. Mental disorders listed on death certificates
c. Admission to psychiatric hospital

1.5.3 Multimorbidity or polypharmacy with dementia outcomes on neuroimaging

Neuroimaging and biomarker studies are common in dementia prevention research as they help identify markers of neurodegeneration before cognitive manifestations emerge.[41] The rationale is that if changes are detected early, disease modification may be possible through pharmacological or lifestyle interventions.[40] Neuroimaging can also help differentiate between biological and psychological causes of cognitive impairment, for example Alzheimer's disease and functional cognitive disorder.[105] Although it is established that multimorbidity and dementia commonly co-exist,[39] there is relatively little published neuroimaging research specifically focusing on multimorbidity, and none on polypharmacy.[98]

1.5.3.1 Hypothesis 3

Physical multimorbidity or greater number of conditions, and polypharmacy or greater number of medications, will be associated with outcomes linked to dementia on structural MRI neuroimaging (periventricular and deep white matter hyperintensities, hippocampal volume and microhaemorrhages)

1.5.4 Multimorbidity with CSF amyloid-β

Of all biomarkers being explored in relation to dementia, amyloid-β is the most studied and is of particular interest in drug development.[106] Previous research into multimorbidity and neurodegeneration found that the association was independent of amyloid,[98] but the evidence is limited and warrants further exploration.

1.5.4.1 Hypothesis 4

Multimorbidity, or having a larger number of chronic conditions, will be associated with lower concentrations of CSF amyloid-β, as a marker of Alzheimer's disease.

In keeping with the multimodal nature of these hypotheses, and in the absence of a single dataset that would allow me to test all these hypotheses, I use data from different sources and tailor my approach to the mental and brain health outcomes available in each. The analytical chapters of this thesis use a range of complementary methods, in keeping with the complex nature of the questions.

The three datasets I use are two cohort studies focused on brain health and dementia, and one population-level dataset of routinely collected NHS data. The latter has the volume and variety common to 'big data', which are increasingly popular in health research for these reasons.[107,108] Other strengths are that the data are real healthcare data from patients, and in the NHS this includes almost all of the population, regardless of socioeconomic status. However, there are recognised limitations, including that routine data do not contain detailed information on confounding factors and cannot confirm the accuracy of clinical diagnoses.[109,110] The smaller cohort studies offer a degree of detail not available in population-level data, for example the ability to examine biomarkers and the presence of both self-reported diagnoses and screening-positive mental health symptoms. These studies carry their own limitations, including selection bias inherent when recruiting relatively healthy volunteers. One way of addressing limitations across different sizes of dataset is to 'triangulate' research by comparing results from two or more different approaches to the same research question.[111] As only initial data are available from each cohort study, I carried out cross-sectional analyses on these data. Although I could not complete exactly the same analyses in each dataset, I address the overall questions in differing datasets to add depth to my results.

1.6 EXPLORATION OF MULTIMORBIDITY MEASUREMENT IN THIS THESIS

There are various methods for measuring multimorbidity, the most common of which is counting conditions from pre-defined lists that vary in length in breadth.[112] Some measures weight individual conditions by their association with outcomes, and others add other relevant factors.[113] There have been two major systematic reviews on

the measurement of multimorbidity, both of which conducted their searches in 2009.[112,113] These are now outdated, particularly in the light of the steep increase in multimorbidity publications since then and ongoing discussion of using appropriate methods for better comparisons.[86,114] There has been a recent narrative review of multimorbidity measurement, but this did not involve a systematic literature search and an update is required.[11]

Before embarking on data analysis, I begin the thesis with a detailed review of available multimorbidity indices in Chapter 2 and a discussion of broad methodological issues in measurement, in Chapter 3.

Chapter 2 Systematic review of multimorbidity indices

2.1 INTRODUCTION

When studying multimorbidity, it is important to consider its definition, as outlined in Chapter 1, but also how it is measured. In existing multimorbidity research, there is relatively little focus on methodology and measurement compared to clinical research questions.[113] Two main numerical methods exist for measuring multimorbidity: counting diseases and using indices. An index quantifying multimorbidity can be used to predict relevant outcomes, to adjust for multimorbidity as a confounding factor or to permit its use as a single variable in statistical models.[11] In this chapter, I present a systematic review on multimorbidity indices which has been accepted for publication in *The BMJ*, preceded by a general introduction and followed by further discussion. Disease counts carry their own methodological issues so are considered separately in Chapter 3.

I used the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines to structure and report this work.[115] I consulted an Academic Liaison Librarian who assisted me to develop the search strategy, initially by combining search terms from previous reviews of multimorbidity measurement with additional synonyms. After test runs of my preliminary search strategy revealed over 42 000 results from one database alone, I refined it under the librarian's guidance. For example, I restricted the search to either titles or titles, abstracts and key words only, in the databases where this was possible. This reduced the number of hits owing to the large number of published papers that mention multimorbidity somewhere in the text but are not specifically focused on the topic. I also added adjacency indicators to words such as 'multiple' and 'conditions', specifying that they should be no more than two words apart.

I screened all search results with two co-authors (LGS and DSM). I extracted data from all papers and scored their risk of reporting bias; both these tasks were duplicated for consistency by DSM. I wrote the first draft of the manuscript and prepared all the tables before making amendments following comments from all co-

authors (the remaining three of whom are my PhD supervisors). I navigated three rounds of peer review, conducting a considerable amount of revision before the final submission. During this process, we received comments on the manuscript from a total of eight unique reviewers, the journal's Head of Research and two editorial committees. Their varied suggestions reflected the heterogeneity of the multimorbidity research field, and the additional information they requested led to the paper growing beyond a narrative review. I added supplementary files detailing index updates, model development and evaluation. We aimed to make the paper more accessible and usable as a guide by adding recommendations for index choice. The final paper was copy-edited by *The BMJ* before publication; I approved or changed all amendments.

2.1.1 Background

There have been several previous systematic reviews of multimorbidity measurement, but an updated search is due. In 2003, De Groot and colleagues published the first systematic review on this topic, listing 13 methods of measuring multimorbidity for both community and hospitalised patients.[116] Another systematic review was published by Diederichs et al. in 2011, finding 39 studies from a search in August 2009.[113] The most recent systematic review on multimorbidity measures in community settings was published by Huntley and colleagues in 2012 after a search in December 2009.[112] There have been additional specific reviews since then, such as one published in 2015 that focused only on indices for use with administrative data.[117]

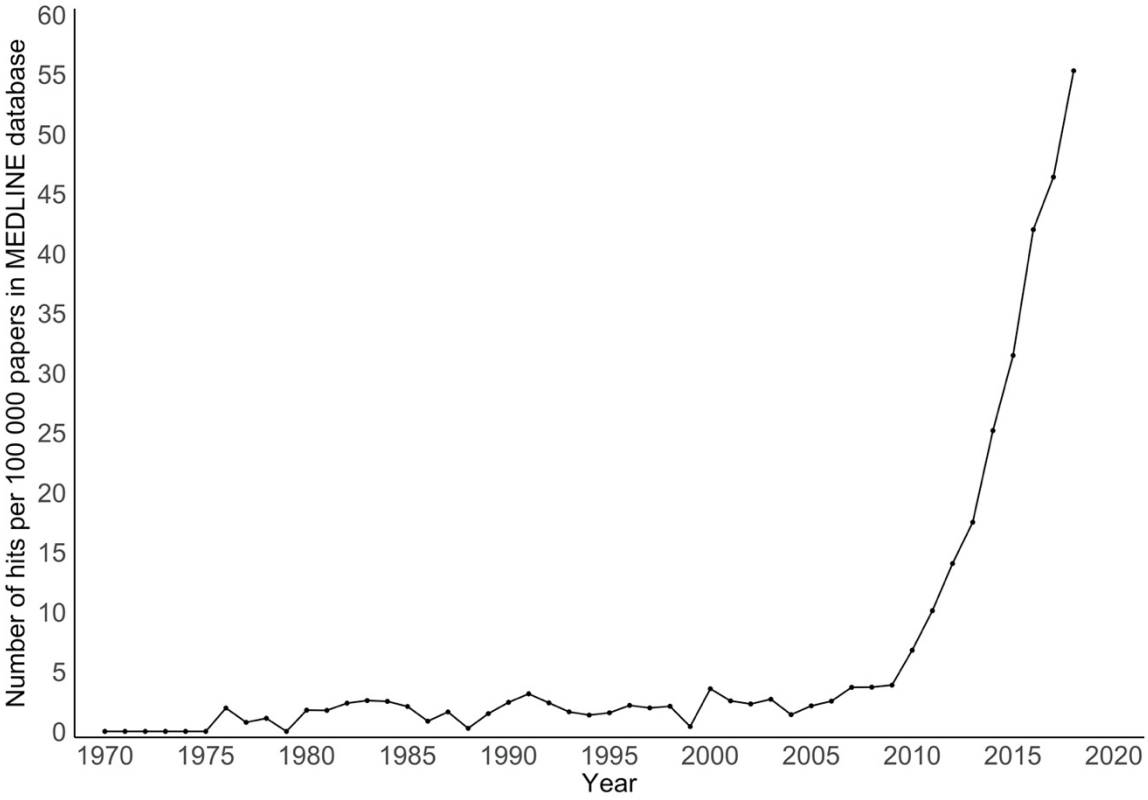
In 2019, a systematic review of systematic reviews on the definitions and measurement of multimorbidity included the reviews mentioned above [118] as well as two further studies discussing definitions.[5,119] This review has a broad scope, including both measurement and definitions.[118] In addition, it is limited by the search dates of the studies included, with the most recent being the review of indices for use in administrative data in October 2013.[117] However, research into multimorbidity has expanded greatly since 2010.[86] Table 2-1 summarises the characteristics of these previous systematic reviews.

Table 2-1: Summary of previous systematic reviews on measurement of multimorbidity

First author	Year published	Number of studies included	Features of review
Johnston [118]	2019	6	Systematic review of systematic reviews, including both measurement and definitions
Yurkovich [117]	2015	76	Includes development and validation studies of comorbidity indices in administrative data. Lists Charlson Index adaptations [120]
Huntley [112]	2012	194	Compares use and predictive validity of 17 different measures including disease counts
Diederichs [113]	2011	39	Among indices, considers lists of conditions: justification, length and composition
De Groot [116]	2003	13	Explores validity and reliability of indices. Also includes disease count.

Further to the growth demonstrated in Figure 1-2 on page 16, I ran an up-to-date measure of hits in MEDLINE for the term ‘multimorbidity’ as a keyword in December 2019 (with data only available until 2018). Figure 2-1 shows the results of this search, with a continued steep increase after 2015 when the previous bibliographic study ended.[121]

Figure 2-1: Hits for the term 'multimorbidity' in MEDLINE, per 100 000 papers each year, 1970-2018



In the context of this rapidly growing field, I conducted a specific and detailed systematic review of the available indices for measuring multimorbidity.

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Measuring multimorbidity beyond counting diseases: systematic review of community and population studies and guide to index choice

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ABSTRACT

OBJECTIVES

To identify and summarise existing indices for measuring multimorbidity beyond disease counts, to establish which indices include mental health comorbidities or outcomes, and to develop recommendations based on applicability, performance, and usage.

DESIGN

Systematic review.

DATA SOURCES

Seven medical research databases (Medline, Web of Science Core Collection, Cochrane Library, Embase, PsycINFO, Scopus, and CINAHL Plus) from inception to October 2018 and bibliographies and citations of relevant papers. Searches were limited to English language publications.

ELIGIBILITY CRITERIA FOR STUDY SELECTION

Original articles describing a new multimorbidity index including more information than disease counts and not focusing on comorbidity associated with one specific disease. Studies were of adults based in the community or at population level.

RESULTS

Among 7128 search results, 5560 unique titles were identified. After screening against eligibility criteria the review finally included 35 papers. As index components, 25 indices used conditions (weighted or in combination with other parameters), five used diagnostic categories, four used drug use, and one used physiological measures. Predicted outcomes included mortality (18 indices), healthcare use or costs (13), hospital admission (13), and health related quality of life (7). 29 indices considered some aspect of mental health, with most including it as a comorbidity. 12 indices are recommended for use.

CONCLUSIONS

35 multimorbidity indices are available, with differing components and outcomes. Researchers and clinicians should examine existing indices for suitability before creating new ones.

SYSTEMATIC REVIEW REGISTRATION

PROSPERO CRD42017074211.

WHAT IS ALREADY KNOWN ON THIS TOPIC

It is common for people to have two or more co-occurring chronic conditions (multimorbidity)

Researchers and clinicians use many different indices to measure multimorbidity

WHAT THIS STUDY ADDS

At least 35 objective measures of multimorbidity are available for people living in the community and each of these uses different variables to generate a score or index, linked with various or no outcome measures

No specific index investigates the interplay between mental and physical multimorbidity, although this is dealt with in a variety of ways across the measures

The recommendations in this study should guide researchers to find a suitable index for their purposes

Introduction

Multimorbidity, usually defined as the coexistence of two or more chronic conditions within an individual, is important for patient outcomes and healthcare costs. Because its prevalence is rising as populations age, multimorbidity is attracting increasing attention from the research community worldwide.[1] More than 2800 publications on multimorbidity appeared between 1900 and 2016, 80% of which were published after 2010.[2] As no universally agreed measure or list of diseases exists to define multimorbidity, numerous indices have been developed. These might be designed, for example, to quantify multimorbidity as a covariate in other analyses, for mortality prediction or for risk adjustment. Previous systematic reviews identified multiple indices, but no searches have been done of indices since 2009.[3 4]

Multimorbidity research most often refers to a count of chronic conditions.[4] This method does not reflect patients' experience or the effects of different combinations or severity of diseases.[5] Some indices, however, combine disease counts with severity measures, physiological factors, or demographic items, thereby allowing a more holistic quantification of illness burden.

The coexistence of both physical and mental illness within multimorbidity is prevalent.[6] A 2018 report identifying priorities for multimorbidity research highlighted the need for more work into this coexistence.[1] Researchers exploring multimorbidity will therefore increasingly need to account for mental disorders. As previous reviews of multimorbidity indices have not covered mental health in depth we identified and summarised all community based multimorbidity measures that include more than simple disease counts, paying particular attention to mental health. This review should help guide clinicians and researchers to select an appropriate index according to their requirements.

Methods

No single accepted term describes the methods of measuring multimorbidity. In this review we use the term "index" to refer to any method of quantifying disease burden or predicting specific outcomes that includes more than a count of conditions. This could be by weighting conditions (for example, by allocating a score to each), adding other elements, or examining other variables such as drug or physiological parameters.

Search

To capture all relevant publications we conducted a broad search. We included a variety of terms for multimorbidity derived from previous systematic reviews on this topic[3 4] and other literature discussing terminology in this area of research.[7] We developed the search strategy iteratively with the support of an Academic Support Librarian. The final search terms are listed in the appendix (appendix eTable 1) and include multimorbidity, comorbidity, polypathology, polymorbidity, pluripathology, multi-condition, and multiple chronic conditions. The search was restricted to adults older than 18 years and to English language publications.

Eligibility criteria

We planned to summarise reports of novel indices and were primarily interested in the original report of each index. Therefore we excluded papers that either used existing indices or measured multimorbidity using only disease counts. In the initial screening process we included only the original form of each scale and not adaptations or updates; these were found later. Records that were not original research papers, such as conference abstracts, letters, and systematic reviews, were excluded. We defined multimorbidity as multiple co-occurring conditions without reference to a specific disease, so excluded papers were those that focused on comorbidities of an index disease or on comorbidities within one disease area (such as the coexistence of several psychiatric conditions). As most people with multimorbidity are adults living in the community and managed in primary care, we excluded articles about children, animals, or people admitted to hospital or living in residential care. We included studies of hospital inpatients when the primary focus was follow-up after discharge (for example, mortality one year later). As resources were limited, we excluded papers when full texts were not available in English.

Information sources

On 19 October 2018 we searched Medline, Web of Science Core Collection, Cochrane Library, Embase, PsycINFO, Scopus, and CINAHL Plus from inception onwards.

Study selection

Two authors used Covidence software independently to screen titles against exclusion criteria and the subsequent abstracts against the same criteria.[8] We then extracted the full texts of relevant abstracts for further screening. Any disagreements at the title, abstract, and full text stages were resolved by discussion, and a third author mediated unresolved conflicts. We excluded papers that referred to an existing index, but listed the indices that were used when excluding them at the abstract stage. We found the original papers describing these indices and returned them to the title screening stage. Additional relevant titles were found by reviewing previous systematic reviews on this topic, searching the bibliographies of included full text papers, and tracking their citations using Google Scholar. Emerging relevant titles were added to the screening process.

Usage, updates, and validation

After the list of included papers had been finalised, we searched their citations on Google Scholar for updates, revisions, or adaptations as well as validation papers. When original indices were adapted and validated numerous times, we listed the original performance and principal adaptations. We did not include adaptations where the original index was translated into another language with no other changes made. To assess the popularity of each index, we took the total number of citations for each original paper from Google Scholar on 7 September 2019, as a proxy for use. We then calculated the number of citations for each whole year since publication. To retain awareness of the context of their initial design and aims, we summarised index updates separately from the original papers.

Data collection process

We created a data extraction tool containing specific elements of interest for each original index. This tool took account of previous reviews on this topic as well as additional information relating to mental health. We used a broad definition of mental health, comprising any mental disorder, including mood disorders, dementia, delirium, and addictions as well as relevant symptoms. Many papers describe validation of the indices used so details on the size and demographic distribution of the populations under test was important.

Two authors independently extracted data from all full texts. We compared the consistency of extracted items and resolved any differences by discussion and reference to the original paper, with a third author available in case of substantially differing data extraction.

Data items

The variables of interest during data extraction were first author, year of publication, and name of index; original purpose of the index; characteristics of the population under test, including type of data source (eg, cohort study), location, number of participants, sex and age distribution, and mean number of concurrent medical conditions (when given); components included in the index; weighting method (if any) and details of model for its development; outcome measures; information and resources required to apply the index; internal validation or comparison

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with another index (if applicable); external validation and performance compared with another index (if applicable); and inclusion of mental health (either in comorbidities or as outcomes).

Risk of reporting bias in original studies

We assessed the risk of bias of study design and reporting and aimed to develop overall recommendations for index choice. The Cochrane Collaboration advises against scales that generate total numerical scores, preferring emphasis on individual papers' performance on each criterion.[9] After our search date the Prediction model Risk Of Bias ASsessment Tool (PROBAST) was published. It focuses on risk of bias and applicability in prediction model studies.[10] As our search was not restricted to prediction models, it was not appropriate to apply this tool to every paper. We therefore developed our own list of criteria having referred to resources available for assessing clinical prediction indices.[11-13] Our assessment aimed to deal with risk of selection, observer, and funding bias. The list contained 10 questions on the population tested, description of the index, statistical methods, validity, and funding. The assessment tool is available in the appendix (appendix eTable 2), including division into domains. We also included an overall impression of the papers' risk of bias based on the Scottish Intercollegiate Guidelines Network standard, which was scored separately to the criteria rather than in an additive fashion.[14] Two reviewers independently assessed each paper and resolved disagreements by discussion.

When choosing an index, its predictive ability and its use elsewhere are important. We generated overall recommendations taking into account the generalisability of participants, selection and clinical relevance of index components, outcome measurement, risk of reporting bias, and model evaluation. These were separated into three main categories: recommended, potentially useful (usually when indices were applicable to certain situations), and not recommended.

Synthesis of results

We anticipated finding a wide variety of indices covering diverse outcome measures and therefore planned to summarise these narratively. Because of the range of outcomes included we did not expect to be able to perform meta-analysis. We listed performance and validity statistics as reported by the original papers or validation studies alongside each other, for comparison.

We did not expect to find indices specifically designed for measuring physical multimorbidity in relation to any aspect of mental health. Therefore, for separate narrative synthesis we planned to seek those indices that mentioned mental illnesses or symptoms, either as comorbidities or as outcomes.

Patient and public involvement

An early draft of this paper was discussed with a lay contributor who has personal experience of multimorbidity. We incorporated her comments into the text—for example, noting in the introduction that the number of conditions a person has might not reflect their experience of health, and in the discussion her suggestions about outcomes that could be important to patients. The lay contributor also commented on a lay summary of the paper (see appendix page 43), which we amended accordingly.

Results

Study selection

The searches yielded 7128 results. A search of bibliographies and citations identified 48 additional relevant titles, and a further 15 titles were added from the list of indices mentioned in excluded abstracts. The total number of titles was therefore 7191. Duplicates were removed using EndNote X8 and Covidence software,[8 15] leaving 5560 unique records for screening (fig 1).[16] Overall, 5236 titles were excluded at the screening stage, leaving 324 abstracts for eligibility assessment. Of these, 86 full texts were assessed and 35 papers finally included.

Study characteristics

Twenty articles originated from the United States[17-36]; three from Australia[37-39]; two each from the United Kingdom,[40 41] Taiwan,[42 43] and Italy[44 45]; and one each from Canada,[46] Spain,[47] Germany,[48] New Zealand,[49] Norway,[50] and India.[51] They were published between 1968 and 2017, with 15 (43%) published since the last systematic review on this topic in 2009.[17-20 40 42-51] The mean number of participants included in the derivation populations of indices developed after 2009 was 356 906, compared with 75 491 before 2009. The newer indices primarily required access to medical records in 11 (73%) cases,[18-20 40 42-45 47-49] and the remainder (4, 27%) self-report[17 46 50 51]; 10 (50%) indices before 2009 primarily used medical records[21 23 26 29 32-36 39] and 10 (50%) used self-report.[22 24 25 27 28 30 31 37 38 41]

The majority of papers described one final multimorbidity index, even if they tested various models in development, and four papers concluded with more than one index or measure.[23 25 30 46] For consistency, when articles were summarised and their quality assessed we considered each paper as a whole and noted when more than one index existed. We did not comment on models that used only unweighted disease counts, in keeping with our overall exclusion criteria.

Index components

Four indices primarily used weighted drug counts to quantify multimorbidity,[33 39 43 45] five used diagnostic groups or clusters,[23 26 34 36 48] and 25 included counts of diseases. Of these, 21 were weighted[17 19 20 22 24 27-29 31 32 35 37 38 40 41 44 46 47 49 50 51] and nine incorporated other parameters, demographic or otherwise.[18 19 22 25 28 30 42 47 51] Four papers used a combination of weighting and additional variables.[19 22 28 47] One index used physiological measurements to diagnose multimorbidity.[21] When

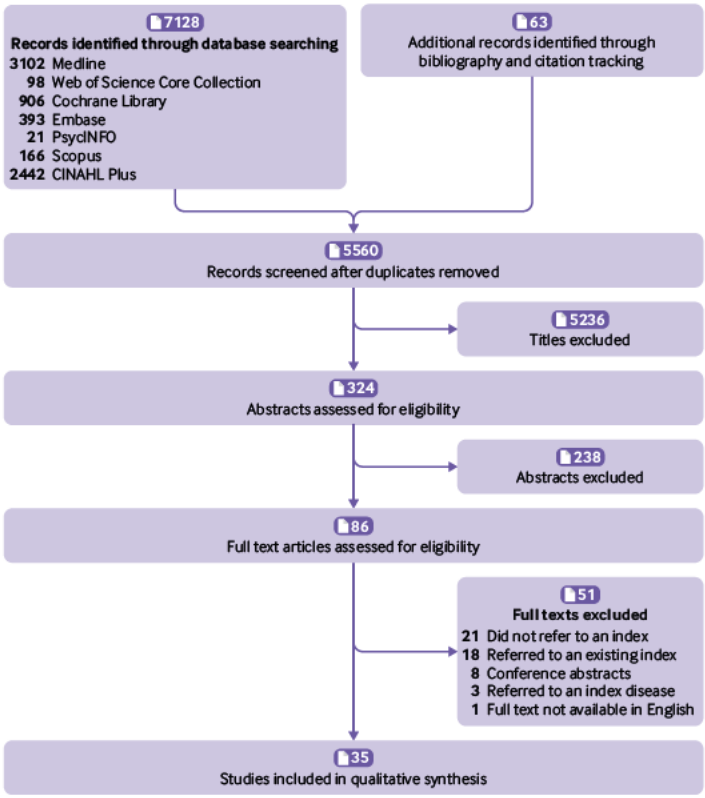

Fig 1 | Screening process according to PRISMA

diagnoses were required, 14 indices took these from medical records[18 19 20 23 26 29 32 35 36 40 42 44 48 49] and 15 from self-report.[17 22 24 25 27 28 30 31 36 37 38 41 46 50 51] Figure 2 is a spider diagram of the papers, displayed according to their broad category of index components.

Outcome measures

The number of outcomes assessed in each paper ranged from none to seven. Eighteen studies measured mortality as an outcome,[19 21 22 25 28 29 33 35-40 42 44 45 47 49] 13 aimed to predict hospital admissions,[18 23 28 31 33 37-39 42-45 49] 10 measured general healthcare use,[18 19 23 25 27 31 33 34 38 46] seven measured independence with daily activities or disability (with or without physical functioning),[19 21 24 31 33 38 41] seven measured health related quality of life,[20 25 27 37 38 46 48] five measured overall self-reported health,[24 33 41 46 50] five measured healthcare costs,[23 26 27 30 44] and four measured drug use.[19 23 27 46] Mental health was a specific outcome in three papers,[24 33 41] with a further six including mental health aspects of established tools (eg, the mental component score of SF-36).[20 25 27 37 38 48] Adherence to screening programmes,[18] specific physiological parameters,[18] and care quality indicators[19] were assessed by one tool each. Ten (29%) papers used cross sectional data to derive their index weighting but measured longitudinal outcomes.[19 21 22 25 33 36 38 39 42 43] Table 1 lists the papers according to their original outcomes and index components.

Applicability

The applicability of each index depends on study design and intended usage. Table 1 summarises index components and outcome variables. Most of the original papers (27, 77%) contained sufficient information for readers to use the index, usually with lists of included conditions with or without weighting. Of the remainder, access to additional free resources was needed in four,[30 43 45 47] information from proprietary scales was needed in one,[51] and two were missing information that would allow the index to be applied.[18 31] One index was only available as proprietary software.[34 52]

Some of the indices, although designed to measure multimorbidity, were developed in cohorts of people

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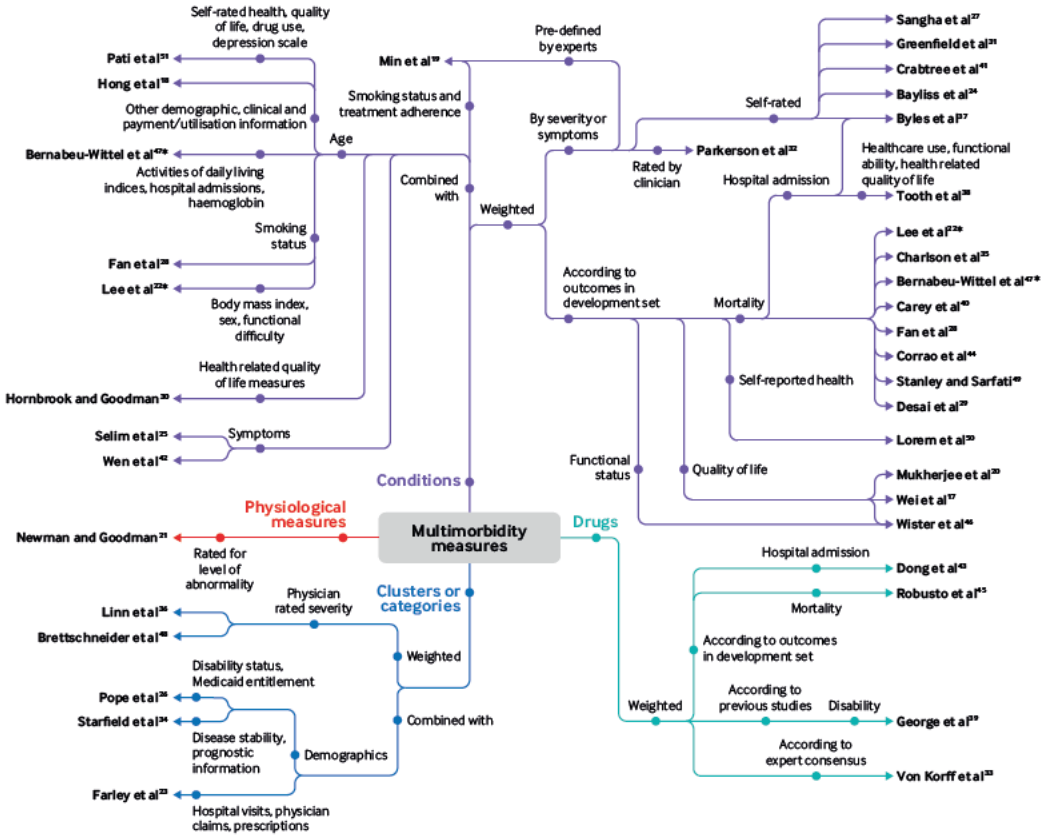

Fig 2 | Spider diagram summarising index components. *Paper appears under more than one category

with a specific disease, and therefore this condition was not included in the list of comorbidities.[23 31] Most indices were based on diagnoses or drugs, but two indices required results of laboratory or other investigations.[21 47]

The provenance of papers will affect their applicability to other settings. For example, the majority of papers came from the US where the predominant health system is commercial and healthcare costs are of interest to insurers. Some of the indices were designed with a particular population in mind, such as the questionnaire for Indian primary care. This included diseases that are less prevalent in other geographical areas, such as filariasis and tuberculosis, which might limit generalisability.[51] Other original indices have domains that might be outdated. One example is the Charlson comorbidity index.[35] This index assigns the maximum weight of 6 points to AIDS, but the life expectancy for HIV/AIDS in high income countries has changed considerably since the index's publication in 1987.[53]

Although several papers mentioned outcomes as relevant to patient experience, only one clearly described involving patients in the study design, by developing their rating scale with focus groups.[37]

Summary of evidence

Appendix eTables 3 to 6 summarise all included papers according to their index's original purpose, components and outcome variables, and information used. The data source, location, and demographics of the population used to derive or test the measure are listed as they are relevant for context. Our overall recommendations are also included. In appendix eTable 3, the index components are weighted condition counts, in appendix eTable 4, the index components are conditions with additional parameters, in appendix eTable 5 they are weighted drug counts, and appendix eTable 6 comprises the remainder, including diagnostic groups and physiological measures.

Weighting

The majority of indices (n=29, 83%) included some form of component weighting. Conditions, diagnostic categories, and drugs were weighted by severity or symptoms, either self-reported or defined by clinicians, or according to their associated outcomes in a derivation cohort. Different methods were used for developing each index, and disparities existed in the level of methodological detail reported. The appendix eTable 7 summarises the method for developing each model, the details provided, and baseline outcome reporting.

Inclusion of mental health

Twenty nine (83%) of the papers contained some measure of mental health or dementia, with 18 of these including mental health markers exclusively as comorbidities (including psychotropic drugs when

Table 1 | Studies classified by components and outcomes of original versions of indices

	Index components					
	Conditions			Categories or clusters		
Original outcomes	Weighted	With additional parameters	Drugs (all weighted)	Weighted	With additional parameters	Physiological measures
Mortality	Corrao et al[44]	Wen et al[42]	Robusto et al[45]	Linn* et al[36]		Newman* et al[21]
	Stanley and Sarfati[49]	Min et al[19]	George et al[39]			
	Min et al[19]	Bernabeu-Wittel et al[47]	Von Korff* et al[33]			
	Carey et al[40]	Lee* et al[22]				
	Bernabeu-Wittel et al[47]	Selim et al[25]				
	Tooth et al[38]	Fan et al[8]				
	Lee* et al[22]					
	Byles et al[37]					
	Fan et al[28]					
	Desai* et al[29]					
	Charlson* et al[35]					
Healthcare use and costs	Corrao et al[44]	Hong et al[18]	Von Korff* et al[33]	Pope* et al[26]	Farley et al[23]	
	Wister et al[46]	Min et al[19]		Starfield* et al[34]		
	Min et al[19]	Selim et al[25]				
	Tooth et al[38]	Hornbrook and Goodman[30]				
	Sangha* et al[27]					
	Greenfield* et al[31]					
Hospital admission	Corrao et al[44]	Wen et al[42]	Robusto et al[45]		Farley et al[23]	
	Stanley and Sarfati[49]	Hong et al[18]	Dong et al[43]			
	Byles et al[37]	Fan et al[28]	George et al[39]			
	Fan et al[28]		Von Korff* et al[33]			
	Greenfield* et al[31]					
Independence or disability	Min et al[19]	Min et al[19]	Von Korff* et al[33]			Newman* et al[21]
	Tooth et al[38]					
	Bayliss* et al[24]					
	Crabtree et al[41]					
	Greenfield* et al[31]					
Self-rated overall health	Lorem et al[50]		Von Korff* et al[33]			
	Wister et al[46]					
	Bayliss* et al[24]					
	Crabtree et al[41]					
Health related quality of life or life satisfaction	Wister et al[46]	Selim et al[25]		Brettschneider et al[48]		
	Mukherjee* et al[20]					
	Tooth et al[38]					
	Byles et al[37]					
	Sangha* et al[27]					
Drug use	Wister et al[46]	Min et al[19]			Farley et al[23]	
	Min et al[19]					
Physical functioning	Bayliss* et al[24]					Newman* et al[21]
	Greenfield* et al[31]					
Mental health, depression or anxiety	Bayliss* et al[24]		Von Korff* et al[33]			
	Crabtree et al[41]					
	Greenfield* et al[31]					
Specific physiological measures		Hong et al[18]				
Quality indicators or adherence to screening	Min et al[19]	Hong et al[18]				
		Min[19]				
No outcomes measured	Wei et al[17]	Pati et al[51]				
	Pati et al[51]					
	Parkerson* et al[32]					

*Studies have been subsequently updated or adapted.

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relevant)[17-19 22 26 30 32 34-36 39 40 42 43 45 47 49 51] and three including mental health markers as an outcome only.[24 31 33] Seven measures included different aspects of mental health as both comorbidities and outcomes,[20 25 27 37 38 44 48] and one paper included anxiety and depression as both a comorbidity and an outcome.[41] In appendix eTable 8, we summarise whether each index dealt with aspects of mental health, as either comorbidities or outcomes, and how these were measured. Where papers discussed specific findings relating to multimorbidity and mental health, we present their conclusions.

Risk of reporting bias within studies

Using our quality assessment tool, we classified six papers as high quality with little or no risk of bias in reporting[22 24 27 32 37 49] and seven as low quality with moderate to high risk of bias.[23 28 34 35 36 41 42] The remaining 22 papers were of satisfactory quality. Of the five domains we assessed, the best reported were index description and funding source. Validity and statistical methods were the least well reported across all papers. Table 2 shows the scores for all papers across each domain. As we had agreed in advance to judge the overall impression without summing domain scores, the domain scores did not always lead to the same overall impression. For example, one study was given an overall impression of satisfactory with a total domain score of 6,[48] whereas another study scored 8 and was also deemed satisfactory.[51]

Risk of bias across studies

It was not possible to quantify publication bias owing to the variety of methods and outcomes used. It is likely that more unpublished methods of measuring multimorbidity exist and are used in clinical practice, especially tailored to specific patient populations or available clinical information.

Usage, performance, and validation

As a proxy for usage, we calculated the number of annual citations for each paper. The number of citations for each year since publication ranged from three[41] to 949,[35] with a median of 8.8 (interquartile range 5.3-16.2). This information is listed alongside measures of the indices' performance at predicting outcomes and validation in appendix eTables 9 (indices without external validation) and 10 (externally validated indices). Sixteen original papers described designing indices within a derivation cohort and testing their ability to predict specific outcomes within a separate validation set.[20 22 28-30 33 35 37 38 40 43 44 45 47 49 50]

Fourteen original papers measured an index's performance at predicting outcomes[17 22 28 30-32 34 36-38 41 42 46 48] and 20 compared an index to an existing measure of multimorbidity.[18-21 23-27 29 33 35 39 40 43 44 45 47 49 50] Fourteen indices were validated elsewhere, of which 11 were compared with other indices[20 22 26 27 33-36 39 43 47] and three only measured ability to predict outcomes.[17 24 32] Among the indices that were externally validated, 11 were tested at predicting different or additional outcomes to those in the original index design.[20 24 26 32-36 39 43 47] Some indices were tested against other indices that had been developed with different original outcomes—for example, the Charlson index where the outcome in question was admission to hospital[43] or health related quality of life.[20]

Updates and adaptations

Thirteen (37%) of the indices had updates or adaptations published, by either original or separate research teams. These revised versions included updated comorbidities or weights, focused on specific patient groups, or mapped a clinical index to codes for administrative data. Two of the indices are risk adjustment methods undergoing regular review and updates.[26 34] The relevant indices are listed in appendix eTable 11 alongside a summary of their adaptations and updates and any reported performance metrics. The older and widely used indices such as Charlson, Chronic Disease Score, and Cumulative Illness Rating Scale have been adapted and updated many times; we include the most cited versions. Most updated indices are broadly based on the aim and outcome measures of the original, with some exceptions.[57-60]

Of the indices that were not updated, in some cases this was because the original index was unsuccessful at predicting specific outcomes[37] or was not designed for use outside of the original study.[30]

Discussion

In this review we collated descriptions of 35 distinct multimorbidity indices. The papers were diverse in study design, intended purpose, and variables included. Similarities did, however, emerge, such as index components concentrating on conditions, diagnostic categories, drug classes, or physiological measures. Mortality was the most commonly studied outcome, with healthcare use, hospital admission, functional ability, and health related quality of life as other important groups. Those that measure mortality will be of most relevance to clinicians and researchers, whereas healthcare use and costs are more useful to healthcare providers and funders, particularly in predominantly private healthcare systems. For patients, the most relevant outcomes might be quality of life or self-reported health.

Strengths and weaknesses of this study

A major strength of this review was the use of an updated search in a rapidly expanding area of research and a focus on multimorbidity measures that specifically include mental health.

Although the medical subject heading (MeSH) term "comorbidity" has existed since 1990, a new MeSH term, "multimorbidity," was introduced in January 2018, after our search had been designed and preregistered.[1 61] We found that the word "indexes" was used in some titles when we had used "indices" in our search terms. One paper was found by citation tracking and had apparently been missed during our search because we had omitted the term "score."[44]

Table 2 | Overall risk of reporting bias: domain scores

Reference	Sample selection (maximum++)	Index description (maximum ++)	Statistical methods (maximum ++)	Validity (maximum +++)	Funding source (maximum ++)	Overall quality
Corrao et al[44]	-	++	+	+	++	Satisfactory
Wen et al[42]	++	++	+	-	++	Low
Stanley and Sarfati[49]	++	++	+	+	++	High
Wei et al[17]	+	++	+	+	++	Satisfactory
Robusto et al[45]	+	++	+	+	++	Satisfactory
Lorem et al[50]	+	++	++	+	++	Satisfactory
Pati et al[51]	++	++	+	++	++	Satisfactory
Hong et al[18]	++	++	+	+	++	Satisfactory
Wister et al[46]	++	+	++	-	++	Satisfactory
Brettschneider et al[48]	++	++	+	-	++	Satisfactory
Min et al[19]	-	++	+	++	+	Satisfactory
Carey et al[40]	+	++	+	+	++	Satisfactory
Dong et al[43]	+	++	+	+	++	Satisfactory
Bernabeu-Wittel et al[47]	++	++	+	+	++	Satisfactory
Mukherjee et al[20]	++	++	+	+	++	Satisfactory
Newman and Goodman[21]	++	++	+	+	++	Satisfactory
Tooth et al[38]	+	++	+	+	++	Satisfactory
George et al[39]	-	++	+	++	+	Satisfactory
Lee et al[22]	++	++	+	+	++	High
Farley et al[23]	-	-	+	+	+	Low
Byles et al[37]	++	++	+	+	-	High
Bayliss et al[24]	++	++	++	+	++	High
Selim et al[25]	+	++	+	+	++	Satisfactory
Pope et al[26]	++	++	+	+	++	Satisfactory
Sangha et al[27]	++	++	+	+++	++	High
Fan et al[28]	+	+	+	+	++	Low
Desai et al[29]	++	++	+	+	++	Satisfactory
Crabtree et al[41]	-	++	+	+	++	Low
Hornbrook and Goodman[30]	+	+	+	+	++	Satisfactory
Greenfield et al[31]	++	++	+	+	++	Satisfactory
Parkerson et al[32]	++	++	+	++	+	High
Von Korff et al[33]	-	+	+	++	++	Satisfactory
Starfield et al[34]	-	++	-	+	++	Low
Charlson et al[35]	-	++	+	+	-	Low
Linn et al[36]	-	+	+	++	-	Low

However, we aimed to minimise the number of missed relevant papers by searching bibliographies, citations, and indices that had been mentioned in the abstracts we excluded. A limitation of this review is that we limited our search to full texts in the medical literature, excluding conference abstracts and other grey literature. This approach might have missed indices in clinical use that are either unpublished or based on guidelines from healthcare quality institutions.

In this review, we excluded papers that used simple counts of conditions to measure multimorbidity, focusing instead on indices. We chose to make this distinction because indices tend to include multiple parameters to quantify different aspects of multimorbidity and use sophisticated models to predict outcomes. However, as disease counts are the most commonly used method of measuring multimorbidity, their exclusion is a limitation of our work.[4] The ease of applying disease counts means they are frequently used and they are comparable between studies as long as the list of candidate conditions is clear.[62] One paper in this review reported that a count of diagnosis clusters was a better predictor of healthcare expenditure than more complex indices.[23] Other research has drawn similar conclusions.[63 64] Reviewing the use of disease counts is outside the scope of this paper and has been discussed elsewhere.[65-67] Simple counts of drugs have also been shown to predict healthcare use and mortality,[68] and using these or disease counts are more practical than indices in many settings. For example, they are used in clinical care, as they do not require calculations or particular software, or in large population studies where the impact of each condition on individuals is unknown.[6]

As this review is aimed at those undertaking population or community research, we also excluded studies of people who had been admitted to hospital or live in residential care. This meant that several commonly used indices were not included in this review, such as the Elixhauser index.[69] We did include the Charlson, PROFUND, Self-Administered Comorbidity Questionnaire, and High-Risk Diagnoses for the Elderly Scale indices as although the studies recruited hospital patients, they did so when the patients were discharged, and the main period of interest was later, in the community setting.[27 29 35 47]

Some of the indices have been in use for many years and have several adaptations. The Charlson index is the most widely known and warranted its own systematic review within a medical specialty (critical care)[70]; we

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Box 1: Guide to selecting an index using this paper when designing a multimorbidity study

- Identify reasons for including multimorbidity—for example, is multimorbidity important because of its association with quality of life or mortality? This will inform which outcomes of original indices are relevant
- Identify the exposure variables available (eg, diagnoses, drugs)
- Identify the outcomes to be measured
- Use figure 3 to choose a recommended index
- Use the information in the appendix (eTables 9 and 10) to compare usage and performance of any suitable indices

have only briefly summarised its performance and the principal adaptations. More information is available in another systematic review on this topic.[71]

Some of the indices were specifically designed for use with administrative data. These might have scored more poorly on quality assessment as our tool focused on reporting and clinical applicability. Our search also included papers that compared different measurements of multimorbidity but that were not intended for clinical use.[46] We included these papers for completeness when they met our inclusion criteria. We aimed to find measures of multimorbidity, and our exclusion criteria included studies of comorbidity with a specific index disease. However, in two of the papers studied the indices had been developed in populations with one condition only, either hypertension[23] or type 2 diabetes.[31] We referred to our protocol and included these studies because their aim was to study multimorbidity rather than comorbidities of those conditions as index diseases. These papers are, however, less generalisable to the general population.

Our search was intentionally broad, using a wide range of search terms in multiple medical research databases. We included a variety of studies measuring multimorbidity from different perspectives, which is a strength over previous more specific reviews.[71]

We generated overall impressions of the risk of reporting bias and recommendations for index use, to provide a guide for researchers when choosing an index. Samples in the included studies were, however, heterogeneous, and the indices had varied purposes and components. Therefore, our recommendations are subjective. Formally comparing the predictive ability of the indices is outside the scope of this work but has been comprehensively performed by other investigators.[68 72-74]

Comparison with previous literature

The two most recent similar systematic reviews to ours did not formally assess the quality of publications.[34] Fifteen (43%) of the indices we included were published after 2009 and therefore would not have been found by the searches in these previous reviews. This is out of proportion to the increase in multimorbidity publications since 2010, suggesting that many recent papers have used either older measures or disease counts.[2] A newer systematic review on this topic focused only on tools used on administrative data and conducted its search in 2012.[71] A systematic review of multimorbidity systematic reviews, published in 2018, focused on definitions and measurement.[5] However, it did not include a search for new indices, thereby also omitting the 15 papers published since 2010.

Recommendations for index selection

We suggest that to select an index for clinical or research use, clinicians or researchers should first consider their desired outcomes and the information available. Box 1 summarises the process of selecting an index using this review.

Appendix eTables 3-6 list our overall recommendations, divided broadly into "not recommended," "potentially useful," and "recommended," and figure 3 displays the 12 indices that we recommend according to their design. The 10 indices that are not recommended could be useful for other purposes, such as recording symptoms[41] or comparing models,[37] but our recommendations focus on those that are practical for designing multimorbidity research.

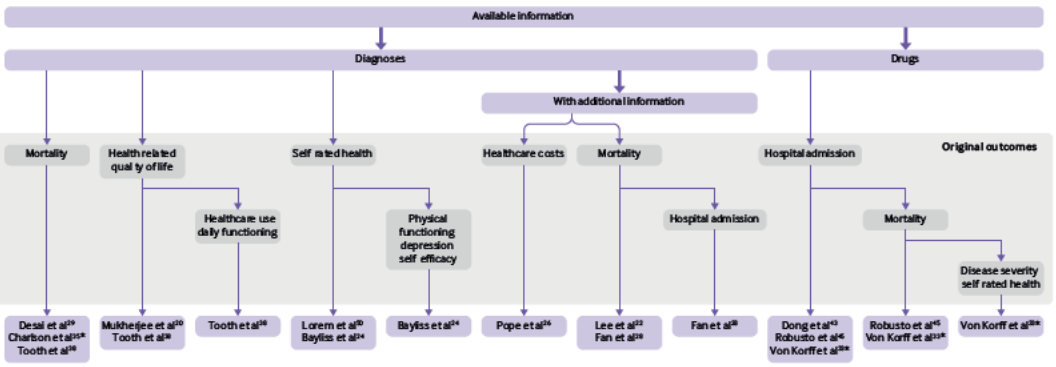

Fig 3 | Flowchart of recommended indices organised by components and original outcomes

Conclusions

At least 35 objective measures of multimorbidity are available for people living in the community, and each of these uses different variables to generate a score or index, linked with various or no outcome measures. We found no specific index for investigating the interplay between mental and physical multimorbidity, although this issue is dealt with in a variety of ways across the measures. The array of index components and outcomes means that a validated measure exists for many applications, including clinical, research, and cost prediction. It is important when choosing an index to consider its original purpose and the outcomes for which it is validated. Given the differing methodologies of multimorbidity research, it would not be appropriate to assume that a single index could definitively measure multimorbidity in all settings. However, with this research area at risk of saturation, we propose that anyone measuring multimorbidity should study existing indices before developing new ones.

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Contributors: LES performed the literature search; screened the titles, abstracts, and full texts; wrote the first draft of the article; and is the guarantor. LG-S and DSM acted as independent second reviewers in the screening process. LES and DSM independently extracted all the data and assessed the reporting quality of all full texts. GM-T provided statistical guidance. TCR, CWR, and GM-T developed the idea for the article with LES and supervised the research process. LES is the guarantor. All authors edited the manuscript. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Ethical approval: Not required.

Data sharing: Search terms and risk of bias assessment questions are available in the appendix. Data extraction and quality assessment pro-formas are available on request from the corresponding author.

The paper's guarantor (LES) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as originally planned and registered have been explained.

Dissemination to participants and related patient and public communities: Owing to the nature of this article compiling and reviewing other researchers' work, we have not contacted specific patient groups. We have provided a lay summary in the appendix.

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Supplementary information: Additional methods and tables

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2.3 SUPPLEMENTARY MATERIAL[4]

eTable 1: Search strategy by database

Database	Search strategy
Web of science core collection "Advanced search"	1. TI=(Multimorbidity or multi-morbidity or comorbidit* or co-morbidit* or polypatholog* or poly-patholog* or polymorbidit* or poly-morbidit* or multipatholog* or multi-patholog* or multicondition* or multi-condition* or pluripatholog* or pluri-patholog* or 'multiple chronic condition*' or 'morbidity burden') 2. TI= ((multiple or coexisting or co-existing or concurrent or comorbid or co-morbid) NEAR/2 (disease* or illness* or condition* or diagnosis or diagnoses or morbid*)) 3. TI=(((index or indices) not ('body mass' or 'body-mass')) or (measure* or tool or instrument or categor* or rating scale* or count) or (classif* not 'international classification of disease*')) 4. #2 or #1 5. #4 AND #3 6. TI=(Community or outpatient* or ambulatory or ambulant or population or generalist* or 'general practi*' or 'primary care' or 'primary health*' or 'primary medic*' or 'family practi*' or 'family physician*' or 'family doctor' or 'family medic*' or 'medical practice*') 7. (#6 AND #5) AND LANGUAGE: (English)
Cochrane Library "Search Manager" tab	1. ((Multimorbidity or multi-morbidity or comorbidity or polypathology or polymorbidity or poly-morbidity or multipathology or multi-pathology or multicondition or multi-condition or pluripathology or pluri-pathology or 'multiple chronic conditions' or 'morbidity burden') or ((multiple or coexisting or co-existing or concurrent or comorbid or co-morbid) NEAR/2 (disease or illness or condition or diagnosis or morbid))) NEAR/5 (((index or indices) not ('body mass' or 'body-mass')) or (measure or tool or instrument or category or rating scale or count) or (classification not 'international classification of diseases'))) 2. (Community or outpatient or ambulatory or ambulant or population or generalist or 'general practice' or 'general practitioner' or GP or 'primary care' or 'primary health' or 'primary healthcare' or 'primary medicine' or 'primary medical' or 'family practice' or 'family practitioner' or 'family physician' or 'family doctor' or 'family medicine' or 'family medical' or 'medical practice') 3. #1 AND #2

[4] References for this supplementary material appear in the thesis References on page 321

Database	Search strategy
Ovid MEDLINE "Advanced Search"	1. ((Multimorbidity or multi-morbidity or comorbidit$ or co-morbidit$ or polypatholog$ or poly-patholog$ or polymorbidit$ or poly-morbidit$ or multipatholog$ or multi-patholog$ or multicondition$ or multi-condition$ or pluripatholog$ or pluri-patholog$ or 'multiple chronic condition$' or 'morbidity burden') or ((multiple or coexisting or co-existing or concurrent or comorbid or co-morbid) adj2 (disease$ or illness$ or condition$ or diagnos#s or morbid$))) adj5 (((index or indices) not ('body mass' or 'body-mass')) or (measure$ or tool or instrument or categor$ or rating scale$ or count) or (classif$ not 'international classification of disease$'))).mp. 2. (Community or outpatient$ or ambulatory or ambulant or population or generalist$ or 'general practi$' or GP$ or 'primary care' or 'primary health$' or 'primary medic$' or 'family practi$' or 'family physician$' or 'family doctor' or 'family medic$' or 'medical practice$').mp 3. 1 and 2 4. Animals/ not Humans/ 5. 3 not 4 6. limit 5 to english language
Embase AND PsycINFO "Advanced Search"	1. ((Multimorbidity or multi-morbidity or comorbidit$ or co-morbidit$ or polypatholog$ or poly-patholog$ or polymorbidit$ or poly-morbidit$ or multipatholog$ or multi-patholog$ or multicondition$ or multi-condition$ or pluripatholog$ or pluri-patholog$ or 'multiple chronic condition$' or 'morbidity burden') or ((multiple or coexisting or co-existing or concurrent or comorbid or co-morbid) adj2 (disease$ or illness$ or condition$ or diagnos#s or morbid$))) adj5 (((index or indices) not ('body mass' or 'body-mass')) or (measure$ or tool or instrument or categor$ or rating scale$ or count) or (classif$ not 'international classification of disease$'))).ti. 2. (Community or outpatient$ or ambulatory or ambulant or population or generalist$ or 'general practi$' or GP$ or 'primary care' or 'primary health$' or 'primary medic$' or 'family practi$' or 'family physician$' or 'family doctor' or 'family medic$' or 'medical practice$').mp 3. 1 and 2 4. Animals/ not Humans/ 5. 3 not 4 6. limit 5 to english language
Scopus "Advanced" tab	((TITLE (({multiple} OR {coexisting} OR {co-existing} OR {concurrent} OR {comorbid} OR {co-morbid}) W/1 (disease* OR illness* OR condition* OR diagnos?s OR morbidit*))) OR (TITLE ({multimorbidity} OR {multi-morbidity} OR comorbidit* OR

Database	Search strategy
	co-morbidit* OR polypatholog* OR poly-patholog* OR polymorbidit* OR poly-morbidit* OR multipatholog* OR multi-patholog* OR multicondition* OR multi-condition* OR pluripatholog* OR pluri-patholog* OR {multiple chronic condition*} OR {morbidity burden}))) AND (TITLE ((measure* OR "tool" OR "instrument" OR category* OR rating AND scale*) OR (classif* AND NOT {international classification of disease*}) OR (({index} OR {indices}) AND NOT ({body mass index} OR {body-mass index})))) AND (TITLE-ABS-KEY ({community} OR outpatient* OR {ambulatory} OR {ambulant} OR {population} OR generalist* OR {general practi*} OR gp* OR {primary care} OR {primary health*} OR {primary medic*} OR {family practi*} OR {family physician*} OR {family doctor} OR {family medic*} OR {medical practice*})) AND (LIMIT-TO (LANGUAGE , "English "))
CINAHL Plus	(TX (((Multimorbidity or multi-morbidity or comorbidit* or co-morbidit* or polypatholog* or poly-patholog* or polymorbidit* or poly-morbidit* or multipatholog* or multi-patholog* or multicondition* or multi-condition* or pluripatholog* or pluri-patholog* or 'multiple chronic condition*' or 'morbidity burden') or ((multiple or coexisting or co-existing or concurrent or comorbid or co-morbid) N2 (disease* or illness* or condition* or diagnos#s or morbid*))) N5 (((index or indices) not ('body mass' or 'body-mass')) or (measure* or tool or instrument or category* or rating scale* or count) or (classif* not 'international classification of disease*')))) AND TX((Community or outpatient* or ambulatory or ambulant or population or generalist* or 'general practi*' or GP* or 'primary care' or 'primary health*' or 'primary medic*' or 'family practi*' or 'family physician*' or 'family doctor' or 'family medic*' or 'medical practice*'))) Limiters: Age group: all adult; Language: English

eTable 2: Risk of bias assessment tool questions, by domain

Questions 1-9 marked as follows: Yes + No or not applicable -

Participant selection (maximum ++)

1. Are the patient/population demographics of this study clearly described?
2. Are the patient/population demographics representative (e.g. Including an appropriate proportion of genders, socioeconomic status etc)

Index description (maximum ++)

3. Are the variables included in the index clearly defined?
4. If the index uses a list of diseases, does it describe the selection process for this list?

Statistical methods (maximum ++)

5. Are the statistical methods used clearly described?
6. Is a sample size calculation included?

Validity (maximum +++)

7. When outcomes were included, were outcome raters blinded to the variables used in the index?
8. Was there a test for inter-rater or test-retest reliability of the index?
9. Was the index validated, either in this paper or elsewhere?

Funding source (maximum ++)

10. Is there a statement of funding or conflicts of interest?

Yes: no likely conflict ++

Yes: possible conflict +

No statement -

Overall quality criteria (based on SIGN Guidelines)[122]

High: Majority of criteria met. Little or no risk of bias

Satisfactory: Most criteria met. Some flaws in the study with an associated risk of bias

Low: Either most criteria not met, or significant flaws relating to key aspects of study design.

eTable 3: Data extracted from original papers where weighted conditions are the index components, displayed in chronological order, with overall recommendation for use

Publication and name of index	Original purpose	Data source and location	Population demographics	Index components	Information used	Original outcomes measured	Recommendation
Corrao 2017 [123] Multisource Comorbidity Score	Predicting mortality, hospitalisation and healthcare costs	Population-based retrospective cohort study of people aged ≥50 years from administrative databases. Italy	Derivation: n=500 000 Validation sets: n=4×500 000 All aged ≥50 years; no further details	34 conditions taken from diagnosis codes and medication use, weighted by association with mortality in derivation set	Inpatient medical records and outpatient prescriptions. Weights and list of conditions given in paper	One- and five-year mortality and hospital admissions, two-year hospital costs	Potentially useful for predicting mortality; requires further evaluation
Stanley 2017 [124] **Measuring multimorbidity (M3) Index**	Predicting mortality	Routinely collected public healthcare data. New Zealand	Derivation: n=2 331 645, 52.2% women Validation: n=1 000 166, 52.2% women	55 conditions, weighted by association with mortality in derivation set	Routinely collected hospitalisation data. Weights and list of conditions given in paper	One-year mortality and one-year non-maternity hospital admission	Potentially useful for predicting mortality; requires further evaluation
Wei 2016 [125] **Multimorbidity Weighted Index**	Measuring disease burden	Prospective cohort studies of nurses and health professionals. USA	n=216 890, mean age 55 years, 80.1% women, mean 3.3 chronic conditions	74 self-reported conditions, weighted by physical functioning domain of SF-36	Self-reported diagnoses. Weights and list of conditions given in paper	None tested in this paper	Potentially useful for predicting physical function; requires further evaluation
Lorem 2016 [126] **Health Impact Index**	Estimating levels of self-reported health	Longitudinal cohort study of all adults aged over 25 years within one region. Norway	Derivation: n=26 684, 52.6% women. Validation: n=804, 55% women. Age distribution not given	19 conditions, weighted according to association with self-reported health in derivation set	Self-reported diagnoses. Weights and list of conditions given in paper	Self-reported health, asked in survey question with four-point self-rating scale	Recommended for measuring disease burden. Needs external validation

Publication and name of index	Original purpose	Data source and location	Population demographics	Index components	Information used	Original outcomes measured	Recommendation
Wister 2015 [127]	Predicting life satisfaction, perceived health, healthcare and medication use	Subsample of cross-sectional study of adults aged over 65 years. Canada	n=16 369, 54.9% women, mean 2.8 conditions	19 self-reported chronic conditions. Six models examined: three count-based, others weighted according to Health Utility Index with and without age and gender, OARS ADL scale	Self-reported diagnoses from survey. Weights and list of conditions given in paper	Score on Satisfaction with Life Scale, self-reported health (one question), self-reported health professional visits, self-reported daily medication use	Not recommended. Primarily comparison of methods; not designed for external use
Carey 2013 [128] **QOF Comorbidity Score**	Mortality prediction	Retrospective cohort study of anonymised primary care records of patients aged ⩾60 years from 375 GP practices. UK	Derivation: n=317 876, mean age 71.6 years, 51.4% women. Validation: n=335 904, mean age 71.6 years, 51.4% women	15 chronic conditions with subgroups for some, weighted based on mortality in derivation set	Primary care records. List of conditions and weighting given in paper	One-year mortality	Potentially useful for predicting mortality in primary care. Needs external evaluation
Mukherjee 2011 [129] **Health-Related Quality of Life Comorbidity Index (HRQL-CI) ***	Predicting health-related quality of life (HRQL)	Medical records from participants in population survey. USA	Derivation: n=12 713, 61.6% women. Validation: n=12 812, 60.5% women. No other details given	26 Clinical Classification Codes, weighted by association with outcomes in derivation set and by clinical judgement	Diagnoses from primary and secondary care health records. Lists of conditions and weighting in original paper	SF-12 health outcome survey, two single-item self-report health status questions	Recommended for predicting health-related quality of life

Publication and name of index	Original purpose	Data source and location	Population demographics	Index components	Information used	Original outcomes measured	Recommendation
Tooth 2008 [130]	Prediction of mortality, health service use, ADL independence and HRQL	Longitudinal population-based survey of women. Australia	Derivation: 5,217, mean age 74.9 years, 100% women, median 2 chronic conditions. Validation: 5,217, mean age 74.9 years, 100% women, median 2 chronic conditions	17 self-reported conditions, of which two include severity scale	Self-reported diagnoses. Conditions and weights listed in original paper	Six-year mortality and self-reported measures from survey follow-up: annual healthcare use, assistance with ADL, SF-36	Recommended for predicting less well studied outcomes. Needs further evaluation in sample including men
Byles 2005 [131]	Prediction of quality of life, mortality and hospitalisation	Veterans and war widows aged ⩾70 years enrolled in RCT. Australia	Derivation: n=869, median age 76 years, 45% women. Validation: n=434, median age 76, 47% women. Mean 7 conditions in both cohorts	25 conditions, each with self-reported severity rating. Weighted depending on outcomes in derivation cohort	Self-reported diagnoses and severity from survey. List of conditions and weighting given in this paper	Two-year mortality, hospital admission, quality of life measured using SF-36	Not recommended; as authors note, using one model is not effective at predicting multiple outcomes
Bayliss 2005 [132] **Disease Burden Morbidity Assessment ***	Quality of life prediction	Postal survey sent to stratified random sample of one healthcare provider's members aged over 65 years. USA	n=156, mean age 75 years, 49.4% women, mean 5.9 chronic conditions	25 chronic conditions (self-report), each weighted by self-reported interference with daily activities	Self-reported diagnoses and severity from survey. List of conditions in original paper	Overall health status, physical functioning (both from SF-36), depression, self-efficacy	Recommended for predicting self-rated health, depression, physical functioning and self-efficacy

Publication and name of index	Original purpose	Data source and location	Population demographics	Index components	Information used	Original outcomes measured	Recommendation
Sangha 2003 [133] **Self-Administered Comorbidity Questionnaire ***	Predicting resource utilisation and health status	Randomly selected patients aged ⩾50 years admitted to general medical and general surgical inpatient units. USA	n=170, mean age 65.3 years, 55% women	13 conditions and space for ⩽ 3 free-text entries, weighted by patient-reported impact on daily life	Self-reported diagnoses and severity weighting in questionnaire. All domains included in paper	Resource utilisation during hospital stay; at one-year follow up: SF-36 and patient-reported visits to physicians and medication use	Potentially useful for predicting HRQL and healthcare costs through self-report methods in research setting
Desai 2002 [134] **High-Risk Diagnoses for the Elderly Scale * (HRDES)**	Predicting mortality	Two prospective cohort studies within hospital general medicine service. USA	Derivation: n=524, mean age 78.7 years, 56% women Validation: n=852, mean age 79.7 years, 61% women	10 conditions, weighted by relative risk for mortality in derivation set	Diagnoses from inpatient discharge records. Lists of conditions and weighting in original paper	One-year mortality	Recommended for predicting mortality – most relevant in inpatients as sepsis is included
Crabtree 2000 [135] **Comorbidity Symptom Scale (CmSS)**	Classification of comorbidities for longitudinal study	Outpatient cataract and geriatric day hospital patients. UK	Derivation: n=50, all aged ⩾65 years (no other details given) Validation: n=183, median age 78.0 years, 68.3% women, mean 6 conditions	22 conditions, some with details about symptoms, self-report severity scale	Self-reported diagnoses, symptoms and severity in questionnaire. Item list included in paper	Activities of Daily Living (NEADL), perceived health status (GHQ-28), anxiety and depression (HAD)	Potentially useful for gathering information on symptoms but not recommended as index due to small sample and minimal validation

Publication and name of index	Original purpose	Data source and location	Population demographics	Index components	Information used	Original outcomes measured	Recommendation
Greenfield 1995 [136] **Total Illness Burden Index (TIBI)***	Measuring functional status and quality of life	Participants of longitudinal cohort study with type II diabetes. USA	n=1,738, mean age 66.3, 50.8% women	15 conditions weighted for symptom severity	Self-reported conditions in questionnaire; list of conditions but not symptom severity given in original paper	Physical function, role function according to SF-36, mental health index. Disability days, doctor visits and hospitalisations within six months	Not recommended. Participants all had diabetes; list of weights not readily available
Parkerson 1993 [137] **Duke Severity of Illness Checklist (DUSOI)***	Controlling for overall illness severity in research	Medical records of convenience sample of primary care attendees aged 18-65 years. USA	n=414, mean age 40.5, 58.7% women, mean 1.9 chronic conditions	All conditions noted in medical records, weighted by rater-judged symptoms, complications, prognosis and treatability	Diagnoses, symptoms, complications, prognosis and treatability from primary care medical records. Sample checklist in original paper	None	Potentially useful for establishing medical history in clinical setting but has no limits on what constitutes conditions so limited applicability in research
Charlson 1987 [120] **Charlson Index***	Classification of comorbidities for longitudinal studies	Derivation: All patients admitted to one hospital during one month, hospital records data collected at discharge.	Derivation: n=604, mean 1.68 conditions. Validation: n=685, 100% women. No other details given	19 conditions, weighted according to mortality in derivation set	Diagnoses from inpatient discharge records. Included conditions and weighting listed in original paper	One-year mortality	Recommended for predicting mortality due to widespread use despite possible flaws in methods. Original weights are outdated; recommend using Quan update [54] (see eTable 11)

Publication and name of index	Original purpose	Data source and location	Population demographics	Index components	Information used	Original outcomes measured	Recommendation
		Validation: all women receiving treatment for primary breast cancer at a single hospital. USA					

* Indices that have an updated or modified version available

eTable 4: Data extracted from original papers where index components include conditions with additional information

Publication and name of index	Original purpose	Data source and location	Population demographics	Index components	Information used	Original outcomes measured	Recommendation
Wen 2017 [138] **Multimorbidity Frailty Index**	Predicting mortality and hospital use	Retrospective cohort study of people aged 65-100 years using national health records database. Taiwan	n=86 133, mean age 73.4 years, 50.2% women	32 codes from ICD-9-CM, of which three are symptoms and 29 diagnoses	Inpatient and outpatient claims records. List of conditions given in paper	Mortality, unplanned hospitalisations and ICU admissions at one, five and eight years	Not recommended: not evaluated and is not a frailty index as it claims
Pati 2016 [139] **Multimorbidity Assessment Questionnaire for Primary Care (MAQ-PC)**	Quantifying multimorbidity for epidemiological work	Systematic random sample of adult primary care attendees. India	n=103, mean age 45.0 years, 45% women, mean 1.6 chronic conditions	18 self-reported conditions, three open-ended diagnosis questions all with self-reported severity, medication use, self-reported HRQL, SF-12, PHQ-9, healthcare utilisation, demographic variables	Self-reported diagnoses and medication from questionnaire. Healthcare use and demographics from medical records. PHQ-9 (free), SF-12 (paid licence)	None reported	Potentially useful for information gathering. Conditions relevant to low-income setting
Hong 2015 [140] **estimated Physician Defined Complexity (ePDC)**	Risk stratification for resource allocation	Electronic health data from adults in primary care research network. USA	n=143 372, mean age 49 years, 57.4% women (split into two-thirds for derivation and	24 variables including 9 chronic conditions, HbA1c, demographic, healthcare	Electronic primary care health records: demographics, diagnoses, HbA1c, appointment and	Hospitalisation, emergency visits, adherence to cancer screening programmes,	Not recommended: not usable as information available is incomplete

Publication and name of index	Original purpose	Data source and location	Population demographics	Index components	Information used	Original outcomes measured	Recommendation
			one-third for validation)	utilisation and medication information	billing data, algorithm to define diabetes (information not provided; tried to contact author without success)	HbA1c, LDL cholesterol in patients with cardiovascular disease	
Min 2013 [141] **Geriatric CompleXity of Care Index (GXI)**	Predicting complicated ambulatory care including polypharmacy	Medical records from participants aged ⩾75 years in cohort study. California, USA	n=644, mean age 81.2, 66.4% women, mean 3.6 chronic conditions	25 conditions and behavioural states, weighted by expert opinion on contribution to complexity	Diagnoses from primary care medical records. List of conditions and weights in original publication	Five-year mortality and functional decline, two provider visit variables, polypharmacy, and number of eligible quality indicators	Potentially useful in older people but needs external evaluation in larger sample
Bernabeu-Wittel 2011 [142] **PROFUND**	Mortality prediction	Consecutive patients with ⩾2 conditions aged over 18 years from internal and geriatric medicine in 33 hospitals, recruited for cohort study at discharge or in community. Spain	Derivation: n=757, mean age 79 years, 45.7% women. Validation: n=768, mean age 78.8 years, 45.3% women	Age, four conditions, haemoglobin, Barthel Index (ADLs), care giver status, hospitalisations in last year. Weighted depending on mortality in derivation cohort	Number of hospitalisations and diagnoses from secondary care records or self-report, age, care giver status. Barthel Index (available for free). Functional status according to NYHA/MRC (available free),	One-year mortality	Potentially useful for predicting mortality but requires specific components that may not be commonly available

Publication and name of index	Original purpose	Data source and location	Population demographics	Index components	Information used	Original outcomes measured	Recommendation
					haemoglobin. Weighting in this paper.		
Lee 2006 [9] *	Mortality prediction	One wave of cohort study of adults aged over 50 years. USA	Derivation: n=11 701, mean age 67 years, 57% women. Validation: n=8,009, mean age 67, 56% women	Age, sex, four chronic conditions, smoking, BMI, four functional measures, weighted based on mortality	Self-report in survey: demographics, diagnoses, smoking status. BMI. Questions on functional ability and weights both listed in paper	Four-year mortality	Recommended for predicting mortality as long as functional measures are available
Selim 2004 [143]	To assess HRQL and predict healthcare utilisation and mortality	Postal survey sent to participants in longitudinal veterans' cohort study. USA	n=2,425, mean age 64, 0% women, mean 6.3 chronic conditions	Combination of 36 self-reported conditions and symptom list, separated into physical and mental conditions. (Three other models purely count-based)	Self-reported diagnoses and symptoms (survey interview). Conditions and symptoms listed in paper	SF-36, number of outpatient visits, 35-week mortality	Not recommended: not designed as index, includes several models and some methods are unclear
Fan 2002 [10] **Seattle Index of Co-morbidity**	Predicting mortality and hospitalisation	Participants of prospective cohort study aged ⩾50 years, various outpatient centres, USA	Derivation: n=5,469, mean age 67.8 years, 2.6% women, mean 3.8 chronic conditions.	7 chronic conditions, weighted based on mortality in derivation set, age, smoking status	Self-reported diagnoses and smoking status (from survey). Age from records. List of conditions and	All-cause mortality, hospitalisation	Recommended for predicting mortality where medical history and smoking status available

Publication and name of index	Original purpose	Data source and location	Population demographics	Index components	Information used	Original outcomes measured	Recommendation
			Validation: n=5,478, mean age 67.8, 2.7% women, mean 3.8 chronic conditions		weighting given in paper		
Hornbrook 1996 [144]	Prediction of healthcare expenditure	Postal survey sent to two random samples of patients from one primary healthcare provider. USA	n=7,739, mean age 42.2 years, 55.4% women (Split in half at random to test different models)	Five models including various combinations of demographics, RAND-36 scales and self-report of six chronic diseases	Self-reported diagnoses, demographics from administrative records, RAND-36 (available free online)	One year's total health plan expenditure	Not recommended; as authors state it is exploratory work and do not identify one model for external use. Useful for comparing cost prediction models

* Indices that have an updated or modified version available

eTable 5: Data extracted from original papers where index components are weighted drug counts

Publication and name of index	Original purpose	Data source and location	Population demographics	Index components	Information used	Original outcomes measured	Recommendation
Robusto 2016 [145] **Drug-Derived Complexity Index**	Predicting mortality and hospitalisation	Population-based retrospective cohort study using record linkage. Italy	Derivation: n=999 391, mean age 60.2 years, 53.7% women. Validation: n=999 557, mean age 60.2 years, 53.7% women	19 classes of drug, weighted based on mortality in derivation set	Community prescribing records organised by WHO ATC codes (available for free). Weights and lists of drugs given in paper	One-year and overall mortality, unplanned hospitalisation	Recommended for measuring multimorbidity using medication data to predict mortality. Needs external validation

Publication and name of index	Original purpose	Data source and location	Population demographics	Index components	Information used	Original outcomes measured	Recommendation
Dong 2013 [146] **Pharmacy-Based Disease Indicator**	Prediction of hospitalisation	Routinely collected pharmacy data from adults aged ⩾18 years from longitudinal health insurance database. Taiwan	Derivation: n=697 823, mean age 43.4, 51.4% women. Validation: n=714 072, mean age 43.6, 51.6% women	37 drug categories, weighted based on hospitalisation in derivation cohort	Prescribing records from primary and secondary care, organised by WHO ATC codes. Weights and lists of drugs in original paper	One-year hospitalisation	Recommended for predicting hospitalisation using prescribing data
George 2006 [147] **Medication-based Disease Burden Index (MDBI)**	Prediction of mortality and hospitalisation	Participants of RCT taking ⩾ 3 medications (and with other risk factors) discharged from two tertiary care	n=317, mean age 71.8 years, (gender breakdown not given), mean 10.4 medications	Drugs corresponding to 20 conditions, weighted based on burden of disease studies	Prescribing records from inpatient discharges. List of drugs and weights given in this paper	Hospital readmission or death within 12 weeks	Potentially useful but requires validation in larger studies

Publication and name of index	Original purpose	Data source and location	Population demographics	Index components	Information used	Original outcomes measured	Recommendation
		hospitals. Australia					
Von Korff 1992 [148] **Chronic Disease Score***	Measuring chronic disease using pharmacy data	Routinely collected prescription data from various healthcare providers. USA	Derivation samples: n=219, n=722, n=1,016, n=2,247. Validation: n=122 911. Overall demographics not given	25 classes of drug, weighted according to expert consensus	Drugs from medical or pharmacy records. List of drugs and weighting given in original paper	Physician rating of physical disease severity (pilot sample). One-year mortality and hospitalisations. In smaller samples, measured self-rated health, chronic pain, functional disability, depression, anxiety and somatisation according to SCL-90-R	Recommended for measuring disease severity and predicting mortality and hospitalisations using drug data. Advise using updated version Rx-Risk for newer list of drugs [55] (see eTable 11)

* Indices that have an updated or modified version available

eTable 6: Data extracted from original papers where index components are diagnostic groups or physiological measures

Publication and name of index	Original purpose	Data source and location	Population demographics	Index components	Information used	Original outcomes measured	Recommendation
Brettschneider 2013 [149]	Quality of life prediction	Cohort study of randomly selected general practice patients. Subset studied had ⩾3 conditions. Germany	n=3,189, mean age 74.4 years, 59.3% women, mean 7 chronic conditions	42 diagnostic groups, each with severity rating	Primary care diagnoses and severity rating of each condition according to participant's GP. List of conditions given in paper	Health-related quality of life according to EQ-5D	Potentially useful for assigning condition weights in other studies
Newman 2008 [150] **Physiologic Index of Comorbidity ***	Predicting mortality and disability	Measurements taken as part of longitudinal cohort study of people aged ⩾ 65 years. USA	n=2,928, mean age 74.5, 57.8% women	Five non-invasive physiological parameters, all graded for abnormality on three-point scale	Carotid ultrasound, pulmonary function testing, brain magnetic resonance scan, serum cystatin-C, and fasting glucose. From cohort study but could be taken from medical records. Weighting given in this paper	Nine-year mortality, mobility disability, ADL disability	Not recommended: requires very specific components. Updated version Healthy Ageing Index more practical [56] (see eTable 11)
Farley 2006 [151]	Prediction of healthcare expenditure	Electronic health records of adults in managed care organisation aged ⩾18 years who filled a	n=20 378, mean age 49.0 years, 47% women, mean 7.1 diagnosis clusters	Two separate final models: Count of hospital visits, physician claims and unique prescriptions with and without	Data on physician and hospital claims, diagnoses, prescriptions and demographics	One-year healthcare expenditure	Not recommended for external use, but provides evidence comparing models with disease counts

Publication and name of index	Original purpose	Data source and location	Population demographics	Index components	Information used	Original outcomes measured	Recommendation
		prescription for an anti-hypertensive. USA		counts of 119 ICD-9-CM diagnostic clusters. With and without age and gender	from health records		
Pope 2004 [152] **The Centers for Medicare and Medicaid Services' Hierarchical Condition Category (CMS-HCC) ***	Predicting medical expense risk	Fee-for-service claims of 5% sample of population covered by large healthcare provider (with specific subsample of nursing home residents). USA	n=1 337 887, no further details given	70 hierarchical condition categories, gender, age, Medicaid enrolment, disability status, interactions between diseases and between diseases and disability status	Diagnosis categories and demographic information from primary and secondary healthcare records. Conditions listed in paper	Healthcare expenditure	Recommended for predicting healthcare expenditure in USA setting

Publication and name of index	Original purpose	Data source and location	Population demographics	Index components	Information used	Original outcomes measured	Recommendation
Starfield 1991 [153] **Ambulatory Care Groups***	Predicting healthcare utilisation and costs	Routinely collected data from outpatients covered by five healthcare providers. USA	Total n=106 551 including adults and children. No further details given	34 diagnostic groups, weighted according to recorded stability and collapsed into 12 overall groups	Requires access to proprietary software. Diagnoses and severity from primary care medical records, demographics from administrative or medical records. Diagnostic groups listed in original paper	Annual number of healthcare visits and healthcare charges	Potentially useful for predicting costs in USA setting but needs proprietary software
Linn 1968 [154] **Cumulative Illness Rating Scale (CIRS) ***	Assessing physical impairment for research	Study of adults aged over 55 years. USA	n=472, no further details given	13 disease areas, each scored for severity by assessing physician	Diagnoses and severity from physician interview or medical records. Body systems listed in original paper	Not assessed in detail but briefly mentions correlation with deaths, vital organ involvement and number of previous illnesses	Potentially useful for information gathering in clinical and research settings although somewhat subjective

* Indices that have an updated or modified version available

Abbreviations in eTables 3 to 6:

ADL: Activities of Daily Living
APR-DRGs: All Patient Refined Diagnosis Related Groups
BMI: body mass index
EQ-5D: EuroQol five-dimension measure of health status

GHQ-28: 28-Item General Health Questionnaire
GP: General Practitioner
HAD: Hospital Anxiety and Depression Scale
HbA1c: (glycated) haemoglobin A1c
HRQL: Health-related quality of life
ICD-9-CM: The International Classification of Diseases, Ninth Revision, Clinical Modification
ICU: Intensive Care Unit
LDL: low-density lipoprotein
MRC: Medical Research Council [classification of heart failure]
NEADL: Nottingham Extended Activities of Daily Living Scale
NYHA: New York Heart Association [classification of heart failure]
OARS ADL: Older Americans Resources and Services Activities of Daily Living Scale
PHQ-9: Nine-item Patient Health Questionnaire
PIP-DCG: Principal Inpatient Diagnostic Cost Group Model for Medicare Risk Adjustment
QOF: Quality and Outcomes Framework
RAND-36: Research And Development Corporation 36-item health survey
RCT: Randomised controlled trial
RxRisk model: A revision and expansion of the Chronic Disease Score [33,55]
RxRiskV: Veterans Health Administration Adapted RxRisk
SCL-90-R: Symptom Checklist-90-Revised
SF-12: 12-item short-form health survey
SF-36: Medical Outcomes Study Short Form
WHO ATC: World Health Organisation Anatomical Therapeutic Chemical classification system

eTable 7: Development of models in original index descriptions

Publication and name of index	Method of developing model	Model details provided	Baseline outcomes reported
Corrao 2017 [123] **Multisource Comorbidity Score**	Parametric survival models for relationship between each condition and time to death, then least absolute shrinkage and selection operator (LASSO) method to select predictor conditions, then coefficients multiplied by 10 and rounded to nearest integer	Regression coefficients of survival model for all included conditions. No intercepts or baseline survival	No mortality figures reported
Wen 2017 [138] **Multimorbidity Frailty Index (mFI)**	Overall index score = number of conditions ("deficits") divided by total candidate conditions. No weighting	Not applicable	30,136 deaths (35.0% sample). No figures for number of hospitalisations or intensive care admissions
Stanley 2017 [124] **Measuring multimorbidity (M3) Index**	Conditions weighted by β coefficient where β>0. Total score = sum of β coefficients	All coefficients listed. No other model details	28,611 deaths (0.9% sample) in derivation and validation sets
Wei 2016 [125] **Multimorbidity Weighted Index**	Used mixed models to predict physical function (PF) of SF-36 for each condition. Pooled coefficients from three samples using fixed-effects meta-analysis to develop condition weights	All coefficients listed. No other model details	PF used for weighting; no clear overall outcome. Summary PF scores given
Robusto 2016 [145] **Drug-Derived Complexity Index**	Weights derived from Cox proportional hazard regression coefficients for mortality divided by 0.3, rounded to the nearest integer	All coefficients listed. No other model details	>213,000 deaths in combined samples (10.7%)
Lorem 2016 [126] **Health Impact Index**	Weights from ordinal logistic regression odds ratios (odds of scoring at lower levels of self-rated health for those with the disease	Odds ratios for all components given. Full model equation given. No intercept	Summary statistics listed for self-rated health across demographic groups

Publication and name of index	Method of developing model	Model details provided	Baseline outcomes reported
	compared with those without), rounded to nearest integer		
Pati 2016 [139] **Multimorbidity Assessment Questionnaire for Primary Care (MAQ-PC)**	Not applicable	Not applicable	Not applicable
Hong 2015 [140] **estimated Physician Defined Complexity (ePDC)**	Logistic regression to identify factors predictive of physician-defined complexity (the odds of being defined as complex by physician)	Odds ratios for all components given. No intercept or further model details	Figures for all relevant outcome events given
Wister 2015 [127]	One model weighted by Health Utility Index (HUI3) correlation, one weighted by OARS functional status scale correlation, one weighted by β coefficients predicting HUI3 in ordinary least squares regression	All coefficients and correlations listed. No intercept or further model details	Summary statistics for all outcomes given
Brettschneider 2013 [149]	Conditions weighted by physician-defined severity	Not applicable	EQ-5D summary scores listed
Min 2013 [141] **Geriatric CompleXity of Care Index (GXI)**	Conditions weighted by physician-defined severity	Not applicable	Summary values for each outcome given
Carey 2013 [128] **QOF Comorbidity Score**	Conditions weighted by Cox proportional hazard ratios for mortality in training set	No coefficients or other model details	10,595 deaths (3.3% of sample)
Dong 2013 [146] **Pharmacy-Based Disease Indicator**	Drugs weighted based on coefficients from logistic regression for hospitalisation in training set	All coefficients listed. Equation given. No intercepts	Approximately 60,000 hospitalisations in each set (8.5% of sample)

Publication and name of index	Method of developing model	Model details provided	Baseline outcomes reported
Bernabeu-Wittel 2011 [142] **PROFUND**	Cox models for one-year mortality; weights generated by β coefficient divided by the lowest β coefficient and rounded to nearest integer. Components included if independently associated with mortality	Odds ratios (not coefficients) for each included component given. No intercepts	Mortality reported as 35% in derivation cohort (n≈265)
Mukherjee 2011 [129] **Health-Related Quality of Life Comorbidity Index (HRQL-CI)**	Predictors selected using LASSO method: regression for each predictor and either PCS or MCS of SF-12. Points generated based on coefficients and clinical judgement	All coefficients listed. Intercepts given for separate physical and mental SF-12 scores. Tested separately for coefficient- or points-based models	Summary statistics for outcomes presented
Newman 2008 [150] **Physiologic Index of Comorbidity**	Parameters weighted by arbitrary abnormality cut-points (tertiles)	Not applicable	No figures listed for number of deaths. Method of measuring disability not given. Summary scores for disability not given
Tooth 2008 [130]	Conditions weighted by regression coefficient (scaled and rounded to nearest integer) from Cox hazard models for mortality, logistic regression for healthcare outcomes, or multiple regression for SF-36. Different weights for each outcome	Hazard ratios and odds ratios for mortality and healthcare measures. Coefficients for all aspects of SF-36 listed. No intercept	14.9% of derivation set died (n≈777). Summary results given for all other outcomes
George 2006 [147] **Medication-based Disease Burden Index (MDBI)**	Weights based on association with disability in previous studies. Clinical panel decided on medications to include	None	Mortality or hospitalisation within 12 weeks (77 occurrences of one or both)
Lee 2006 [9]	Used backward elimination (P<0.05) to choose variables that improved predictive value of	Odds ratios but not coefficients given. No intercepts	1,361 (12%) deaths

Publication and name of index	Method of developing model	Model details provided	Baseline outcomes reported
	model, then further selected using Schwarz Bayesian Information Criterion (BIC). Weighting developed by dividing logistic regression β coefficients by the lowest coefficient and rounding to the nearest integer		
Farley 2006 [151]	Addition of various variables (e.g. count of physician visits and unique prescriptions). No weighting	Not applicable	Summary statistics for specific expenditure-related outcomes given
Byles 2005 [131]	Weights generated using hazard ratios for mortality and odds ratios for admission. Weights with and without health self-rating	Lists of odds and hazard ratios given but no coefficients or intercepts	51% admitted to hospital (485 patients), 7% died (n=59 in derivation sample, n=29 validation)
Bayliss 2005 [132] **Disease Burden Morbidity Assessment**	Conditions weighted by self-reported severity	No; correlations between overall score and outcomes for testing only	Summary statistics for each outcome provided
Selim 2004 [143]	Components chosen by availability and expert panel. Weighting was not beneficial to model so was not used (data not shown in original paper)	Not applicable	77 patients (4%) died. No summary statistics for other outcomes
Pope 2004 [152] **The Centers for Medicare and Medicaid Services' Hierarchical Condition Category (CMS-HCC)**	Developed using weighted least squares multiple regression	Coefficients for all parameters included. No intercepts	Detailed summary statistics of all expenditures given
Sangha 2003 [133] **Self-Administered Comorbidity Questionnaire**	Conditions weighted by patient-reported severity	Not applicable	Summary statistics given for SF-36, hospitalisation and inpatient cost outcomes

Publication and name of index	Method of developing model	Model details provided	Baseline outcomes reported
Fan 2002 [10] **Seattle Index of Co-morbidity**	Conditions weighted by regression coefficients from Cox hazard models for mortality, multiplied by four then rounded to the nearest integer	Hazard ratios and coefficients for mortality for each parameter listed	396 (7.2% of sample) deaths, 1,383 (25.3%) hospitalisations
Desai 2002 [134] **High-Risk Diagnoses for the Elderly Scale**	Conditions weighted by hazard ratio for one-year mortality, rounded to the nearest integer	Hazard ratios listed. No coefficients or intercepts	154 (29%) died within one-year follow-up
Crabtree 2000 [135] **Comorbidity Symptom Scale (CmSS)**	Conditions weighted by self-reported severity	Not applicable	Appropriate scales used for each outcome but no summary statistics given
Hornbrook 1996 [144]	In one model, conditions weighted by interaction effects with RAND-36	Full model including intercepts given	No summary data given on healthcare cost outcomes
Greenfield 1995 [136] **Total Illness Burden Index (TIBI)**	Conditions weighted by severity; each group's weight calculated by summing each condition's regression coefficients for functioning, combined with clinical opinion	Coefficients for one example condition included. No intercepts	Physical function and role functioning from SF-36. Summary data given
Parkerson 1993 [137] **Duke Severity of Illness Checklist (DUSOI)**	Conditions weighted by severity for each patient	Not applicable	Not applicable
Von Korff 1992 [148] **Chronic Disease Score**	Drugs weighted based on expert opinion	Not applicable	Summary data for outcomes in population validation cohort. 1,053 deaths (0.9%), 8,585 hospitalisations (8.0%)
Starfield 1991 [153] **Ambulatory Care Groups**	Conditions classified into groups then treating as counts; no weighting	Not applicable	Summary measures for healthcare visits given

Publication and name of index	Method of developing model	Model details provided	Baseline outcomes reported
Charlson 1987 [120] **Charlson Index**	Conditions weighted by adjusted relative risks for one-year mortality, rounded to nearest integer	Relative risks listed. No coefficients or intercepts	Mortality (in-hospital and at one year) figures listed for each condition
Linn 1968 [154] **Cumulative Illness Rating Scale (CIRS)**	Conditions weighted by physician-defined severity	Not applicable	None measured in original paper

Abbreviations in eTable 7:
AUC: Area under the curve
BIC: Bayesian Information Criterion
CDS: Chronic Disease Score
EQ-5D: EuroQol five-dimension measure of health status
IDI: Integrated discrimination improvement
LASSO: Least absolute shrinkage and selection operator
MCS: Mental component summary
NRI: Net reclassification improvement
PCS: Physical component summary
PF: 10-item physical functioning scale of SF-36
ROC: Receiver operating characteristic
SF(-36 or -12): Medical Outcomes Study Short Form

eTable 8: Original indices that include aspects of mental health as comorbidities or outcome variables

First author and year	Comorbidities or index components	Outcomes	Findings, if applicable
Corrao 2017 [123]	Alcohol abuse, psychoses, anxiety and dementia included as comorbidities, defined by use of relevant medications	All-cause hospitalisation as outcome; no separation of admission types to include psychiatric	Regression coefficients with time to death: alcohol abuse β=0.99 (SE=0.16), psychoses β=0.77 (SE=0.05), anxiety β=0.52 (SE=0.23), dementia β=0.51 (SE=0.06). Weights allocated in model accordingly
Wen 2017 [138]	Comorbidities include "senile and presenile organic psychotic conditions." Diagnoses from claims records	Does not specify subtypes of hospital admissions (e.g. psychiatric)	Not separately examined
Stanley 2017 [155]	Comorbidity variables: alcohol abuse, anxiety and behavioural disorders, dementia, drug abuse, major psychiatric disorder, mental and behavioural disorders due to brain damage, mental retardation. Diagnoses from routinely collected healthcare data	None	β coefficients for one-year mortality (log hazard ratios (95%CI)): alcohol abuse=0.58 (0.47 to 0.68), anxiety and behavioural disorders=0.12 (0.04 to 0.21), dementia=1.02 (0.97 to 1.07), drug abuse=0.56 (0.38 to 0.74), major psychiatric disorder=0.21 (0.13 to 0.29), mental and behavioural disorders due to brain damage=0.04 (−0.17 to 0.24), mental retardation=1.41 (1.21 to 1.60)
Wei 2016 [125]	Weighted comorbidities include alcohol abuse, depression and dementia. Taken from self-reported conditions	None	Depression and dementia both significantly associated with poorer scores on physical functioning subscale of SF-36
Robusto 2016 [145]	Drugs in model include anti-depressants, anti-psychotics, anti-dementia drugs. Data from record linkage	Does not specify whether hospitalisation outcome includes psychiatric admissions	Hazard ratios (95% CI) for mortality with each class: antipsychotics=2.32 (2.24 to 2.40), anti-dementia drugs=3.10 (2.92 to 3.29), antidepressants=1.09 (1.06 to 1.11). Weighted accordingly
Pati 2016 [139]	Comorbidities include dementia (self-report), depression (PHQ-9) and mental aspects of HRQL (SF-12)	None	Self-reported depression did not correlate well with PHQ-9 scores, suggesting under-diagnosis (no details given)
Hong 2015 [140]	Comorbidities include: anxiety, post-traumatic stress disorder, bipolar disorder, dementia, depression, drug or alcohol addiction-related conditions, personality disorder, schizophrenia or other psychotic disorders, chronic pain, eating disorders, or history of domestic violence, situational stress/depression/anxiety or adjustment reactions, attention deficit disorder,	None	High risk psychiatric and behavioural disorders were significantly associated with physician-defined complexity whereas post-traumatic stress disorder was not

First author and year	Comorbidities or index components	Outcomes	Findings, if applicable
	dementia, marijuana use, history of drug or alcohol addiction. Diagnoses from health records		
Brettschneider 2013 [149]	Depression, anxiety and somatoform disorders included as comorbidities in weighted count. Taken from self-report questionnaire. (Dementia was an exclusion criterion)	Anxiety/depression is one dimension of EQ-5D which was outcome	Weighted count of morbidities significantly associated with all domains of EQ-5D: b=-1.02 (SE 0.06). No information on weighted count's association with specific dimensions. Participants with depression had increased odds of poor scores across all EQ-5D domains. Depression, anxiety and insomnia were each significantly associated with EQ-5D anxiety/depression dimension
Min 2013 [141]	Dementia, anxiety and depression as comorbidity variables. Taken from medical records, weight assigned by expert consensus	None	Not examined separately
Carey 2013 [128]	Dementia, depression and psychotic disorders all included as comorbidities. Taken from medical records	None	All included mental disorders were individually associated with increased mortality risk in derivation set (dementia hazard ratio=2.83 (95% CI 2.63 to 3.04), depression HR 1.11 (1.05 to 1.18), psychotic disorders HR 1.74 (1.49 to 2.04))
Dong 2013 [146]	Psychiatric medication included as an index component	Does not specify whether outcome includes psychiatric hospitalisation	Weights in index: antidepressants=0.23, antipsychotics=0.40, lithium=0.85, anxiolytics=0.14. No specific outcomes given
Bernabeu-Wittel 2011 [142]	Dementia and delirium (in last hospital admission) as comorbidities in index. From records or self-report	None	Odds ratio for 12-month mortality with dementia=1.89 (95% CI 1.1 to 3.1), P=0.019, for delirium in last hospital admission=2.1 (1.5 to 4.9), P=0.001
Mukherjee 2011 [129]	Comorbidities include: affective disorders, schizophrenia, other psychoses, anxiety, depression. Diagnoses from medical records. Cognitive impairment codes excluded	SF-12 mental component score, two core health status questions	Mental health diagnoses had strong association with worse SF-12 MCS scores, as did asthma, heart failure, neurological conditions and pain-related conditions
Tooth 2008 [130]	Depression, anxiety, Alzheimer's disease (self-reported)	SF-36 as outcome, includes mental component scale. Healthcare visits (self-reported) as outcome – does not specify which specialty	Alzheimer's disease found to be associated with higher risk of mortality, functional dependency and poorer social functioning and mental health. Depression had a weak link with poor functional ability

First author and year	Comorbidities or index components	Outcomes	Findings, if applicable
George 2006 [147]	Alzheimer's and other dementias included as comorbidity (identified by prescription of drugs for dementia)	Does not specify whether outcome includes psychiatric hospitalisation	MDBI reported as 100% sensitive and 100% specific for Alzheimer's and other dementias when measured against medical records
Lee 2006 [9]	Two functional questions (difficulty managing finances and personal hygiene) refer to "health or memory problems"	None	Difficulty bathing and managing finances each assigned two points in overall model
Byles 2005 [131]	Depression and forgetfulness included as comorbidities. Self-reported with severity rating	Mental Component Score (MCS) of SF-36	Increasing scores on all versions of the multimorbidity index were associated with worse scores on the SF-36 MCS
Bayliss 2005 [132]	None	Depression screen from Behavioural Risk Factor Surveillance System	Being less depressed was significantly negatively correlated with self-reported disease burden (P<0.001) and number of conditions (P=0.002) but not with Charlson index or RxRisk score
Selim 2004 [143]	Comorbidity variables include self-reported schizophrenia, depression, bipolar disorder, anxiety disorder, post-traumatic stress disorder, alcohol abuse	Mental health outpatient visits from administrative data, SF-36	Mental disorders on comorbidity index correlated better with the mental than physical scale of the SF-36. Comorbidity index including mental disorders was not significantly associated with mortality
Pope 2004 [152]	Comorbidity variables: Drug or alcohol psychosis, drug or alcohol dependence, schizophrenia, major depressive, bipolar, and paranoid disorders. Diagnoses taken from claims data	None	Not separately examined
Sangha 2003 [133]	Depression (self-reported diagnosis) included as a comorbidity	Mental Component Score (MCS) of SF-36	Spearman correlation of SF-36 MCS score at one-year follow-up with baseline comorbidity score R^2=-0.03 (P>0.05).
Crabtree 2000 [135]	Anxiety/depression (self-report) included as one comorbidity	Anxiety/depression measured by Hospital Anxiety and Depression (HAD) scale and GHQ-28	Overall score on the CmSS correlated with GHQ-28 (r=0.48) and HAD (r=0.52) with P<0.01

First author and year	Comorbidities or index components	Outcomes	Findings, if applicable
Hornbrook 1996 [144]	Depression as comorbidity (self-report diagnosis); some models included elements of SF-36, which includes mental health	None	Depression performed poorly at explaining variance in costs, both as a reported comorbidity and through SF-36
Greenfield 1995 [136]	Not clearly included as comorbidity (may be counted under "neurologic problems")	"Mental health index" (assume part of SF-36)	Global severity measure significantly associated with mental health index score (F statistic 51.7, P<0.001)
Parkerson 1993 [137]	Any condition could be a comorbidity (Diagnoses from medical records, weighted by rater's clinical judgement)	None	Participants with the highest scores were those with depression and at least one other condition
Von Korff 1992 [148]	Psychotropic drugs not included	Depression, anxiety, somatisation as outcomes in one test (symptoms measured with SCL-90-R)	Chronic Disease Score was not correlated with depression and anxiety
Starfield 1991 [153]	Three of 34 listed diagnoses are psychosocial, separated into chronic, other and psychophysiologic. Taken from health records	Does not specify subtype of outpatient visits (e.g. mental health	Individuals with psychosocial diagnoses, whether alone or in combination with other diagnoses, have relatively high levels of healthcare use
Charlson 1987 [120]	Dementia, according to medical records, included as comorbidity	None	Dementia alone carried relative risk of one-year mortality of 1.4
Linn 1968 [154]	Psychiatric disease listed as disease area (severity scored by physician)	None	Not examined separately

eTable 9: Usage, validation and performance of multimorbidity indices – indices without external validation[5]

Publication and name of index	Citations since publication	Citations per year[6]	Internal validation and/or comparison	Predictive accuracy measurement	Performance
Corrao 2017 [123] **Multisource Comorbidity Score**	9	9.0	Tested n or g na paper on one nterna (sp t-samp e) and three externa va dat on sets. Compared to Char son, E xhauser and Chron c D sease Score (CDS) nd ces	D scr m nat on: AUC for one-year morta ty	AUCs for one-year morta ty: Mu t source Comorb d ty Score=0.78 (95% CI 0.77 to 0.79), Char son=0.69 (0.68 to 0.70), E xhauser=0.65 (0.64 to 0.66), CDS=0.69 (0.68 to 0.70)
Wen 2017 [138] **Multimorbidity Frailty Index (mFI)**	8	8.0	ROC ana ys s of outcomes w th n or g na dataset on y	D scr m nat on: AUC for a outcomes by categor sed mFI scores	C-stat st cs for: a -cause morta ty=0.67 (95% CI 0.66 to 0.68), unp anned hosp ta sat on=0.65 (0.65 to 0.66) and ICU adm ss on=0.68 (0.67 to 0.69) (a at one year)
Stanley 2017 [124] **Measuring Multimorbidity (M3) Index**	12	12.0	Va dated n or g na paper on va dat on set (random y ass gned sp t-samp e). Compared w th Char son and E xhauser nd ces	D scr m nat on: C-stat st cs for morta ty and hosp ta sat on (a so used ntegrated d scr m nat on mprovement (IDI) and Aka ke nformat on cr ter on)	C-stat st cs for one-year morta ty: M3 + age + gender=0.92 (95% CI 0.93 to 0.93), Char son + age + gender=0.92 (0.92 to 0.92), E xhauser + age + gender=0.92 (0.92 to 0.93); One-year hosp ta sat on: M3 + age + gender=0.70 (95% CI 0.70 to 0.71), Char son + age + gender=0.68 (0.68 to 0.69), E xhauser + age + gender=0.68 (0.67 to 0.68)
Robusto 2016 [145] **Drug-Derived Complexity Index (DDCI)**	10	5.0	Va dated w th n or g na paper on va dat on cohort (random y ass gned sp t-samp e). Compared w th Char son ndex n subsamp e of 125,094 hosp ta sed pat ents	D scr m nat on and net rec ass f cat on mprovement (NRI) measured for morta ty and hosp ta sat on	C-stat st cs for one-year morta ty: DDCI=0.81 (0.81 to 0.82), age, sex and Char son comb ned=0.80 (0.79 to 0.80); overa morta ty: DDCI=0.80 (0.79 to 0.80), age, sex and Char son comb ned=0.79 (0.78 to 0.79); f rst unp anned hosp ta sat on: DDCI=0.62 (0.62 to 0.62), age, sex and Char son comb ned=0.62 (0.62 to 0.62)
Lorem 2016 [126] **Health Impact Index (HII)**	11	5.5	Va dated n or g na paper n separate cohort. Compared ab ty to pred ct se f-rated hea th w th Char son ndex	Ca brat on: used Spearman s corre at on to compare the assoc at on of se f-rated hea th to both Hea th Impact Index and the Char son ndex (wh ch was or g na y	Spearman corre at on (R_S) w th se f-rated hea th: HII= -0.36, P<0.001, Char son= -0.25, P<0.001

[5] Validation of original indices only; validation of index updates not included. Papers marked with * have updates available

[6] Citations per full year since publication according to Google Scholar, as at 7th September 2019

Publication and name of index	Citations since publication	Citations per year[6]	Internal validation and/or comparison	Predictive accuracy measurement	Performance
				deve oped to pred ct morta ty)	
Pati 2016 [139] **Multimorbidity Assessment Questionnaire for Primary Care (MAQ-PC)**	7	3.5	Tested for nterna cons stency w th n or g na cohort. Compar son between pat ent se f-report of d agnoses and phys c ans' prescr pt ons. Not compared w th other sca es	Compared se f-report w th d agnoses apparent from prescr pt ons	Overa Cronbach's a pha=0.69. Concordance (Scott Kappa) between se f-report and prescr pt on-based d agnoses ranged from 0.58 for hear ng prob em to 1.00 for tubercu os s
Hong 2015 [140] **estimated Physician Defined Complexity (ePDC)**	15	5.0	Test character st cs ca cu ated n va dat on set w th n or g na paper. Bootstrapp ng n random th rd of samp e. Compared w th outpat ent Char son score and propr etary commerc a r sk pred ctor, but no comparab e pred ct on scores g ven	D scr m nat on: C-stat st cs for phys c an-def ned comp ex ty. Compared to Char son and Commerc a R sk Pred ctor, but no c ear compar son resu ts ava ab e	In own va dat on set: Accuracy=0.82, Sens t v ty=0.47, Spec f c ty=0.95, Pos t ve Pred ct ve Va ue=0.77, Negat ve Pred ct ve Va ue=0.83. C-stat st cs for mode s' pred ct on of phys c an-def ned comp ex ty: <45 years=0.82, 45–64 years=0.82 and ≥65 years=0.77
Wister 2015 [127]	15	5.0	Measured construct va d ty of s x mode s w th each other w th n or g na paper	None	B var ate corre at on coeff c ent for mu t morb d ty add t ve sca e (best perform ng mode) w th fe sat sfact on= -0.23 (compared to d chotom sed 0/≥1 cond t ons= -0.10), perce ved hea th= -0.39 (-0.15), hea th profess ona v s ts= 0.22 (0.14), da y med cat on use= 0.50 (0.30)
Brettschneider 2013 [149]	85	17.0	None	None	Ord nary east squares regress on for assoc at on between mu t morb d ty measured by we ghted count score w th overa HRQL (EQ VAS), b= -1.02 (SE=0.06)
Min 2013 [141] **Geriatric CompleXity of Care Index (GXI)**	26	5.2	In or g na paper, measured corre at on and compared pred ct ve ab ty w th s mp e d sease count, mod f ed Char son ndex (mCCI) and H erarch ca Cond t on	D scr m nat on: AUC for a outcomes compared to mod f ed Char son ndex (mCCI) and mod f ed HCC (mHCC)	Adjusted R^2s for pr mary care v s ts: GXI=14.3, mHCC=6.1, mCCI=3.8; spec a ty v s ts: GXI=9.1, mHCC=9.9, mCCI=2.9; qua ty nd cators (med ca records on y): GXI=32.8, mHCC=15.8, mCCI=19.6. Adjusted AUCs for 5-year morta ty: GXI=76.2, mHCC=78.7, mCCI=77.5; 5-year funct ona dec ne: GXI=83.8, mHCC=89.6, mCCI=77.5; Po ypharmacy (≥14 med cat ons): GXI=81.5, mHCC=76.9, mCCI=70.1

Publication and name of index	Citations since publication	Citations per year[6]	Internal validation and/or comparison	Predictive accuracy measurement	Performance
			Category score (mHCC) n same cohort		
Carey 2013 [128] **QOF Comorbidity Score**	44	8.8	Tested w th n or g na paper on va dat on cohort (sp t-samp e); a so compared morta ty pred ct on w th Char son ndex	D scr m nat on: C-stat st cs for morta ty compared to Char son ndex	C-stat st cs for one-year morta ty: standard QOF score=0.83, extended QOF score=0.83, Char son ndex=0.82
Newman 2008 [150] **Physiologic Index of Comorbidity * (PIC)**	98	9.8	Compared w th age a one and s mp e cond t on count w th n same cohort n or g na paper	D scr m nat on: surv va mode s by ndex score	AUCs for n ne-year morta ty n or g na paper: age a one=0.67, PIC=0.71, PIC adjusted for age, sex, race=0.73
Tooth 2008 [130]	86	8.6	Va dated w th n or g na paper on va dat on set (random sp t-samp e)	Exp a ned var at on: compared R^2 of we ghted and unwe ghted scores for nd v dua cond t ons across 13 ana yses	Re at ve d fferences n R^2 for we ghted scores: 0.2-1.3% (med an=0.9%), unwe ghted scores 4.9%-35.0%, med an=13.3%
Farley 2006 [151]	167	13.9	Compared w th Char son-Romano ndex, E xhauser ndex and RxR sk-V n same cohort n or g na paper	D scr m nat on: C-stat st c for nd v dua s spend ng at the 90th percent e for each mode	C-stat st cs for nd v dua s spend ng at 90th percent e on hosp ta and phys c an c a ms: Far ey d agnos s c uster ng=0.69 (0.68 to 0.70), Char son=0.66 (0.65 to 0.67), RxR sk-V 0.64 (0.63 to 0.65), E xhauser=0.66 (0.66 to 0.66)
Byles 2005 [131]	94	7.2	Tested d fferent mode s on va dat on cohort w th n or g na paper (random sp t-samp e)	None	HRs for two-year morta ty us ng sever ty-we ghted ndex based on morta ty=1.3 (*P*<0.001), sever ty-we ghted ndex based on hosp ta sat on=1.1 (*P*>0.05). ORs for two-year hosp ta sat on us ng sever ty-we ghted ndex based on morta ty=1.2 (*P*>0.05), sever ty-we ghted ndex based on hosp ta sat on=1.7 (*P*<0.01). Authors adv se that a s ng e ndex cannot pred ct a var ety of outcomes
Selim 2004 [143]	191	13.6	Compared one mode to D sease Burden Index (DBI) n same cohort n or g na paper [156]	L near regress on for var ance n outcomes exp a ned by ndex mode s. No d scr m nat on or ca brat on	Pearson corre at ons: comb ned phys ca /menta comorb d ty mode w th: SF-36 PCS= -0.39, SF-36 MCS= -0.31. Cond t on/symptom comorb d ty ndex w th: PCS= -0.50, MCS= -0.39. Hazard rat o for 35-week surv va w th each add t ona un t n phys ca ndex= 0.14. For MCS, a) R^2 for regress on mode s: DBI=15%, comb ned phys ca + menta ndex=33%; b) regress on coeff c ents: DBI= −1.32, comb ned phys ca + menta ndex= −5.50 (*P*<0.001). For psych atr c outpat ent c n c v s ts, R^2: DBI=2.3%, comb ned phys ca + menta ndex=14%; coeff c ents DBI=0.06, Comb ned ndex=0.40; (*P*<0.001)

Publication and name of index	Citations since publication	Citations per year[6]	Internal validation and/or comparison	Predictive accuracy measurement	Performance
Fan 2002 [10] **Seattle Index of Co-morbidity (SIC)**	160	10.0	Tested w th n or g na paper on va dat on cohort (random sp t-samp e)	D scr m nat on: ROC and Kap an-Me er curves for morta ty and hosp ta sat on	In va dat on set for a) two-year surv va , AUCs: SIC=0.71, comb ned PCS+MCS= 0.71; b) two-year hosp ta sat ons, AUCs: SIC=0.61, PCS+MCS=0.64
Desai 2002 [134] **High-Risk Diagnoses for the Elderly Scale * (HRDES)**	85	5.3	Va dated w th n or g na paper; compared w th Char son-Deyo ndex and APR-DRGs n separate va dat on cohort	D scr m nat on: Kap an-Me er curves for morta ty by score r sk eve	For one-year morta ty n va dat on cohort, C-stat st cs: HRDES=0.69, Char son-Deyo=0.65 (*P*<0.05 compared to HRDES), tota d agnoses=0.59 (*P*<0.05 compared to HRDES), APR-DRGs=0.67 (*P*=0.43 compared to HRDES)
Crabtree 2000 [135] **Comorbidity Symptom Scale (CmSS)**	55	3.1	Corre at ons w th outcomes tested n separate va dat on set n or g na paper. Not compared to another sca e	None	Spearman's coeff c ent for corre at on between CmSS score and act v t es of da y v ng (NEADL)=0.56; perce ved hea th status (GHQ-28)=0.48; anx ety and depress on (HAD)=0.52 (*P*<0.01 for a va ues)
Hornbrook 1996 [144]	168	7.6	Mode s compared w th each other on ha f of the samp e n or g na paper (random sp t-samp e). Not compared to other sca es	Ca brat on: regress on of pred cted versus actua costs	Grouped R^2s for f t of pred cted to actua costs: D sease count=0.56, D sease count + age + gender =0.68, D sease count, age, gender and funct on=0.80
Greenfield 1995 [136] **Total Illness Burden Index (TIBI)***	133	5.8	Corre at ons w th outcomes tested n s ng e cohort n or g na paper. Not compared w th any other sca es	None	Pearson's *r* for corre at on w th g oba sever ty measure: phys ca funct on= -0.55 (*P*<0.001); ro e funct on ng due to phys ca hea th= -0.54 (*P*<0.001); og(d sab ty days)=0.43 (*P*<0.001); og(phys c an v s ts)=0.28 (*P*<0.001); og(hosp ta sat ons)=0.15 (*P*<0.001)

eTable 10: Usage, validation and performance of multimorbidity indices – Indices with external validation

Publication and name of index	Citations since publication	Citations per year[7]	Validation and/or comparison	Predictive accuracy measurement in original paper	Performance (original outcomes)	Additional outcomes tested in external validation
Wei 2016 [125] **Multimorbidity Weighted Index (MWI)**	22	11.0	Interna y va dated through bootstrapp ng and cross-va dat on to test we ght ng. Tested for spec f c outcomes n fo ow-up paper by same author group. 157] Not compared to another mode	None	Externa y va dated n 20,509 part c pants of the Hea th and Ret rement Survey. Mean (SD) age 64.7 (10.7) years, 54.1% women. On mu t var ab e regress on, adjusted β for each po nt ncrease n MWI: phys ca funct on ng score= -3.73 (95% CI -3.84 to -3.62), gr p strength= -0.27kg (-0.32 to -0.22), ga t speed= -0.29m/s (-0.35 to -0.23), TICS-m score= -0.06 (-0.07 to -0.04) [157]	None
Dong 2013 [146] **Pharmacy-Based Disease Indicator (PBDI)**	18	3.6	Pred ct on of hosp ta sat on compared w th Char son-Deyo ndex n separate samp e n or g na paper. Compared to med cat on and cond t on counts n subsequent paper by d fferent authors.[158]	D scr m nat on: C-stat st cs and IDI. Ca brat on: Br er score. Compared performance w th Char son-Deyo us ng net rec ass f cat on mprovement (NRI)	C-stat st cs for one-year hosp ta sat on: a) n or g na paper: PBDI=0.72 (adjusted for age + sex), Char son-Deyo=0.69 (adjusted for age + sex).[146] b) In va dat on paper (449,715 French workers, approx mate y 52% fema e): PBDI=0.68 (ad usted for age + gender), ad usted cond t on count=0.64, a ternat ve med cat on ndex (Ind v dua Chron c Cond t on score)=0.68 [158]	One-year morta ty. C-stat st cs for one-morta ty PBDI=0.90 (adjusted for age + gender), ad usted cond t on count=0.90, a ternat ve med cat on ndex (Ind v dua Chron c Cond t on score)=0.89 [158]
Bernabeu-Wittel 2011 [142] **PROFUND**	133	19.0	Compared w th Char son-Deyo ndex (w th and w thout age ad ustment) n separate va dat on cohort n or g na paper. Va dated n four subsequent	Ca brat on: compared ndex-pred cted to observed morta ty. D scr m nat on: ROC curves for f na mode n der vat on and va dat on sets	AUCs (95% CI) for one-year morta ty n or g na paper: PROFUND=0.73 (0.71 to 0.76), Age-adjusted Char son-Deyo=0.62 (0.59 to 0.65).[142] AUCs for four-year morta ty: a) n 768 peop e w th mu t morb d ty (45.3% women, mean (SD) age 78.8 (9.8) years) PROFUND=0.71 (0.67 to 0.77), Age-ad usted Char son-Deyo=0.61 (0.56 to 0.67) [159]	Unp anned hosp ta sat on. In 1,033 card o ogy npat ents, mean (SD) age 67 (13.1) years 35.1% women, HR for morta ty=1.13 (1.01-1.27) and e ther morta ty or hosp ta sat on=1.09

[7] Citations per full year since publication according to Google Scholar, as at 7th September 2019

Publication and name of index	Citations since publication	Citations per year[7]	Validation and/or comparison	Predictive accuracy measurement in original paper	Performance (original outcomes)	Additional outcomes tested in external validation
			papers, three of wh ch nc uded an or g na author.[159–161]		b) n 441 peop e w th mu t morb d ty (mean (SD) age 80.9 (8.7) years, 55.6% women) 160] PROFUND n nterna med c ne=0.75 (0.69-0.81), Ger atr c med c ne=0.52 (0.37 to 0.67). C-stat st c for one-year morta ty n 333 nterna med c ne pat ents w th mu t morb d ty (mean (SD) age 79.3 (9.0) years, 50.3% women)=0.73 (0.67 to 0.78), 132 ger atr c med c ne pat ents w th mu t morb d ty (mean (SD) age 84.6 (7.1) years, 65.0% fema e)=0.55 (0.45 to 0.64) [161]	(1.01-1.18), both at 12 months.[162]
Mukherjee 2011 [129] **Health-Related Quality of Life Comorbidity Index (HRQL-CI) ***	32	4.6	Interna va dat on w th 10-fo d cross-va dat on. Compared w th Char son ndex n separate va dat on cohort n or g na paper. Va dated n two subsequent papers, one by separate authors [163]	Ca brat on: corre at on between observed and pred cted MCS or PCS	Corre at on between observed and pred cted a) PCS: HRQL-CI=0.57, Char son=0.38 b) MCS: HRQL-CI=0.37, Char son=0.11. D scr m nat on of mu t p e outcomes assessed among 9,832 pat ents w th type 2 d abetes (mean (SD) age 44.8 (11.6) years, 73.1% fema e) n externa va dat on paper.[164] HRQL-CI phys ca =0.66 (0.65 to 0.68), HRQL-CI menta =0.66 (0.64 to 0.68). In 13,289 adu ts w th d abetes (mean (SD) age 60.5 (13.7) years, 49.0% fema e), ad usted R^2 for pred ct ng a) PCS: HRQL-CI=29.1 (27.5 to 30.6), Char son=19.1 (17.6 to 20.5), E xhauser=21.1 (19.6 to 22.4), CDS=26.3 (24.7 to 27.7) b) MCS: HRQL-CI=15.0 (14.3 to 17.4), Char son=5.6 (4.7 to 6.6), E xhauser=14.3 (12.8 to 15.8), CDS=14.7 (13.3 to 16.2) [163]	Hea thcare costs, med cat on adherence, hosp ta sat on and outpat ent attendance. C-stat st cs for hea thcare costs: Char son=0.64 (95% CI 0.62 to 0.66), E xhauser=0.70 (0.68 to 0.71), CDS=0.65 (0.64 to -0.67).[164]
George 2006 [147] **Medication-based Disease Burden Index (MDBI)**	44	3.7	Compared w th Chron c D sease Score and Char son ndex on s ng e cohort n or g na paper. Later va dat on papers by d fferent authors	Tested pred ct ve va d ty us ng odds rat os for outcomes	At pred ct ng death and hosp ta readm ss on, ORs (95% CI): MDBI=4.7 (1.4 to 15.5), CDS=1.13 (1.0 to 1.3), Char son=1.4 (1.2 to 1.7). In externa va dat on on 212 acute ger atr c npat ents, mean (SD) age 81 (7.3) years, 62% fema e, pred ct on of three-month morta ty or readm ss on: MDBI=2.99 (0.99 to 9.03), CIRS-G=1.2 (1.1 to 1.3), Char son ndex=1.39 (1.12	Se f-rated hea th. Reported as a stat st ca y s gn f cant assoc at on between MDBI scores and decreas ng se f-rated hea th (P<0.001) [166]

Publication and name of index	Citations since publication	Citations per year[7]	Validation and/or comparison	Predictive accuracy measurement in original paper	Performance (original outcomes)	Additional outcomes tested in external validation
			compared to CIRS-G, Char son and cond t on count [165] and tested assoc at on w th morta ty and se f-rated hea th [166]		to 1.72), chron c d sease count=1.22 (1.08 to 1.38).[165] In 776 cohort study part c pants (mean age 83.5 years, 58% fema e), adjusted HR for morta ty=3.69 (95% CI 2.26-6.02) [166]	
Lee 2006 [9] *	656	54.7	Tested w th n or g na paper on separate va dat on cohort and by or g na authors n ten-year fo ow-up. 167] Subsequent va dat on by d fferent authors compared to Char son ndex [168]	Ca brat on: compared pred cted w th actua morta ty n der vat on and va dat on cohorts. D scr m nat on: ROC curves n der vat on and va dat on cohorts	C-stat st cs for four-year morta ty: deve opment cohort=0.84, va dat on cohort=0.82. In fo ow-up of or g na part c pants for pred ct ng ten-year morta ty, C-stat st c (va dat on cohort)=0.83 (0.82 to 0.84) [167] Externa va dat on tested ten-year morta ty n 735 pat ents undergo ng rad ca cystectomy (med an age 67 years): HR (95% CI) per un t ncrease n nd ces: Lee=1.06 (1.00 to 1.12, *P*=0.04), age-ad usted Char son=1.08 (1.02 to 1.15, *P*=0.01).[168]	None
Bayliss 2005 [132] **Disease Burden Morbidity Assessment * (DBMA)**	200	15.4	Compared survey resu ts w th Char son and RxR sk nd ces n s ng e cohort n or g na paper. Va d ty tested n three subsequent papers by d fferent authors [169–171]	D scr m nat on: C-stat st cs for se f-reported d seases on y, not overa score	For overa hea th status score as outcome n or g na paper, Spearman corre at ons DBMA=0.60 (*P*<0.001), Char son=0.48 (*P*<0.001), RxR sk=0.17 (*P*=0.037). 132] In subsequent paper (307 part c pants, mean age 59 years), Cronbach's a pha for nterna cons stency of the tota DBMA score=0.69.[169] Subsequent va d ty paper created a near measure n 1,747 adu ts aged over 50 years. Spearman's corre at ons w th: phys ca funct on ng= −0.48, perce ved hea th=−0.47, depress on (score ≥3 on CES-D-10)=0.32, qua ty of fe −0.24 [171]	Morta ty. F ve-year morta ty va dat on n 625 commun ty-dwe ng adu ts aged ≥65 years for h gher compared to ower DBMA scores HR=1.07 (95% CI 1.00–1.15, *P*=0.044) [170]

Publication and name of index	Citations since publication	Citations per year[7]	Validation and/or comparison	Predictive accuracy measurement in original paper	Performance (original outcomes)	Additional outcomes tested in external validation
Pope 2004 [152] **The Centers for Medicare and Medicaid Services' Hierarchical Condition Category (CMS-HCC) ***	731	52.2	In s ng e cohort n or g na paper, compared to r sk adjustment mode PIP-DCG. Eva uated pred cted versus actua costs n subsequent papers by externa groups 172,173] and report by or g na authors [174]	Ca brat on: Tests of pred cted versus actua costs; pred ct ve rat os g ven	In or g na paper, R^2 for one-year expend ture: age-sex mode 1.0%, PIP-DCG 6.2%, DCG/HCC 11.2%.[152] Among 1,441,247 Med care benef c ar es, rat o of pred cted to actua hea thcare costs n a age and gender groups=1.000 [174]	Morta ty. In 170,342 pat ents adm tted to hosp ta (mean age 78 years, 60% fema e), C-stat st cs for s x-month morta ty: CMS-HCC=0.72 (*P*>0.05), Char son=0.71 (*P*<0.05), E xhauser=0.70 (*P*<0.05) [172] Hosp ta sat on In 83,187 managed care pat ents w th mean age 46.9 years, 54.6% fema e, c-stat st c for pred ct ng hosp ta sat on=0.67, emergency v s ts=0.58 [173]
Sangha 2003 [133] **Self-Administered Comorbidity Questionnaire * (SCQ)**	966	64.4	In s ng e samp e n or g na paper, tested corre at on w th Char son ndex. Va dated n two ater papers by d fferent authors [175,176]	None	In or g na paper, Spearman coeff c ents for a) corre at on between SCQ and Char son ndex=0.32 (0.55 when truncat ng to conta n on y comparab e tems); b) number of prescr pt ons at one year, SCQ=0.37, Char son=0.02; c) frequency of doctor v s ts: SCQ=0.15, Char son=0.09. R^2s for a) PCS at one year: Char son="non-s gn f cant", SCQ=0.22 (69.3% var at on exp a ned by comorb d ty); b) MCS: SCQ and Char son both "non-s gn f cant". [133] In externa va dat on of 525 pat ents after acute coronary syndrome (mean (SD) age 59.7 (12.0) years, 36.4% fema e), R^2 for EQ-5D scores at e ght months: Char son=0.25 (*P*=0.132), SCQ=0.27 (*P*<0.001); Act v ty Status Index, a measure of phys ca funct on, at e ght months:	None

Publication and name of index	Citations since publication	Citations per year[7]	Validation and/or comparison	Predictive accuracy measurement in original paper	Performance (original outcomes)	Additional outcomes tested in external validation
					CCI=0.37 (*P*<0.001), SCQ=0.36 (*P*<0.001).[175] In 98 outpat ents w th anky os ng spondy t s (mean (SD) age 53.9 (11.4) years, 29.6% fema e), Spearman coeff c ents for a) corre at on between SCQ and Char son=0.24; b) PCS: SCQ= -0.45, Char son= -0.17; b) MCS: SCQ= -0.10, Char son=0.09 [176]	
Parkerson 1993 [137] **Duke Severity of Illness Checklist (DUSOI)***	193	7.7	Compar son between c n c ans rat ngs and aud tor for nter-rater re ab ty n s ng e samp e n or g na paper. Not compared to another sca e. Pred ct on of one-year hea thcare usage tested n ater paper by same authors [177]	None	Intrac ass corre at on coeff c ents (ICC) of agreement for prov der-comp eted ana ogue sca e of overa ness sever ty for: DUSOI prov der overa sever ty scores=0.61 (*P*<0.001); DUSOI aud t check st scores=0.42 (*P*<0.001). Externa va dat on tested nter-rater re ab ty n 14 sets of records by 33 c n c ans 178]: ICC=0.43 (95% CI 0.27 to 0.61).	Hea thcare usage. In 1,202 pr mary care pat ents (mean (SD) age 47.6 (16.6) years, 65.0% fema e), ad usted R^2 var ance exp a ned by DUSOI n a hea thcare v s ts =0.05.[177]
Von Korff [148] **Chronic Disease Score***	942	36.2	Compared w th phys c an rated sever ty sca e n p ot samp e and separate random samp e. Compared w th ADGs for cost pred ct on n ater paper by the same authors [179]	None	In or g na paper, Pearson corre at on between CDS and phys c an-rated phys ca d sease sever ty n p ot samp e (n=219) *r*=0.57, n second samp e (n=722) *r*=0.46.[148] A so used as comparator when deve op ng severa other nd ces [123,129,147]	Hea thcare costs. In ater paper exam n ng 254,694 managed care enro ees (no demograph cs ava ab e), ord nary east squares regress on R^2s exp a n ng var ance n s x-month tota cost for age and sex=0.02, CDS ad usted for age and sex=0.09, ADGs ad usted for age and sex=0.19 and rev sed

Publication and name of index	Citations since publication	Citations per year[7]	Validation and/or comparison	Predictive accuracy measurement in original paper	Performance (original outcomes)	Additional outcomes tested in external validation
						CDS (d fferent we ght ng method) ad usted for age and sex=0.19 [179]
Starfield 1991 [153] **Ambulatory Care Groups***	574	21.3	In or g na paper, compared d str but on of d agnost c groups n subsamp es from across f ve hea thcare prov ders. Severa externa va dat ons by d fferent authors test ng cost pred ct on, hea thcare use and morta ty [180]	None	In or g na paper, for pred ct ng one-year tota costs, adjusted R^2s: age group + sex=0.04, age group, sex, b nary ADG=0.19, 51 ACGs=0.15.[153] Mu t p e externa rev ews n d fferent sett ngs test ts pred ct ve va ue.[180] In one cohort of 59,384 Med ca d members (no demograph cs g ven), AUC for 90th percent e of costs: Chron c ness and d sab ty payment system (CDPS)=0.69 (95% CI 0.67 to 0.70), d agnost c cost groups (DCG)=0.75 (0.74 to 0.76), ACG-PM vers on 7.0 (ad usted c n ca groups- pred ct ve mode [an adaptat on])=0.79 (0.78 to 0.80).[181]	Morta ty. In popu at on of 10,498,413 adu ts (med an age 46 (IQR 34-59) years, 51% women), one-year morta ty C-stat st cs: age + sex=0.88, Char son=0.91, 32 ADGs=0.87, age, sex + 32 ADGs=0.92 [182]
Charlson 1987 [120] **Charlson Index***	29408	948.6	Tested w th n or g na paper on separate va dat on cohort. Compared w th Kap an-Fe nste n method. Extens ve y va dated and used e sewhere by d fferent authors, often as comparator when generat ng new nd ces	D scr m nat on: Kap an-Me er p ots of morta ty w th d ffer ng ndex eve s compared to Kap an-Fe nste n method	W th n or g na paper, RR for one-year morta ty for: ncreas ng Char son ndex by 1 po nt=2.3 (95% CI 1.9-2.8), each decade of age=2.4 (2.0-2.9) In surv va ana ys s, var ance exp a ned: Char son=0.41, Kap an-Fe nste n=0.41.[120] A so used as comparator for many other nd ces sted n th s tab e [1,3,4,5,7,10,11,32,35,40,41,47,49,60]	Severa other outcomes tested nc ud ng HRQL, med cat on use, ength of hosp ta stay, readm ss on [117]
Linn 1968 [154] **Cumulative Illness**	1863	37.3	Va dat on br ef y ment oned n or g na paper.	None	Or g na study reports that "tota scores corre ated w th death, v ta organ nvo vement,	In study of 181 ger atr c npat ents (mean (SD) age 79 (7.4) years),

Publication and name of index	Citations since publication	Citations per year[7]	Validation and/or comparison	Predictive accuracy measurement in original paper	Performance (original outcomes)	Additional outcomes tested in external validation
Rating Scale (CIRS) *			Externa y va dated n severa p aces by d fferent authors [183–186]		number of prev ous nesses at P<0.01" (but not age) w th no further deta s.[154]	corre at ons between or g na CIRS and act v t es of da y v ng *r*=-0.49 (*P*<0.001), pat ent mora e= -0.30 (*P*<0.001), days n hosp ta =0.21 (*P*=0.001), number of med cat ons=0.31 (*P*<0.001).[183] In compar son of 238 adu ts n pr mary care (mean (SD) age 59.0 (14.3) years, 71.0% fema e), Pearson corre at on coeff c ents for PCS: CIRS= -0.54 (*P*<0.01), Char son= -0.31 (*P*<0.01).[186] In 103 npat ents aged 90-99 years (mean age 92 years, 71% fema e), CIRS corre ated w th ength of hosp ta stay, Pearson s *r*=0.4, *P*<0.05.[185] Among 439 res dents of a care fac ty w th mean (SD) age 84.1 (5.7) years, 72.4% fema e, CIRS corre ated w th funct ona d sab ty accord ng to Phys ca Se f-Ma ntenance Sca e *r*=0.322 (*P*=0.001) and tota number of med cat ons (*r*=0.301).[184]

* Indices that have an updated or modified version available

Abbreviations in eTables 9 and 10:
APR-DRGs: A Pat ent Ref ned D agnos s Re ated Groups
AUC: Area under the Curve
CDS: Chron c D sease Score
CES-D: Center for Ep dem o og c Stud es Depress on sca e
CI: Conf dence nterva
CIRS-G: Cumu at ve I ness Rat ng Sca e – Ger atr c
EQ 5D: EuroQo f ve-d mens on measure of hea th status
EQ VAS: EuroQo -v sua ana ogue sca e
HR: Hazard rat o
HRQL: Hea th-re ated qua ty of fe
IDI: Integrated d scr m nat on mprovement
mFI: Mu t morb d ty Fra ty Index
mHCC: Mod f ed H erarch ca Cond t on Categor es
mCCI: Mod f ed Char son Comorb d ty Index
MCS: Menta Component Score of SF-36
NEADL: Nott ngham Extended Act v t es of Da y L v ng Sca e
NRI: Net rec ass f cat on mprovement
OR: Odds rat o
PCS: Phys ca Component Score of SF-36
PIP-DCG: Pr nc pa Inpat ent D agnost c Cost Group Mode for Med care R sk Ad ustment
QOF: Qua ty and Outcomes Framework
ROC: Rece ver Operat ng Character st c
RR: R sk rat o
RxR sk: A rev s on and expans on of the Chron c D sease Score (w th and w thout Veterans adaptat on)
TICS-m: Mod f ed Te ephone Interv ew for Cogn t ve Status

eTable 11: Index updates and adaptations

Publication and name of index	Updates or adaptations	Aim compared to original index	Details	Performance or comparison
Mukherjee 2011 [129] **Health-Related Quality of Life Comorbidity Index (HRQL-CI)**	Ou 2016 [187]	Measur ng hea th-re ated qua ty of fe (same as or g na)	Comb nes phys ca and menta subsca es of or g na measure nto one sca e	Regress on coeff c ents for a) genera hea th: ref ned HRQL-CI=0.25, Char son=0.10 b) SF-6D: ref ned HRQL-CI=0.25, Char son=0.09; c) EQ-5D: ref ned HRQL-CI=0.28, Char son=0.06
Newman 2008 [150] **Physiologic Index of Comorbidity**	Mod f ed Phys o og c Index [188]	Pred ct ng morta ty (same as or g na)	Adapted to nc ude more eas y ava ab e measures n ep dem o og ca stud es. Parameters: systo c b ood pressure, forced v ta capac ty, D g t Symbo Subst tut on Test score, serum cystat n-C, serum fast ng g ucose	C-stat st cs for morta ty (mean fo ow-up 9.3 years): Unadjusted ndex=0.66 (95% CI 0.64 to 0.68), Age a one=0.59 (0.57 to 0.61), Index + age=0.67 (0.65 to 0.69)
	Hea thy Ag ng Index [189]	Pred ct ng morta ty (same as or g na)	Adapted for use n ep dem o og ca stud es. Components nc ude: systo c b ood pressure, pu monary v ta capac ty, creat n ne, fast ng g ucose, and Mod f ed M n -Menta Status Exam nat on (MMSE) score	C-stat st cs for morta ty (med an fo ow-up 12.8 years): ndex a one=0.64 (0.63 to 0.66), age a one=0.70 (0.68 to 1.72)
Lee 2006 [9]	Kobayash 2016 [190]	Pred ct ng ten-year morta ty (compared to four n or g na ndex)	We ghted to pred ct ten-year morta ty. Ass gns d fferent we ghts to age, nc udes a var ab e on ack of phys ca act v ty. Exc udes some var ab es from or g na ndex (d abetes, BMI<25 kg/m^2, d ff cu ty bath ng)	AUC for ten-year morta ty n va dat on cohort, w th new ndex=0.84, w th or g na ndex=0.81
Bayliss 2005 [132] **Disease Burden Morbidity Assessment**	Bay ss 2009 [191]	Pred ct ng genera hea th/d sease burden (same as or g na)	Inc uded 21 cond t ons nstead of or g na 25 (exc udes ver d sease, k dney d sease, a coho sm, nerve cond t ons)	Corre at on coeff c ents w th Char son-Quan=0.23 (*P*<0.001) and CDS=0.26 (*P*<0.001)
	Po tras 2012 [192]	Pred ct ng genera hea th/d sease burden (same as or g na)	Added depress on to 2009 adaptat on cond t ons and trans ated nto Canad an French	Compared w th CIRS two weeks after n t a assessment, Pearson corre at on coeff c ent=0.56 (0.38 to 0.70, *P*<0.01)
Pope 2004 [152] **The Centers for Medicare and Medicaid Services'**	Regu ar updates [193]	Pred ct ng hea thcare expend ture (same as or g na)	Updated annua y w th amended ICD-10 mapp ngs and software	Regu ar reports; 2018 report sts deta ed pred ct ve expend ture accuracy for comb nat ons of cond t ons of CMS-HCC.[69] Rat o of one-year pred cted to actua

Publication and name of index	Updates or adaptations	Aim compared to original index	Details	Performance or comparison
Hierarchical Condition Category (CMS-HCC)				expend ture=1.00 (but g ves caveat that th s s an average n a very arge group)
Sangha 2003 [133] **Self-Administered Comorbidity Questionnaire**	Hudson 2008 [194]	Pred ct ng hea th-re ated qua ty of fe (nc uded n or g na)	Adapted for peop e w th system c auto mmune d seases: removed rheumato d arthr t s from cond t on st	Kenda s Tau b corre at on between SCQ and a) PCS: System c sc eros s= -0.26, system c upus= -0.31 b) MCS: System c sc eros s= -0.14, system c upus= -0.12
	Sr dharan 2014 [195]	Pred ct ng morta ty (d fferent from or g na)	Adapted for pat ents w th end-stage rena d sease: added e ght preva ent cond t ons n th s group and space for free-text answers; removed quest on on k dney d sease	AUC for 18-month morta ty: mod f ed SCQ=0.72 (0.65 to 0.80), Char son=0.75 (0.68 to 0.82)
Desai 2002 [134] **High-Risk Diagnoses for the Elderly Scale (HRDES)**	Burden of I ness Score for E der y Persons (BISEP) [196]	Pred ct ng morta ty (same as or g na)	Added serum a bum n and creat n ne, dement a and wa k ng mpa rment to ten we ghted cond t ons from HRDES	C-stat st cs for one year morta ty n va dat on cohort: HRDES=0.59, BISEP=0.77
Greenfield 1995 [136] **Total Illness Burden Index (TIBI)**	TIBI-P [197]	Pred ct ng hea th-re ated qua ty of fe (same as or g na) and morta ty (d fferent)	Mod f ed for men w th prostate cancer. Reduced doma ns on some tems, nc uded d abetes and non-prostate cancers	R^2 for PCS: ad usted TIBI-P=0.35, demograph cs a one=0.16. 3.5-year morta ty: adjusted HR for h ghest scor ng group compared to owest=13.1 (6.3 to 27.4) [198]
Parkerson 1993 [137] **Duke Severity of Illness Checklist (DUSOI)**	Duke Case-M x System (DUMIX) [199]	Pred ct ng hea thcare expend ture (d fferent from or g na)	Adds demograph c nformat on and se f-reported funct ona hea th status to DUSOI	Var ance n future c n c charges exp a ned by DUMIX=17.1%, age + gender a one=9.1%
Von Korff 1992 [148] **Chronic Disease Score**	Rx-R sk [200]	Pred ct ng hea thcare expend ture (hea thcare use nc uded n or g na)	We ghted drug groups ncreased to 57 from 25 n CDS. Inc udes ch dren. W de y used and va dated	In or g na paper, cost var ance exp a ned (R^2): RxR sk=8.7%, CMS-HCCs=15.4%, ACGs=10.2%. In ater va dat on, C-stat st cs for one-year morta ty: we ghted RxR sk=0.79 (0.78 to 0.79) [201]
	Rx-R sk-V [202]	Pred ct ng hea thcare expend ture (hea thcare use nc uded n or g na)	Adapted for use n veteran popu at on and updated to nc ude newer drugs. Inc udes 45 drug c asses	Or g na paper quotes var ance exp a ned (R^2) for concurrent costs=0.18 and prospect ve costs=0.10. Compared to other sca es n or g na Far ey paper (see eTab e 9) [151]

Publication and name of index	Updates or adaptations	Aim compared to original index	Details	Performance or comparison
	McGregor 2006 [203]	Pred ct ng spec f c d agnoses (d fferent from or g na)	Adaptat ons for nosocom a nfect ous d seases: MRSA and VRE. Comb ned ndex (CDS-ID) conta ns s x cond t ons	C-stat st cs for pred ct ng MRSA d agnos s: CDS-ID=0.57, CDS=0.52; for pred ct ng VRE d agnos s: CDS-ID=0.64, CDS=0.57
Starfield 1991 [153] **Ambulatory Care Groups**	Regu ar ongo ng updates [204]	Pred ct ng hea thcare expend ture (same as or g na)	Updates to d sease markers, v s t c ass f cat ons and software. Vers on 12.0 re eased March 2019	See eTab e 10
Charlson 1987 [120]	Deyo 1992 [205]	Pred ct ng morta ty (same as or g na) and other outcomes	A gned cond t ons w th ICD-9 codes. Comb ned eukaem a/ ymphoma w th other ma gnanc es g v ng 17 cond t ons	Used as comparator n other stud es – see eTab es 9 and 10
	Romano 1993 [206] (Dartmouth-Man toba)	Pred ct ng morta ty (same as or g na)	Adapted for use w th adm n strat ve data us ng ICD-9-CM codes; broader def n t ons than Deyo	Compared to other sca es n or g na Far ey paper (see eTab e 9) [151]
	D Hoore 1993 [207]	Pred ct ng morta ty (same as or g na)	Uses f rst three d g ts of ICD-9	In th s paper, C-stat st c for n-hosp ta morta ty=0.83
	Gha 1996 [208]	Pred ct ng morta ty (same as or g na)	Ass gns new we ghts to Deyo s system, accord ng to study-spec f c morta ty. Inc udes on y f ve cond t ons	In th s paper, C-stat st c for n-hosp ta morta ty=0.74, or g na Char son ndex=0.70
	Quan 2005 [209]	Pred ct ng morta ty (same as or g na)	Adapted for ICD-10, nc udes 12 cond t ons. Later rev s on ass gns new we ghts to cond t ons [210]	In th s paper, C-stat st cs d scr m nat ng n-hosp ta morta ty n one cohort: Quan=0.83, or g na Char son=0.81
Linn 1968 [154] **Cumulative Illness Rating Scale (CIRS)**	CIRS-G [211]	Pred ct ng overa ness sever ty (same as or g na) and funct ona mpa rment (d fferent)	Mod f ed for o der popu at on. Added haematopo et c category, c ar f ed where to st dement a and breast d sorders. On ne ca cu ators ava ab e w th examp es [212]	W de y used. Th s paper reports Spearman corre at on between CIRS-G and a) OARS ADL=0.58 (P<0.02) and b) ncreas ng overa med ca mpa rment=0.45 (*P*=0.002)
	CIRS-SA [213]	Pred ct ng overa ness sever ty (same as or g na)	Substance abuse vers on. Has 13 tems nc ud ng HIV status and gu dance on where to record hepat t s. Removed psych atry category	Cronbach s coeff c ent for nterna cons stency=0.57. Kenda s tau for agreement between overa CIRS-SA and consu tant assessment of ness sever ty=0.58 (*P*<0.01)
	M stry 2004 [214]	Pred ct ng morta ty (d fferent from or g na)	Two subsca es, nc ud ng (CIRS-IP) and exc ud ng (CIRS-PH) acute cond t ons	Cox proport ona hazards regress on for age-adjusted days of surv va , standard sed β CIRS-IP=0.55 (0.14-0.96), CIRS-PH=0.70 (0.28-1.11)

Abbreviations in eTable 11:
AUC: Area under the curve
BMI: Body mass ndex
EQ-5D: EuroQo f ve-d mens on measure of hea th status
ICD-9-CM: Internat ona C ass f cat on of D seases, N nth Rev s on, C n ca Mod f cat on
ICD-10: Internat ona Stat st ca C ass f cat on of D seases and Re ated Hea th Prob ems 10th Rev s on
MCS: Menta Component Score of SF-36
MRSA: Meth c n-res stant *Staphylococcus aureus*
OARS ADL: O der Amer cans Resources and Serv ces Act v t es of Da y L v ng Sca e
PCS: Phys ca Component Score of SF-36
SF-6D: Shortened rev sed vers on of SF-36
VRE: Vancomyc n-res stant enterococc

Appendix lay summary - "Ways of measuring multiple conditions"

Title of research article: *Measuring multimorbidity beyond counting diseases: systematic review of community and population studies and guide to index choice.*

This research is funded by the Medical Research Foundation and the Medical Research Council through a grant to Dr Lucy Stirland.

What is a systematic review?

A systematic review is a common type of research. It's a way of finding lots of published research articles and summarising them together.

What do we know about this topic already?

It's common for people to have two or more chronic conditions at once. This is often called multimorbidity. Researchers and clinicians measure multimorbidity in many different ways.

What questions does this review ask?

1. What methods exist for measuring multimorbidity?
2. How good are they?
3. Do they include mental health?

How was the search carried out?

We decided in advance which topics to include. In October 2018, we searched seven online medical research databases. Two researchers separately checked 5,560 article titles. We discarded irrelevant articles.

What did the review find?

We ended up with 35 papers, each describing a way to measure multimorbidity. Most of them combined the number of chronic conditions with other things like age. Some counted people's prescribed drugs and others included medical test results.

Most of the tools aimed to predict health in some way. For example, 18 of them looked at death rates, 13 at hospitalisations and six at quality of life.

Nearly all the papers considered mental health, with 18 counting it as part of multimorbidity. Eleven measures aimed to predict some aspect of mental health.

Only one paper mentioned including patients in their research design.

How good were the papers?

We graded each paper according to set standards. Six were high quality, 22 were satisfactory and seven were low quality. Three of the papers didn't mention who funded their research. Four were funded by drug companies – this might make them biased. The other 28 papers had no funding bias.

What does this mean for patients?

These tools might help make other research more relevant to people with multiple conditions. For example, drug trials use very healthy people who are not like most patients. Researchers could use these tools to account for multimorbidity in a wider range of people.

Healthcare officials can also use the tools to predict how services will be used and plan how to fund them.

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2.4 FURTHER DISCUSSION

Of the 35 indices found, we recommended 12 which would be most relevant for use in research. As emphasised in the paper, it is crucial to take into account the population in question and the outcomes of interest when employing an index. I detail further limitations and issues that were not covered in the paper in the rest of this chapter.

2.4.1 Terminology

My search strategy included a variety of synonyms for multimorbidity in order to capture as many relevant papers as possible. This could have introduced ambiguity, however, as there may be nuances of meaning between terms. For example, the term 'polypathology' is linked to the French expression *polypathologie en cascade.* This concept suggests a number of conditions that flow from an original index condition, also known as concordant multimorbidity.[2] However, when reviewing the final papers this was not an evident issue as they all used the terms multimorbidity, comorbidity and polypathology to denote the same state or concept.

Throughout the paper, I used the term 'multimorbidity' even when some indices referred to themselves as comorbidity indices.[120,123,150,151,129,132,133,135,137,141,143,146] I had included 'comorbidity' as a search term as it is sometimes used to mean multimorbidity.[2] In a paper published by Dutch primary care researchers in 1996, there was a call to differentiate between comorbidity (implying the presence of an index disease) and multimorbidity (the general state of having multiple conditions).[2] However, even in

papers published since then, there continued to be instances where the word comorbidity was used to mean both.[215] In addition, I uniquely used the term 'index' for consistency, as suggested by a peer reviewer, where some of the papers did not technically generate an index and would be better described as a tool, measure or model. Four papers compared several models [127,143,144,151] and one was mostly designed around information gathering rather than quantifying multimorbidity.[139] These dissimilarities in terminology may have led to some papers being considered in line with weighted indices when they were not intended to be used in this way.

Another terminology issue is that one index included is titled the Multimorbidity Frailty Index, but does not measure frailty.[138] It counts 'deficits', which are usually included in definitions of frailty, but the 'deficits' mentioned are actually conditions, so it measures multimorbidity alone. Although the concepts of multimorbidity and frailty have some overlap, as explained in section 1.2.7, they measure different states and are not equivalent.[216] This is a limitation of that particular paper, rather than my work.

2.4.2 Search limitations

2.4.2.1 Contemporaneity

As with all systematic reviews, conducting a formal literature search and screening all the resulting titles means that research published after the search date is missed. This is a particular risk in such a dynamic and growing research field as multimorbidity. I originally submitted the paper to *The BMJ* in July 2018 based on a search conducted in August 2017. The first round of editorial board review recommended an updated search, so I ran the search again using the same strategy in October 2018. Since then, however, there have been at least two papers published presenting new indices, despite the field being seemingly saturated already.

In the first of these new papers, Constantinou and colleagues proposed two new indices, the Mortality-Related Morbidity Index (MRMI) and the Expenditure-Related Morbidity Index (ERMI).[217] These include 16 conditions, gender and age, all

weighted based on the outcomes stated in the name of each index. Secondly, Quinzler et al. developed a medication-based Chronic Disease Score (medCDS) using drugs as markers for common chronic conditions and weighting them according to their coefficients for association with mortality.[218]

The Cambridge Multimorbidity Score is another new index.[219] It includes 37 weighted conditions and was designed around three outcomes: primary care consultations, unplanned hospital admissions and mortality. Each of these outcomes carries its own weights in the index. The heterogeneity between indices' derivation and use of weighting is further discussed in Chapter 3.

A new solution to the issue of review searches becoming dated quickly is the living systematic review approach, which usually involves monthly updated searches and combines human paper selection with machine automation.[220] This would not have been feasible within the scope of this PhD but is a promising technique for the future of systematic reviews.

2.4.2.2 Limitations in search terms

My search strategy did not find the Multimorbidity Interaction Severity Index, published in 2017, which is described as a web-based decision support tool, designed for use with individual patients.[221] The search terms referring to community or population studies may have obscured this reference from emerging during the search, and it was not found in the citation searching. This index could be practical as the majority of multimorbidity indices are best used in research or service planning rather than with individual patients.[222] In addition, a team of Canadian primary care researchers has developed a new questionnaire for gathering information from patients which would be useful in practice and was also not found by our search.[223] It has some general similarities to two tools that were included so would have met inclusion criteria.[133,139]

I used the expression ‘rating scale’ in my search terms so may have missed tools that used the word ‘scale’ alone. I also did not include the term ‘score’ in my search strategy. This may have led to me missing the Complexity Score, which includes a count of conditions and medications, but it is published in a journal that is not indexed in MEDLINE so would probably not have appeared in the search.[224] The article does not describe the list of conditions or medications from which the counts were derived.

The MeSH term ‘multimorbidity’ was launched in January 2018, after my search strategy had been developed and pre-registered, so I did not use it; it should be included in future searches.[24]

2.4.2.3 Research published in ‘predatory’ journals

When reviewing citations, I came across the Institutionalization Comorbidity Index, which used prescription data to predict institutionalisation and was derived from a population of 61 172 community-dwelling older adults in Québec.[225] Although the paper was written by a bona fide group of pharmacy researchers, it was published in the *Journal of Gerontology & Geriatric Research*. This is one of many journals published by OMICS International, which is widely understood to be a predatory publisher with little to no peer review process.[226] The company has been successfully sued for deceptive academic practice by the US Federal Trade Commission.[227] I had not considered the possibility of finding predatory journal articles when designing my search. In discussion with my co-authors and reference to my pre-registered protocol, we agreed to exclude the paper as it did not emerge during formal citation tracking.

As the predatory publishing field grows, there have been new recommendations to screen included papers for the journal’s quality and exclude those from predatory publishers from systematic reviews.[228] While this approach ensures that included papers are thoroughly peer-reviewed, it could also lead to the omission of genuine research unwittingly submitted to these less rigorous journals.

2.4.2.4 Potentially useful excluded indices

Another commonly used tool is that developed by Gagne and colleagues in 2011, which combines elements from the Charlson and Elixhauser indices.[229] The paper did not meet our inclusion criteria as it did not include a novel index, and was additionally not discussed when reviewing updates as it clearly states its objective was to predict mortality by combining the two existing comorbidity indices. However, this index was developed to address the outdated list of conditions in the Charlson index so could be useful in practice.

2.4.2.5 Limitations in assessing risk of reporting bias

It is generally preferable to use a validated pre-existing quality or risk of bias assessment tool, but when planning the review, I searched the literature and did not find one that was suitable. A peer reviewer suggested the comprehensive Prediction model Risk Of Bias ASsessment Tool (PROBAST).[230] This is designed specifically for diagnostic and prognostic prediction models and was therefore not applicable to all the included indices. In addition, it was published after our review was pre-registered. We therefore developed our own list of quality or reporting bias questions based on available resources. We aimed to keep the list relatively concise so that readers could refer to it easily. This approach drew criticism from some peer reviewers, who pointed out that the list included mostly reported details and was less sensitive at detecting bias or assessing quality. We did consider removing mention of the tool, but kept it in accordance with PRISMA recommendations that risk of bias within and across studies be assessed and reported.[115] Instead of using a new tool post-hoc, we included more detail on index development and validation elsewhere in the paper. This allowed in-depth comparisons between the indices' methods and application that would not be as clearly captured using a risk of bias tool.

Our overall recommendations for index use, which were an addition requested by peer reviewers, drew on the risk of bias assessment, generalisability and validation results. However, they had the limitation of being subjective.

2.4.2.6 Further limitations

My search focused only on studies of multimorbidity and excluded those that centred on an index condition. A 2016 systematic review of multimorbidity definitions found that a small number of studies used comorbidity indices, developed around an index disease, that were not designed to measure multimorbidity.[119] When using an index disease, for example studying the comorbidities of patients with coronary artery disease, these people still have multimorbidity but it has been approached from a specific viewpoint. My justification for focusing only on multimorbidity was to include all relevant people, not only those selected due to having a particular diagnosis. Two of the final included studies in my review were developed in populations of people with specific diseases,[136,151] but their focus was on multimorbidity rather than comorbidities alongside these conditions. However, we excluded multimorbidity indices that were developed in a cohort with a specific disease, even if they were later useful for measuring multimorbidity, for example the Index of Co-existent Disease, whose original patients were undergoing total hip replacement.[231] This is a limitation of the resulting list of indices we generated, but our focus was on the methodology and design of original studies, rather than their eventual uses.

We excluded studies that measured multimorbidity within a single disease area. A 2018 analysis of the use of the term ‘multimorbidity’ within the literature found that it was most prevalent within psychiatric publications.[87] Its use there is as a replacement for the previous concept ‘dual diagnosis’, usually referring to the co-existence of substance use disorders with another psychiatric disorder.[232] Using multimorbidity in this context reminds psychiatrists that although patients in drug trials may only have one mental disorder, in reality this is rarely the case. However, studies on multimorbidity within psychiatry usually fail to capture physical comorbidities and as such do not fit with the definition of multimorbidity used elsewhere in research and in this thesis, which refers to the whole person.[232]

It is a limitation common to all systematic reviews that by setting and adhering to specific inclusion and exclusion criteria, occasionally important or prominent studies will be excluded.[113]

2.4.3 Comparison of indices

One peer reviewer suggested conducting a direct comparison of the indices' performance at predicting certain outcomes. This would have been difficult due to the diversity of index components and predicted outcomes. Numerous studies have explored this question, and a systematic review of studies that compared any index to either the Charlson or Elixhauser index found 54 titles; this review is discussed further in section 3.2.5, page 99.[233] I therefore chose not to compare indices as this was not directly linked to my aim of identifying and summarising indices for measuring multimorbidity.

2.4.4 Other relevant recent publications

There have been two recent review articles on measuring multimorbidity, one a detailed narrative review [11] and the other documentation of an expert group discussion and consensus.[114] In the narrative review, Nicholson and colleagues recommended that researchers and clinicians pay attention not only to the original outcomes used in developing indices, but also the population in which they were derived, for example a cohort study or population-based sample.[11] They also highlighted the fact that multimorbidity indices are not usually designed to capture or predict multiple outcomes, and that in fact it may be sometimes be useful to use more than one index for different purposes in a study.[11,186] They considered the measurement of mental health within multimorbidity, which is generally under-researched. The second review was a report from a meeting and survey of 29 Canadian experts on ageing and multimorbidity research.[114] They emphasised that most indices do not address social factors contributing to outcomes for people with multimorbidity, or conditions that vary in severity over time. Similarly to my review, they concluded that there is not a single multimorbidity measure that is universally suitable and that researchers should find one that fits the study purpose and includes an appropriate list of conditions.

2.5 CHAPTER CONCLUSIONS

This chapter has presented a comprehensive review of indices for measuring multimorbidity. The commonest, and often most practical, method of measuring multimorbidity is counting diagnoses. This, along with other methodological issues, and the process of developing my own methods, are discussed in more detail in Chapter 3.

Chapter 3 Methodological issues when measuring multimorbidity

3.1 INTRODUCTION

Chapter 2 consisted of a review of multimorbidity measurement methods. Most papers included in the systematic review used weighted indices, with weights generated in diverse ways. This chapter explores the methods of developing indices in more detail, including their limitations. There are several other ways to quantify multimorbidity. Disease counts are the most commonly used and warrant methodological consideration, for example regarding the length and content of lists of candidate conditions.[112,119] This chapter also outlines alternative data-driven methods such as clustering and network analyses, before concluding with justification of the methods I used in data analysis in Chapters 4, 5 and 6.

3.2 ISSUES WITHIN MULTIMORBIDITY INDICES

3.2.1 Weighting methods

Among the 35 indices studied in the previous chapter, 29 used some form of weighting for the index components, whether they were diseases, drugs or other parameters. Twelve of these used relatively subjective ratings of condition severity, either as decided by clinicians,[136,137,141,148,149,153,154] or reported by patients,[132,133,135] based on previous research,[147] or on abnormality of physiological markers.[150] Depending on the outcome of interest, self-report can be an appropriate weighting method. For example, the Disease Burden Morbidity Assessment (DBMA) asks patients to report which conditions they have from a list of 25, and their relative interference with daily activities.[132] This is relevant to the predicted outcomes, which include self-rated health. Weighting by subjective measures of disease severity was commoner in older papers, whereas more recent indices tended towards more objective models. One older example is the widely-used Chronic Disease Score, developed in 1992 to predict mortality and hospitalisation, which defined its weights based on expert consensus rather than statistical models.[148]

The most common method for deriving weights in indices is to attribute a score for each condition based on its association with the outcome in question. Among indices that used this approach, the majority used regression coefficients for weighting. As listed in eTable 7 of section 2.3, these indices summed the coefficients for each parameter (either raw or rounded to integers) to generate the overall score.[9,10,152,155,123,125,127,129,130,142,145,146] These coefficients were primarily from survival analyses, but as noted on page 30, in some indices, the weights were generated based on cross-sectional analyses and then used to predict longitudinal outcomes.[9,141,147,154] This may limit their validity when used in this way.

Table 3-1 shows an example weighting method: that used in the Charlson Index.[120] For each condition the patient has, the weight for that condition is added to create an overall score. An illustrative patient with dementia, diabetes (with no end-organ damage) and a peptic ulcer would receive a score of 3.

Table 3-1: Weights used in Charlson Index [120]

Condition	**Assigned weight**
Myocardial infarct	1
Congestive heart failure	
Peripheral vascular disease	
Cerebrovascular disease	
Dementia	
Chronic pulmonary disease	
Connective tissue disease	
Ulcer disease	
Mild liver disease	
Diabetes	
Hemiplegia	2
Moderate or severe renal disease	
Diabetes with end organ damage	
Any tumour	
Leukaemia	
Lymphoma	
Moderate or severe liver disease	3
Metastatic solid tumour	6
AIDS	

3.2.2 Methodological limitations of the Charlson Index

In five of the studies included in my systematic review, weights for each index component were generated using a hazard ratio, odds ratio or relative risk.[120,126,128,131,134] The index developed by Charlson and colleagues is the most prominent and commonly applied for measuring multimorbidity and uses this approach.[112,120] There has been some dissent about the validity of deriving index weights by summing hazard ratios. Charlson and colleagues' methods were first questioned in the *Journal of Clinical Epidemiology* in 1993, with Romano et al. pointing out that relative hazards are multiplicative, not additive, and that adding coefficients would better fit the underlying assumptions of the Cox model.[206] Following further debate in 1996, Dr Charlson wrote to the journal defending her index, saying that it had been able to predict a surprising range of outcomes and that:

> *"The original index was never envisioned as the final definitive statement, but instead as an important foundation on which to build."* [234]

Mehta and colleagues tested the importance of the limitations in Charlson's work in 2016.[235] They studied 766 208 general practice patients, comparing hazard ratio weights and coefficients from the original Charlson Index and different adaptations. Their own coefficients were from multivariate Cox proportional hazards models for one-year mortality. The authors reported that models using regression coefficients were slightly better at predicting mortality than those derived from hazard ratios.[235] In order to truly test the index's predictive value, this paper kept Charlson's original list of conditions, even though some of them (such as ulcer disease) were less relevant to mortality in 2016 than they were in 1987, when the original paper was published.[235,236] In the same 2016 issue of the *Journal of Clinical Epidemiology*, Dr Charlson criticised Mehta and colleagues' methods and maintained that her weighting was valid.[237] The editors' comment suggested that previous research using the Charlson Index should be re-evaluated. They emphasised that *"using correct algebra is surely not up for debate."*[238]

3.2.3 Applicability of indices

Many index weights were derived in specific populations, for example hospital inpatients or survey volunteers, and are less applicable to different groups such as population studies. To address this issue, Diederichs and colleagues aimed to calculate suitable weighting for ten chronic conditions using individual participant data from people aged 65 years and older in five population-based studies in Germany.[239] They generated the pooled odds ratios for reporting fair or poor health for each condition across all the studies. If there was sufficient similarity across studies, they considered that these ratios would be meaningful weights for a multimorbidity index. They listed each condition's weight separately and did not propose adding all of them to create an overall score or index. However, this approach has two limitations. The first is transforming a Likert scale about self-rated health into a dichotomous variable, which not only assumes that a largely subjective measure can be split into two outcomes, but also loses statistical power.[240] The second is that the authors suggested that researchers sum odds ratios, with the resulting limitations discussed earlier.[239] In addition, using self-rated health as the outcome limits their usefulness in other studies, for example those predicting mortality, similarly to other indices.

All multimorbidity indices are limited by the fact that they usually neglect to capture interactions between conditions, treatment effects and functional parameters. One commentator has remarked that the indices work based on the assumption that the functional decline preceding death is related to the patient's comorbid conditions when in fact these processes may develop in parallel.[241]

3.2.4 Rasch models

An alternative method of attributing weights or scores to conditions is the Rasch model, originally developed for psychometric tests.[242] It is based on the theory that an individual's outcome on a test is dependent on their attributes (for example, ability) and the difficulty of the test. It can be used to generate a linear score from categorical test items. None of the indices studied in Chapter 2 used this method, although a follow-up study of the DBMA tested its validity using Rasch analysis.[132] The authors found that according to this method, the index's reliability was low. However, a linear

transformation of the total DBMA score generated using the Rasch model discriminated better between age groups than the original raw score.[171] The DBMA was designed to calculate disease burden by summing the interference of each condition with patients' lives according to a Likert scale. For this reason, it is suited to psychometric test analysis.

Another example of using Rasch models in multimorbidity research is in the development of the Multimorbidity Illness Perceptions Scale (MULTIPleS), a scale for measuring the perceived impact of multimorbidity.[243][8] The authors' explanation for using Rasch analysis was to allow for comparisons between patients and across patients over time. Similarly to the DBMA, MULTIPleS used a Likert scale for each item of measurement. The Rasch approach is less likely to be relevant for indices that include binary markers for the presence or absence of conditions.

3.2.5 Comparing indices

Numerous studies have compared the performance of two or more multimorbidity indices at predicting specific outcomes (construct validity). The original Charlson Index and its later adaptations have been used in studies to illustrate the discrepancies between multimorbidity prevalence when using different measures.[186,244] They are also used as benchmarks in the development and validation of new measures, for example the Measuring Multimorbidity (M3) Index.[155,245]

A systematic review published in 2011 found 54 articles that compared at least two comorbidity measures in administrative datasets.[233] Its search strategy specified that one of these must be the Charlson or Elixhauser Index.[246] The authors found that both methods predicted mortality better over longer (>30 days) rather than shorter periods, and that the Elixhauser index performed the best.[233] This review was very broad and included comorbidity with index diseases in addition to multimorbidity.

[8] This paper was not included in my systematic review as it focuses on measuring illness perceptions rather than multimorbidity itself.

Another systematic review of comorbidity indices for use in administrative data found 76 papers in 2015.[117] Its search strategy was not limited to specific indices. A total of 35 studies used the Charlson Index or its adaptations as comparators and 24 further studies compared other commonly used indices. This review provided a narrative description of the differences between indices rather than meta-analysing comparisons. Comparing indices has the benefit not only of testing each one's validity but can also measure the robustness of multimorbidity prevalence estimates within large-scale studies.

3.3 DISEASE COUNTS

Chapter 2 reviewed methods of measuring multimorbidity beyond counting diseases. A previous systematic review of all methods of quantifying multimorbidity found that among 194 studies, 98 (51%) used disease counts.[112] As the authors observed, there is evidence to suggest that counts can perform as well as other measures and are often used for practical reasons.[143,151,247] A study comparing five count-based measures found that continuous disease counts, either of all possible conditions or of those on the list from Barnett and colleagues, performed similarly to the Charlson Index and RxRisk-V at predicting hospital admissions and functional decline.[39,248] The developers of the Functional Comorbidity Index tried weighting conditions based on regression coefficients where functional ability was the outcome. This method provided similar explanations for variance in physical functioning to disease counts, so they chose to use counted conditions for ease.[249][9]

Counting conditions does have limitations. If each condition is allocated a count of one, i.e. is unweighted, this assumes they all have a similar impact on the patient. For example, there are likely to be differences in prognosis and illness experience between two patients who each have two conditions: a patient with treated hypertension and hypothyroidism may not be comparable to one with heart failure and dementia.[250] Disease counts do not capture the severity of individual diseases

[9] This index was also excluded from my review as its final model was an unweighted count.

either, which differ from person to person.[114] This is often the rationale for using weighted indices as discussed in section 3.2.1.

These limitations are relevant not only in continuous disease counts but also when considering a cut-off of two or more conditions to define multimorbidity. However, counts are easier to calculate than index scores, especially in large primary care or population studies where the impact of each disease on each patient is heterogeneous and difficult to measure. Where prevalence of multimorbidity is the main research question, or there is no clear defined outcome to guide the choice of an index, counts are the most suitable method.[39] In addition, using an index that includes weighting based on previous associations may in fact bias the results of a new study. As long as the list of conditions is justified, it is therefore appropriate to use counts in studies such as mine that examine under-researched areas with diverse outcomes.

3.3.1 Justification of candidate conditions

In all measures of multimorbidity, including weighted indices or unweighted disease counts, the list of candidate conditions should be clearly stated. Having a list clearly communicates what researchers mean by multimorbidity and permits comparison between studies.[251] Decisions on what constitutes multimorbidity and which conditions to include may be taken a priori, using a list published elsewhere, or as a result of evidence review.[118]

Within the papers reviewed in Chapter 2, only one did not justify its choice of potential conditions.[144] This is less than would be expected from previous research; the 2011 systematic review by Diederichs and colleagues found that among 39 studies using disease counts or indices, 59% did not specify the criteria for the selection of conditions.[113] The majority of studies reviewed in Chapter 2 used the conditions' associations with their outcomes of interest to refine the list. The others used pre-existing research, prevalence data, expert and clinician consensus or a combination of these approaches. One study considered any condition that each patient

reported.[199] Pragmatic reasons were also used, for example which conditions were asked about in the medical history of a cohort study or survey.[113,127] Whatever the process of list selection, it can always be considered arbitrary; the best approach is to give clear justification for which conditions were chosen.

As well as how the list was developed, it is important to understand which conditions it includes. For example, 'heart disease' in one study may be separated into atrial fibrillation, coronary artery disease and arrhythmia in another study, thereby under-estimating multimorbidity in one list compared to the other. Similarly, cancer may count as one condition or be separated by type. When generating a new list, another issue to consider is conditions directly caused by another disease, such as consequences of diabetes, and whether these should be treated as separate conditions.[113] There is no agreed solution to this problem, apart from to decide early in the study design process how to account for them.[252]

To improve comparability between studies, Diederichs and colleagues proposed a list of eleven conditions to be included as a minimum in future indices.[113] The list was based on the use of these conditions in multimorbidity studies of people aged over 65 years, and prevalence in this age group in Germany. The conditions are: cancer, diabetes mellitus, depression, hypertension, myocardial infarction, chronic ischaemic heart disease, heart arrhythmias, heart insufficiency [failure], stroke, chronic obstructive pulmonary disease, and arthritis. Missing from this list are thyroid disorders, any gastrointestinal conditions and common eye diseases such as glaucoma. In addition, myocardial infarction and stroke are acute conditions, which although may have important sequelae, do not in themselves meet the usual definition of chronic diseases. The list is therefore useful as a starting selection of conditions but should not be used alone.

3.3.2 Counts using established lists of conditions

A 2016 systematic review of multimorbidity definitions highlighted that among 163 articles studied, 115 (71%) generated their own definition of multimorbidity with a

unique list of conditions.[119] This approach introduces heterogeneity between studies and using one of the available established lists allows better comparability. For example, when counting conditions, several recent studies have used the list of 40 conditions published in Barnett and colleagues' major multimorbidity epidemiology paper.[39,253,254] These diagnoses were selected based on the 11 conditions recommended by Diederichs et al., population prevalence and clinical consensus.[113] This list has some limitations, for example that it includes some vague conditions such as low vision; these are discussed in more detail in section 5.5.3 on page 191. Another list of 60 conditions has been more recently developed, based on guidance from other studies and application of chronicity criteria to disease categories in the International Statistical Classification of Diseases and Related Health Problems, 10th revision (ICD-10).[255] This list includes states such as obesity, whose definition as a disease is contentious, and allergy, which may vary widely in severity. Its advantage over the list produced by Barnett and colleagues is that it does not contain symptoms such as 'painful condition'. There are specific lists that have been developed in primary care, such as that published by O'Halloran and colleagues in 2004.[13] The authors defined a list of chronic conditions according to the International Classification of Primary Care-Version 2 (ICPC-2), which was later revised for relevance to include 75 conditions.[256]

When choosing a list, there are practical issues to consider, such as its mapping to diagnostic criteria (for example, ICD-10), which can ensure generalisability between studies.[255] This is important where definitions of conditions differ between classification systems. In addition, condition selection should be justified within the age range being studied. For example, if the list was developed according to condition prevalence, this can differ between older and younger, often socioeconomically deprived, people.[11] The aim of the study that developed the list should also be considered, for example whether the conditions were chosen for their association with quality of life or mortality. Lists can often be arbitrary or based on practical, rather than scientific, reasons. Researchers should therefore be aware of the selection process of conditions on pre-defined lists before using them.

3.3.3 Length of condition lists

The number of conditions on a list is important, as the range of possible conditions limits comparability, particularly between prevalence studies. The number of candidate conditions included in counts has been found to be as high as 147.[257] A 2012 systematic review compared multimorbidity prevalence across 21 studies.[258] The authors found that although various aspects of study design affected prevalence rates, the number of conditions was the most important factor. There was minimal variation in prevalence between studies that used 12 or more conditions, and the authors recommended that this be the minimum number. This was confirmed by a population study in Australia that found a list of the 12 most prevalent chronic conditions detected 80% of multimorbidity found by using all possible conditions.[259] Another systematic review on this topic recommended a list of between 25 and 74 conditions to optimise estimation of population multimorbidity prevalence.[260] One of the indices included in my review accounted for this issue by dividing the number of conditions experienced by participants by the total number listed, giving a proportion of possible diseases instead of a continuous count.[138] However, this is rarely done, so attention should always be paid to the number of conditions listed. Alternatively, it can be argued that each condition is so different that a continuous count may be less meaningful than an overall dichotomy.

If a list is to be used directly with or by patients or participants, it should be of manageable length and in understandable language.[223] For example, it is relatively straightforward to gather data from a list of 40 conditions when using electronic medical records, but if they were presented as a list for self-report in an observational study, this may be too long for participants. Fortin and colleagues proposed that a suitable list length for self-report would be between 12 and 20 conditions.[223] In longitudinal studies with several waves, it should be decided in advance how to deal with inconsistency of self-report, for example when patients report that they have a chronic life-long condition in one wave and then not report it at follow-up.[261]

3.3.4 Cut-offs for defining multimorbidity

In general, it is most appropriate to analyse a count of any parameter as a pseudo-continuous variable, i.e. a variable that is discrete, with an upper bound and that only

includes integers, but treated as continuous. Dichotomising continuous variables loses much of the information available.[262] However, strictly adhering to the accepted and most commonly used definition of multimorbidity uses a cut-off of at least two conditions.[119] A limitation of this approach is that there is a ceiling effect; having two conditions is treated the same as having many more.

A 2014 systematic review of multimorbidity studies found 31 papers that compared cut-offs of both two and three conditions for detecting prevalence.[263] Overall, there was little difference in prevalence rates whether a cut-off of two or three conditions was used. A cross-sectional study of a Canadian cohort of 1 710 individuals found that, using a list of 21 conditions, the prevalence of multimorbidity was lower when using a cut-off of three rather than two conditions.[264] Prevalence was also lower when using a list of six, instead of 21 candidate conditions. The authors also found that participants defined as having multimorbidity by the list of six conditions and cut-off of ≥3 had poorer health-related quality of life than those defined by the list of 21 conditions and a cut-off of ≥2 conditions. It therefore seems relatively unimportant which cut-off is used, but again its use should be justified.

3.4 OTHER MEASUREMENT METHODS

3.4.1 Cluster analysis

Newer methods of measuring multimorbidity include clustering and network analyses. Clustering uses various methods to identify groups of conditions that co-exist, depending on their correlations with each other, within large datasets. The use of clustering methods in multimorbidity research is based on the premise that we are interested in comorbid conditions that co-exist in a non-random fashion. Given that it is a data-driven approach, clustering does not usually use pre-defined information about group structure, instead allowing patterns to emerge.[265] This can be with a pre-defined number of co-existing conditions (such as two, or ‘disease pairs’),[266] or whichever corresponding conditions appear in the data. Alternatively, cluster analysis can be used to find groups of people with similar multimorbidity profiles, rather than groups of co-existing conditions.[267] The Academy of Medical Sciences’ 2018 report on multimorbidity identified outstanding areas of research which included the

prevalence, trends and outcomes relating to disease clusters, highlighting their current pertinence.[7]

A common method for identifying clusters in multimorbidity is to conduct multiple correspondence analysis to detect underlying structures in the data, and derive continuous measures from the original binary or categorical variables.[268] The next step is to use K-means clustering on these results. This well-established algorithm generates groups and allocates each object (or condition) to the group to whose mean it was closest. It then iteratively recalculates the group means and re-allocates each object.[269,270]

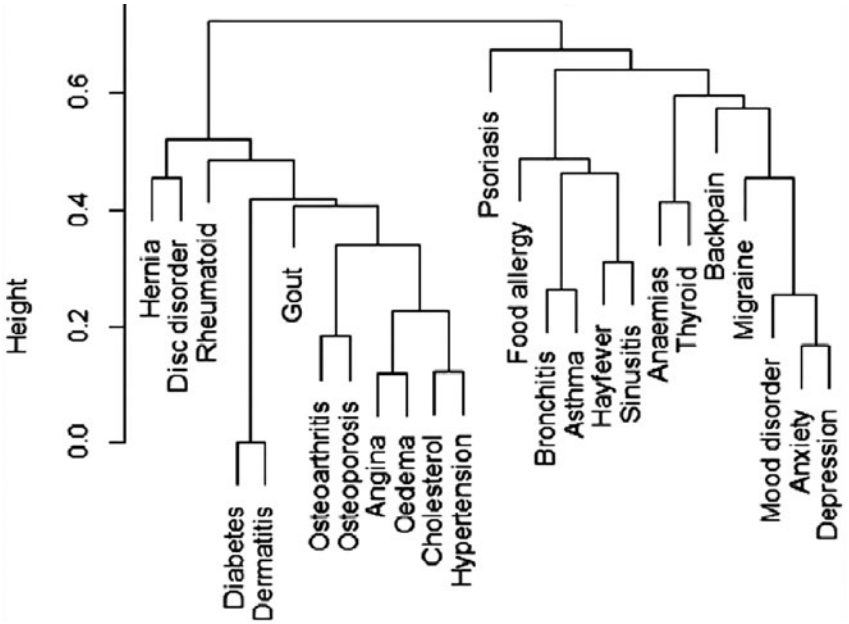
There have been three systematic reviews exploring clustering in multimorbidity. A review in 2013 found 19 articles containing 165 combinations of two diseases.[271] The authors reported that depression, hypertension and diabetes were the diseases that most commonly appeared in clusters. This was due to both their prevalence and their co-existence with other conditions. Prados-Torres and colleagues' systematic review focused on associative comorbidity, thereby including 14 articles that established the co-existence of conditions was not due to chance.[272] Among these, they found 97 patterns of two or more, and 63 of three or more conditions. These were broadly separated into cardiovascular and metabolic conditions, mental disorders and musculoskeletal conditions.

3.4.1.1 Hierarchical clustering

The third systematic review of clustering in multimorbidity, published in 2018, found 41 studies.[273] The study identified five different analytical methods for identifying clusters, with the most common being factor analysis or hierarchical clustering. Hierarchical clusters can be represented as dendrograms, which are created by algorithms that identify overlapping groups of comorbid conditions and their similarity (known as distance between clusters). Highly correlated clusters are near the bottom of the dendrogram and those with less correspondence are displayed the furthest away from each other.[273,274] Figure 3-1 is an example of this method, presenting

25 chronic conditions among 20 788 participants of the Australian National Health Survey.[273] Height on the y-axis represents the dissimilarity between clusters and the distance at which they diverge.[274]

Figure 3-1: Dendrogram showing hierarchical clustering of conditions, from Ng et al, 2018.[273] [10]



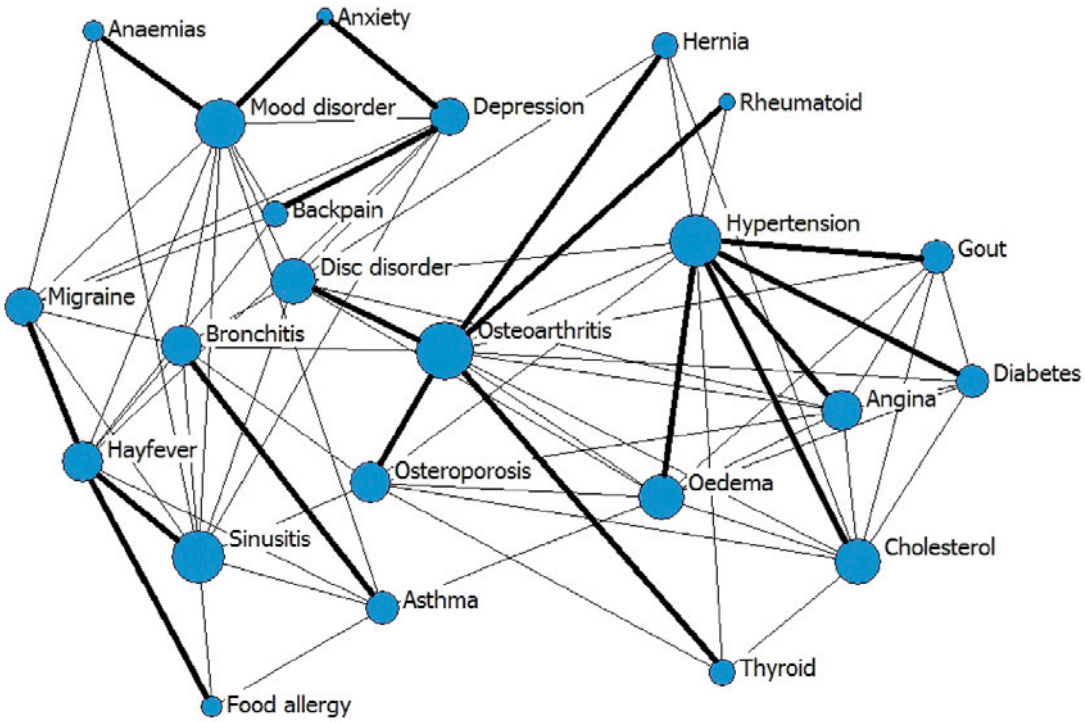
A population study of the associations between multimorbidity and health-related quality of life in 8 841 people compared count-based with hierarchical cluster methods, from a list of ten conditions.[275] The authors reported that the hierarchical clustering was effective and had the advantage of identifying specific conditions of interest contributing to the outcome in question, which is not possible using disease counts. Highly prevalent conditions may form part of several clusters, so all clustering methods sometimes lead to groups of conditions that are not clinically meaningful. The conditions included in the list has an impact on the number and composition of clusters. A disadvantage of these methods is therefore that both a large number of conditions needs to be included, as well as a large sample size.

[10] Used by permission of the International Epidemiological Association (through Oxford University Press) for print and electronic reproduction in PhD thesis: licence 4625360146955

3.4.2 Network analysis

Some studies that employ clustering techniques also use network analyses. These display the connections between comorbid conditions. Figure 3-2 is an example network diagram presenting the same conditions from the Australian National Health Survey as in Figure 3-1.[273] It highlights the conditions that most commonly co-exist with others by proportional node sizes, with bold connecting lines (edges) emphasising the common disease pairs.

Figure 3-2: Network diagram of co-existing conditions, from Ng et al., 2018.[273] [11] *Node size is proportional to the condition's number of comorbid conditions; bold lines highlight the most frequently co-occurring pairs*



It is also possible to map disease clusters onto network diagrams by colour-coding conditions.[276] Network analyses have clear applications in visually presenting the constituents of multimorbidity within a sample. Clustering and network analyses can

[11] Used by permission of the International Epidemiological Association (through Oxford University Press) for print and electronic reproduction in PhD thesis: licence 4625300894002

present quantitative data on the prevalence of each condition and its co-existence with others.

3.4.3 Association Rules

A method for assessing multimorbidity similar to network analysis is Association Rules. This process, used in machine learning, finds combinations of conditions based on both prevalence and their co-existence being more likely than chance. It can identify relationships between conditions and quantify how often each relationship occurs and its likelihood of occurring. A 2016 study used this technique among 1 464 men aged 70 years and over in Australia.[277] The authors reported that it identified predictable clusters such as congestive heart failure co-existing with angina and 'heart attack', but also a clear association between anxiety and heart failure. A 2018 paper using the UK Biobank cohort used a two-step method to map networks of conditions with their likely temporality.[278] The authors first used hierarchical clustering to generate dendrograms, then used Association Rule Mining to more closely explore the links between the conditions, including which ones were likely to be antecedent or consequent to each other. They identified three clusters, the first of which contained only myocardial infarction and angina. This may not clinically be considered a cluster, rather two manifestations of one disease process. The study also found a strong association between anxiety and depression which again may represent symptoms of one condition rather than two separate ones. The Association Rules method has rarely been used in multimorbidity research so far to date but may increase in prominence with the rise in the application of machine learning techniques.

3.4.4 Duration of illness

Another methodological issue to acknowledge when comparing multimorbidity prevalence or outcome studies is the length of time over which diagnosis data were collected.[20,251] A count-based method can give the same weight to two recently diagnosed conditions as two that were diagnosed ten years ago. This is more problematic when exploring associations with specific outcomes than in prevalence studies. An approach to this is to use a longer retrospective period in which to identify diagnoses (for example, in medical records).[279] Alternatively, the cumulative duration method has been used recently by Maciejewski and colleagues.[280] This

involves summing together the time since diagnosis for all of a patient's conditions from a pre-defined list. For example, a patient with one condition lasting 20 years would be assigned 20 patient-years and a patient with three conditions for five, two and three years respectively would have a total of 10 patient-years. The authors found that there was significant variation in cumulative duration even among people with multimorbidity, but that a count of diseases was a better predictor of healthcare expenditure than this cumulative count. The time of diagnosis is sensitive to bias, for example in that people with better access to healthcare will be diagnosed sooner and will have longer duration of illness. In general, it has been identified that there is little work addressing whether, and how, to include conditions that are either episodic or of short duration within multimorbidity research.[114]

3.4.5 Multimorbidity as a dynamic variable

Multimorbidity is mostly presented as static, a single count. This may be necessary and appropriate in cross-sectional analyses, but multimorbidity can change and develop over time. Ageing plays a crucial part in the pathology of conditions, and psychosocial factors such as access to healthcare and care-seeking behaviour are relevant to the acquisition of diagnoses. In addition, successful treatment of a condition may make it less relevant to an individual's disease burden.

Only a few studies have examined changes in multimorbidity over time and used diverse methods. A paper using latent class growth analysis examined primary care records of 24 615 people aged over 50 years and identified five clusters depending on their multimorbidity status and its trajectory.[281] The authors tested this method in a smaller population of 4 532 patients by assigning them to the same clusters. Scores on health-related quality of life were worse, as expected, in groups with evolving or chronic multimorbidity compared to no or recently diagnosed multimorbidity. An 11-year longitudinal study of 335 people with dementia in Utah found that the number of comorbidities fluctuated over time and that this number did not predict poorer cognitive outcomes.[282] A study of 756 adults aged ≥65 years without cognitive impairment in Baltimore counted from a list of 13 conditions and used linear mixed models to explore multimorbidity trajectories.[283] The authors reported that a faster accumulation of chronic conditions was associated with decline

in fluency, but not on memory tests. This study is likely limited by the use of linear mixed models with a relatively small number of conditions. An approach that includes change in multimorbidity burden is therefore valuable when designing longitudinal research.

Network analyses can also be used to monitor changing multimorbidity. For example, researchers at Harvard University developed a network of data from all claims in the USA's Medicare system from over 13 million patients.[284] In several stages, they explored the relative risk of developing each condition compared to the others, generating a phenotypic disease network to track progression from one condition to another and to identify mortality risk. These maps currently represent phenotypes but could be used in future to identify common molecular or genetic aetiologies between conditions or inform new treatments such as by drug repurposing.[285]

3.5 CONCLUSIONS

3.5.1 Summary of methods of measuring multimorbidity

Multimorbidity research usually explores the complex co-existence of multiple conditions within individuals, and there are methodological factors to consider when interpreting existing research and planning analyses. Table 3-2 briefly outlines these issues relating to each method discussed in this chapter.

Table 3-2: Summary of measurement methods, their advantages and disadvantages

Measurement method	Advantages	Disadvantages
Disease counts	- Common, so comparable to other studies - Easily applicable - Produces numerical value	- Assumes the same importance of each condition - Dependent on the length and content of lists of candidate conditions
Weighted indices	- Relatively easy to use if appropriate information available - Usually produces numerical value	- Many indices are not well validated and have limited comparability - The most commonly used index, the Charlson Index, is dated and has possible methodological flaws [120]
Clustering	- Provides information on disease co-occurrence - Hierarchical clustering allows visual representation of similarities	- High prevalence conditions can appear in many clusters - Clusters are not always clinically meaningful
Network analysis	- Visually displays information about relative disease connections - Can be used to show temporality	- Can become difficult to interpret with large numbers of conditions
Association rules	- Identifies the prevalence and likelihood of diseases co-occurring	- Requires understanding of advanced methods - May find associations that are not clinically meaningful

3.5.2 Methods used in this thesis

In Chapter 4, I present the first data analyses in this thesis, exploring the impacts of chronic diseases and medication use on varying mental and brain health outcomes. I use a pragmatic approach to counting diseases based on which ones were included in the PREVENT Dementia study's Case Report Form, then applying chronicity criteria to them.[42] In the European Prevention of Alzheimer's Disease (EPAD) study used in Chapter 5, the medical history collection was limited by there being no marker of whether conditions had resolved or were continuing, so I used Barnett and colleagues' list as it defines most conditions based on ever being diagnosed.[39,52] I present network analyses in Chapters 4 and 5. This method permits visual representation of frequently co-occurring conditions and complement the information presented in disease counts. I investigated the possibility of hierarchical and non-hierarchical cluster analyses in these data, but owing to having ordinal binary variables for disease presence or absence, this was not immediately appropriate.

The majority of multimorbidity research quantifies multimorbidity by counting diseases and uses either a pseudo-continuous count, a dichotomous measure of multimorbidity or both.[112] In keeping with this, and accounting for the fact that the PREVENT Dementia and EPAD datasets had different lists of conditions, I opted to use disease counts and dichotomous multimorbidity measures. When designing my analyses, I maintained awareness of important methodological issues, particularly stating a priori the content and length of lists of candidate conditions.

Chapter 6 focuses on polypharmacy in NHS routinely collected data. Although some indices studied in Chapter 2 use weighted counts of medication to measure multimorbidity,[145–148] polypharmacy itself is measured by medication count in the vast majority of studies.[32] Therefore, when exploring polypharmacy in Chapters 4 and 6, I used continuous and categorical counts of all relevant medications as the exposure variables.

Chapter 4 Cross-sectional analyses in the PREVENT Dementia Study

4.1 INTRODUCTION

As outlined in Chapter 1, population studies have shown that around a third of people with multimorbidity have both physical illness and mental disorders.[38,39] These mental disorders include depression, anxiety and neurodegenerative diseases such as dementia.[39] The co-existence of physical multimorbidity and mental disorders results in greater treatment burden for individuals and costs to healthcare services.[71] However, understanding of specific mental health outcomes in people with multimorbidity remains limited. This chapter will explore associations between multimorbidity and polypharmacy with specific mental health, cognitive testing and neuroimaging outcomes in a mid-life cohort from the PREVENT Dementia study.

4.1.1 Associations between multimorbidity and depression or anxiety

Depression has a worldwide prevalence of 2-15% and can lead to substantial disability across the life course.[286] There are known links between individual physical conditions, such as stroke, and depression,[287] but the relationship between multiple chronic conditions and depression, especially in mid-life, is less well understood. A 2017 systematic review of multimorbidity and depression including 40 papers and meta-analysis revealed that people with multimorbidity had a three times greater risk of depression than people with no chronic physical conditions.[288] The majority (26, 65%) of studies included in this review were undertaken in older adults, with only one in a mid-life sample.[289] The review suggested healthcare-related explanations for this physical-mental multimorbidity, for example that people with chronic conditions may receive better attention to their mental health than people who do not regularly attend primary care. It also highlighted previous work on depression that found negative cognitions were precipitated by genetic risk, early trauma and biological stress reactivity, all of which are additionally relevant to physical health.[290]

The co-occurrence of multimorbidity and anxiety is less frequently studied, but one cross-sectional study of 138 858 patients' medical records in Minnesota has shown they do co-exist.[50]

4.1.2 Polypharmacy and mental or brain health

The associations between polypharmacy and mental or brain health outcomes have rarely been studied. A 2014 systematic review of outcomes associated with polypharmacy included 58 papers, of which five studied cognitive impairment or dementia as outcomes.[291] Two of these showed no convincing associations between polypharmacy and these cognitive outcomes. One paper examined depression using the Center for Epidemiologic Studies Depression (CES-D) scale and found an association between increasing numbers of medication and higher scores on the CES-D (β=0.13, P<0.01, adjusted for age, education and physical health).[95] This paper, published in 1989, is the only example of work exploring the association between polypharmacy and depression to date. It proposed potential explanations for their co-existence, including that drug adverse effects can include lethargy and depression, that people with depression are likely to seek more care for their physical health, and that co-existent multimorbidity physically predisposes patients to depression.

4.1.3 Multimorbidity with cognitive impairment and neurodegeneration

There have been three studies into associations between multimorbidity and neuroimaging biomarkers.[98,99,292] One of these studies included 1 449 people aged 70-89 years with no cognitive impairment.[98] It found that people with multimorbidity (≥2 conditions) had increased odds of fluorodeoxyglucose hypometabolism (odds ratio (OR) 2.03, 95% confidence interval (CI) 1.10 to 3.77, adjusted for age, sex and education) and reduced MRI cortical thickness (OR=1.53, 95% CI 1.09 to 2.16 adjusted for age, sex and education), both in regions of interest for Alzheimer's disease. These associations were further increased in people with four or more conditions. Another study, of 318 people aged 70-85 years, found an association between greater numbers of chronic conditions and decreased hippocampal volume (–0.03 ± 0.01cm^3; P=0.012).[99] The third study suggested links between multimorbidity and combinations of markers of neurodegeneration including

amyloid.[292] The importance of amyloid in these papers is discussed in more detail in Chapter 5.

The co-existence of multimorbidity and neurodegeneration may be explained by common biological aetiology such as inflammatory or vascular pathways.[293] Physical conditions contributing to multimorbidity could be either risk factors for clinical dementia, such as hypertension or diabetes, or conditions associated with dementia in their own right, such as Parkinson's disease or stroke.[48]

4.1.4 Mid-life approach

Most research investigating multimorbidity and polypharmacy has been conducted in older people, amongst whom they are common.[3] However, the majority of people with multimorbidity are middle-aged.[39] Although clinically manifest cognitive impairment is more prevalent in older age, there is increasing evidence that pathological changes of Alzheimer's disease are present in mid-life.[41] This is in the broader context of a life-course approach to dementia epidemiology, purporting that intrauterine and childhood factors, as well as behavioural factors in adulthood, can contribute to later dementia risk.[294] Therefore, the focus of dementia prevention research is turning towards detailed studies of middle-aged people.[41] In research and clinical settings, old age is most commonly defined as being aged over 65 years with middle age being between 45-65 years, although it is acknowledged that risk factors exist at all ages and that biological age differs between individuals.[40]

Depression and anxiety in mid-life have been identified as risk factors for dementia,[43,44] although the direction of the association remains uncertain.[46] They are clinically important in this age group due to the potential disability caused in working-age adults.[286] Understanding the interplay between multimorbidity and polypharmacy with depression and anxiety is therefore not only valuable in its own right, but adds to the knowledge on factors leading to poor brain health and dementia. This is best explored in a mid-life cohort before substantial cognitive impairment has developed. The PREVENT Dementia study offers opportunities to explore the

associations between multimorbidity, polypharmacy, depression and anxiety in mid-life.

4.2 HYPOTHESES

This chapter explores associations between physical multimorbidity and polypharmacy with mental disorders and relevant neuroimaging outcomes in a middle-aged cohort. The following hypotheses are in keeping with the overall hypotheses of this PhD presented in section 1.5 on page 18.

1. Physical multimorbidity (or having a larger number of chronic conditions) will be associated with an increased risk of mental disorders. The greater the burden of multimorbidity, the higher the individual's risk of developing a mental disorder. These include:
    a. Depression
    b. Anxiety
    c. Cognitive impairment (specific deficits on cognitive testing)
2. Polypharmacy, or using larger numbers of medications (accounting for antidepressant drugs) will be associated with poorer mental health, and the greater the burden of polypharmacy, the higher a person's risk of developing a mental disorder as above
3. Physical multimorbidity (or having more chronic conditions) will be associated with outcomes linked to dementia on structural MRI neuroimaging (periventricular and deep white matter hyperintensities, hippocampal volume and microhaemorrhages)
4. Polypharmacy, or using more medication, will be associated with the same MRI outcomes

4.3 METHODS

4.3.1 The PREVENT Dementia Study

PREVENT Dementia is a prospective cohort study which was initiated in 2013 with the aim of identifying risk factors for dementia in mid-life to inform strategies for

secondary prevention.[42] The study population was phenotyped in detail, paying particular attention to known risk factors for dementia such as family history and *APOE* ε4 status. As well as in-depth medical and lifestyle history, mental health questionnaires and rigorous cognitive testing, biomarkers were measured including various blood tests and brain MRI and fMRI.

The PREVENT Dementia study was given ethical approval by the NHS Research Ethics Committee London Camberwell St Giles, reference 12/LO/1023. My analyses did not require separate ethics permissions, as I was not collecting new data or re-contacting participants. The principal investigators published the study protocol prospectively.[51] I submitted an application to the steering group and was granted access to the data.

4.3.2 Participants

Participants were recruited through the dementia register database of West London Mental Health NHS Trust, which holds records of people with dementia who have consented to be contacted for research and their carers (usually offspring).[295] Recruitment was also undertaken through the Join Dementia Research website and via publicity online and at public presentations.[296] People were eligible to participate if they were aged 40-59 years at baseline and were fluent in English. Exclusion criteria were a diagnosis of, or reported cognitive impairment or dementia and known contraindication to MRI.

The original pilot study was designed to include three groups of 50 participants each, stratified by risk of developing dementia. These included offspring of patients diagnosed with Alzheimer's disease who had an *APOE* ε4 allele, offspring of patients with dementia without an *APOE* ε4 allele and participants without a parent with dementia who had an *APOE* ε2, but not *APOE* ε4 allele.[51] Power calculations were based on existing studies of biomarkers in mid-life, of which there were few at the time of study design.[297,298] The calculations found that with 50 participants per group, mean differences in hippocampal volume of 0.327cm^3 and mean differences

in plasma $A\beta_{42}$ of 8.07 pg/ml could be detected between groups, with α=0.05 and 0.90 power in both cases.[51]

There were 210 participants in the initial wave, with a total of 700 currently participating across London, Edinburgh, Dublin, Cambridge and Oxford sites. The first follow-up visits took place two years after initial assessments and are planned every five years thereafter. This chapter contains cross-sectional analysis of quality-controlled data from the pilot phase in London in 2014-15.

4.3.3 Exposure variables

4.3.3.1 Chronic conditions

In keeping with other research into multimorbidity and polypharmacy, I used counts of chronic physical conditions and medications for these analyses. Based on a combination of definitions from the International Classification of Primary Care, version 2,[13] and from NHS Scotland Information Services Division,[14] I developed a definition of chronic conditions, as described in section 1.2.2 on page 2. Conditions should last at least six months, have an impact on quality of life (either directly or through sequelae), clearly meet diagnostic criteria, and have a pattern of recurrence or deterioration. I therefore excluded conditions that may have significant impact on life but are not chronic such as myocardial infarction, and procedures reported such as carotid artery surgery.

The PREVENT Dementia participant case report form names 69 conditions in the medical history, with space for other conditions to be entered. These are categorised by body system as shown in Table 4-1. I read each free-text 'other' entry to decide whether the condition fitted the chronicity criteria, and if so, coded it according to body system. This created a new 'other' category within each body system. The medical history in the PREVENT Dementia assessment was collected by a qualified doctor. They asked if the participant had ever had each of the conditions, and if so, recorded its date of onset, whether it was currently active and whether the participant had required hospitalisation. Any uncertainties were clarified by reference to the

participant's medical records, with their consent. I took the outcomes self-reported active depression and anxiety disorder from this medical history.

Table 4-1: Number of conditions by body system

System	Number of conditions in full list	Number of conditions included in analyses (includes 'other')
Blood	2	2
Cardiovascular	17 (including 6 procedures)	12
Gastrointestinal	12	13
Genitourinary/reproductive	4	4
Eyes, ears, nose and throat	2	2
Metabolic	5	4
Musculoskeletal	5	5
Neurological/Psychiatric	13	7
Pulmonary	4	3
Whole body	4	2 (both immunological)
Cancer	1	1
Total	69	55

The focus of multimorbidity in these analyses is physical, with mental disorders the outcomes of interest. I therefore excluded psychiatric disorders from my disease count. These included 'alcoholism' and 'drug abuse' which appeared in the 'whole body' category. I also excluded obesity, as body mass index (BMI) was included as a potential covariate in preliminary analyses. In addition, obesity is usually seen as a risk factor rather than a disease in itself.[119] Hearing loss is included in some studies counting multimorbidity [39] but as its definition can vary widely, as a functional impairment rather than physical disease, I excluded it from these analyses. My final chronic condition list therefore included 55 diagnoses.

For analyses on depression and anxiety outcomes, I used two measures of multimorbidity: pseudo-continuous counts of any chronic conditions the participant reported, and binary measures of ≥2 versus 0-1 conditions. This was in anticipation that, owing to the overall sample size, there would be few participants reporting each number of chronic conditions. It also aligns with other multimorbidity research.[119] I did not use the binary variables where the outcomes were cognitive test scores or

MRI markers of neurodegeneration after preliminary analyses revealed they had no likely associations with the exposure variables.

4.3.3.2 Medication history

At the initial interview, study doctors collected information on current medication according to participant self-report. This included drug name, dose, frequency and indication. The reported medications were then coded according to the World Health Organization's (WHO) Anatomical Therapeutic Chemical (ATC) classification.[299] This is a hierarchical system of five levels: a letter denoting the anatomical or broad pharmacological group, a number for the therapeutic group, two further letters for pharmacological subgroups and a final number for the chemical substance. For example, fluoxetine has ATC code N06AB03, which consists of the following levels:

N	Nervous system
N06	Psychoanaleptics
N06A	Antidepressants
N06AB	Selective serotonin reuptake inhibitors
N06AB03	Fluoxetine.

This system allowed me to find and segregate antidepressants by searching for ATC codes starting with the string 'N06A'. I then created an indicator for whether each participant took an antidepressant. I was particularly interested in this as it could influence their outcomes regarding depression and anxiety, regardless of the drug indication. I used the indicator to account for antidepressant use in these analyses. I used the same method to ascertain whether participants took anxiolytics and account for this. For both antidepressants and anxiolytics, I reviewed free-text entries stating treatment indication as both groups can be used for non-psychiatric indications.

I checked free-text medication entries where there was no ATC code and assigned the relevant code as per the ATC online index, where sufficient information existed.[299] Most polypharmacy studies use prescribed medication from electronic health records.[35] However, the PREVENT Dementia case report form allowed

participants to record any medications they took, whether prescribed or not. I therefore excluded medications that appeared to be primarily over-the-counter vitamins or health supplements, or where insufficient free-text information was recorded to generate an ATC code, for example ‘eye drops’.

Similarly to my chronic condition measures, I used two exposure variables for quantifying the number of medications. One was a continuous count of any relevant medication reported by the participant. I excluded antidepressants from this total count as I hypothesised that antidepressant use would be linked to depression and anxiety outcomes. I also planned to use antidepressant use as a covariate so including them in the exposure would lead to them being counted twice. I used the count of medications excluding antidepressants as the medication exposure variable in all analyses, regardless of the outcome, for consistency. To further explore the concept of polypharmacy, I also used a dichotomous measure of ≥3 versus 0-2 medications. Although the majority of studies use a cut-off of ≥5,[32] in this cohort of mid-life healthy volunteers, I discovered after exploring the data that very few participants were taking ≥5 drugs.

4.3.4 Outcome variables

The primary variables of interest in PREVENT Dementia are the detailed cognitive test battery and biomarkers including neuroimaging. Participants also completed validated questionnaires on symptoms of depression, anxiety and resilience, with these considered risk factors for dementia or cognitive impairment. To complement the mental health outcomes used elsewhere in this thesis, I chose to analyse scores on the Center for Epidemiologic Studies Depression (CES-D) scale [300] and the Spielberger State and Trait Anxiety Inventory (STAI);[301] participants’ self-report of depression and anxiety; neuroimaging measures and detailed cognitive outcomes from the COGNITO battery.[302]

4.3.4.1 Depression measures

The CES-D is a self-administered scale containing 20 questions about depressive symptoms in the past week.[300] The questions cover mood, cognitive and somatic symptoms of depressive disorder, and are equally weighted (see Appendix 1, page 357). Participants answer each question on a scale of zero (rarely or none of the time) to three (most of the time, or five to seven days). Four of the questions ask positive questions, for example *"I am happy"*, so their scores are inverted. Overall scores are calculated by summing the scores for each answer, giving a maximum total of 60.[300] As it was originally designed as a continuous scale to measure symptoms, I treated it as such.

The CES-D has been validated in several settings, and a cut-off score of ≥16 is generally used to distinguish between people with and without depression.[303] A systematic review and meta-analysis of studies using the CES-D found a sensitivity of 87% and specificity of 70% using this cut-off.[304] I therefore additionally derived a binary measure of scores ≥16 to account for the small sample size.

I also used self-reported medical history of active depression as an outcome, to correspond with other datasets which only use diagnoses rather than test outcomes and to add further detail beyond test scores. Depression appears on a list of conditions in the PREVENT Dementia case report form medical history, which is collected by a qualified doctor. The list does not offer further details such as whether depression was diagnosed by a doctor or is under treatment, but does specify whether this is currently active.

4.3.4.2 Anxiety measures

The Spielberger State-Trait Anxiety Inventory (STAI) has two sub-tests measuring state and trait anxiety.[301] The state sub-test asks about current symptoms at the time of inventory completion, and only this was used in PREVENT Dementia. It consists of 20 self-report questions on symptoms of anxiety, scored from one to four. Ten of the questions are positive statements, such as *"I feel at ease"* and the other

ten are negative, for example, *"I am tense"*.[12] The scale for the positive questions is inverted before generating the overall score, so that higher total scores indicate more symptoms of anxiety. The maximum possible score is 80. A cut-off of 40 was found to have specificity of 75% and sensitivity of 68% in 40 adults aged over 65 years, compared to a structured clinical interview conducted by a psychiatrist.[305] Although this sample is older than the one used in my analyses, I chose to use the cut-off of 40 to indicate clinically significant anxiety as it is the most frequently used.[306,307] Similarly to CES-D, I used both the continuous score and binary measures for comparative analyses.

To strengthen my results, as with depression, I additionally used a dichotomous self-reported diagnosis of active anxiety disorder from the medical history.

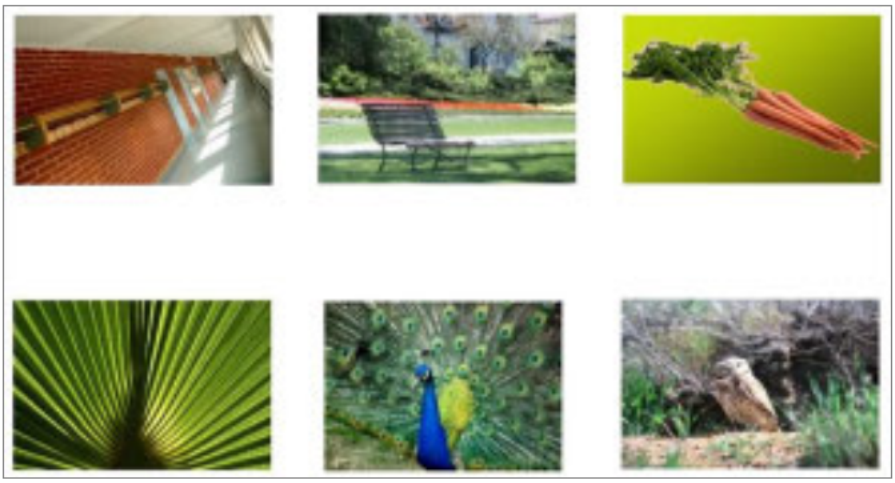
4.3.4.3 Cognitive outcomes

COGNITO is a computerised neuropsychometric test battery designed for epidemiological cognition research.[302] It covers attention, memory, visuospatial processing and language. There are 20 tasks which generate detailed results as well as an overall score for each task. Due to the relatively small size of this initial phase cohort, I chose not to include all COGNITO outcomes. Instead, I referred to those previously reported to be significantly associated with risk of dementia. In a 2017 publication using PREVENT Dementia data, Karen Ritchie and colleagues found an association between higher Cardiovascular Risk Factors, Aging, and Incidence of Dementia (CAIDE) score and poorer performance on the COGNITO name-face associative learning task (OR=1.4, 95% CI 1.04 to 1.26; *P*=0.008) and phoneme comprehension time (β (standard error)=16.7 (7.24); *P*=0.02).[308] I therefore chose the phoneme comprehension and name-face associative learning tests as outcomes for analysis.

[12] The Spielberger State-Trait Anxiety Inventory is copyrighted by Mind Garden, who provided it under paid licence to PREVENT Dementia; I could not obtain permission to reproduce it here

For the phoneme comprehension test, the tester reads and shows a word to the participant. The participant then sees six pictures containing distractors and must select the correct picture that matches the word. Figure 4-1 illustrates the choices relating to the word 'peacock'.

Figure 4-1: Example images for participant to match with 'peacock' [13] [309]



To harmonise with previously published work, I used mean time for a correct response (in milliseconds) to the phoneme comprehension test, with longer times suggesting poorer function at this task.

In the name-face associative learning task, the participant sees 18 faces, of which nine had been associated with names earlier in the test. The score of interest is the number of correctly recalled names, with a maximum possible score of nine. Previous authors using this variable chose to dichotomise the results around the median, as the overall results were not normally distributed.[308] For consistency, I used the same approach, creating a binary variable.

4.3.4.4 Imaging outcomes

Participants underwent multimodal 3T structural MRI on a single scanner.[308] Scan results were reported by a neuroradiologist and analysed by a single rater blinded to

[13] Reproduced from COGNITO manual (available at https://edin.ac/2QNCurJ)[309] with permission from Prof Karen Ritchie

all clinical and genetic study data.[310] The imaging outcome variables of interest were hippocampal volume, white matter hyperintensities (quantified by Fazekas score) and cerebral microhaemorrhages. Smaller hippocampal volume is associated with an increased risk of Alzheimer's disease, and decreasing hippocampal volume can be an early marker of memory deterioration and dementia.[311] The Fazekas score was initially proposed in 1987 as a measure of white matter hyperintensities to quantify vascular damage. It grades periventricular hyperintensity and deep white-matter hyperintensity, each on a scale of zero to three based on appearance.[312] Risk of dementia and severity of cognitive impairment are associated with more periventricular hyperintensities, whereas the risk of mood disorders and their severity are associated with deep white-matter hyperintensities.[313] I therefore analysed each score as a separate outcome measure. In this study, white matter hyperintensities were quantified using specific validated automatic methods.[310]

Cerebral microhaemorrhages, also known as microbleeds, are perivascular deposits of haemosiderin that have leaked from small vessels and indicate susceptibility to haemorrhage.[314] In general, arteriosclerosis leads to white matter damage and deep microbleeds whereas amyloid angiopathy causes white matter damage and lobar microbleeds. One study found that overall burden of cerebral microbleeds was associated with a higher risk of developing dementia compared to people without them, independent of vascular risk factors (hazard ratio 1.74, 95% CI 1.00 to 3.01).[315] PREVENT Dementia imaging analysis used the Microbleed Anatomical Rating Scale (MARS) to evaluate whether each participant had at least one definite microbleed in each anatomical area.[310]

The hippocampal volume variable was a mean of left and right grey matter hippocampal volume and had already been adjusted for total brain volume.[308] The scan images had been processed by a colleague working on imaging within the PREVENT Dementia study and I received numerical variables only.

4.3.5 Covariates

I generated an initial list of potentially relevant covariates comprising established risk factors for dementia and depression. Age was recorded in whole years and participants reported their gender and race.[14] Owing to the expected ethnic mix of the sample, I used a dichotomous race variable of Caucasian and non-Caucasian for analyses.

Data on head injuries were collected using the Brain Injury Screening Questionnaire (BISQ). I used a sum variable of the number of self-reported episodes of loss of consciousness following a blow to the head.[316] I used separate binary indicators of whether the participant was taking at least one antidepressant or anxiolytic for a psychiatric indication.

The CAIDE score, as mentioned in section 4.3.4.3, is a validated risk score comprising weightings for the following participant characteristics: age, gender, education, systolic blood pressure, body mass index (BMI), total cholesterol, physical activity and *APOE* status. Scores vary from 0 to 15, with higher scores conferring a higher risk of dementia.[317] I treated the score as a continuous covariate in relevant analyses with outcomes relating to cognition or neurodegeneration. The CAIDE score includes age and gender so I did not include age and gender when using it as a covariate.

I adjusted appropriate neuroimaging outcomes for total intracranial volume, which was calculated as the sum of grey matter, white matter and cerebrospinal fluid.

[14] Gender describes a person's self-representation as male or female, whereas sex is determined by biological features including reproductive organs.[591] The PREVENT Dementia Participant Case Report Form asks participants their gender. This term is therefore used throughout this chapter.

4.3.6 Statistical analysis

I used R version 3.4.3 with RStudio for all analyses.[318] I initially investigated the overall characteristics of the sample, including age distribution, prevalence of diagnoses and medication use, and generated bar graphs.

4.3.6.1 Network analyses

In order to investigate the co-occurrence of conditions and prescribed medications, I employed network analysis. Firstly, I grouped medications into their ATC therapeutic subgroup, giving 39 groups. I used the R package `igraph` to create adjacency matrices of chronic physical conditions and medication subgroups separately.[319] In an adjacency matrix, the terms (conditions or medications) appear in both rows and columns and each entry represents the co-occurrence of two terms. The `igraph` package then graphs this adjacency matrix. I generated network analysis graphs with the Fruchterman-Reingold layout, which aims to produce edges of equal length.[320] Some vertices needed manually adjusting to prevent overlap of their labels. In keeping with other similar research, I restricted my network analyses to participants with at least three conditions or medications, as this allowed exploration of their connections.[276]

4.3.6.2 Regression models

Prior to conducting regression analysis, I tested model assumptions by examining diagnostic plots of condition or medication counts against the continuous outcomes.[321] These graphical analyses revealed that the appropriate assumptions were met. I used linear regression models for continuous outcome variables (raw CES-D and STAI scores, phoneme comprehension time, hippocampal volume, Fazekas scores and microhaemorrhage count). An illustration of the R code is as follows:

```
library(tidyverse)

linear_model = lm(continuous_outcome ~ exposure +
covariate, data=dataset)

tidy(linear_model, conf.int = TRUE)
```

For binary outcomes including self-reported depression or anxiety disorder, I used logistic regression. I also generated binary variables based on accepted cut scores for the COGNITO name-face association test, as well as CES-D and STAI. For these binary variables, I anticipated small numbers in each sub-group so used Student's t-test to compare the means. On plotting standardised residuals of these models with condition and medication counts as exposure variables, there were no influential observations. The code used for logistic regression followed the following template:

```
library(tidyverse)

logistic_model = glm(dichotomous_outcome ~ exposure +
covariate, data=dataset, family=binomial(link='logit'))

tidy(logistic_model, exponentiate = TRUE, conf.int =
TRUE)
```

I tested each covariate using logistic or linear regression against all exposure and outcome variables. If the variable was associated with both exposure and outcome (P<0.05), I included it as a covariate in preliminary analyses. I included age and gender in all models, with additional relevant covariates for each group of outcomes.

The analyses were grouped by outcome variable. For each outcome, I ran the appropriate regression model with number of chronic conditions and number of medications as exposure variables. I conducted the analyses initially unadjusted and then included specific combinations of covariates, presenting the adjusted model results.

4.3.6.3 Sensitivity analyses

In analyses with depression and anxiety outcomes, I conducted additional analyses in a subsample of participants not taking antidepressants for a psychiatric indication, to explore the importance of this variable beyond including it as a covariate. I also

tested for interaction effects between the number of chronic conditions and antidepressant use.

4.4 RESULTS

4.4.1 Description of the sample

The sample consisted of 210 individuals, 148 (70.5%) of whom were women. Self-reported race was Caucasian for 89.5% of participants with the next largest groups being black (n=7, 3.3%) and Indian subcontinent (n=7, 3.3%). Further demographic details are listed in Table 4-2. This section focuses on the key exposure and outcome variables; further information about the sample has been published elsewhere.[308,322]

Table 4-2: Sample characteristics, n=210

Variable	Missing	N (%)	Mean (SD)
Gender (female)	0	148 (70.5%)	
Race (Caucasian)	0	188 (89.5%)	
Currently have depression (self-report)	0	16 (7.6%)	
Currently taking antidepressant	0	26 (12.4%)	
Taking antidepressant for psychiatric indication	0	18 (8.6%)	
Currently taking anxiolytic	0	1 (0.5%)	
Current anxiety disorder (self-report)	0	21 (10.0%)	
Head injuries leading to loss of consciousness	0	0 = 129 (61.4%) 1-2 = 70 (33.3%) 3 or more = 11 (5.2%)	
≥2 chronic conditions	0	119 (56.7%)	
Taking ≥3 medications (excluding antidepressants)	0	39 (18.6%)	
Age in years	0		52.0 (5.47) Women: 51.7 (5.42) Men: 52.7 (5.56)
Years of education	0		15.9 (3.44)
Number of chronic physical conditions	0		2.17 (1.86) Women: 2.34 (1.97) Men: 1.76 (1.50)
Number of current medications	0		1.65 (2.15)
Number of current medications excluding antidepressants	0		1.52 (2.00) Women: 1.47 (1.89) Men: 1.66 (2.25)

Variable	Missing N (%)	Mean (SD)
CES-D total score	0	9.2 (8.15)
STAI total score	0	30.4 (9.40)
Mean time for correct response on phoneme comprehension test (milliseconds)	0	1585.7 (304.24)
Number of names correctly recalled on name-face association (maximum 9)		5.34 (2.21)
CAIDE Dementia risk score	2	5.9 (2.81)
Total intracranial volume / cm^3	17	1389 (131.1)
Periventricular Fazekas score	17	1.1 (0.42)
Deep white matter Fazekas score	17	0.68 (0.57)
Hippocampal volume / cm^3	17	73.72 (0.34)
Cerebral microhaemorrhages	17	0.28 (1.22)

4.4.1.1 Chronic conditions

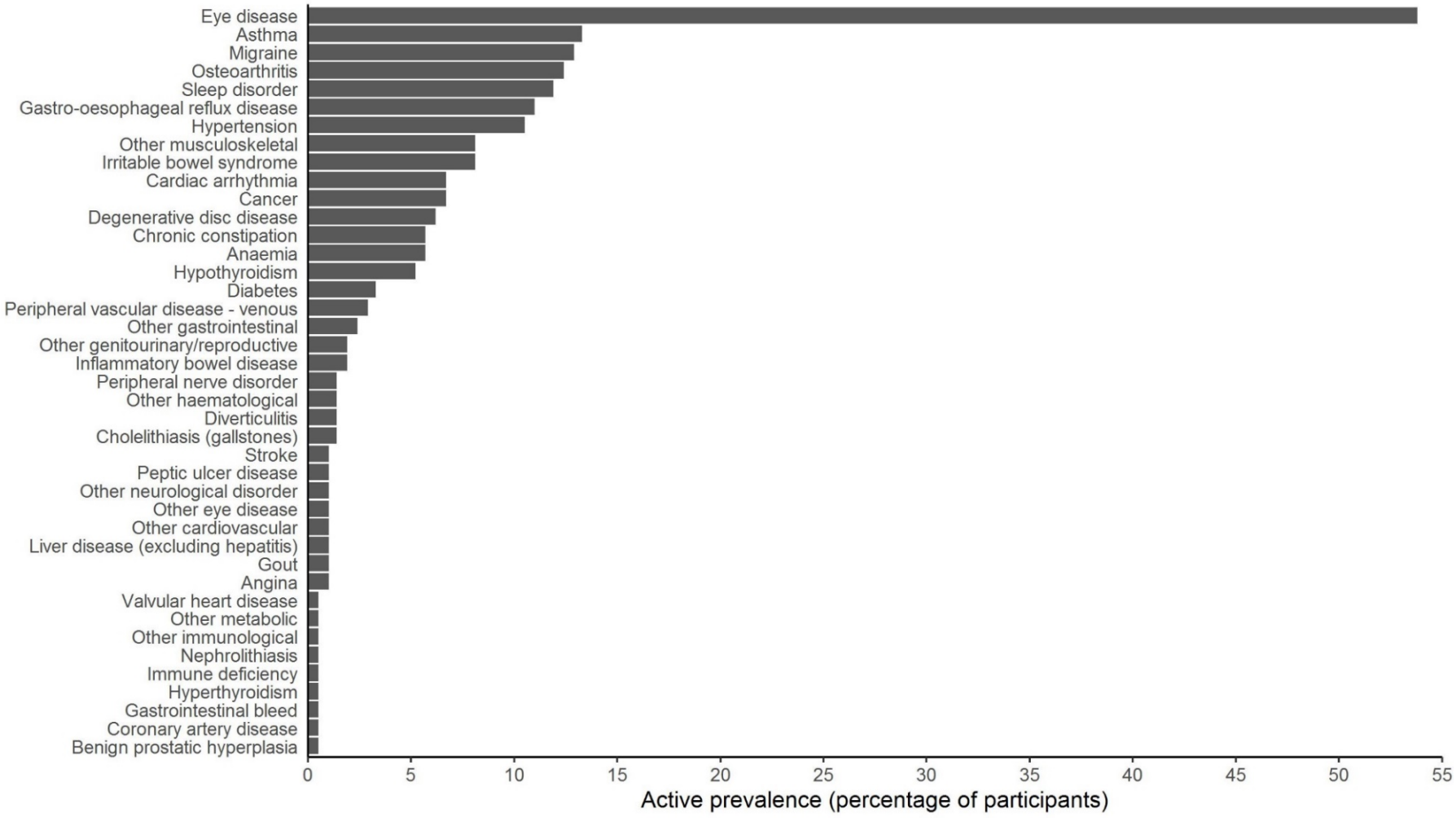
After excluding conditions not deemed to be chronic, I calculated the prevalence of each listed condition, as shown in Table 4-3 and displayed in Figure 4-2 on page 134. Of these 55 conditions, 14 were not reported by any participants. It is apparent that eye disease is the most prevalent condition. This may be due to the method of information gathering, which did not allow any sub-categories of eye disease and therefore may include a variety of conditions such as glaucoma or presbyopia.

Table 4-3: Prevalence of all conditions. Total n=210

Body system	Condition	Active prevalence
Blood	Anaemia	12 (5.7%)
	Other haematological	3 (1.4%)
Cardiovascular	Angina	2 (1.0%)
	Congestive heart failure	0
	Hypertension	22 (10.5%)
	Cardiac arrhythmia	14 (6.7%)
	Peripheral vascular disease – arterial	0
	Peripheral vascular disease – venous	6 (2.9%)
	Congenital heart disease	0
	Valvular heart disease	1 (0.5%)
	Coronary artery disease	1 (0.5%)
	Aortic aneurysm (surgery)	0
	Pacemaker	0
	Other cardiovascular	2 (1.0%)
Gastrointestinal	Peptic ulcer disease	2 (1.0%)
	Gastro-oesophageal reflux disease	23 (11.0%)

Body system	Condition	Active prevalence
	Liver disease (excluding hepatitis)	2 (1.0%)
	Hepatitis	0
	Pancreatitis	0
	Gastrointestinal bleed	1 (0.5%)
	Cholelithiasis (gallstones)	3 (1.4%)
	Cholecystitis	0
	Inflammatory bowel disease	4 (1.9%)
	Diverticulitis	3 (1.4%)
	Irritable bowel syndrome	17 (8.1%)
	Chronic constipation	12 (5.7%)
	Other gastrointestinal	5 (2.4%)
Genitourinary or reproductive	Kidney disorder	0
	Benign prostatic hyperplasia	1 (0.5%)
	Nephrolithiasis	1 (0.5%)
	Other genitourinary/reproductive	4 (1.9%)
Ears, eyes, nose, throat	Eye disease	113 (53.8%)
	Other eye disease	2 (1.0%)
Metabolic	Diabetes	7 (3.3%)
	Hyperthyroidism	1 (0.5%)
	Hypothyroidism	11 (5.2%)
	Other metabolic	1 (0.5%)
Musculoskeletal	Gout	2 (1.0%)
	Osteoarthritis	26 (12.4)
	Collagen vascular disease	0
	Degenerative disc disease	13 (6.2%)
	Other musculoskeletal	17 (8.1%)
Neurological	Seizure/convulsion disorder	0
	Migraine	27 (12.9%)
	Stroke (ever)	2 (1.0%)
	Parkinson’s disease	0
	Peripheral nerve disorder	3 (1.4%)
	Sleep disorder	25 (11.9%)
	Other neurological disorder	2 (1.0%)
Immunological	Immune deficiency	1 (0.5%)
	Other immunological	1 (0.5%)
Cancer	Cancer (ever)	14 (6.7%)
Pulmonary	Chronic obstructive pulmonary disease	0
	Asthma	28 (13.3%)
	Tuberculosis	0

Figure 4-2: Prevalence of chronic conditions



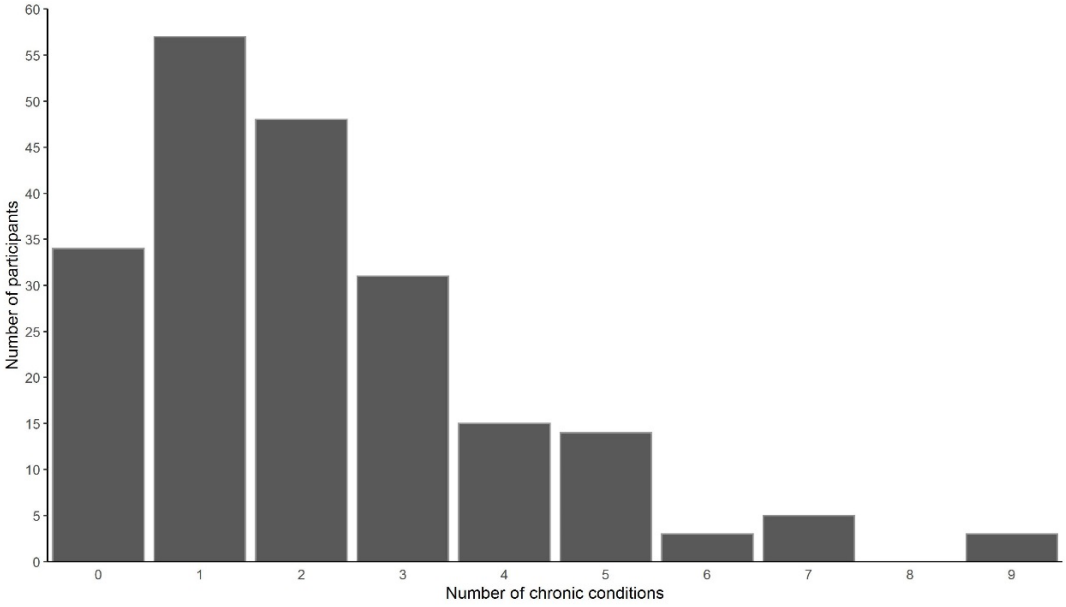
The mean number of chronic physical conditions was 2.17 (SD=1.86), with a range of 0-9 and median 2. Women reported more physical conditions than men; a Student's t-test identified a difference in the means (μ_{men}=1.76 [SD_{men}=1.50]; μ_{women}=2.34 [SD_{women}=1.97], t= -2.34, *P*=0.020). Table 4-4 shows the prevalence of multimorbidity using different cut-offs.

Table 4-4: Prevalence of multimorbidity

Number of conditions	**n (%)**
0	34 (16.2%)
1	57 (27.1%)
≥2	119 (56.7%)
≥3	71 (33.8%)
≥4	40 (19.0%)

Figure 4-3 shows the distribution of participants' total number of chronic conditions.

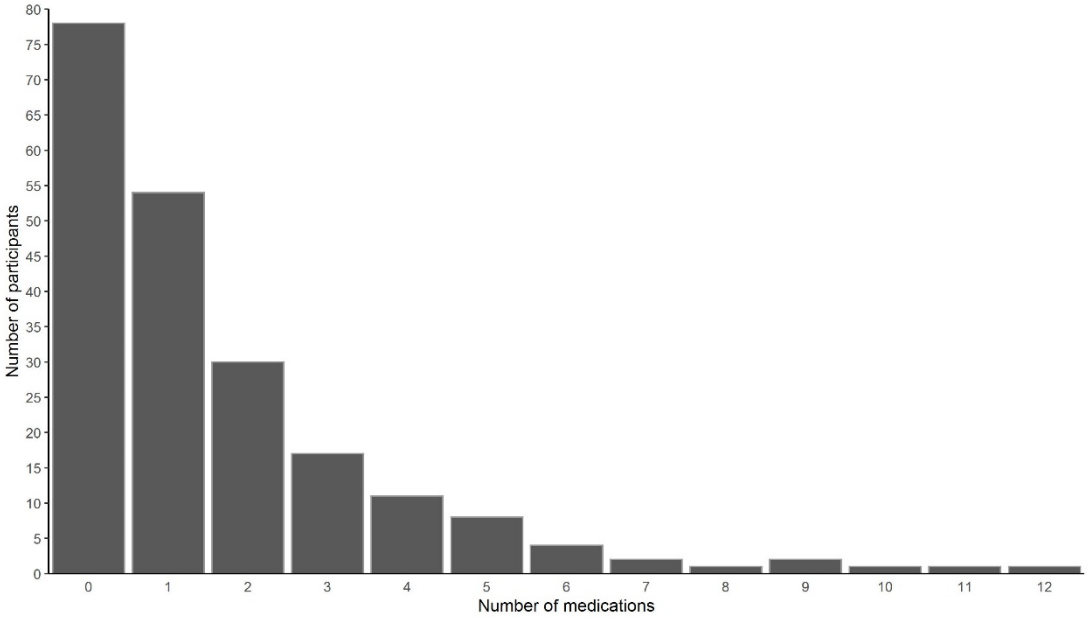
Figure 4-3: Distribution of chronic physical conditions



4.4.1.2 Medications

The mean number of medications reported was 1.65 (SD=2.15), median 1 and range 0-12, and the distribution is displayed in Figure 4-4.

Figure 4-4: Distribution of total number of current medications



Twenty-six (12.4%) participants took antidepressants, with indications as follows: ten for depression, eight for anxiety, obsessive-compulsive disorder or bipolar disorder and eight for other diverse indications including pain relief, pre-menstrual tension and hot flushes.

When adding an interaction term to the model, there was no statistically significant interaction between chronic condition count and antidepressant use. After excluding antidepressants, the mean number of medications was 1.52 (SD=2.0), median 1 and range 0-11. The distribution is shown in Figure 4-5. On Student's t-test, there was no difference between the mean medication use, excluding antidepressants, for men and women (μ_{men}=1.66 [SD_{men}=2.25]; μ_{women}=1.47 [SD_{women}=1.89] , t=0.60, *P*=0.551).

Figure 4-5: Distribution of number of current medications, excluding antidepressants

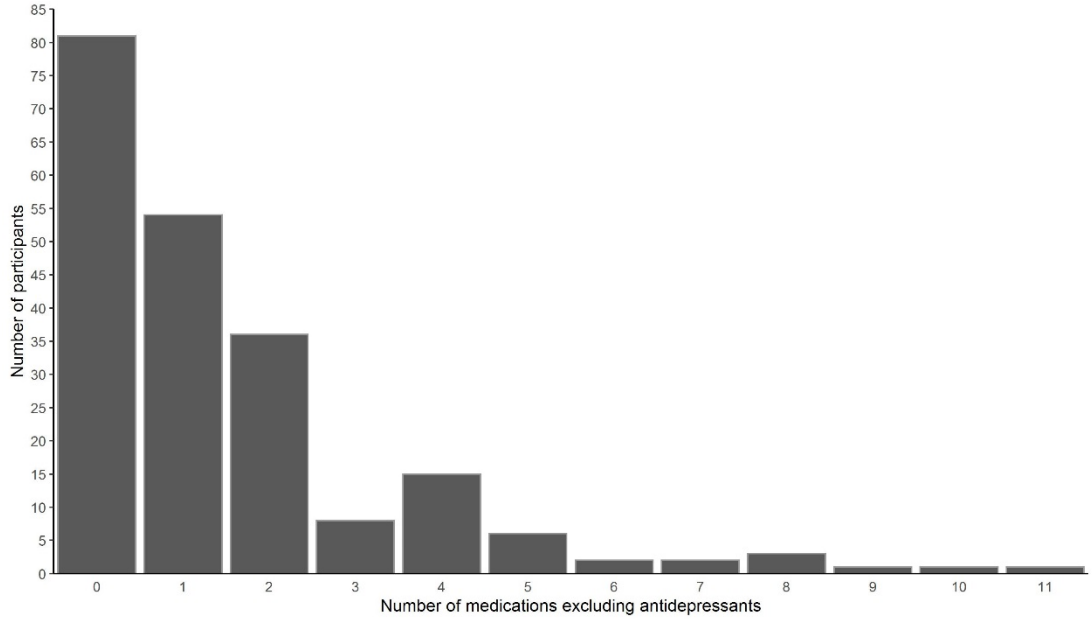
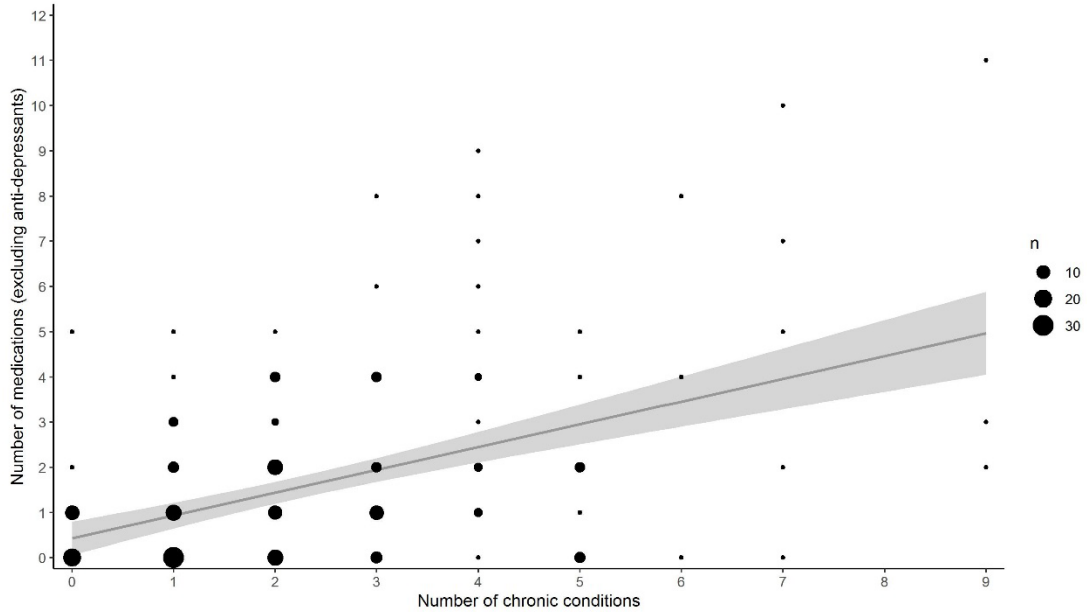


Figure 4-6 shows the number of medications, excluding antidepressants, compared to the total number of chronic physical conditions. For those participants with at least one chronic condition, the mean number of medications per condition was 0.72 (SD 0.85), median 0.5 and range 0.2-5.0.

Figure 4-6: Number of medications by chronic physical conditions



Only one participant was taking an anxiolytic medication, and not for a psychiatric indication, so this was abandoned as a covariate.

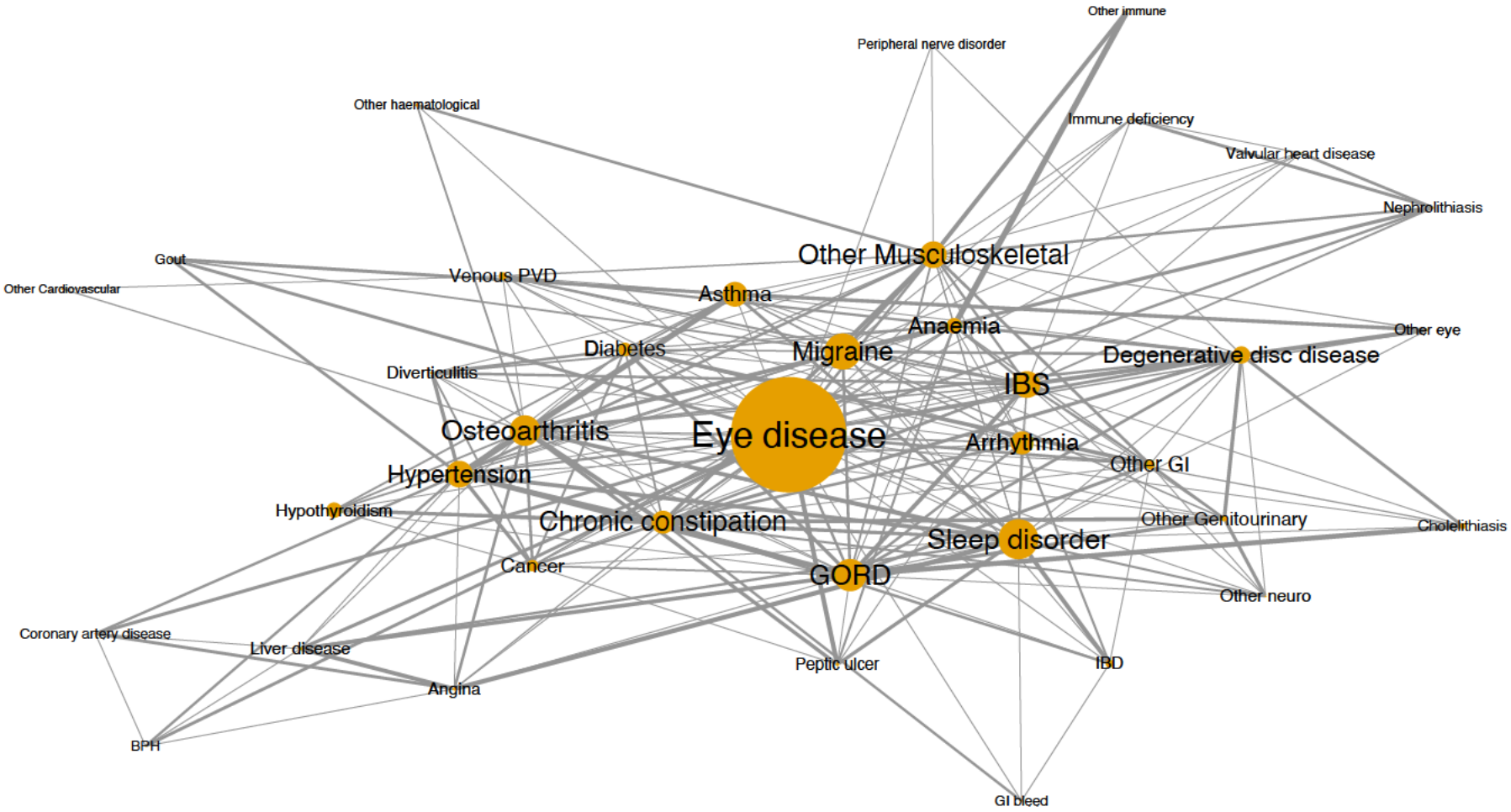
4.4.2 Network analyses

Seventy-one participants had three or more conditions and 48 people took three or more medications (including antidepressants). I only included participants with at least three conditions or medications in the network analyses in keeping with similar published research.[276]

Among the participants with three or more concurrent conditions, 38 conditions were reported by at least one participant. Figure 4-7 is a network analysis diagram of the interaction between the conditions. The label size of each node reflects its number of connections to other conditions, whereas the node size represents the prevalence of that condition. The thickness of lines between nodes displays the relative frequency of that connection.

Due the disproportionately high prevalence of eye disease and therefore its high rates of comorbidity, I generated another sample of people with three or more conditions, excluding all eye disease from the condition list. This sample included 48 participants. I produced another network analysis diagram of this sample, seen in Figure 4-8. Figure 4-9 is a network graph of the medications used by participants who took at least three medications. It shows that psychoanaleptics (the ATC term that includes antidepressants, stimulants and anti-dementia drugs, but in this sample only antidepressants were relevant) were the most connected group. Acid-related drugs and antihypertensives were the most prevalent but were relatively less frequently co-existent with other medications.

Figure 4-7: Network diagram of chronic conditions among people with ≥3 conditions (n=71)



Abbreviations: PVD: peripheral vascular disease; IBS: irritable bowel syndrome; GI: gastrointestinal; GORD: gastro-oesophageal reflux disease; BPH: benign prostatic hypertrophy; IBD: inflammatory bowel disease.

Figure 4-8: Network diagram of chronic conditions among people with ≥3 conditions, excluding eye conditions (n=48)

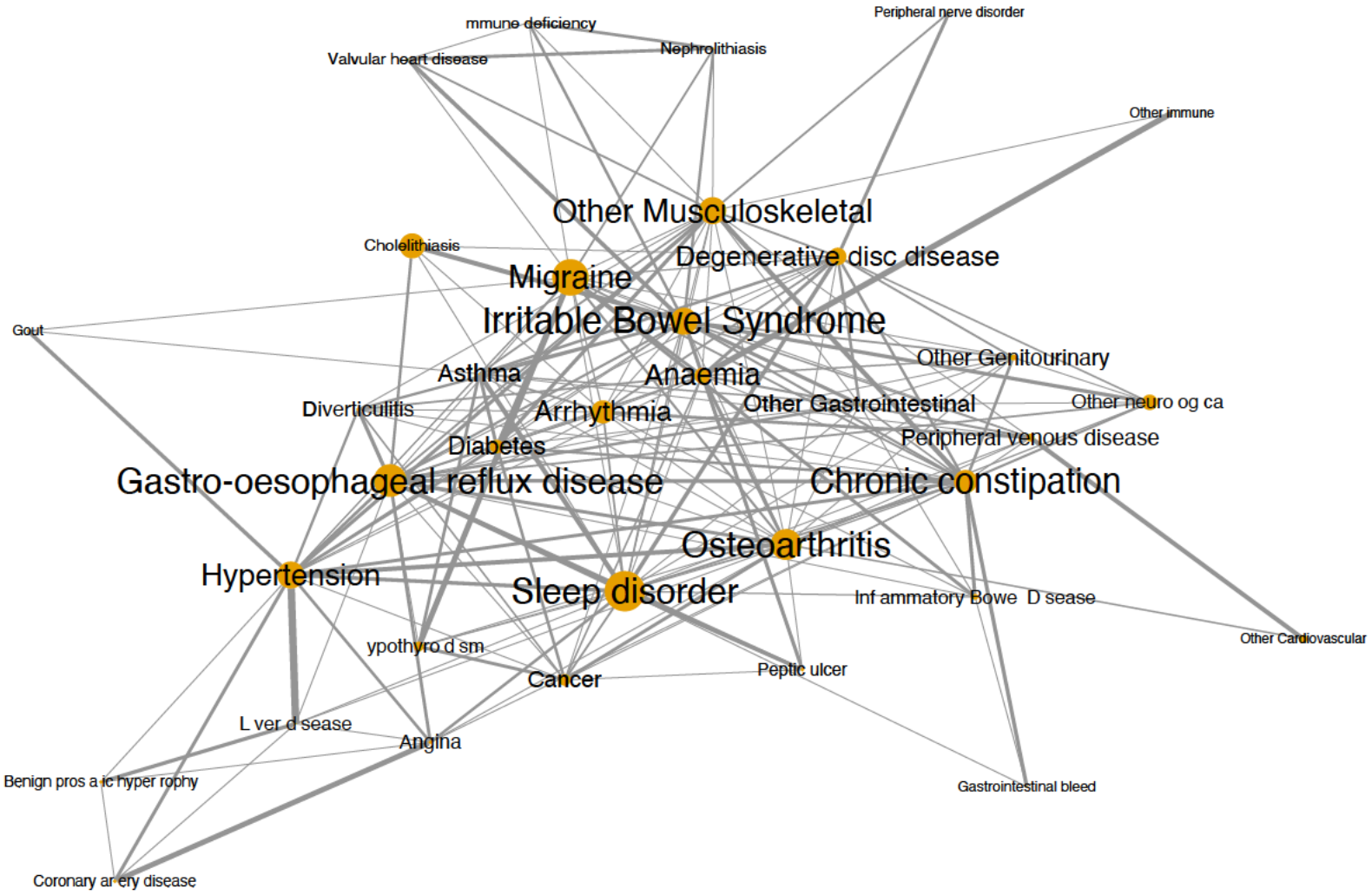
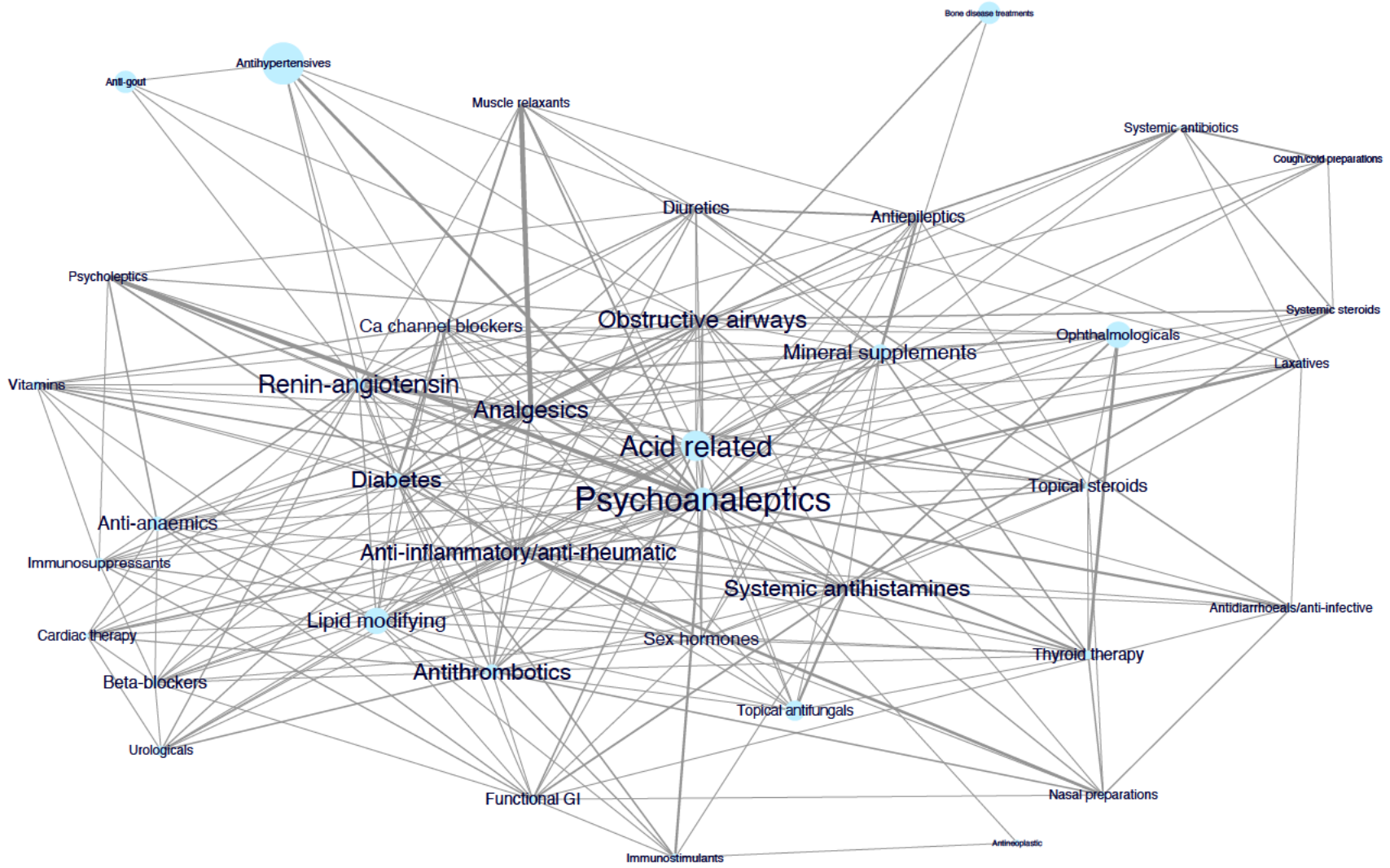


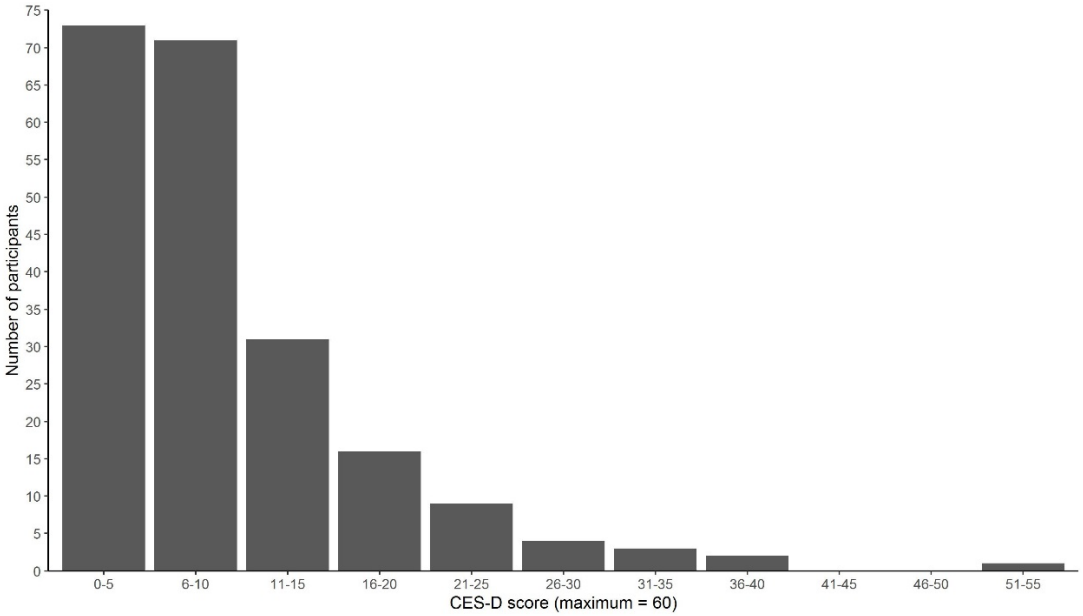
Figure 4-9: Network diagram of medications among participants taking ≥3 medications (n=48)



4.4.3 Depression outcomes

The mean score on the CES-D was 9.2 (SD 8.1), median 7 and range 0-52. Figure 4-10 shows the distribution of the scores, with clear right skew. A total of 35 (16.7%) participants scored 16 or over.

Figure 4-10: Distribution of CES-D scores



I adjusted for age and gender in all models. Other variables that were associated (P<0.05) with at least one outcome and at least one exposure variable were number of head injuries, antidepressant use and any reported history of depression. I did not include any history of depression in these analyses, as there was too much overlap with self-reported history of current depression. In order to minimise the number of covariates used in this relatively small sample, I did not include head injuries as it was less clinically relevant. I added race as a covariate in order to harmonise with the anxiety outcomes, where it was significantly associated with the exposure variables. I used the same covariates across all exposure variables for both CES-D and self-reported depression outcomes.

In all the results for depression and anxiety outcomes, I list three models: Model 1 with age, gender and race as covariates, Model 2 with the addition of antidepressant use and Model 3 as the sensitivity analyses in participants not taking antidepressants for a psychiatric indication (adjusted for age, gender and race).

4.4.3.1 Chronic conditions and CES-D score

There were relatively few participants with each number of chronic physical conditions according to binary CES-D score, as shown in Table 4-5.

Table 4-5: Number of participants with each number of conditions, by CES-D score

Number of conditions	CES-D <16	CES-D ≥16	CES-D <16	CES-D ≥16
0	29	5	75	16
1	46	11		
2	41	7	100	19
3	27	4		
≥4	32	8		

On linear regression, there was an association between continuous condition count and continuous CES-D score that met conventional statistical significance when adjusted for demographics, as shown in Table 4-6. This suggested an increase in CES-D score by 0.62 points (95% CI 0.04 to 1.20) with each additional chronic condition. However, the association was no longer significant when additionally adjusting for antidepressant use or in a subsample not taking antidepressants. In addition, the positive associations had wide confidence intervals, likely due to small numbers of people attaining each score on the CES-D (all results are shown in Table 4-6). To address this, I also used a binary outcome variable of ≥16, which showed no significant associations with continuous conditions. Multimorbidity (≥2 conditions) was not significantly associated with either continuous or binary CES-D scores.

Table 4-6: Results of regression models for depression outcomes dependent on chronic physical conditions

Exposure / Outcome	Model	Chronic physical conditions			Multimorbidity (≥2 compared to 0-1 conditions)		
		Coefficient (95% CI)	OR[a] (95% CI)	*P*-value	Coefficient (95% CI)	OR (95% CI)	*P*-value
CES-D continuous	Model 1	**0.62 (0.04 to 1.20)**		**0.035**	1.72 (-0.44 to 3.89)		0.118
	Model 2	0.46 (-0.13 to 1.05)		0.126	1.26 (-1.02 to 3.54)		0.278
	Model 3	0.37 (-0.26 to 1.00)		0.250	0.91 (-1.31 to 3.14)		0.420
CES-D ≥16	Model 1		1.06 (0.86 to 1.29)	0.573		0.86 (0.39 to 1.88)	0.698
	Model 2		1.01 (0.81 to 1.24)	0.904		0.75 (0.36 to 1.68)	0.486
	Model 3		0.94 (0.72 to 1.19)	0.629		0.63 (0.27 to 1.45)	0.283
Self-reported depression	Model 1		**1.41 (1.11 to 1.80)**	**0.005**		2.38 (0.77 to 9.02)	0.159
	Model 2		1.25 (0.82 to 1.90)	0.295		0.81 (0.10 to 5.72)	0.833

Model 1: Adjusted for age, gender, race

Model 2: Adjusted for age, gender, race, antidepressant use for psychiatric indication

Model 3: Adjusted for age, gender, race in sample not taking antidepressants for psychiatric indication (n=192)

[a] Odds ratio per unit increase in number of chronic conditions

4.4.3.2 Chronic conditions and self-reported depression

Sixteen (7.6%) people reported a current diagnosis of depression, and of those, seven (43.7%) scored 16 or more on the CES-D (Table 4-7).

Table 4-7: CES-D scores compared to self-report

Self-reported depression	CES-D <16	CES-D ≥16
Current depression	9	7
No current depression	166	28

I calculated the mean of each exposure variable according to participants' self-reported depression status, and used a Student's t-test to examine the differences between the means, as shown in Table 4-8. There was a difference between the mean number of chronic physical conditions among people with and without self-reported depression (*P*=0.025), but not their number of medications.

Table 4-8: Mean chronic conditions and medications according to depression status

	Mean (SD) in participants with self-reported depression	Mean (SD) in participants with no depression	T-test for means (*P*)
Number of chronic conditions	3.63 (2.50)	2.05 (1.75)	**0.025**
Number of medications	2.69 (3.20)	1.43 (1.85)	0.140

Again, the numbers of people with each number of chronic conditions and depression were small, as shown in Table 4-9.

Table 4-9: Number of conditions by self-reported depression status

	No depression	Depression
0 conditions	34	0
1 condition	53	4
2 conditions	45	3
3 conditions	29	2
≥4 conditions	33	7

I carried out logistic regression of continuous number of physical conditions as the exposure variable to predict self-reported depression. There was an association between these two, shown in Table 4-6, which remained when adjusting for demographic covariates (OR for depression with each additional condition=1.41, 95%

CI 1.11 to 1.80, *P*=0.005) but not for antidepressant use (OR=1.25, 95% CI 0.82 to 1.90, *P*=0.295). However, the numbers in each group were small. When treating multimorbidity as dichotomous, there was no significant association with self-reported depression.

I did not conduct analyses in the subsample of people not taking antidepressants for psychiatric indication with the outcome of self-reported depression, as the overlap between this outcome and taking antidepressants was high, and numbers of participants were small.

4.4.3.3 Medication use and CES-D score

In these analyses, the count of medications excludes antidepressants. Similarly to chronic conditions, the number of people with individual numbers of medications according to CES-D score was relatively small, as shown in Table 4-10.

Table 4-10: Number of participants with each number of medications (excluding antidepressants), by CES-D score

Number of medications	CES-D <16	CES-D ≥16
0	67	14
1	48	6
2	32	4
3	5	3
4	13	2
≥5	10	6

With each additional medication, the CES-D score increased by 0.66 points (95% CI 0.12 to 1.21, *P*=0.017), until adjusted for antidepressant use (β=0.52, 95% CI -0.03 to 1.07, *P*=0.062), as shown in Table 4-11. The association between continuous conditions and scoring ≥16 on CES-D was only significant in the unadjusted model (OR with each additional medication=1.20, 95% CI 1.02 to 1.40, *P*=0.022).

Polypharmacy (≥3 medications) was only associated with continuous and binary CES-D scores in unadjusted models (continuous: β=3.52, 95% CI 0.71 to 6.34 and binary: OR=2.41, 95% CI 1.03 to 5.39). The adjusted results are shown in Table 4-11.

Table 4-11: Results of regression models for depression outcomes dependent on medication use

Exposure / Outcome	Model	Medications excluding antidepressants			Polypharmacy (≥3 compared to 0-2 medications)		
		Coefficient (95% CI)	OR[a] (95% CI)	*P*-value	Coefficient (95% CI)	OR (95% CI)	*P*-value
CES-D continuous	Model 1	**0.66 (0.12 to 1.21)**		**0.017**	2.59 (-0.22 to 5.40)		0.071
	Model 2	0.52 (-0.03 to 1.07)		0.062	2.30 (-0.48 to 5.08)		0.104
	Model 3	0.38 (-0.23 to 0.99)		0.220	1.60 (-1.33 to 4.53)		0.283
CES-D ≥16	Model 1		1.17 (0.98 to 1.39)	0.078		2.13 (0.83 to 5.24)	0.106
	Model 2		1.14 (0.94 to 1.36)	0.169		2.02 (0.77 to 5.03)	0.139
	Model 3		1.05 (0.84 to 1.29)	0.651		1.42 (0.48 to 3.81)	0.499
Self-reported depression	Model 1		**1.36 (1.07 to 1.73)**	**0.010**		1.80 (0.42 to 6.55)	0.392
	Model 2		1.11 (0.76 to 1.71)	0.621		1.21 (0.12 to 10.3)	0.865

Model 1: Adjusted for age, gender, race

Model 2: Adjusted for age, gender, race, antidepressant use for psychiatric indication

Model 3: Adjusted for age, gender, race in sample not taking antidepressants for psychiatric indication (n=192)

[a] Odds ratio per unit increase in number of medications

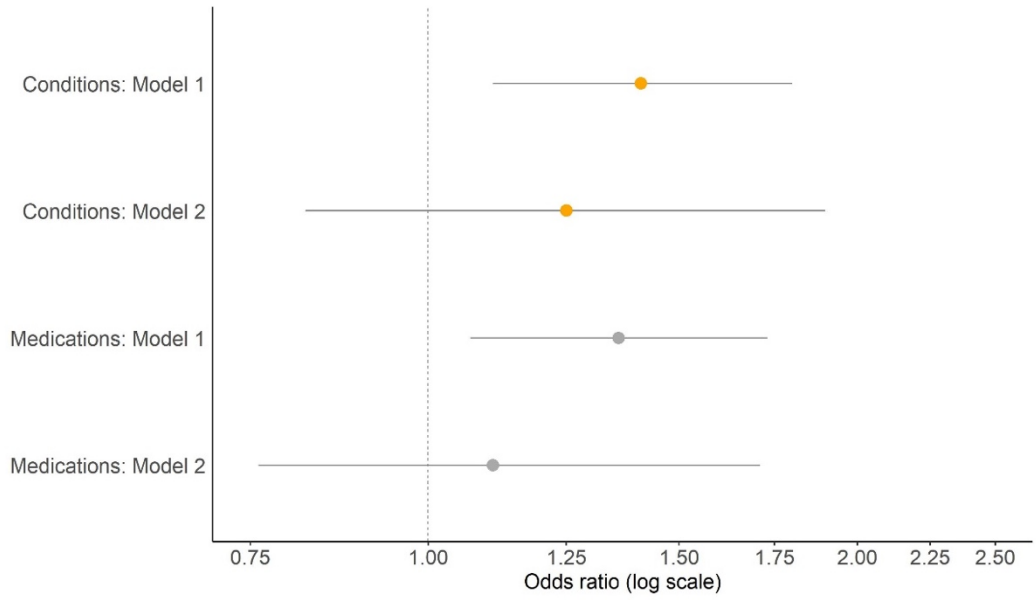
4.4.3.4 Medication use and self-reported depression

On logistic regression, there was an association between number of medications and self-reported depression (OR with each additional medication=1.36 (95% CI 1.07 to 1.73, *P*=0.010), except when adjusting for antidepressant use (OR=1.11, 95% CI 0.76 to 1.71, *P*=0.621). These results are shown in Table 4-11 and, along with the models where conditions were an exposure, are displayed in Figure 4-11.

Owing to the small number of people with self-reported depression, I used a binary polypharmacy exposure variable of ≥3 compared to 0-2 medications. There was no significant association between this and the occurrence of self-reported depression.

In summary, increasing conditions and medications were associated with self-reported depression. Increasing numbers of conditions and medications were associated with increasing scores on CES-D. These associations were attenuated when accounting for antidepressant use.

Figure 4-11: Odds ratio for reporting depression in medical history with larger (continuous) numbers of conditions or medications



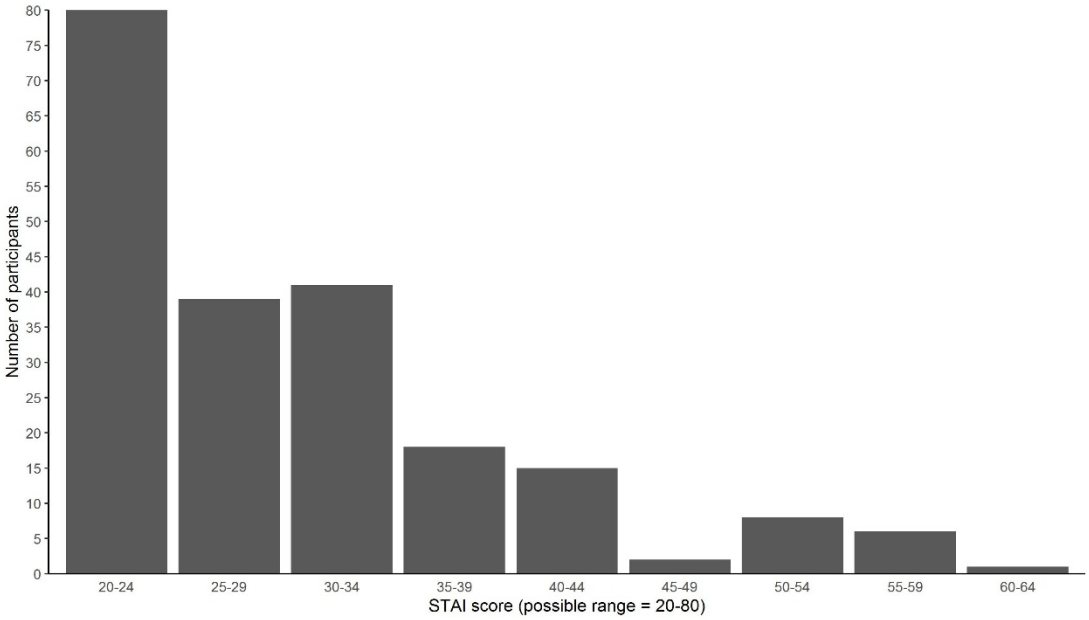
Model 1: Adjusted for age, gender, race
Model 2: Adjusted for age, gender, race, antidepressant use for psychiatric indication

4.4.4 Anxiety outcomes

The range of possible scores on the STAI is 20-80. The mean score in the PREVENT Dementia cohort was 30.4 (SD 9.4), median 28 and range 20-60. I used the continuous measure to better understand symptoms, as well as a dichotomous outcome. Figure 4-12 shows the distribution of scores, again with right skew.

In preliminary analyses with the outcomes of the Spielberger State-Trait Anxiety Inventory (STAI) (state questions only) and self-reported anxiety disorder, I tested control variables using linear regression. Race, antidepressant use and head injuries were associated (P<0.05) with at least one of the two anxiety outcomes and at least one of the exposure variables (number of chronic conditions and medications). I included age, gender and race as covariates, for consistency with the depression outcome analyses.

Figure 4-12: Distribution of STAI scores in PREVENT



4.4.4.1 Chronic conditions and Spielberger State Anxiety Inventory score

Using linear regression, I examined the association between numbers of chronic physical conditions (continuous and dichotomous) and STAI scores (both continuous

and dichotomised). None of the models attained conventional statistical significance; all results are shown in Table 4-13.

4.4.4.2 Chronic conditions and self-reported anxiety disorder

Due to the relatively small numbers of people reporting an anxiety disorder diagnosis, I present the characteristics of each exposure variable between the groups in Table 4-12. A Student's t-test showed a difference between the means of chronic conditions (*P*<0.001) in people with and without an anxiety disorder, whereas the mean numbers of medication were not significantly different.

Table 4-12: Exposure variable characteristics by anxiety disorder diagnosis

	Mean (SD) in participants with self-reported anxiety	**Mean (SD) in participants with no anxiety disorder**	**T-test for means (*P*)**
Number of chronic conditions	4.2 (2.44)	1.95 (1.65)	**<0.001**
Number of medications	2.24 (2.51)	1.44 (1.93)	0.174

Logistic regression of continuous chronic conditions showed an association between increasing morbidity and self-reported anxiety disorder, which remained when adjusting for all relevant covariates, including antidepressant use (OR with each additional condition=1.74 (95% CI 1.31 to 2.39, *P*<0.001), as shown in Table 4-13.

Table 4-13: Results of regression models for anxiety outcomes dependent on chronic conditions

Exposure / Outcome	Model	Chronic physical conditions			Multimorbidity (≥2 compared to 0-1 conditions)		
		Coefficient (95% CI)	OR[a] (95% CI)	*P*-value	Coefficient (95% CI)	OR (95% CI)	*P*-value
STAI continuous	Model 1	0.06 (-0.64 to 0.76)		0.860	1.20 (-1.39 to 3.79)		0.361
	Model 2	-0.07 (-0.78 to 0.65)		0.855	0.92 (-1.70 to 3.53)		0.490
	Model 3	0.02 (-0.75 to 0.78)		0.963	0.62 (-2.08 to 3.32)		0.651
STAI ≥40	Model 1		0.69 (0.22 to 1.84)	0.485		0.74 (0.33 to 1.64)	0.451
	Model 2		0.72 (0.23 to 1.92)	0.532		0.77 (0.34 to 1.72)	0.517
	Model 3		0.68 (0.21 to 1.89)	0.487		0.73 (0.32 to 1.64)	0.443
Self-reported anxiety disorder	Model 1		**1.71 (1.35 to 2.21)**	**<0.001**		**5.35 (1.68 to 23.9)**	**0.011**
	Model 2		**1.74 (1.31 to 2.39)**	**<0.001**		**4.50 (1.13 to 24.9)**	**0.051**

[a] Odds ratio per unit increase in number of chronic conditions

Model 1: Adjusted for age, gender, race

Model 2: Adjusted for age, gender, race, antidepressant use for psychiatric indication

Model 3: Adjusted for age, gender, race in sample not taking antidepressants for psychiatric indication (n=192)

4.4.4.3 Medication use and Spielberger State Anxiety Inventory score

Twenty-one (10.0%) participants reported a diagnosis of anxiety disorder in the medical history. Of these, seven (33.3%) scored ≥40 on the STAI and 12 (46.2%) took antidepressants, as displayed in Table 4-14.

Table 4-14: Characteristics of participants reporting anxiety disorder

	Self-reported anxiety disorder	**No anxiety disorder**
STAI <40	14	164
STAI ≥40	7	25
Not taking antidepressants	9	175
Taking antidepressants	12	14

On linear regression analyses, there were no significant associations between medications, either continuous or dichotomised, and continuous or dichotomised STAI scores. These results are listed in Table 4-15.

4.4.4.4 Medication use and self-reported anxiety disorder

Results of logistic regression with self-reported anxiety as the outcome and medications, both continuous and binary, as exposure variables, are shown in Table 4-15. Although there was a marginal association in the model adjusted for age and gender, there was overall no association to suggest rejecting the null hypothesis in these analyses. The results of the odds ratios for self-reported anxiety disorder with chronic conditions and medication use are represented in Figure 4-13 on page 154.

In summary, increasing numbers of chronic physical conditions and multimorbidity were associated with self-reported anxiety, although absolute numbers were small. Scores on the STAI were not linked to chronic conditions or medications.

Table 4-15: Results of regression models for anxiety outcomes dependent on medication use

Exposure / Outcome	Model	Medications excluding antidepressants			Polypharmacy (≥3 compared to 0-2 medications)		
		Coefficient (95% CI)	OR[a] (95% CI)	*P*-value	Coefficient (95% CI)	OR (95% CI)	*P*-value
STAI continuous	Model 1	0.10 (-0.56 to 0.75)		0.766	0.62 (-2.75 to 3.98)		0.717
	Model 2	-0.01 (-0.68 to 0.66)		0.973	0.42 (-2.94 to 3.79)		0.805
	Model 3	0.08 (-0.65 to 0.82)		0.823	0.61 (-2.95 to 4.17)		0.737
STAI ≥40	Model 1		0.92 (0.73 to 1.12)	0.452		0.69 (0.22 to 1.84)	0.485
	Model 2		0.94 (0.74 to 1.14)	0.547		0.72 (0.23 to 1.92)	0.532
	Model 3		0.91 (0.70 to 1.14)	0.447		0.68 (0.21 to 1.89)	0.487
Self-reported anxiety disorder	Model 1		**1.24 (1.00 to 1.53)**	**0.043**		1.76 (0.50 to 5.53)	0.350
	Model 2		1.05 (0.78 to 1.40)	0.760		1.41 (0.28 to 6.05)	0.656

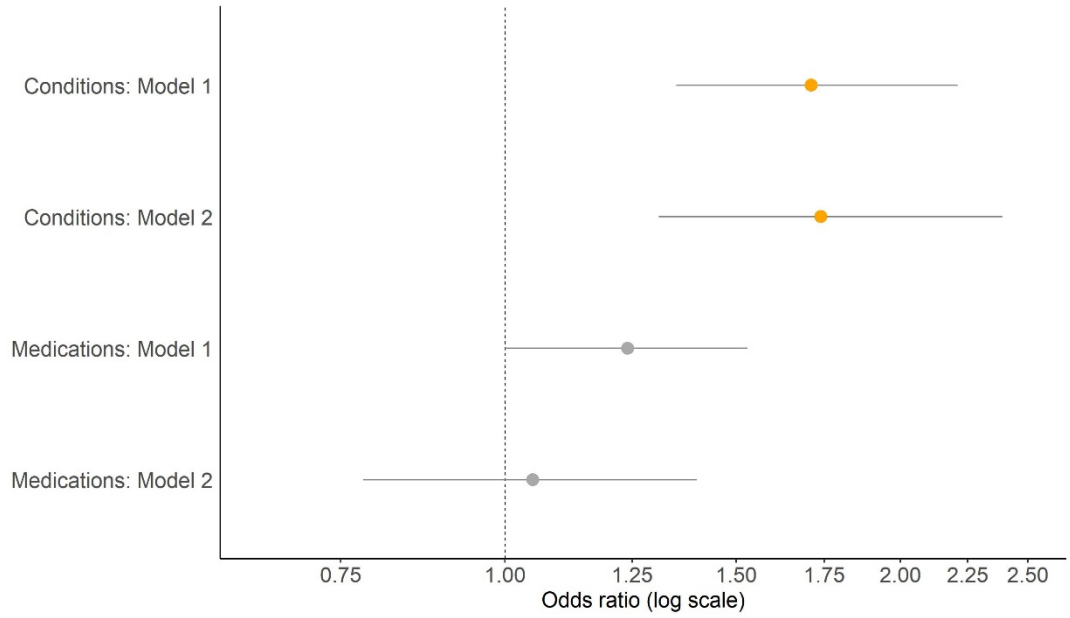
Model 1: Adjusted for age, gender, race

Model 2: Adjusted for age, gender, race, antidepressant use for psychiatric indication

Model 3: Adjusted for age, gender, race in sample not taking antidepressants for psychiatric indication (n=192)

[a] Odds ratio per unit increase in number of medications

Figure 4-13: Odds ratios for reporting anxiety disorder in medical history with increasing numbers of conditions and medications



Model 1: Adjusted for age, gender, race
Model 2: Adjusted for age, gender, race, antidepressant use for psychiatric indication

4.4.5 Cognitive test outcomes

When choosing covariates for the cognitive test outcomes, I found that age, gender, race, years of education and CAIDE score were each associated with at least one outcome and at least one exposure variable.

4.4.5.1 Chronic conditions and phoneme comprehension time

The range of mean times on the phoneme comprehension test was 1000-2654 milliseconds, with a median of 1527. On linear regression with this as a continuous outcome and continuous chronic conditions as the exposure, the results (shown in Table 4-16) showed no support for rejecting the null hypothesis. Anticipating no further associations, I did not further categorise conditions or medications into a binary multimorbidity measure.

Table 4-16: Results of regression models for cognitive test outcomes in relation to continuous condition and medication counts

Exposure / Outcome	Model	Chronic physical conditions			Medications (excluding antidepressants)		
		Coefficient (95% CI)	OR[a] (95% CI)	*P*-value	Coefficient (95% CI)	OR[b] (95% CI)	*P*-value
Phoneme comprehension time	Model 1	-0.08 (-22.4 to 22.3)		0.994	-4.62 (-25.3 to 16.1)		0.661
	Model 2	-0.87 (-23.7 to 21.9)		0.940	-5.50 (-26.8 to 15.8)		0.611
	Model 3	-0.93 (-23.3 to 31.5)		0.935	-3.31 (-24.7 to 18.1)		0.760
Name-face association score ≥6	Model 1		1.01 (0.86 to 1.17)	0.948		1.06 (0.92 to 1.23)	0.419
	Model 2		0.99 (0.84 to 1.16)	0.873		1.09 (0.93 to 1.28)	0.277
	Model 3		1.03 (0.89 to 1.20)	0.664		1.07 (0.93 to 1.23)	0.375

Model 1: Adjusted for age, gender

Model 2: Adjusted for age, gender, race, years of education

Model 3: Adjusted for CAIDE score

[a] Odds ratio per unit increase in number of conditions

[b] Odds ratio per unit increase in number of medications

4.4.5.2 Medication use and phoneme comprehension time

There was no significant association between continuous number of medications and phoneme comprehension time, as shown in Table 4-16 on page 155. I therefore did not pursue using a dichotomous polypharmacy variable.

4.4.5.3 Chronic conditions and name-face association

The median score on name-face associative learning was six out of a maximum of nine. Using a binary variable around this median, in keeping with previously published research using this measure, I performed logistic regression according to continuous number of chronic conditions.[308] I found no significant associations. (Table 4-16).

4.4.5.4 Medication use and name-face association

Using continuous number of medications (excluding antidepressants) as the exposure variable, I found no association with binary name-face association scores on logistic regression, as shown in Table 4-16.

In summary, there was no suggestion of any associations between increasing conditions or medications and either of the cognitive test outcomes.

4.4.6 MRI Outcomes

Seventeen (8.1%) participants did not have an MRI, so all the following results apply to the 193 (91.9%) participants that did. The following covariates were associated (P<0.05) with at least one exposure variable and at least one outcome: age, gender, race, CAIDE score, and total intracranial volume (except for hippocampal volume, which had already been adjusted for total brain volume). To avoid including too many covariates in this small sample, I did not include race.

4.4.6.1 Chronic conditions and hippocampal volume

On linear regression analyses, a negative coefficient would suggest that increasing chronic conditions was associated with smaller hippocampal volume (which is in turn associated with cognitive impairment and dementia). Table 4-17 shows the results, which include only a marginal association between the two when adjusting for CAIDE score (β= -0.03, 95% CI -0.05 to 0.00, *P*=0.040).

4.4.6.2 Medication use and hippocampal volume

In keeping with previous analyses, the medication variable excluded antidepressants, although this is less likely to affect MRI outcomes than depression or anxiety. I used linear regression to model the association between increasing medications and increasing hippocampal volume, and found no significant association, as shown in Table 4-17.

In summary, there was only weak evidence in support of an association between chronic conditions and decreasing hippocampal volume.

Table 4-17: Regression results for MRI findings in relation to conditions and medication use

Exposure / Outcome	Model	Chronic physical conditions		Medications (excluding antidepressants)	
		Coefficient (95% CI)	*P*-value	Coefficient (95% CI)	*P*-value
Hippocampal volume	Model 1	-0.01 (-0.04 to 0.01)	0.294	-0.01 (-0.04 to 0.01)	0.230
	Model 2	**-0.03 (-0.05 to 0.00)**	**0.040**	-0.02 (-0.05 to 0.01)	0.167
Periventricular Fazekas score	Model 1	**-0.04 (-0.07 to 0.00)**	**0.027**	-0.02 (-0.06 to 0.01)	0.175
	Model 2	-0.03 (-0.06 to 0.01)	0.112	-0.02 (-0.06 to 0.01)	0.112
	Model 3	-0.02 (-0.06 to 0.01)	0.184	-0.02 (-0.06 to 0.01)	0.184
Deep white matter Fazekas score	Model 1	-0.02 (-0.07 to 0.02)	0.360	0.02 (-0.03 to 0.06)	0.458
	Model 2	-0.02 (-0.06 to 0.03)	0.486	0.02 (-0.03 to 0.06)	0.479
	Model 3	-0.02 (-0.07 to 0.02)	0.300	0.01 (-0.03 to 0.06)	0.534
Microhaemorrhage count	Model 1	0.03 (-0.07 to 0.12)	0.596	-0.02 (-0.12 to 0.08)	0.716
	Model 2	0.03 (-0.07 to 0.13)	0.555	-0.01 (-0.11 to 0.09)	0.825
	Model 3	0.03 (-0.07 to 0.13)	0.539	-0.01 (-0.12 to 0.09)	0.780

Model 1: Adjusted for age, gender

Model 2: Adjusted for CAIDE score

Model 3: Adjusted for age, gender, total intracranial volume

4.4.6.3 Chronic physical conditions and Fazekas scores

I analysed each sub-test of the Fazekas score separately, firstly using the periventricular hyperintensity scale as the outcome. The results of linear regression analysis with chronic conditions as the exposure showed a marginal association between increasing chronic conditions and decreased score on the periventricular Fazekas score when adjusted for age and gender only (β= -0.04, 95% CI -0.07 to 0.00, *P*=0.027). Again, this association was attenuated when adjusted for CAIDE score or intracranial volume. The results are listed in Table 4-17 on page 158.

On linear regression with deep white matter Fazekas subscore as the outcome, there was no evidence to suggest an association with total chronic conditions (Table 4-17).

4.4.6.4 Medication use and Fazekas scores

I used linear regression of continuous number of medications with periventricular Fazekas score, and then deep white matter Fazekas score, as the outcomes. Neither of these analyses revealed a significant association, as seen in Table 4-17.

4.4.6.5 Chronic conditions and microhaemorrhage count

The mean number of cerebral microhaemorrhages was 0.28 (SD 1.22), with a range of 0-15. In linear regression analyses with continuous chronic conditions as the exposure variable, there was no evidence to support an association between these variables (see Table 4-17).

4.4.6.6 Medication use and microhaemorrhage count

With continuous medications as the exposure variable, I used linear regression with microhaemorrhage count as the outcome. There was no apparent association, as shown in Table 4-17.

In summary, there was no convincing evidence for associations between increasing chronic conditions or medications with any MRI outcomes suggestive of neurodegeneration.

4.5 DISCUSSION

4.5.1 Summary of main findings

Findings from this initial wave of the PREVENT Dementia study show that participants had a mean of 2.2 (SD 1.9) chronic physical conditions. It is difficult to compare multimorbidity between studies, as the lists used to generate condition counts vary considerably.[264] A recent English primary care cohort study found that people aged 45-54 years had a mean of 0.8 (SD 1.2) chronic conditions,[38] and Scottish data showed 45-64 year-olds had a mean of 1.2 conditions (SD 1.5).[39] The apparently above-average prevalence of multimorbidity in PREVENT Dementia participants may reflect the high number of conditions enquired about and the method of self-report at a detailed interview by a doctor.

The majority of PREVENT Dementia participants (n=132, 62.9%) were taking at least one medication, and among those, the mean medications taken was 2.6 (SD 2.2). This compares to a study of all adults in one area of Scotland aged over 20 years which found 58.2% of the population were prescribed any drugs, and of those, the mean of drugs dispensed was 4.4.[323] PREVENT Dementia participants therefore take on average fewer medications than the general population, which is likely due to the mid-life age range and that participants are healthy volunteers.

As discussed in section 4.4.1.2 on page 137, the mean number of medications per condition was 0.72, which is less than figures reported in the literature. For example, a 2018 Swedish register-based population study of adults aged over 75 years found a mean of 2.4 chronic conditions and 4.6 medications, that is a mean of 1.92 medications per condition.[78] The discrepancy may be explained in PREVENT Dementia by the detailed medical history interview revealing more conditions than

would be found in medical records, but the number of medications remaining the same.

4.5.1.1 Hypotheses addressed

1. a) There was an association between increasing chronic conditions and self-reported depression (adjusted OR with each additional condition=1.41, 95% CI 1.11 to 1.80, *P*=0.005) and increasing CES-D scores (adjusted model β=0.62, 95% CI 0.04 to 1.20, *P*=0.035). Dichotomous multimorbidity was not associated with these outcomes. In all cases, the associations were attenuated when accounting for use of antidepressants for psychiatric indications.

   b) An increasing number of chronic conditions was associated with self-reported anxiety disorder, which was maintained when adjusting for antidepressant use (adjusted OR=1.74, 95% CI 1.31 to 2.39, *P*<0.001). There was no association between chronic conditions and increasing scores on the STAI.

   c) There were no associations between multimorbidity and cognitive test scores.

2. a) There was an association between increasing numbers of medication increasing scores on the CES-D (adjusted β for each additional medication=0.66 (95% CI 0.12 to 1.12, *P*=0.017). The association was not convincing when adjusted for antidepressant use. Increasing numbers of medication were also associated with self-reported depression (OR=1.36, 95% CI 1.07 to 1.73, *P*=0.010), but not when adjusting for antidepressant use. A dichotomous marker of polypharmacy was not significantly associated with depression outcomes in adjusted models.

   b) There were no associations between medication use and either self-reported anxiety disorder or increasing scores on STAI.

   c) I found no associations between medication use and cognitive impairment according to COGNITO test scores.

3. There was no association between increasing numbers of chronic conditions and decreasing hippocampal volume, cerebral microhaemorrhages or increasing Fazekas score.

4. There were no associations between increasing medication use and MRI outcomes linked to dementia and cognitive impairment.

4.5.2 Comparison with other literature

A systematic review and meta-analysis of 40 papers studying multimorbidity and depression found that people with multimorbidity were at over twice the risk (risk ratio 2.13 (95% CI 1.62 to 2.80)) of developing depression compared to those without.[288] My findings support this result, albeit with a smaller odds ratio and treating chronic conditions as continuous (OR with each condition for self-reported depression=1.41, 95% CI 1.11 to 1.80, *P*=0.005).

There was an association between increasing number of medications and scores on the CES-D, which supports previously published findings using this measure.[95] However, the results differed when I dichotomised medications into a polypharmacy variable. I am aware of the dangers of over-analysing data, particularly in a relatively small dataset. I consider that if changing the parameters could substantially alter the strength of an association, the association should be considered modest at best. There is little in the literature about polypharmacy and specific anxiety outcomes so my positive findings in this area are new.

Previous work reported from a longitudinal study has also found that people with multimorbidity are at increased risk of having increased anxiety symptoms (OR=2.30, 95% CI 1.44 to 4.01).[324] I did not find a similar association on testing for anxiety symptoms, but did find an association between increasing physical conditions and reporting a diagnosis of anxiety disorder (fully adjusted OR=1.74 95% CI 1.31 to 2.39, *P*<0.001). This difference between reported diagnosis and objective measurement may reflect the fact that those who report a diagnosis are likely to be receiving treatment and therefore report fewer active symptoms.

There is little published literature on multimorbidity and neuroimaging outcomes and none on polypharmacy.[98,99] Either this is a novel area for exploration, or my negative findings in this area may suggest publication bias, in that other researchers have found no associations and therefore have not published their results. There is more evidence of a link between multimorbidity and cognitive decline,[47] and the co-existence of dementia with multiple physical conditions.[39] The only findings of interest on neuroimaging were marginal associations between chronic conditions with decreased hippocampal volume and decreased periventricular Fazekas scores. These contradict each other, as smaller hippocampal volume and higher Fazekas scores are markers of neurodegeneration. Previous research has established a link between multimorbidity and lower hippocampal volumes.[99]

Other research has examined links between polypharmacy and worsening cognition, with variation between studies on whether they found an association or not.[291,325] There is no single agreed definition of a cut-off for polypharmacy, and many of these studies use different parameters. In addition, my analyses did not support an association between chronic condition count and poorer performance on cognitive testing. This may be due to the mid-life age profile of the PREVENT Dementia cohort. Its design aims to detect subtle longitudinal changes in cognition, which is outside the scope of this cross-sectional work.

4.5.3 Strengths

This chapter investigates the risk factors of chronic conditions and medications in a thoroughly phenotyped ageing cohort. The outcomes examined include not only validated rating scales and cognitive tests but also MRI measures and participant-reported clinical diagnoses. This selection of measures therefore adds considerable breadth compared to existing research in this area. In addition, most previous studies only measure continuous or dichotomous measures of chronic conditions or medications, whereas this chapter includes both.[288]

In all but one analysis, apparent associations between multimorbidity or polypharmacy and depression or anxiety outcomes ceased when including antidepressant use as a control variable. This implies that taking antidepressants, perhaps as a marker for mental disorders (fully or partially treated), is an important explanation in the pathway between chronic conditions, medication use and anxiety and depression. This overlap between physical and mental illness is complex and difficult to capture but I attempted to understand it by approaching it from several different angles. To my knowledge, no previous research on these topics has attempted to account for this example of confounding by indication; this is a strength of my work.[95,288,324,326]

4.5.4 Limitations

4.5.4.1 Study characteristics

The data available were collected in the baseline pilot phase of the PREVENT Dementia study, so allow only cross-sectional analyses of 210 participants. The cohort was designed as a longitudinal study. Cross-sectional analysis leaves questions about direction of causality unclear. It is known, for example, that all mental disorders are associated with later physical health consequences, so the findings from this study may reflect people who were originally depressed experiencing physical health deterioration.[286] Although relevant covariates were considered, the possibility of residual confounding remains.

With such a sample size, groups within the dataset can be small, for example only 26 participants reported current use of antidepressant medication. There are also more women (148, 70.5%) than men in the sample, so when groups are subdivided by gender they can become very small. For example, only seven men took antidepressants. It is important to recognise the role of chance in analyses on these numbers, and effect size could be over-estimated.

The cohort in general is relatively young and consists of healthy volunteers. I expected an under-estimation of levels of multimorbidity and polypharmacy through selection

bias. However, following up a young cohort allows investigation of the theory that the genesis of later-life depression associated with polypharmacy may originate in mid-life. The results compared to other published data suggest that under-estimation is unlikely.

There was a high prevalence of previous head injuries within the cohort, with 81 (38.6%) participants reporting at least one head injury that led to loss of consciousness. This may have been relevant to cognitive or neuroimaging outcomes, but was deemed less important than other confounding factors when selecting covariates.

Seventeen (8.1%) of the sample did not have an MRI, for reasons unknown. This is another potential source of selection bias for the MRI outcome variables. My analysis with cerebral microhaemorrhages as an outcome looked only at total load rather than presence in specific regions. When analysing future waves I will include a breakdown of lobar versus deep microbleeds, which could differentiate between microvascular and Alzheimer's pathology.[314]

4.5.4.2 Medical history

The nature of the PREVENT Dementia initial visit is that all the medical history and medications are self-reported at interview with a doctor. This can lead to several types of bias including recall bias and social desirability bias.[327] Self-reported depression may be more sensitive than CES-D for identifying people with a clinical diagnosis who have received treatment and therefore perform better on testing than they might have done untreated. However, participants may also report depression that has not been clinically diagnosed, more so perhaps than a physical condition. Previous studies comparing self-report with diagnostic or screening tests for depression have remarked upon this complex relationship.[328] Self-reported antidepressant use in cohort studies, however, has been found to correlate strongly with prescription records.[329]

Some of the medical history obtained in PREVENT Dementia is rather ambiguous; for example, there is no differentiation between type I and type II diabetes, which differ pathologically and prognostically. There were incidences where significant conditions were only included in the free-text 'other' section, such as rheumatoid arthritis and sarcoidosis. There is potential for overlap between some listed conditions, such as irritable bowel syndrome and chronic constipation.

There is only one option for recording any eye disease, with no possibility of adding free text. Therefore, the relatively high proportion of people reporting 'eye disease/disorder' may be explained by myopia or presbyopia. There is no way of establishing whether this is the case, though, and the category would also include common ophthalmic conditions such as glaucoma and age-related macular degeneration. A systematic review and meta-analysis on the prevalence of depression among people with eye disease found a pooled odds ratio of depression of 1.59 (95% CI 1.40 to 1.81) compared to healthy controls, across 13 studies.[330] The study also found that the eye condition with the highest prevalence of depression was dry eye disease, which could be considered a relatively minor diagnosis. This highlights that mental health implications of common conditions may not correlate with clinicians' perceived severity of illness. Owing to these associations, I chose not to exclude all eye disease from the main analyses, as doing so would make assumptions that what was recorded was not important. I did remove eye diseases from some of my network analyses.

The inclusion of eye diseases which had unexpectedly high prevalence is likely to have artificially increased the mean number of conditions and the prevalence of multimorbidity. It may have led to over-estimated associations between chronic condition count and the mental health outcomes. If future similar analyses are performed in this dataset, I will advise conducting sensitivity analyses to assess the importance of eye diseases.

For these analyses, I included all conditions listed in the PREVENT Dementia participant case report form that I deemed chronic. There have been numerous publications discussing how many and which conditions should be included when investigating multimorbidity, as discussed in detail in Chapter 2. Previous research has recommended using a list of between 25-75 conditions, so the 55 I included is likely to be an appropriate number.[260] My selection could be seen to be subjective. Future work on this dataset may benefit from redefining the list of conditions based on previous publications, although it would not possible to fully harmonise the list used in PREVENT Dementia with that of Barnett et al.[39] For example, the lack of free text options means that conditions like glaucoma included in Barnett and colleagues' list could not be separated.

I applied my definition of chronic disease broadly to each diagnosis. No information on individual participants' disease severity was collected so this process may have over- or under-estimated the impact on each individual. I excluded conditions that are nonetheless important risk factors for significant disease, such as hyperlipidaemia, based on this definition. There is no separate category for gynaecological disorders so these were recorded under 'other genitourinary/reproductive'. There is no space on the participant case report form to record 'other pulmonary disease'. I excluded all dermatological conditions recorded in 'other' categories as none of them met the criteria above. I list prevalence for all conditions in Table 4-3 on page 132, even those where no participants reported the condition, to allow harmonisation with analysis of future waves of the PREVENT Dementia study.

4.5.4.3 Sample size

The most obvious limitation of this work compared to that in other datasets is its relatively small size. I chose to conduct these analyses partly to inform further the questions I would ask in bigger datasets, and to prepare the practicalities of doing so. PREVENT Dementia contains detail on many measured parameters that may be confounding factors, and this level of information is not available in extremely large datasets such as the linked NHS prescribing data presented in Chapter 6. In addition, the cognitive tests used in PREVENT Dementia are rigorous and well validated.

The pilot phase of PREVENT Dementia was powered to detect changes in hippocampal volume and plasma $A\beta_{42}$, not the other outcomes examined. However, where I did see results suggesting statistical significance, I reported raw *P*-values to allow cautious interpretation rather than relying upon an arbitrary cut-off.

4.5.4.4 Other measurements and analyses

I included all medication that had a WHO ATC code. This included all regularly taken prescription medicines, but also included some that may be less relevant, such as three-monthly depot progesterone injection and an adrenaline EpiPen that would only be used infrequently as required. This does not match with my analyses in Chapter 6 and could be reconsidered in future work with these data.

PREVENT Dementia used the original CES-D, as opposed to the 2004 revised version, in order to harmonise with other similar cohort studies. The revised version replaces the inverted questions (for example *"I was happy"*) with their opposites (*"nothing made me happy"*). It also includes questions on somatic and psychomotor symptoms of depression and thoughts of self-harm and death. Nine of the twenty questions were replaced with completely different ones, so the scales are not interchangeable. The total scores are comparable, but there is an additional option for answering 'nearly every day for two weeks' as a symptom measure for use when making a diagnosis.[331] This limits the comparability of some of my findings to other research using the revised CES-D.

Owing to the small sample size, I only used outcomes of two subtests of the COGNITO battery that had previously been found to be of interest in this cohort.[308] The phoneme comprehension task tested semantic memory and name-face associative learning tested episodic memory.[332] Changes in episodic and semantic memory have been identified as early markers of prodromal Alzheimer's disease.[333,334] However, restricting my analyses to these tests neglected other

important cognitive domains for detecting preclinical disease including psychomotor speed and verbal fluency.[334]

Network analysis has limitations depending on the specific methods used, and in this chapter I present the graphs only for description of the sample rather than to infer the existence of statistical networks.[335]

4.5.5 Implications

The presence of associations between condition count and medication use with depression, and condition count with anxiety, lends support to my overall thesis hypotheses of the important influence of physical health and resulting medication burden on mental health. The modest nature of these results in a small sample size limits the certainty with which conclusions can be drawn, but reinforces the need to corroborate them in much larger datasets. A particular strength of completing this work in a pilot wave of an ongoing longitudinal study is the opportunity to revisit the analyses when data from future waves are available.

4.6 CONCLUSIONS

In this cross-sectional study of a middle-aged cohort of healthy volunteers, I found associations between increasing chronic conditions and both self-reported depression and self-reported anxiety disorder. In addition, there were associations between medication use and depression (both self-reported and according to a screening scale).

I found evidence of a marginal association between multimorbidity and decreasing periventricular Fazekas score. I found these associations in the context of numerous other calculations, the remainder of which suggested no association. The findings should therefore be interpreted with caution. This work is not able to support the idea that mechanisms leading to late-life depression or dementia may appear in the

decades before clinical concern arises, but follow-up of these same participants may be able to examine this link.

The work on depression and anxiety outcomes in this chapter has been published in the *Journal of Comorbidity* and is presented in Appendix 2.

In Chapter 5, I focus in more depth on a specific biomarker of Alzheimer's disease, amyloid-β, as measured in cerebrospinal fluid in a different cohort optimised for measuring the preclinical phase of neurodegenerative brain disease.

Chapter 5 Cross-sectional analyses in the EPAD cohort

5.1 INTRODUCTION

In Chapter 4, I explored the relationship between multimorbidity and clinical mental health outcomes including self-reported diagnoses and scores on cognitive and psychological tests. I also assessed some imaging outcomes, finding no strong associations between multimorbidity, polypharmacy and markers of neurodegeneration. In this chapter, I build on that biological investigation by focusing in depth on one biomarker of Alzheimer's disease in the European Prevention of Alzheimer's Dementia (EPAD) longitudinal cohort study.

This work has been published in the *Journal of Alzheimer's Disease* and is presented below after a general introduction, then followed by further discussion. I prepared and analysed the data, created the figures, wrote the first draft of the manuscript and made revisions following comments from the co-authors (who are my PhD supervisors) and peer reviewers.[15]

5.1.1 Background

Dementia is a common mental disorder, with an estimated prevalence of 7.1% in people aged 65 and over in the UK.[336] It is associated with adverse outcomes for individuals including reduced independence and increased mortality. There are economic costs to health and social care providers as well as personal costs to unpaid carers.[40] Diagnoses of dementia are made clinically and in most patients cannot currently be confirmed by imaging or biomarker investigations. Estimates suggest that clinically overt Alzheimer's disease accounts for 62% of dementia in the UK.[336]

[15] A reviewer from the *Journal of Alzheimer's Disease* pointed out the difference between the terms sex and gender. The EPAD participant case report form used the word 'sex' so I have used this term throughout the chapter.

5.1.1.1 Amyloid hypothesis

Alzheimer's disease pathology is defined as the presence of plaques formed of extracellular amyloid-β (Aβ) deposits, neurofibrillary tangles of abnormal tau filaments and evidence of neurodegeneration.[337] Around 95% of cerebral Aβ is $A\beta_{40}$ (the peptide terminating at carboxyl 40), but $A\beta_{42}$ is believed to initiate the formation of plaques.[338] The amyloid cascade hypothesis states that an increase in Aβ leads to its aggregation, impaired synaptic function and resulting neuronal damage.[337] $A\beta_{42}$ is secreted into cerebrospinal fluid (CSF), so is accessible in clinical and research settings. Low CSF amyloid β_{42} is a marker of brain Aβ deposition and is used to identify preclinical Alzheimer's disease that is present before the emergence of cognitive symptoms.[339,340] Cerebral amyloid is also important as a therapeutic target, and there have been several trials of drugs, for example that decrease Aβ production or aggregation, or act as immunotherapy against Aβ.[341] Some of these trials, for example of aducanumab, have shown promising results but there is as yet little evidence that they will be clinically or cost effective.[342]

5.1.1.2 Amyloid and vascular disease

It has previously been established that systemic vascular disease is associated with cerebral amyloid angiopathy, where amyloid is deposited in arterial walls, increasing arterial stiffness.[343] This in turn reduces amyloid clearance and further increases deposition within both brain vasculature and parenchyma.[344] Epidemiological studies have found associations between mid-life hypertension and Alzheimer's disease.[345] While this relationship between vascular and amyloid processes has been thoroughly studied both in fundamental science and at population level, there has to date been very little research into the biological mechanisms between multimorbidity and neurodegeneration.

5.1.1.3 Existing evidence

To inform my analysis, I first conducted a literature search in MEDLINE for relevant papers on amyloid and multimorbidity (updated 16th January 2020), then checked their bibliographies. There are three publications, reflecting two unique studies, on multimorbidity and amyloid neuroimaging biomarkers, all published since 2016.[98,99,292] They all report no association between numbers of chronic

conditions and amyloid status, and are explored in more detail in the paper's Discussion. I found no published research investigating multimorbidity and CSF Aβ.

The majority of people with dementia have at least one other comorbid condition. A cross-sectional study carried out in 291 169 adults aged over 65 years in Scottish primary care found that 10 258 (3.5%) had a recorded diagnosis of dementia.[346] Using a list of 32 possible physical conditions, the authors found that people with dementia were more likely to have five or more physical conditions than people without (age and sex adjusted OR=1.42, 95% CI 1.35 to 1.50; $P<0.001$) and had increased levels of polypharmacy. Data from 21 917 patients in The Health Improvement Network (THIN) in England, albeit with a shorter list of ten conditions, showed that 77% of people with dementia had at least one other condition.[48] A cross-sectional Spanish study of 72 815 people aged over 64 years explored the comorbidities of dementia in detail. The authors reported that the most common comorbidity was hypertension but that comorbidities differed by gender, with a prominence of comorbid anxiety disorders in women.[347] In addition, a cross-sectional examination of the World Health Organization Study on Global Ageing and Adult Health included six low and middle income countries and found an association between multimorbidity (≥2 conditions) and mild cognitive impairment in these settings (multiply-adjusted OR=1.40, 95% CI 1.23 to 1.58).[348]

Up to 35% of risk factors for dementia are thought to be potentially modifiable.[40] A major report on this topic in 2017 estimated that hypertension contributes 2% and diabetes 1% to a person's lifetime risk of dementia.[40] Optimal management of these conditions, whether existing alone or as aspects of multimorbidity, could prevent or delay progression to dementia. It is therefore worthwhile exploring the area of chronic illnesses as a potential candidate for dementia prevention. This fits with one of the stated aims of the European Prevention of Alzheimer's Dementia (EPAD) Consortium, *"to improve the understanding of the early stages of Alzheimer's disease"*.[349]

The relationship between multimorbidity and dementia is clinically relevant, but mechanisms are unclear. There is a particular gap in the literature on multimorbidity and CSF amyloid, so this chapter addresses the following question in the EPAD Cohort:

5.1.2 Hypothesis

Multimorbidity, or having a larger number of chronic conditions, will be associated with lower concentrations of CSF amyloid-β, as a marker of Alzheimer's disease.

5.2 ARTICLE FULL TEXT

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Associations Between Multimorbidity and Cerebrospinal Fluid Amyloid: A Cross-Sectional Analysis of the European Prevention of Alzheimer's Dementia (EPAD) V500.0 Cohort

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Abstract.
Background: Multimorbidity (the co-occurrence of multiple chronic conditions) is increasingly common, especially among people with dementia. Few neuroimaging studies have explored amyloid biomarkers in people with multimorbidity.
Objective: We aimed to conduct the first study of the association between multimorbidity and cerebrospinal fluid amyloid-β_{42} (CSF Aβ).
Method: The European Prevention of Alzheimer's Dementia (EPAD) Longitudinal Cohort Study V500.0 dataset includes volunteers aged $\geq$50 years from 12 sites. Participants undergo detailed phenotyping, including CSF measures and a self-reported medical history. Using logistic and linear regression analyses, we explored the association between multimorbidity and continuous chronic condition count with CSF Aβ positivity ($A\beta_{42}$ <1000pg/ml) and continuous CSF Aβ concentration. All models were adjusted for age, sex, *APOE* status, education, and family history of dementia.
Results: Among 447 eligible participants without dementia, the mean (SD) age was 66.6 (6.6) years, 234 (52.3%) were women, and 157 (35.1%) were amyloid positive. With chronic conditions regarded as pseudo-continuous, each additional condition carried a decreased likelihood of amyloid positivity (OR = 0.82, 95%CI: 0.68–0.97; $p = 0.026$). With CSF Aβ as a continuous variable, each additional condition was associated with an increase of 54.2 pg/ml (95%CI: 9.9–98.5, $p = 0.017$). Having $\geq$2 conditions was inversely associated with amyloid positivity (OR 0.59, 95%CI: 0.37–0.95, $p = 0.030$) compared to one or none.

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Conclusion: Our findings suggest that the established association between multimorbidity and dementia may be due to a pathway other than amyloid. However, this cross-sectional study does not allow us to make causal inferences. Longitudinal work is required to confirm the inverse association found.

Keywords: Alzheimer's disease, amyloid, dementia, multimorbidity

INTRODUCTION

Multimorbidity, the co-occurrence of multiple chronic diseases within one individual, is increasing in prevalence. It is costly to health services and has been shown to be associated with poor quality of life in adults of all ages [1, 2]. A recent report highlighted its importance and identified it as a priority for research [3].

The literature on multimorbidity and dementia is limited. For example, a cross-sectional study of the Scottish population found that 82% of people with dementia had two or more comorbid conditions [4]. Investigators from the longitudinal Mayo Clinic Study of Aging (MCSA) reported that people with $\geq$2 conditions were at increased risk of cognitive impairment or dementia compared to individuals with 0–1 conditions (hazard ratio, 95% confidence interval [CI] 1.38, 1.05–1.82) [5]. However, three recent papers, describing cross-sectional analyses of two cohort studies, reported no association between the total number of conditions and amyloid deposition on neuroimaging [6–8].

Cerebrospinal fluid (CSF) amyloid-$\beta_{1\text{-}42}$ (Aβ) is a biomarker that represents soluble amyloid. Low levels of CSF Aβ may reflect plaque deposition under the peripheral sink hypothesis and are associated with Alzheimer's disease and dementia [9, 10]. Cerebral amyloid is of interest both for use in clinical diagnosis and as a focus for stratification into Alzheimer's disease drug trials [11, 12]. We found no published research into multimorbidity and amyloid status as determined using CSF. Consequently, we present the first study investigating associations between multimorbidity and CSF Aβ_{42}.

METHODS

Study participants

The European Prevention of Alzheimer's Dementia (EPAD) study is a pan-European multi-site project consisting of a cohort without dementia (ClinicalTrials.gov #NCT02804789). It allows both longitudinal research into potential preventative strategies for neurodegeneration and a cohort prepared for clinical trials of dementia drugs [13, 14]. Participants aged over 50 years were recruited from parent cohorts across twelve trial delivery centers in Europe. To be eligible, they had to have at least seven years of formal education and have a study partner willing to provide collateral information. Potential participants were excluded if they fulfilled diagnostic criteria for dementia, had a known genetic mutation associated with autosomal dominant Alzheimer's disease, had active cancer within the last five years (except basal or squamous skin carcinoma or localized prostate cancer), had a significant unstable physical or mental illness or were unable to consent. All participants provided informed consent and ethical approval was obtained from ethics committees local to each study site. Numerous biological, psychometric, and imaging measures were taken to allow detailed phenotyping. In this study, we used the EPAD V500.0 data release, which contains initial visit data from the first 500 participants across all twelve sites. The sample characteristics were described in detail in a previous publication [15].

Study variables

Each EPAD study visit included a detailed medical and medication history, collected by a study doctor. Participants reported their own diagnosed conditions and current medications. To define chronic conditions for these analyses, we adapted a list from a previous multimorbidity publication (Supplementary Table 1 lists the 39 possible conditions and their relevant definitions in this dataset) [4]. This list has been used in other epidemiological multimorbidity studies so we chose to use it to improve comparability with other research [16–20]. We calculated a count of the total number of conditions on this list for each participant and used this as a pseudo-continuous variable. In keeping with the commonly used definition of multimorbidity being two or more concurrent conditions, we also generated a dichotomous variable for multimorbidity ($\geq$2 versus 0–1 conditions).

Participants reported their own number of years of education, and age in years at initial interview

Table 1
Sample characteristics according to CSF amyloid β status

Variable	Total	N missing	Aβ positive (<1000 pg/ml)	Aβ negative (≥1000 pg/ml)	*p* for difference between Aβ groups
Total sample (%)	447	NA	157 (35.1)	290 (64.9)	–
Mean age in years (SD)	66.6 (6.58)	0	67.8 (6.96)	65.9 (6.31)	0.005
Female (%)	234 (52.3%)	0	73 (46.5)	161 (55.5)	0.085
Mean years of education (SD)	14.1 (3.68)	0	13.9 (3.80)	14.1 (3.62)	0.506
Mean chronic conditions (SD)	1.1 (1.27)	0	0.94 (1.27)	1.15 (1.26)	0.102
≥2 chronic conditions (%)	128 (28.6)	0	37 (23.6)	91 (31.4)	0.102
Carrier of ≥1 *APOE* ε4 allele (%)	178 (39.8)	5	80 (51.6)	98 (34.2)	0.001
≥1 first-degree relative with dementia (%)	265 (59.3)	0	96 (61.1)	169 (58.3)	0.625

was calculated from their date of birth. We treated both of these as continuous variables. Sex was self-reported and treated as dichotomous. Participants also reported any family history of dementia, which we converted into a dichotomous variable of having at least one first-degree relative (sibling or parent) with dementia. Blood was taken for *APOE* genotyping and we generated a dichotomous variable for having at least one *APOE* ε4 allele.

At the initial visit, doctors at each EPAD site carried out lumbar punctures on all participants and the CSF samples collected were analyzed centrally at the University of Gothenburg, Sweden, with the automated Elecsys immunoassay [21]. Previous research examining multimorbidity and amyloid on neuroimaging has used dichotomous variables to represent amyloid abnormality [8], and the commonly used A/T/N (amyloid, tau, neurodegeneration) system for classifying biomarkers also relies on "positive" and "negative" results for each parameter [22]. We therefore used a dichotomous variable for CSF $A\beta_{42}$ to allow comparison between groups, and as the outcome in our primary analyses. There is no universally agreed cut-off for CSF $A\beta_{42}$ as assays vary [23], but other studies using the same assay have used a cut-off of 1092 pg/ml [24] and 1100 pg/ml [25,26]. The EPAD Consortium agreed to lower the cut-off to 1000 pg/ml to balance sensitivity and specificity, giving a dichotomous variable for CSF $A\beta_{42}$: <1000 pg/ml (amyloid positive) or ≥1000 pg/ml (amyloid negative). To assess the robustness of our results to decisions made regarding the CSF cut-off points, we conducted sensitivity analyses excluding participants whose Aβ was between 1000 pg/ml and the highest previously published cut-off using this assay of 1100 pg/ml [26]. Concentrations between these values are the most relevant in comparing the difference in performance between our cut-off and that used by others. To investigate the association further, taking into account the continuum of possible amyloid concentrations, we also used a continuous amyloid outcome measure.

Statistical analysis

We used Student's *t*-test to compare the means of demographic variables between Aβ groups, and Chi-squared test to compare proportions of binary variables (for example, sex). We used logistic regression analyses to model the association between the number of chronic conditions, both as a pseudo-continuous variable and dichotomized as 0–1 versus ≥2 conditions, with dichotomous CSF $A\beta_{42}$. We further adjusted for age, sex, carriage of at least one *APOE* ε4 allele, family history of dementia (at least one first-degree relative) and years of education. We used linear regression to explore the association between chronic conditions, multimorbidity and continuous CSF $A\beta_{42}$.

In all models, when analyzing continuous number of chronic conditions, we added number of conditions squared to the model to explore a possible non-linear association between the number of conditions and amyloid positivity. This would test whether any association between chronic conditions and amyloid changes at extreme numbers of conditions. We also tested for an interaction effect between age and chronic conditions. All analyses were performed using R version 3.4.3 [27].

Finally, given the complexity of counting combinations of conditions, we employed network analyses, an increasingly important method for data visualization, to represent combinations of conditions graphically [28]. We used the R package igraph to generate network graphs for chronic conditions present in amyloid positive and negative participants separately, in circular and alphabetical layout to allow visual comparisons [29]. Participants with fewer than two conditions were excluded from the network analyses so we could investigate links between

conditions. Conditions therefore only appear on the graph when they are reported by at least one participant who has at least two conditions.

RESULTS

Sample description

CSF $A\beta_{42}$ data were missing for 53 participants, resulting in an analytical sample of 447 participants, of whom 157 (35.1%) were amyloid positive and 290 (64.9%) amyloid negative. The overall range of $A\beta_{42}$ concentrations was 277.5 to 3909.0 pg/ml, with a mean of 1330.5 pg/ml and SD 614.1pg/ml. Within the amyloid positive group, the range of Aβ concentrations was 277.5 to 996.0 pg/ml with mean (SD) 714.6 (187.7) pg/ml. In the amyloid negative group, the range was 1005.0 to 3909.0 pg/ml and mean (SD) 1664.0 (495.3) pg/ml, and 108 participants' Aβ concentration was ≥1700 pg/ml. The overall age range was 51.1 to 88.7 years. The amyloid-positive group was older than the amyloid-negative group (mean [SD] 67.8 [6.96] versus 65.9 [6.31] years; $t = 2.83$; $p = 0.005$). Further demographic details are in Table 1.

The mean (SD) number of chronic conditions in those with amyloid positivity was similar to the amyloid negative group (0.94 [1.27] versus 1.15 [1.26]; $t = -1.64$; $p = 0.102$). Ninety-one (31.4%) amyloid negative participants and 37 (23.6%) with amyloid positivity had at least two chronic conditions. Figure 1 displays participants' total number of conditions according to their CSF Aβ status and Fig. 2 shows the relative prevalence of each chronic condition by CSF Aβ.

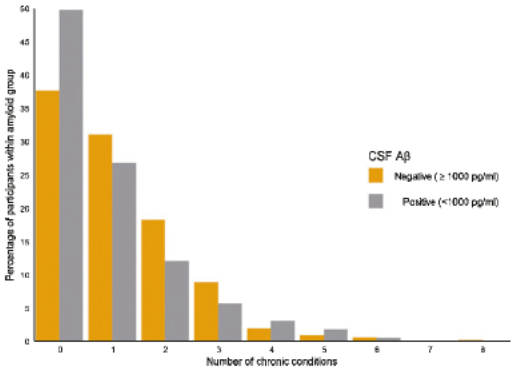

Fig. 1. Participants' total number of chronic conditions by CSF $A\beta_{42}$ status.

Logistic regression analyses with dichotomous Aβ outcome

With chronic conditions as a pseudo-continuous variable, each additional comorbid condition carried an approximately 20% decreased likelihood of amyloid positivity (OR = 0.82, 95%CI: 0.68–0.97; $p = 0.026$, adjusted for age, sex, *APOE* status, family history of dementia, and years of education). To explore potential non-linearity, we additionally adjusted for the square of the number of chronic conditions which reduced the OR to 0.59 (95%CI 0.41–0.85, $p = 0.004$). We tested for an interaction between age and chronic conditions and this emerged as non-significant. People with ≥2 conditions were approximately 40% less likely to be amyloid positive than people with 0–1 conditions (OR adjusted for age, sex, *APOE* status, family history of dementia and years of education 0.59, 95%CI 0.37–0.95, $p = 0.030$). Results of all regression analyses are listed in Table 2.

Linear regression analyses with continuous Aβ outcome

Each additional condition was associated with an increase in $A\beta_{42}$ concentration of 54.2 pg/ml (95% CI 9.9 to 98.5, $p = 0.017$), adjusted for age, sex, *APOE* status, family history of dementia, and years of education. Additionally, adjusting for the number of conditions squared increased the β coefficient to 98.6 (2.4 to 194.9, $p = 0.045$). Compared to participants with 0–1 conditions, those with ≥2 conditions had an increase in $A\beta_{42}$ by 115.7 pg/ml, but this did not reach conventional statistical significance (95% CI –7.7 to 239.0, $p = 0.066$). These results are displayed in Table 2.

Sensitivity analyses

There is currently no universally accepted cut-off for dichotomous Aβ using the Elecsys immunoassay [23]. We therefore conducted sensitivity analyses, excluding participants whose Aβ was between our cut-off of 1000 pg/ml and the highest cut-off used elsewhere, 1100 pg/ml [25]. After excluding participants with Aβ between 1000–1100pg/ml, there were 422 participants remaining. In this group, the odds ratio for amyloid positivity (<1000 pg/ml) with increasing chronic conditions was 0.84 (95% CI = 0.70–1.00, $p = 0.053$), adjusted for age, sex, *APOE*, years of education, and family history of

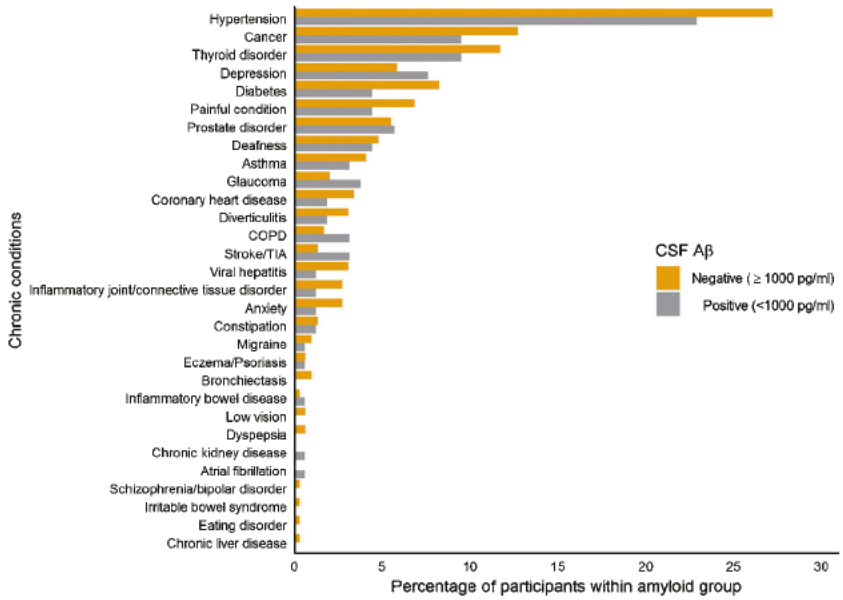

Fig. 2. Prevalence of each chronic condition according to CSF $A\beta_{42}$ status COPD, chronic obstructive pulmonary disease; TIA, transient ischemic attack.

Table 2
Results of regression analyses

Number of conditions	Outcome			
	Continuous Aβ concentration: linear regression		Dichotomous Aβ positivity (<1000 pg/ml): logistic regression	
	β (95% CI)	*p*	Odds ratio (95% CI)	*p*
0–1	Reference	Reference	Reference	Reference
≥2: Model 1	115.7 (–7.7 to 239.0)	0.066	0.59 (0.37 to 0.95)	0.030
Increasing by one: Model 1	54.2 (9.9 to 98.5)	0.017	0.82 (0.68 to 0.97)	0.026
Increasing by one: Model 2	98.6 (2.4 to 194.9)	0.045	0.59 (0.41 to 0.85)	0.004

Model 1: adjusted for age, sex, *APOE* status, family history of dementia, and years of education Model 2: adjusted for age, sex, *APOE* status, family history of dementia, years of education, and number of conditions squared.

dementia. The adjusted OR for amyloid positivity with ≥2 compared to 0–1 conditions was 0.63 (0.39–1.02, $p = 0.062$). Results from linear regression analysis in this group indicate that per additional chronic condition, CSF Aβ increased by 54.0 pg/ml (95% CI = 7.6 to 100.4, $p = 0.023$). Having ≥2 compared to 0–1 conditions suggested an increase in Aβ of 118.65 pg/ml, but did not meet conventional statistical significance (95% CI = –11.97 to 249.27, $p = 0.075$).

Network analyses

The network graphs in Fig. 3 display the co-existing conditions for people with ≥2 conditions in each amyloid status group separately. This includes 20 conditions in the amyloid positive group and 24 in the amyloid negative group.

DISCUSSION

Summary of evidence

We found that both an increasing number of conditions and categorically-defined multimorbidity were associated with lower odds of amyloid positivity in people aged over 50 years without dementia. This finding was less convincing on sensitivity analysis for the Aβ cut-off, but this may relate to reduced statistical power. Increasing chronic conditions was associated with an increase in continuous Aβ concentration (suggesting less Aβ deposited in plaques).

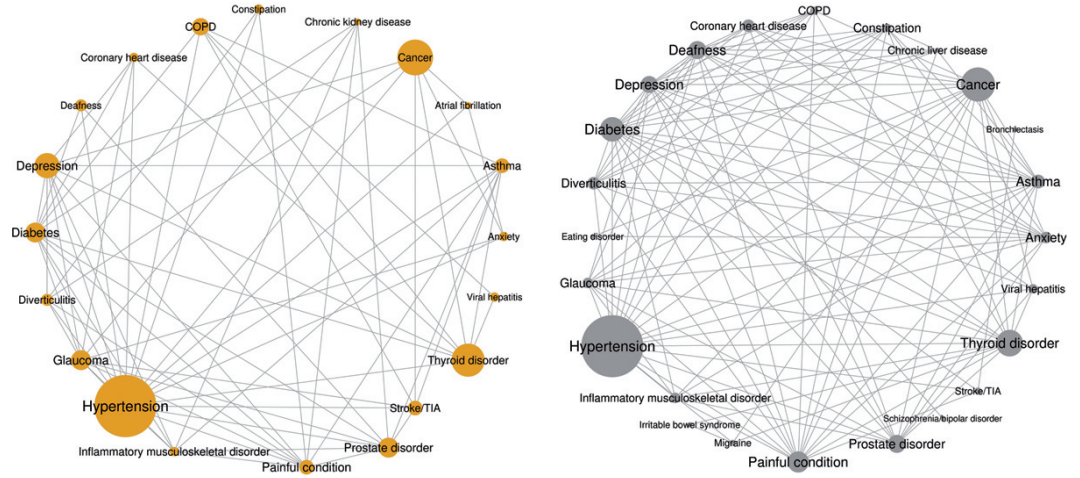

Fig. 3. Network analyses of self-reported chronic conditions according to amyloid status, in participants with ≥2 chronic conditions Amyloid negative participants (CSF $A\beta_{42}$ ≥1000 pg/ml), $n = 91$ Amyloid-positive participants (CSF $A\beta_{42}$ <1000 pg/ml), $n = 37$ COPD, chronic obstructive pulmonary disease; TIA, transient ischemic attack Node sizes represent relative prevalence of each condition and text size the relative number of connections for that condition.

These associations were present when adjusting for age, sex, years of education, *APOE* status, and family history of dementia. There was no significant association between categorical multimorbidity (0–1 versus ≥2 conditions) and continuously measured Aβ. This may reflect the fact that using a continuous count of conditions is more robust than choosing an arbitrary number of conditions to define multimorbidity.

Comparison with other literature

Previous research found no association between multimorbidity and brain amyloid deposition in people without cognitive impairment [6, 7]. Cross-sectional analysis of the Mayo Clinic Study of Aging (MCSA), where participants had a mean age of 79 years and 85% had two or more chronic conditions, found an association between multimorbidity and other imaging biomarkers of brain pathology but not amyloid [6]. The authors concluded that multimorbidity's association with brain pathology was independent of amyloid deposition. Our findings tend to support this, albeit in a younger sample. In further work on MCSA, the same team found that multimorbidity was only associated with amyloid positivity when there was other imaging evidence of neurodegeneration [8].

It is challenging to compare multimorbidity across studies that use different methods to record and count conditions.[30] For example, the MCSA studies used medical records for chronic condition diagnoses, and counted from a list of 19 possible conditions [6]. The INSIGHT-PreAD study, however, used self-reported diagnoses from a list of 14 conditions [7]. Our chosen list of 39 chronic conditions has been used in other multimorbidity research [16–20], but we may have over-estimated multimorbidity compared to the studies with shorter lists. The list of chronic conditions we chose has several limitations. For example, it does not include hyperlipidemia, which is the most prevalent condition in similar studies [8]. It also includes the term "painful condition" which could represent a number of diagnoses, and other conditions which could be better classified as symptoms, such as "low vision". Discrepancy between potential conditions is another recognized disadvantage of using disease counts for multimorbidity research and limits our ability to meaningfully compare the prevalence of conditions with other studies [31].

Potential mechanisms

Given the previously discussed association between multimorbidity and dementia [4,5], it seems unlikely that multimorbidity is protective against amyloid positivity. Our study, although examining a biomarker rather than a clinical outcome, supports the suggestion that this association may not be driven by amyloid [6]. Instead, it is likely that the

impact of multimorbidity on brain health in general is multifactorial.

Using an overall disease count groups all conditions (and therefore biological mechanisms) together, when in fact they may each be risks, neutral or even protective for cerebral amyloid deposition. For example, hypertension, a key vascular risk factor, was highly prevalent in both amyloid groups and may have influenced amyloid burden regardless of whether or not the participant had multimorbidity. Vascular pathology has an important contribution to the development of Alzheimer's disease, and hypertension has been shown to be separately associated with low CSF Aβ [32, 33]. There is evidence that cognitive function declines faster in people with amyloid positivity in midlife if they have hypertension or obesity [34]. Therefore, it is difficult to elucidate mechanisms when measuring multimorbidity purely by disease counts.

An alternative explanation for the contrast between our findings and previous research that found an association between multimorbidity and dementia may be age differences (for example, a mean age of 78.5 years in the MCSA, compared to 66.6 years in our sample). In addition, Vassilaki et al.'s outcome was clinically diagnosed dementia or mild cognitive impairment, suggesting a more advanced neurodegenerative process than amyloid positivity in our population [5]. Given that the prevalence of both multimorbidity and amyloid positivity increase with age [4, 10], it may be that age is the most important factor driving both variables.

Strengths and limitations

To our knowledge, this is the first exploration of the association between multimorbidity and a CSF marker of Alzheimer's disease. We tested the association for both categorically-defined multimorbidity and a pseudo-continuous count of chronic conditions with both dichotomous and continuous amyloid measures.

Given the research participants' age and that they are volunteers, EPAD is a generally healthy cohort. Relatively few participants had two or more conditions in each amyloid status group compared to population-based estimates of multimorbidity in similar age groups [4]. This reflects the ongoing under-representation of people with multimorbidity in clinical trials.[35] EPAD participants reported a mean of 1.1 chronic conditions. A population-based study using the same list of conditions found a mean of 1.0 conditions across all ages, with this rising to 2.6 in people aged 65 to 84 years and 3.6 in those aged 85 years and over [4]. Our study's exclusion criteria mean that the reported conditions are less severe than might occur in a population-based sample. Potential research participants with a diagnosis of cancer (except non-melanoma skin cancer and localized prostate cancer) within the last five years were excluded, meaning that a cancer diagnosis reported by EPAD research participants is most likely historical. The selection of EPAD participants limits this study's generalizability and may not reflect associations in the general population. One aim of EPAD is to investigate people without dementia who may go on to develop it. This means that the cohort was relatively young, so amyloid evidence of neurodegeneration, whether related to multimorbidity or not, may not yet be apparent.

People with dementia were excluded from this study, meaning our findings are only applicable to people with amyloid positivity who have not developed dementia. In addition, we did not examine cognitive outcomes in these analyses, focusing only on biomarkers.

The Elecsys immunoassay's performance has not been formally established at Aβ concentrations above 1700 pg/ml [36]. Similarly to other studies using this assay, we have cautiously included values in this range to allow treatment of Aβ as a continuous variable, as they clearly represent Aβ negativity [25]. However, when using continuous Aβ as the outcome for linear regression models, higher concentrations are likely to be less accurate. We accounted for this by using both continuous and dichotomous Aβ as separate outcomes.

The medical history collected did not include timing of diagnoses, meaning that any recorded diagnosis may not reflect a current or recent one. We managed this by choosing the list of chronic conditions based on a paper which originally defined most conditions according to whether they had ever been recorded [4]. Furthermore, using self-reported conditions, although a commonly used method, has limitations, especially in a cohort at risk of cognitive impairment where recall bias may be a particular problem. This may lead to the under-estimation of multimorbidity. The sample size of this initial release of EPAD data, which is smaller than some comparable studies [6,8], may also mean that a true association was missed because of limited statistical power.

Conclusions

Our finding that multimorbidity is inversely associated with amyloid positivity in a cross-sectional study is novel, so needs to be replicated longitudinally. The lack of association between a dichotomous measure of multimorbidity and continuous amyloid suggests this result needs further exploration.

EPAD's longitudinal cohort study design will allow us to replicate these analyses in future, and confirm whether the inverse association found persists on follow-up as the participants age. In addition, this cross-sectional study does not allow us to make causal inferences, so further research could explore the mechanisms explaining the inverse association between multimorbidity and amyloid positivity. An upcoming release of the larger dataset V1500.0 by the end of 2019 will also permit more detailed analysis of the associations between specific clusters of conditions, amyloid and cognitive change.

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SUPPLEMENTARY MATERIAL

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5.3 SUPPLEMENTARY MATERIAL

Supplementary Table 1. List of chronic conditions and definitions, adapted from Barnett et al., *Lancet* **380**, 37–43, 2012.

Condition	Definition
Hypertension	Recorded diagnosis
Depression	Recorded diagnosis and current prescription of antidepressant
Painful condition	Prescription-only analgesic
Asthma	Recorded diagnosis and current prescription of asthma medication
Coronary heart disease	Recorded diagnosis
Dyspepsia	Recorded diagnosis and current prescription of acid-reducing medication except for antacids
Diabetes	Recorded diagnosis
Thyroid disorders	Recorded diagnosis
Inflammatory joint or connective tissue disorders	Recorded diagnosis
Hearing loss	Recorded diagnosis
COPD	Recorded diagnosis
Anxiety & other neurotic, stress-related & somatoform disorders	Recorded diagnosis and current anxiolytic or antidepressant medication
Irritable bowel syndrome	Recorded diagnosis
Cancer	Recorded diagnosis
Constipation	Current prescription of laxatives
Stroke or transient ischemic attack	Recorded diagnosis
Chronic kidney disease	Recorded diagnosis
Diverticulitis	Recorded diagnosis
Atrial fibrillation	Recorded diagnosis
Prostate disorders	Recorded diagnosis
Glaucoma	Recorded diagnosis
Schizophrenia, non-organic psychosis or bipolar disorder	Recorded diagnosis
Psoriasis or eczema	Recorded diagnosis and related prescription (excluding emollients)
Inflammatory bowel disease	Recorded diagnosis
Migraine	Prescription-only migraine medication
Low vision	Recorded diagnosis
Eating disorder	Recorded diagnosis
Bronchiectasis	Recorded diagnosis
Viral hepatitis	Recorded diagnosis
Chronic liver disease	Recorded diagnosis
Alcohol problems	Recorded diagnosis
Other psychoactive substance misuse	Recorded diagnosis
Peripheral vascular disease	Recorded diagnosis
Heart failure	Recorded diagnosis
Epilepsy (currently treated)	Recorded diagnosis and prescription of anti-epileptic medication
Chronic sinusitis	Recorded diagnosis
Learning disability	Recorded diagnosis
Parkinson's disease	Recorded diagnosis
Multiple sclerosis	Recorded diagnosis

5.4 ADDITIONAL ANALYSES

5.4.1 Cut-offs for defining categorical multimorbidity

As stated in the paper's Results, the relationship between multimorbidity (0-1 versus ≥2 conditions) and continuously measured Aβ concentration did not meet conventional statistical significance. I hypothesised that this may be because using an arbitrary cut-off for the number of conditions is less sensitive than a continuous count. However, the continuous count includes the increase from 0 to 1 condition, which does not fall under the usual definition of multimorbidity. To explore the importance of where the cut-off for multimorbidity lies in this case, I performed additional analyses, presented in Table 5-1 on page 186. These show that the strength of association and significance levels vary depending on the number of conditions chosen to define multimorbidity. Of note, where ≥2 conditions was used, splitting 0 and 1 conditions into separate levels gave a result that did not meet conventional statistical significance when continuous Aβ concentration was the outcome. This suggests that in the continuous count, the difference between 0 and 1 conditions was unlikely to be important in the overall results.

It has been shown that there is little difference in the sensitivity of detecting multimorbidity between using cut-offs of ≥2 or ≥3 conditions, as discussed in Chapter 3 (section 3.3.1.4, page 104).[263] As in other analyses in this thesis, and the most commonly used approach, the cut-off of 0-1 and ≥2 seems most appropriate for binary multimorbidity, especially alongside complementary continuous measures.[119] Using a binary exposure variable has lower statistical power than continuous measures owing to the information lost.[240] There is also a risk of over-analysing these data in a relatively small sample.

Table 5-1: Results of logistic and linear regression when using different definitions of categorically-defined multimorbidity

Number of conditions	n (%)	Outcome			
		Continuous Aβ concentration		Dichotomous Aβ positivity (<1000pg/ml)	
		β (95% CI)	*P*-value	Odds ratio (95% CI)	*P*-value
0-1	319 (71.4)	Reference		-	-
≥2	128 (28.6)	115.7 (-7.7 to 239.0)	0.066	0.59 (0.37 to 0.95)	0.030
0	187 (41.8)	Reference	-	-	-
1	132 (29.5)	132.1 (-0.40 to 264.7)	0.051	0.54 (0.32 to 0.88)	0.014
≥2	128 (28.6)	171.3 (36.3 to 306.4)	0.013	0.46 (0.27 to 0.76)	0.003
0	187 (41.8)	Reference	-	-	-
1-2	204 (45.6)	134.6 (16.2 to 253.1)	0.026	0.49 (0.31 to 0.77)	0.002
≥3	56 (12.5)	212.9 (33.4 to 392.5)	0.020	0.51 (0.26 to 0.99)	0.005
0-2	391 (71.4)	Reference	-	-	-
≥3	56 (12.5)	141.8 (-27.2 to 310.9)	0.100	0.74 (0.39 to 1.38)	0.352

All models adjusted for age, sex, *APOE* status, family history of dementia and years of education

5.4.2 Rates of amyloid positivity

In the EPAD v500.0 sample, 157 (35.1%) participants were amyloid-β positive using the cut-off of 1000pg/ml. Reported rates of amyloid positivity in the general population without cognitive impairment vary from 0% to 47%, with most estimates between 10-30%.[350] The variation is likely due to differing methods and cut-offs used, and the age ranges of participants. EPAD aimed to recruit participants across a range of dementia risk profiles, so the amyloid positive prevalence of 35.1% is relatively high

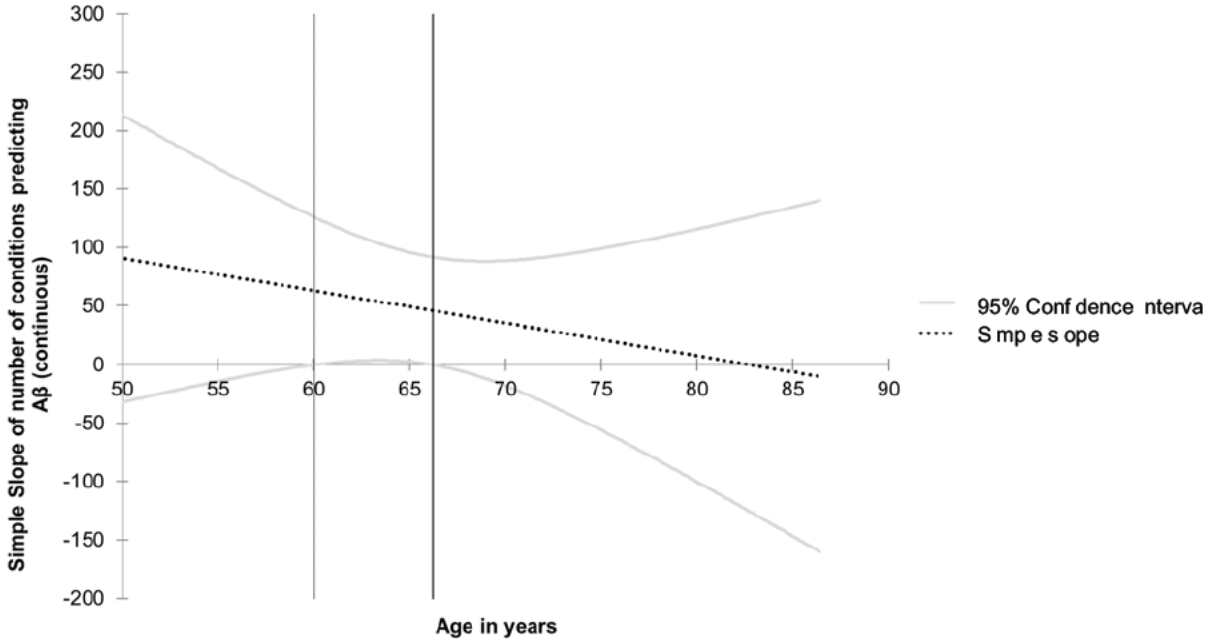
given its age range.[52] A positron emission tomography (PET) imaging study of 1 671 participants in the population-based Mayo Clinic Study of Aging, where the mean age was 71.3 (SD=9.8) years at baseline, explored amyloid positivity in relation to age and cognitive impairment status.[351] The authors reported that the prevalence of amyloid positivity in participants without cognitive impairment was 2.7% (95% CI 0.5% to 4.9%) in those aged 50 to 59 years compared to 41.3% (95% CI 33.4% to 49.2%) in those aged 80 to 89 years. This study emphasises the importance of age when studying amyloid positivity.

5.4.3 Importance of age in the association between multimorbidity and amyloid

Although my analyses were adjusted for age, a possible explanation for the association between chronic conditions and Aβ could be that age is the main factor driving both variables. In univariate analysis of age as a predictor for continuous Aβ, age explained a minimal amount of the variance in Aβ (multiple R^2= 0.05%, adjusted R^2= -1.79%). A moderation analysis is therefore useful in this instance to investigate the impact of age on each of the variables.

The Johnson-Neyman technique calculates the value of the moderator variable (in this case, age) for which the effect of the exposure (chronic conditions) on the outcome (Aβ) are significant.[352,353] Figure 5-1 shows the Johnson-Neyman plot for the slope of continuous chronic conditions predicting continuous Aβ by age. With α=0.05, the region of significance of the simple slope is between 60.0 and 66.2 years. This suggests that age could explain the relationship between chronic conditions and Aβ between these ages, but not in the rest of the sample, where the overall range is 51.1 to 88.7 years. It is counterintuitive that age should explain this association, as increasing age would be expected to be associated with both increasing number of conditions and decreasing CSF Aβ.[354] The relatively young age of my sample is a limitation in this regard, and it is possible that there could be a positive association between chronic conditions and amyloid positivity in older people. There also may be a non-linear relationship between age and CSF amyloid.

Figure 5-1: Johnson-Neyman plot of simple slope of chronic conditions predicting continuous Aβ by age. Vertical lines indicate region of significance

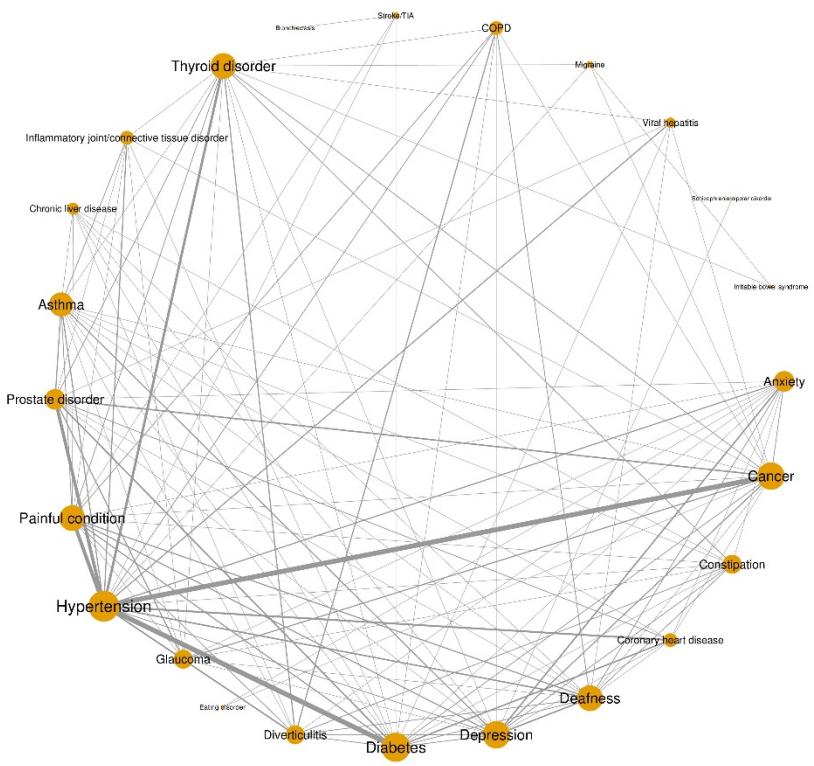


5.4.4 Network analyses

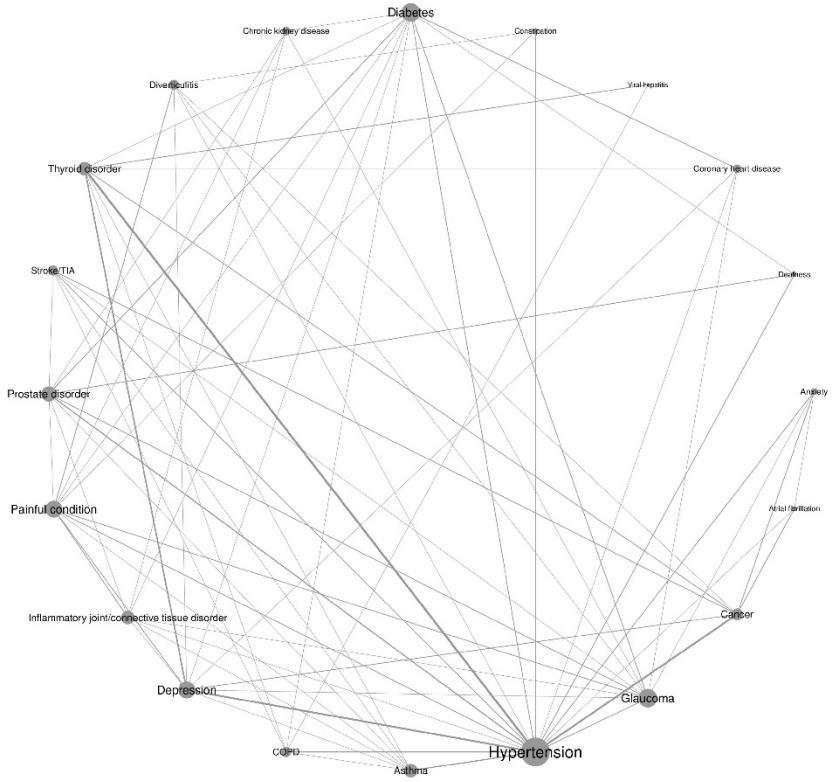
As introduced in section 3.4.2, network analyses are useful for visualising comorbidities within a sample and provide information about multimorbidity beyond simple disease counts. Using the same network analysis methods described in section 4.3.6.1, I generated diagrams of the co-existence of conditions. Similarly to some other publications, the diagrams in the published paper showed connections and condition prevalence without informative line thicknesses.[276] Figure 5-2 is a further network analysis diagram of the conditions according to CSF $A\beta_{42}$ status.

Figure 5-2: Network analyses of self-reported chronic conditions according to CSF Aβ status

Amyloid negative (CSF $A\beta_{42}$ ≥1000pg/ml), n=91



Amyloid positive (CSF $A\beta_{42}$ <1000pg/ml), n=37



The node sizes and text size represent the relative number of connections for each condition, and line thickness the relative frequency of that connection. A limitation of conducting network analyses in this dataset is the small size of the groups analysed (n=37 and n=91), meaning that some connections may appear prominent but that this can be explained by chance. In addition, the small sample means the line thickness on the amyloid positive graph is less informative. Conducting these analyses was valuable preparation for me to both understand similar analyses in other publications and to familiarise myself further with techniques to apply in larger datasets.

5.5 FURTHER DISCUSSION

5.5.1 Hypothesis addressed

There was an inverse association between multimorbidity or having a larger number of chronic conditions and a lower concentration of CSF amyloid-β, a marker of Alzheimer's disease.

5.5.2 Potential mechanisms

In the context of previous research reporting associations between multimorbidity and dementia, the finding that a larger number of chronic conditions is inversely associated with amyloid positivity was unexpected. An explanation for this may be that amyloid is less important in the development of dementia in people with multimorbidity than those without. There is evidence from post-mortem and positron-emission tomography (PET) imaging studies that people with pathological features of Alzheimer's disease may not all have cognitive impairment.[355–359] Additionally, those with a clinical diagnosis of Alzheimer's dementia have evidence of neurodegeneration with multiple pathologies, for example vascular. People with multimorbidity are likely to have multiple cerebral pathologies that contribute to neurodegeneration and clinical manifestations of dementia.[98]

Cerebral amyloid load does not correlate with clinical dementia or severity.[360] There have been clinical trials of drugs that successfully reduced amyloid plaques and neurofibrillary tangles on neuroimaging.[361] However, the majority of these studies

have failed to show evidence of improvement in participants' cognitive and functional abilities.[362,363] Cerebral amyloid deposition may be a marker of a process, for example attempts at brain repair, rather than the pathological cause of neurodegeneration.[364] This would explain why its removal does not tend to improve clinical outcomes in people with cognitive impairment. There are ongoing studies exploring the hypothesis that clearing amyloid before the onset of symptoms may be effective, rather than after cognitive impairment has manifested clinically.[363] My findings, although only from cross-sectional analyses, may support the understanding that clinical dementia is multifactorial and not solely related to amyloid.[365–367]

5.5.3 Additional limitations

People with a contraindication to lumbar puncture or MRI scan were excluded from the EPAD cohort, as is the case in similar CSF studies. This would include participants taking anticoagulant medication for conditions such as atrial fibrillation, adding to the limitation of only including healthy volunteers. In addition, CSF Aβ concentrations can be useful in clinical practice but are not diagnostic when used in isolation. These results should therefore be viewed in the context of adding specific knowledge to a defined area of dementia research, and not extrapolated beyond this.

In these analyses, I used the list of conditions from the influential 2012 primary care multimorbidity epidemiology paper by Barnett and colleagues.[39] As highlighted in section 3.3.1 on page 101, it is important to have a clear definition of multimorbidity, and when counting conditions the list of potential diagnoses should be clearly justified and contain a robust number of conditions. Using an established list improves comparability with other similar studies. Unlike in the PREVENT Dementia study, where participants reported their medical history according to a pre-defined list in the Case Report Form, EPAD participants reported any medical conditions without guidance. They thereby self-selected what counted as a condition. The EPAD Case Report Form did not include any indication of whether a condition was current or previously diagnosed. I therefore chose to count the conditions from the list in Barnett and colleagues' paper.[39] The list specifies the criteria for recording each condition, and this is often 'ever recorded'. I amended the list to remove dementia, as people with pre-existing dementia were excluded from the study, and to adapt some of the

disease definitions to a cohort study case report rather than its original design for primary care records. This list includes some mental disorders, namely depression, schizophrenia or bipolar disorder, eating disorders, learning disability and anxiety or other neurotic and somatoform disorders. I chose to include these conditions to preserve the list's comparability with other studies. However, these inclusions should be taken into account when comparing results in this chapter with those of Chapter 4, where mental disorders were specifically excluded. I made this decision because Chapter 4 examined a range of mental and brain health outcomes, whereas in this chapter the outcome of interest was a specific biomarker related to Alzheimer's disease.

The sample size was too small to conduct analyses accounting for specific disease groups with multimorbidity. Future work could explore the contribution of vascular disease, for example, to any effect seen between multimorbidity and CSF amyloid concentration.

5.5.4 Longitudinal comparisons

The theory that amyloid is a marker, rather than cause, of neurodegeneration may fit with my results,[368] and leads to the hypothesis that longitudinal follow-up may reveal more association between multimorbidity and clinical dementia than with Alzheimer's pathology. A systematic review of multimorbidity and progression of dementia found six longitudinal studies.[369] The authors concluded that the association between increasing multimorbidity and cognitive decline was dynamic and less likely to be detected in cross-sectional analyses. This is a possible explanation for the results seen in my work. A more recent longitudinal study of 14 265 people without dementia found that increasing scores on the Multimorbidity Weighted Index were associated with worse scores on global cognition and recall.[370] Two studies have longitudinally explored not only cognitive outcomes but also varying levels of multimorbidity.[282,283] This approach is a strength over studies that artificially treat multimorbidity as a static state. Future investigations into multimorbidity and amyloid in the EPAD Cohort could explore the association longitudinally, possibly with the addition of measures of cognitive function.

5.5.5 Outcomes of multimorbidity that includes dementia

There is clear evidence that multimorbidity is common in people with dementia.[39] A recent study of quality of life in people with dementia captured 23 chronic conditions using an adapted Charlson Index through an interview with the person with dementia and a carer.[371] The median number of conditions was one. Increasing numbers of conditions was associated with worse scores on mobility, self-care, functioning, pain and anxiety and depression scores within the EuroQol five-dimension measure of health status (EQ-5D). Having dementia alongside other comorbidities is also associated with increased use of health services and costs.[372,373] Multimorbidity in people with dementia is therefore associated with adverse outcomes for the patient, regardless of the underlying mechanisms.

5.5.6 Implications

High quality healthcare should integrate both physical and mental health and account for their complex interactions.[374] My cross-sectional findings should be understood in the context of previous research reporting high levels of comorbidity in people with dementia. They are insufficient to confirm a mechanism or suggest changes in practice. The paper will form a valuable part of the body of research exploring biomarkers in this area, and could direct longitudinal investigation in a larger, or older group. Replicating the analyses in the same participants, especially as some begin to develop dementia, will inform this further. Perhaps biomarkers are of less importance in older people with multimorbidity and this should be taken into account when designing memory or brain health clinics.[375] If amyloid is confirmed not to be important in the relationship between multimorbidity and dementia, this should only reinforce the need for person-centred healthcare that acknowledges the importance of both physical and brain health.

5.6 CHAPTER CONCLUSIONS

This chapter has focused closely on multimorbidity in relation to one biomarker of brain health, CSF amyloid-β. These cross-sectional results show that there is an inverse relationship between having multiple chronic conditions and lower CSF

amyloid concentrations, which are linked to Alzheimer's disease. Chapter 6 will explore longitudinal associations between medication use (a marker of multimorbidity) and clinical manifestations of brain health.

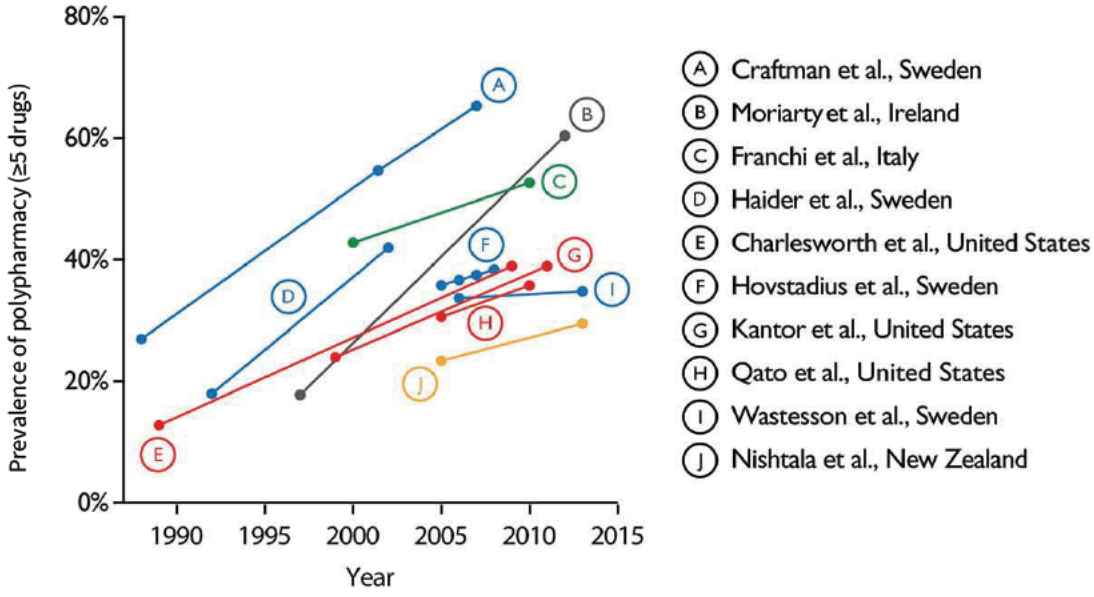
Chapter 6 Longitudinal analyses of routinely collected NHS data

6.1 INTRODUCTION

Polypharmacy is defined as the concurrent prescription of several medications, with the most commonly used cut-off being five.[32] It usually co-exists with multimorbidity.[26] There is clear evidence that as the number of prescribed drugs rises, there is an increase in prescribing errors, high risk prescribing, and adverse drug events, as highlighted in a major 2013 report from the King's Fund.[376]

Rates of polypharmacy are increasing, as demonstrated by an international review of polypharmacy studies from 1990 to 2018, shown in Figure 6-1.[377] This may reflect the rise in multimorbidity, as there is an established link between the two.[78] In addition, they both increase with age, and as populations age worldwide, the prevalence of multimorbidity and polypharmacy rises.[71]

Figure 6-1: Prevalence of polypharmacy (≥5 drugs) from international longitudinal studies. From Wastesson et al., 2018 [377] *with amended y axis label*[16]



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6.1.1 Associations between polypharmacy and mortality

A 2017 systematic review and meta-analysis of polypharmacy as a risk factor for mortality found 47 studies on this topic.[33] Polypharmacy was measured in five main ways and overall, meta-analysed results showed an increased risk of death with increasing medication use. The largest of these studies included 1 917 646 people aged 65 to 94 years in Italy.[378] It found that with chronic use of ≥5 compared to 0-4 drugs, the hazard ratio for death within one year was 1.11 (95% CI 1.08 to 1.14, adjusted for year, sex, age and raw number of drugs). However, a 2017 longitudinal German study of 2 687 people aged 58-82 years found the opposite, with an adjusted hazard ratio for non-cancer mortality in those taking ≥10 drugs of 1.42 (95% CI 0.57 to 3.57) in participants without multimorbidity, and 0.51 (0.11 to 2.27) in people with multimorbidity.[379] The authors reported a significant interaction between taking ≥10 medications and having multimorbidity, defined as severe or very severe disease in more than one organ system (P=0.019). The size of the Italian study and the meta-analysis findings suggest there is an association between polypharmacy and mortality, but none of these studies examined specific causes of death.

This observational association is likely due to the co-existence of polypharmacy and multimorbidity, in that polypharmacy is a marker of severity of comorbid illnesses, which in itself increase the risk of death.[379] There may also be specific adverse effects from individual drugs or an increased risk of drug interactions, each of which is associated with increased mortality.[291]

6.1.2 Polypharmacy and cognitive impairment or dementia

There is some evidence to suggest that polypharmacy is associated with worse cognitive outcomes and poorer mental health in older age. As discussed in Chapter 4 (section 4.1.2 on page 116), a 2014 systematic review of outcomes associated with polypharmacy found 58 papers, of which the most common outcomes were those relating to falls (23 studies), adverse drug events (14 studies) and hospitalisation or mortality (10 studies).[291] Six included papers investigated mental health outcomes, of which five explored cognitive impairment or dementia and one depressive symptoms. This reflects the fact that research into polypharmacy rarely investigates

mental or brain health outcomes, and of studies that do, most focus on cognitive impairment or dementia.

A systematic review exploring polypharmacy and dementia published in 2019 found seven studies, a relatively small number compared to the 47 included in the review on polypharmacy and mortality.[33,35] Polypharmacy did appear to be a risk factor for dementia in most of the studies, with an adjusted risk ratio of 1.30 (95% CI 1.16 to 1.46) on meta-analysis. However, the meta-analysis included papers that used different cut-offs for polypharmacy so this figure should be interpreted with caution. It is clearer that polypharmacy is common among people with existing dementia, with one cross-sectional Scottish population study finding that people with dementia were more likely to be prescribed 5-9 medications (OR=1.46 (1.40 to 1.52, P<0.001)) and ≥10 medications (OR=2.01, 1.90 to 2.12; P<0.001) compared to people without dementia.[346]

At least two relevant studies have been published since this systematic review's search date. A cross-sectional study of 2 122 people aged 69 years found a difference of -2.0 points (95% CI -2.8 to -1.1) on the Addenbrooke's Cognitive Examination version III in those taking 5-8 medications compared to 0-4, and -2.9 points (95% CI -4.4 to -1.4) in those taking ≥9 medications.[325] However, a study of over 15 000 people with dementia in London found no statistically significant difference in the rate of cognitive decline as measured on the Mini-Mental State Examination (MMSE) between those taking 0-4, 5-9 or ≥10 medications.[380] Limitations of this study were that it used the MMSE, which has a known ceiling effect, and that 21.3% of the original sample was excluded due to insufficient MMSE data.[381] In addition, a recent review of 12 studies found that the prevalence of potentially inappropriate prescribing for people with dementia was 31% (95% CI 9 to 52%) in the community and 42% (95% CI 30 to 55%) in residential care settings.[382]

Along with evidence of harms associated with polypharmacy, specific medications have been associated with cognitive decline and dementia, including

benzodiazepines,[102] anticholinergics [383–385] and anti-convulsants.[386] The use of these drug groups may explain a large proportion of the association apparently seen with polypharmacy.

6.1.3 Polypharmacy and delirium

A Spanish study of 457 patients with multimorbidity admitted to medical wards, with a mean age of 81 years, found that patients were prescribed a mean number of 8.2 drugs (standard deviation 3.4).[387] The researchers found no significant difference in one-year survival between patients on 0-4, 5-9 or ≥10 drugs. They also found that people on ≥10 medications were less likely to have been diagnosed with delirium on a previous hospital admission (13.1% v 24.0%, Student's t-test P=0.006), with adjusted OR=0.48 (95% CI 0.25 to 0.91). They postulated that this may be because delirium and cognitive impairment are signs of advanced disease and less intensive treatment regimes. This could also be due to patients undergoing medication reviews as a result of developing delirium on a previous admission. A systematic review of risk factors for in-hospital delirium, however, identified that polypharmacy carried a relative risk of 2.9 (95% CI 1.6 to 5.4) or OR=1.9 (95% CI 1.1 to 3.2).[388] The authors suggested that these positive associations may be due to confounding factors such as the presence of dementia, long hospital stay and severity of physical illness, which are all associated with both polypharmacy and delirium. Individual drugs' mechanism of action, adverse effects and interactions may also be an explanatory factor.[389] Some research exists linking polypharmacy with in-hospital delirium,[388,389] but no research exists exploring broader mental health outcomes in people with polypharmacy at a population level.

6.1.4 Associations between polypharmacy and mental disorders

A cross-sectional study of 5 502 women aged 76 to 81 years in Australia linked prescribing records to mental health scores on the Medical Outcomes Study 36-item Short-Form Health Survey (SF-36).[390] The authors reported that compared to taking no medications, people taking 1-3 medicines had better mental health scores (adjusted β=1.53, 95% CI 0.02 to 3.09, P=0.05), people taking ≥10 medications had worse mental health scores (adjusted β= -2.89, 95% CI -5.05 to -0.73, P<0.009) and there was no statistically significant difference for those taking 4-9 medications. This

longitudinal cohort study had the advantage of including detailed phenotypes, but may have limited generalisability to the population.

A general practice records study of 4 506 people aged ≥50 years in England linked prescribing data to physical and psychological scores on the Short-Form 12 (SF-12) questionnaire at three year follow-up.[391] The author reported that with increasing drug use between four categories (1-4, 5-7, 8-11 and ≥12 drugs), there was a significant association towards poor physical health (*P* for trend=0.025) but no significant association with psychological scores. However, this single-author paper reports unusual methods, for example using logistic regression to test for longitudinal changes between dichotomised SF-12 scores, so is of limited value.

A 2016 systematic review of seven papers on polypharmacy and medication adherence found an association between taking increasing numbers of drugs and worse medication adherence.[392] It has been suggested that this in turn could contribute to the development of mental disorders, due to the under-treatment of a physical or mental illness.[35]

6.1.5 Scottish context

There have been no population-level studies of polypharmacy in Scotland with longitudinal outcomes. A repeated cross-sectional study exploring the dispensed community prescriptions of over 300 000 patients aged over 20 years in Tayside found that 50.6% of people were dispensed one or more drugs in the previous 84 days in 1995, compared to 58.9% in 2010.[37] The proportion of people dispensed 5-9 drugs rose from 9.7% to 16.3% and 10-14 drugs from 1.5% to 4.7% in the same period. A study of electronic primary care records of 180 815 adults aged over 20 years using data from 2006 found 16.9% of adults were prescribed 4-9 medications and 4.6% ten or more.[393] These data were from 40 demographically representative GP practices in Scotland. A cross-sectional study of 1 424 378 people aged over 18 years, also from representative primary care practices using 2007 data, compared people with and without a history of stroke, so does not allow population-level estimates for the

number of medications used.[394] There is therefore an opportunity for research investigating polypharmacy in Scotland longitudinally, at population level and with a particular focus on psychiatric outcomes.

Scotland has arguably the most complete and best quality healthcare data in the UK.[395] Every person registered with a GP in Scotland has a unique ten-digit identifier, the Community Health Index (CHI) number. The CHI number can also be generated following other healthcare contacts such as hospital admissions.[22] It identifies the patient at any healthcare contact and its ubiquitous use allows for linkage between the datasets held by the NHS as well as by other agencies, such as National Records of Scotland (NRS) death certificate information.[107,396] The data are collected and managed by NHS Information Services Division (ISD) and, at the time I accessed the data, were hosted within the Farr Institute of Health Informatics Research.[17]

The use of unconsented routinely collected healthcare data for research is common, but public perception of this practice varies. In general, attitudes are positive as long as data are carefully stored with restrictions to prevent inadvertent identification of individuals.[397,398] In Scotland, unconsented data are stored in Safe Havens, which are secure environments for data linkage and analysis.[399] They are covered by strict governance procedures and robust security. All researchers wishing to access these data must apply by submitting a research proposal to the Public Benefit and Privacy Panel for Health and Social Care.

Given that the evidence for associations between polypharmacy and mental health outcomes is mixed, this chapter explores these links. It takes advantage of the very large sets of routinely collected data available in Scotland to address the lack of longitudinal population-wide studies in this area.

[17] The Farr Institute was named after William Farr (1807-1883) who set up the first system for routinely recording causes of death. It closed in 2018 and has been replaced by Health Data Research UK

6.2 HYPOTHESES

In keeping with the overall hypotheses of this thesis presented in Chapter 1 (section 1.5, page 18), this chapter addresses the following hypotheses:

1. Using larger numbers of medications (accounting for psychotropic prescriptions) will be associated with poorer mental health, as demonstrated by
    a. Presence of a mental disorder on death certificate
    b. Admission to psychiatric hospital

In order to understand mental disorders on death certificates in context, I will also approach the following hypothesis:

2. Using larger numbers of medications (accounting for psychotropic prescriptions) will be associated with increased all-cause mortality.

6.3 METHODS

In this chapter, I describe analyses of routinely collected data provided by NHS National Services Scotland Information Services Division (ISD). I aimed to follow up members of the population dependent on their medication use at baseline. I therefore accessed data from the Prescribing Information System (PIS), NRS death certificate data and hospital records from the Scottish Morbidity Record for psychiatric hospital admissions (SMR04). Demographic data were also required and available via the CHI database.

6.3.1 Access application and procedures

I prepared an application to the Public Benefit and Privacy Panel for Health and Social Care (PBPP), outlining my proposal and plans for data analysis and management. Prior to submitting the application, I presented my plans to lay members of the Farr Institute Scotland Public Panel, who gave positive feedback. I then applied to the PBPP with the proposal and plans presented in Appendix 3. After revisions, my proposal was approved on 22nd June 2017. Ethical approval has previously been granted for the broader electronic Data Research and Innovation Service (eDRIS) by

the East of Scotland NHS Research Ethics Service (reference 16/ES/0112), so an individual ethics application was not required.

6.3.2 Dataset

6.3.2.1 Prescribing Information System

The NHS ISD Prescribing Information System (PIS) collects information on every prescription dispensed in the community and claimed for payment by pharmacies in Scotland. This does not include medication dispensed in hospital or those dispensed but not reimbursed (numbers of which are likely to be very small).[53,400]

6.3.2.2 Death certificate data

National Records of Scotland (NRS) is responsible for registering all deaths that occur in Scotland. ISD's eDRIS provided a linked dataset featuring all deaths in the study period. For every death, a doctor records the causes of death on the Medical Certification of Cause of Death (hereafter referred to as death certificate). NRS then codes the diagnoses according to the International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10). This is initially done by specialist software, then checked by a medical coder.[401] The first field on the death certificate is primary or underlying cause of death, which is the diagnosis considered primarily responsible for the death. Secondary causes of death are those that did not primarily cause the death but are considered relevant to it. Other comorbid diagnoses that are not deemed relevant to the death are not included on the death certificate.

6.3.2.3 Scottish Morbidity Record

The Scottish Morbidity Record (SMR) captures healthcare data for individual patients and reporting of episodes by health boards is mandatory.[402] SMR04 contains data on psychiatric inpatient and day case care. Data have been recorded in SMR04 since the 1960s and are routinely available from 1981 onwards.

6.3.2.4 CHI database

The CHI database holds basic demographic details of registered people, including their address, from which Scottish Index of Multiple Deprivation (SIMD) and care home status are generated. My data extract included these variables at the beginning of each quarter. It also allowed identification of individuals with a CHI number who were not prescribed medication in the final quarter of financial year 2008-2009. This dataset allowed for an overall mean of drugs used to be calculated, but since other essential variables including age were only included in the PIS extract, analyses were only possible among those receiving one or more medications.

6.3.2.5 Data linkage

The data from these four databases (PIS, SMR04, NRS death certificates and CHI) were linked by an eDRIS analyst. Patients' CHI numbers had been removed and replaced with a unique pseudonymised identifier before being made available to me. Table 6-1 summarises the raw variables extracted from each database. The raw data were only available for viewing and analysis via remote access to the Farr Institute Safe Haven, to which access is strictly controlled. Results, including descriptive statistics, outputs of statistical tests and data visualisation, were only released after approval by an eDRIS Information Analyst and data controller.

Table 6-1: List of variables from each ISD dataset

Linked dataset	Variables	Time period
Prescribing Information System (PIS)	Age at start	1st January 2009
	Gender	1st January 2009
	Count of unique medicines dispensed	First quarter of 2009
	List of all unique medicines	First quarter of 2009
Community Health Index (CHI)	Care home residency status	1st January 2009
	Scottish Index of Multiple Deprivation (SIMD)	
National Records of Scotland (NRS) deaths	Age at death	January 2009 to June 2017
	Causes of death	
Scottish Morbidity Record for psychiatric hospital admissions (SMR04)	Age at admission to psychiatric hospital	January 2009 to June 2017

6.3.3 Variables

6.3.3.1 Medications

From the PIS data extract, I received two main drug variables, a count of unique drugs and a concatenated variable of all unique drug names reimbursed between 1st January and 31st March 2009. The inclusion of only unique medications meant that repeat prescription items would not be counted more than once. In keeping with a previous similar study that examined prescriptions over 84 days, my data were extracted by quarter. Guthrie and colleagues stated that the most common prescription length for repeat drugs is 56 days (usual range 28-84 days).[37] They justified using a longer window to capture routinely collected data as the interval between a patient requesting prescriptions does not match exactly with the length of the prescription.

I chose to request dispensing, rather than prescribing, information in order to minimise over-estimation occurring with prescriptions that are not filled. I received access to all prescriptions where a CHI number was present, which is estimated to be almost 100% of dispensed prescriptions.[53] PIS data are organised by the financial quarter in which the dispensing pharmacy was reimbursed for the prescription. Reimbursement usually takes place around two months after dispensing, meaning that for example, medication appearing in a quarter from 1st January to 31st March 2009 would have been prescribed and dispensed between 1st November 2008 and 31st January

2009.[53] Until April 2011, flat-rate prescription charges of £5 per item were applicable in Scotland for people aged under 60 years who did not have an exemption due to certain chronic illnesses or low income. Medication was free for all other patients.[403]

In keeping with a previous similar study, I excluded devices that did not actually deliver drugs, and any other preparations that were prescribable but did not constitute active medications.[37] I addressed this in two ways. Firstly, I reviewed the NHS Scotland Prescription Cost Analysis which lists all items dispensed in Scotland, to find specific formulations that could be considered irrelevant.[404] I then requested the following formulations be excluded: aerosols, cleansing agents, crystals, flour, gum, jelly, mouthwash, oil, paint, paste, rinses, rubs, scrubs, soup, tinctures, vaccines, washes, water and wax. Secondly, I examined the structure of the British National Formulary (BNF) and excluded chapters 14 (immunological products and vaccines) and 18 to 23, sometimes called appendices and indices, which include for example dressings and appliances for incontinence.[405] [18] Then at paragraph level, which mostly represents drug classes, I excluded items which were either not medications (such as foods for special diets) or had little pharmacological action (for example, emollients, throat lozenges, artificial saliva and aromatic inhalations). I included prescribed oxygen as it is a drug and its use is likely to represent significant illness.[406]

The primary exposure variable was the count of unique medications dispensed within one quarter. This is a continuous variable so I primarily treated it as such. However, anticipating a wide range, when comparing hazard ratios for each level of medication use I collapsed the categories at ≥20. When comparing groups of patients by their level of medication use, for example to allow clearer visual comparison on a Kaplan-Meier graph, I used the groups 1-4, 5-9 and ≥10 medications. These cut-offs have been used in several similar studies.[32]

[18] The BNF structure changed in 2017; I referred to the original chapter structure as in BNF 69 (September 2015), now called BNF Legacy

6.3.3.2 Outcome variables

6.3.3.2.1 Deaths

From the NRS linked extract, I received data on any person who was aged over 50 years on 1st January 2009 and died between then and 30th June 2017. The variables included their age at death in months, their primary cause of death and any listed secondary causes of death (of a possible maximum of ten). From these data, I used two time variables, age at death and time to death (age at death minus age at 1st January 2009). I generated a binary variable for mortality to allow analyses on all-cause mortality, and inform and contextualise specific examination of psychiatric causes. I then created a concatenated variable of all causes of death and searched this and the primary cause of death variable separately for psychiatric codes.

I reviewed ICD-10 Chapter V, Mental and Behavioural Disorders, for relevant diagnosis codes.[407] In keeping with my hypotheses that polypharmacy might increase mental disorders, I was interested in those mental disorders that can develop or worsen in ageing. Therefore I excluded intellectual disabilities (*"mental retardation"* in ICD-10) and other neurodevelopmental disorders, and all disorders of adult personality and behaviour (F60-69). This includes specific personality disorders and gender identity disorders, which are by definition lifelong. The disorders included are listed in Table 6-2. I used the `grepl` function to search for the codes and any extensions thereof.

Table 6-2: Mental and behavioural disorders included in definition of psychiatric causes of death

Overall group of disorders	Disorders included	ICD-10 codes
Dementia or mild cognitive impairment	All subtypes of dementia (including unspecified), mild cognitive disorder	F00, F01, F02, F03, F67, G30
Delirium	Delirium not induced by alcohol and other psychoactive substances	F05
Other organic disorders	Organic amnesic syndrome, mental, personality or behavioural disorders due to brain damage and dysfunction or physical disease, unspecified organic mental disorder	F04, F06, F07, F09
Mental and behavioural disorders due to use of alcohol	Includes harmful use, dependence syndrome, acute intoxication, withdrawal state, amnesic syndrome	F10
Mental and behavioural disorders due to other psychoactive substance use	Includes harmful use, dependence syndrome, acute intoxication, withdrawal state, amnesic syndrome	F1, excluding F10
Schizophrenia and other non-organic psychotic disorders	Schizophrenia, persistent delusional disorder, acute and transient psychotic disorder, schizoaffective disorder, other or unspecified nonorganic psychosis. Not schizotypal disorder	F20, F22, F23, F25, F28, F29
Depression and other mood (affective) disorders	Depressive episode, recurrent depressive disorder, other or unspecified mood disorders	F32, F33, F34, F38, F39
Bipolar affective disorder and mania	Bipolar affective disorder, manic episode	F30, F31
Anxiety and adjustment disorders	Obsessive-compulsive disorder, adjustment disorder, phobic and other anxiety disorders	F40, F41, F42, F43
Somatoform, dissociative and other neurotic disorders	Dissociative disorder, somatoform disorder, other neurotic disorders	F44, F45, F48
Eating disorders	Anorexia nervosa, bulimia nervosa, other psychogenic eating disorders	F50
Other disorders	Unspecified mental disorder, psychological and behavioural factors associated with physical disorders or diseases	F99, F54

I created two binary variables, one for death where the primary cause was a mental disorder and another for death with a mental disorder listed as any (including primary) cause of death. For each of these variables, a psychiatric cause of death was coded as 1 and either survival or death without a psychiatric cause was 0.

6.3.3.2.2 Psychiatric admissions

Using the SMR04 dataset, which records all admissions to psychiatric hospital in Scotland, I made a binary variable of whether all linked patients were admitted to psychiatric hospital within the study period. For people with multiple admissions, I took the first admission only. Age at admission was also available from SMR04.

6.3.3.3 Covariates

6.3.3.3.1 Age

The follow-up begins on 1st January 2009, which was when Scotland's prescribing records were linked to other health datasets. This is an arbitrary time point in relation to the exposure and outcome variables, so time in follow-up is therefore irrelevant for most analyses. Patients' ages are more relevant to mortality and hospital admission in this age group. The most appropriate metric of time is therefore age at event (death or hospital admission), with age at entry to the cohort (on 1st January 2009 in all cases) as a covariate.[408–410] This starting age, in months, was taken from the PIS extract.

I generated a time at censoring variable where those who did not die or have a hospital admission were allocated 102 months (the length of follow-up duration). For hospital admission analyses, I used informative censoring with death as a competing event, in that patients who died were censored at their death and did not continue contributing to the hazards of hospital admission. Age was treated as a continuous variable in most analyses, but age groups were used to stratify analyses where appropriate.

6.3.3.3.2 Psychotropic drug use

Medication is the primary form of treatment for most people who seek medical attention for mental disorders.[79] In the UK, psychotropic medication is only prescribed where it has an evidence base for clinical effectiveness, so in theory, taking psychotropic medication should reduce the incidence of mental health outcomes if it effectively treats them. In any case, in this dataset where diagnoses are not available, psychotropic medication use can act as a marker for a pre-existing psychiatric diagnosis. It was therefore important to account for psychotropic drug use in analyses.

I used the concatenated variable of all dispensed drug names to find specific psychotropic medications for descriptive analyses, for use as a covariate and to create a subsample of people not taking psychotropic drugs. I defined drugs as psychotropic if they appeared in the following sections of the British National Formulary (BNF):

4.1 Hypnotics and anxiolytics

4.2 Drugs used in psychoses and related disorders (includes those used in mania)

4.3 Antidepressant drugs

4.11 Drugs for dementia [405]

I did not include any of section 4.10, drugs used in substance dependence (which includes methadone and nicotine replacement), as their effects are not primarily psychotropic. I considered including stimulants used for attention deficit disorder such as atomoxetine, dexamfetamine and methylphenidate, but preliminary analyses showed these to be negligibly small in number, given the age population studied. Table 6-3 lists the drugs included within the psychotropic drug marker. I used the R function `grepl` to include the strings below and any surrounding letters; asterisks in the table represent possible truncations.

Table 6-3: Drugs counted in psychotropic variable

Overall group	Class	Drugs
Antidepressants	Tricyclics and related drugs	Amitriptyline, clomipramine, dosulepin, doxepin, imipramine, lofepramine, nortriptyline, trimipramine, mianserin, trazodone
	Serotonin-specific reuptake inhibitors	*citalopram (includes escitalopram), fluoxetine, fluvoxamine, paroxetine, sertraline
	Monoamine oxidase inhibitors	Phenelzine, isocarboxazid, tranylcypromine, moclobemide
	Other	Mirtazapine, venlafaxine, agomelatine, duloxetine, reboxetine
Antipsychotics	First generation	Benperidol, flupentixol, haloperidol, levomepromazine, pericyazine, trifluoperazine, perphenazine, pimozide, prochlorperazine, *promazine, sulpiride, zuclopentixol
	Second generation	Amisulpride, aripiprazole, clozapine, lurasidone, olanzapine, paliperidone, quetiapine, risperidone, fluphenazine, pipotiazine
Anxiolytics, hypnotics and sedatives	Benzodiazepines	*azepam, *azolam, chlordiazepoxide
	'Z' drugs	Zaleplon, zolpidem, zopiclone
	Antihistamines used primarily for sedation	Promethazine, hydroxyzine
	Other sedatives	Chloral hydrate, clomethiazole, meprobamate, buspirone, phenobarbital
Mood stabilisers		Lithium, asenapine, carbamazepine, valpro*, lamotrigine
Drugs for dementia		Donepezil, galantamine, rivastigmine, memantine

For use as a covariate, I generated a binary variable of whether a patient received one or more of any of these psychotropic medicines. Anticipating that this psychotropic drug use marker might be informative in its own right, I conducted secondary analyses with dichotomous psychotropic drug use as the exposure variable for all outcomes as below and adjusted for the number of unique drugs as well as the other covariates.

6.3.3.3.3 Other covariates

Average life expectancy at birth in Scotland in 2016 was 77.0 years for men and 81.1 years for women, so gender is relevant to these analyses and was included as a

covariate.[411] Gender were taken from the PIS extract and recorded as at 1st January 2009.[19]

I had intended to include ethnic group as this is relevant to multimorbidity prevalence and by extension polypharmacy,[278] but this is only recorded in SMR from hospital contacts, and even then is not recorded well. There was a large proportion of missing data for this variable in exploratory work so I excluded it from further analyses.

Socioeconomic status is strongly associated with multimorbidity, and with mortality relating to this. A seminal multimorbidity paper studying a cross-section of Scotland in 2007 found around a ten-year gap in prevalence of multimorbidity in younger ages between the most and least deprived deciles of deprivation.[39] This has recently been replicated in an English study, which found a ten-year gap in middle age which decreased with increasing age.[412] Polypharmacy has also been shown to be associated with socioeconomic deprivation in Scotland, with people in the most deprived quintile at over twice the risk of being prescribed ≥10 drugs than those in the least deprived quintile (adjusted OR=2.36 (95% CI 2.22 to 2.51).[27,37] The prescription charge of £5 that was applicable to some included patients in 2009 may have reduced medication uptake in people on low incomes who had not met the criteria for exemption due to low income.

The Scottish Index of Multiple Deprivation (SIMD) is a relative measure of deprivation calculated across seven domains: income, employment, health, education, skills and training, housing, geographic access and crime.[413] Scotland is split into 6976 data zones of approximately equal population (around 760 people) which are then ranked according to these domains. The SIMD therefore allows comparison of deprivation in different areas, but relates to the area of residence rather than circumstances of an individual. My CHI extract included the 2016 SIMD decile of each individual, thus representing their deprivation based on their postcode, relative to other places in

[19] The variable provided by ISD was called gender, and as it is possible to request a change to the gender code in a CHI number,[592] I have used this term throughout this chapter

Scotland, with 1 the most deprived and 10 the least deprived. Specific SIMD rank or postcode would have included too much identifiable information. Deciles of other similar scores (for example, Carstairs) have been used in similar population-level studies.[39] The Scottish Government's latest polypharmacy guidance document used SIMD quintiles to demonstrate the disparities in polypharmacy by socioeconomic group.[27]

I also included care home residency as a covariate because people living in care homes or institutions have higher rates of polypharmacy than the general population. For example, a Scottish polypharmacy study found that compared to people living in their own home, the odds ratio of being prescribed ≥10 medications for those living in care homes was 2.88 (95% CI 2.65 to 3.13).[37] A Swedish population-based study of people who died aged 65 years or over found that 37.2% of people living in institutions were taking ≥10 drugs.[414] People living in care homes also have high rates of multimorbidity and frailty so it is important to take this group into account.[415] A care home residency flag was included in the CHI extract. This marker has been found to have 97-99% positive predictive value and sensitivity of 55-89%.[416]

6.3.4 Statistical analysis

The primary methods in this chapter are survival analyses of mortality (all-cause and with mental or behavioural disorders on the death certificate, either as primary or any cause of death) and psychiatric admission, according to the number of medications dispensed.

6.3.4.1 Descriptive statistics

All analyses were conducted within the Farr Institute Safe Haven remote desktop, in R version 3.5.1.[417] For descriptive cross-sectional analyses at the study start date, I used linear regression, using the same template code as detailed in section 4.3.6.2, for example to assess the relationship between age and number of drugs dispensed. I used Student's t-test to compare means and χ^2 tests to compare proportions between groups, for example when describing the characteristics of participants

receiving and not receiving psychotropic drugs. To prevent the inadvertent identification of individuals, outliers on graphs at extreme old age were removed. Where there were fewer than ten patients in a group of patient characteristics, this was presented as only '<10'.

6.3.4.2 Survival analyses

The longitudinal analysis approaches used were Cox proportional hazards regression and the Kaplan-Meier method. The follow up period for longitudinal analyses was 1st January 2009 to 30th June 2017: 8.5 years or 102 months. Ages were given in months, so I used months as my time scale.

6.3.4.2.1 Cox proportional hazards models

Survival analyses are concerned with whether participants met an outcome event (including death) or not, and if they did, the time taken to reach that event. They also account for censoring, that is whether the participant's time to outcome is unknown because it did not occur during the study period. A hazard is the risk of reaching an outcome at a certain time, given that it has not been reached already.[418] Cox proportional hazard ratios, first developed in 1972, are a version of survival models used to investigate the simultaneous effects of multiple explanatory variables on the hazard.[419] The assumption is that the ratio of hazards remains constant over time, and Cox regression coefficients are exponentiated to generate a hazard ratio.

After checking model assumptions graphically using Schoenfeld residuals, I used the R package `survival` to conduct Cox proportional hazards regression models, with right censoring applied.[420] Right censoring means that although patients' starting age was known, if they survived the study period, their age when the outcome occurred was unknown. An example of the code used was as follows:

```
library(survival)

summary(coxph(Surv(censor_time, outcome==1,
type="right") ~ exposure_continuous + covariate,
data=dataset))
```

Included covariates were starting age, gender, care home status and SIMD in all models. The psychotropic medication marker was an additional covariate.

6.3.4.2.2 Kaplan-Meier method

The Kaplan-Meier method, originally described in 1958, represents the estimated probability of survival (or an event not occurring) for a member of the population at that age or time.[421] The method estimates conditional probabilities: the probability of surviving to the end of a time interval given that the participant has already survived to the beginning of it. Survival probability is then calculated as the product of the conditional probabilities of surviving that time interval.[422] Plotting a Kaplan-Meier estimate of the survivor function shows the crude association between the exposure variable at baseline and cumulative probability of the outcome during the follow-up period. The survival probability only changes when an event occurs, which appears as a step on the graph. The step height relates to the remaining sample at risk of the event. In large sample sizes such as mine, the large number of steps makes the curve appear smooth. A disadvantage of using the Kaplan-Meier method is that covariates cannot be included.[418]

I used the R packages `survival` and `survminer` to generate and plot Kaplan-Meier curves as follows:[420,423]

```
library(survival)
library(survminer)

fit = survfit(Surv(censor_time, outcome==1, type="right")
~ exposure_category, data=dataset)

ggsurvplot(fit, censor=FALSE) # with additional details
for adjusting size, colours, guides and legends
```

I did not include censoring ticks on the curves as there were too many events to be meaningfully visible. I separated the sample into subsets of age bands, 50-64 years,

65-79 years and ≥80 years. These age groups are commonly used in longitudinal studies of ageing where the minimum age is 50 years,[424] and have the benefit of including a cut-point at 65 years, which is when older adult healthcare provision begins in much of the UK. This approach allowed some comparison between the age groups.

I used both age at event and time to event (age at event minus age at start) as time variables for comparison, given that it was not possible to adjust for starting age. The explanatory variable was number of drugs categorised into 1-4, 5-9 and ≥10 for ease of interpretation.

6.3.5 Treatment of missing data

Patients whose age at death or admission was less than their starting age were excluded. If the difference between age at death or admission and the starting age was greater than 102 months, these patients were also excluded. Patients with a starting age of less than 50 years were excluded. There were small numbers of these patients and these anomalies were assumed due to errors in either data entry or during the linkage process.

SIMD was the only included variable which contained missing data. Patient characteristics between the groups of those with SIMD available and missing were calculated and compared using χ^2 and t-tests. This preliminary analysis suggested SIMD was missing at random; I excluded those with missing SIMD from the main analyses and conducted sensitivity analyses as follows:

i) Including people with missing SIMD but excluding SIMD as a covariate
ii) Generating estimated SIMD by multiple imputation

Multiple imputation was performed using the R package `mice` (Multivariate Imputation by Chained Equations).[425] The imputation process generates multiple copies of the dataset, simulating possible options for the missing data based on regression models using the non-missing variables. Residual error is added via the regression model's

parameter estimates to create imputed values.[426] The convention is to generate three to five imputations, but White and colleagues suggest the fraction of missing information is often lower than the percentage of missing cases, so the number of imputations should be at least equal to the percentage of missing cases.[427] As 8.96% of the total sample had SIMD missing, I generated nine imputations twice, based on the cumulative hazard for each all-cause mortality and psychiatric admission. For each of these imputations I used five iterations, where the first generates random possible values for the missing data and each iteration refines these using regression coefficients and residual error. The final iteration generates the first imputed dataset and the process is repeated in the next imputation.

The following code is an example of how I generated the imputation:

```
library(mice)

d = data.frame(dataset)

cumulative_hazard = nelsonaalen(d, censor_time, outcome)

d2 = data.frame(d, cumulative_hazard)

imputation1 = mice(d2, m=1, maxit=0, seed=100)

Pred = imputation1$predictorMatrix

Pred[2, “censor_time”] = 0 # the variable to impute is
in column 2

Full_imputation = mice(d2, m=9, maxit=5, seed=100,
predictorMatrix = Pred)
```

The analysis, in this case Cox proportional hazards, is conducted in each of the imputed datasets as normal.[428] It generates an estimate for each parameter for each imputation. The `pool` function of the `mice` package then calculates the mean of these estimates (in this case, Cox regression coefficients), along with the total variance over the repeated analysis according to Rubin’s rules, giving one point estimate.[425,429,430] An example of the code used to do this is as follows:

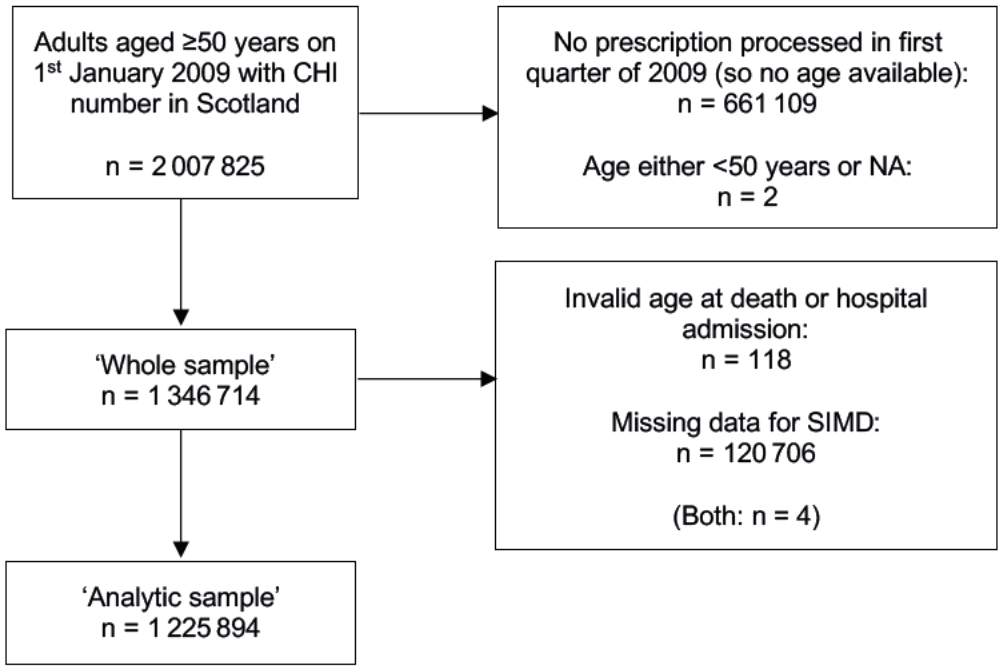
```
library(mice)
library(survival)

cox_model = with(data = Full_imputation,
exp=coxph(Surv(censor_time, outcome) ~
exposure_continuous + covariate))

pool_cox_model = summary(pool(cox_model, dfcom =
1346595))

pool_hr = exp(cbind(pool_cox_model[,1],
(pool_cox_model[,1] - 1.96*(pool_cox_model[,2])),
(pool_cox+model[,1] + 1.96*(pool_cox_model[,2]))))
```

6.4 RESULTS

6.4.1 Sample overview

There were 2 007 825 people aged 50 years and over with a CHI number in the study period. Of these, 661 109 did not have a prescription processed in the first quarter of 2009 so were excluded from further analyses. After removing those in the remaining sample with ages either NA or under 50 years (n=2), 1 346 714 people were in the whole sample for descriptive analyses. After removing 118 patients whose age at death or admission was either less than their starting age or >102 months and the 120 706 with missing SIMD (four people met both these exclusion criteria), the analytic sample comprised 1 225 894 individuals. Figure 6-2 displays the number of participants included and excluded at each stage.

Figure 6-2: Flowchart of sample derivation



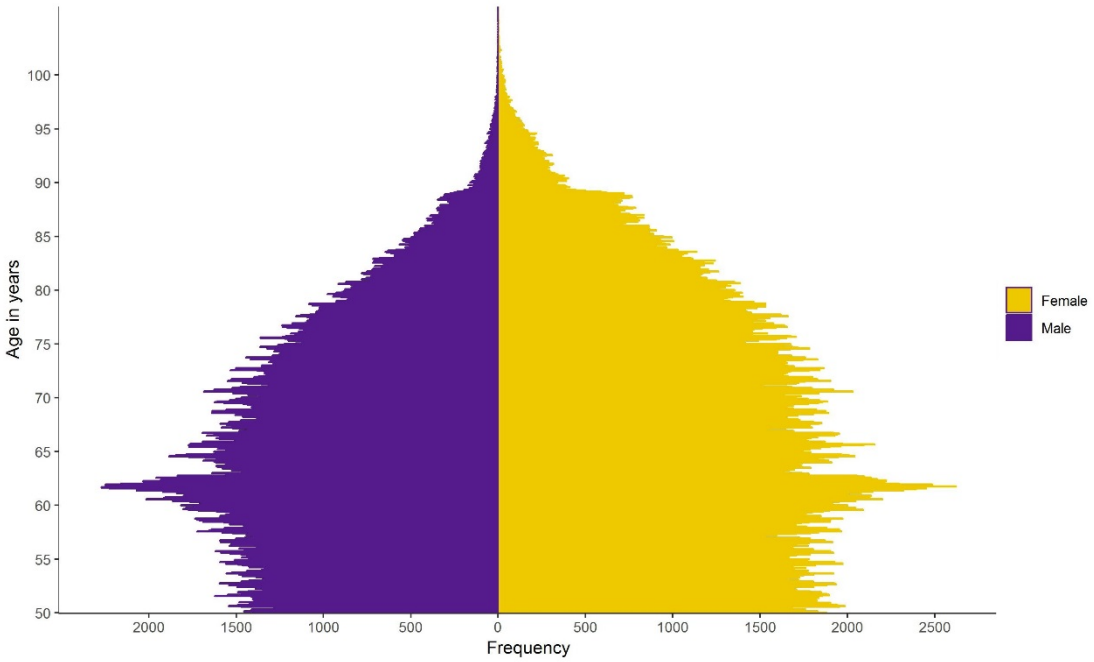
In the analytic sample, the mean starting age was 67.37 (SD=10.80) years, with men younger than women (μ_{men}=66.49 [SD_{men}=10.14]; μ_{women}=68.06 [SD_{women}=11.24] years). Psychotropic medications were supplied to 303 743 (24.78%) people, and 45 925 (3.75%) had a care home residency flag. During the 8.5 year study period, there were 336 244 deaths, of which 63 974 (19.03%) had any psychiatric cause listed and 32 737 (9.74%) had a mental disorder as the primary cause of death. There were 23 747 (1.94%) people admitted to psychiatric hospital, of whom 11 553 (48.65%) later died during the study period. Of these, 7 337 (63.51%) had a psychiatric cause anywhere on their death certificate and 4 275 (37.00%) had a psychiatric primary cause of death. Table 6-4 shows these descriptive statistics for the sample comprising only complete cases, in which analyses were carried out, compared to the whole sample.

Table 6-4: Characteristics of whole sample (including those with missing SIMD), and analytic sample (complete cases) during study period January 2009 to June 2017

	Whole sample		Analytic sample	
	Mean (SD)	**N (%)**	**Mean (SD)**	**N (%)**
All		1 346 714		1 225 894
Starting age (years)	67.37 (10.77)		67.37 (10.80)	
Starting age: men (years)	66.48 (10.12)		66.49 (10.14)	
Starting age: women (years)	68.06 (11.20)		68.06 (11.24)	
Female gender		757 552 (56.25)		687 431 (56.08)
Number of medications	4.98 (3.64)		4.99 (3.65)	
Dispensed any psychotropic medication		332 954 (24.72)		303 743 (24.78)
Dispensed antidepressant		217 546 (16.15)		198 213 (16.17)
Dispensed anxiolytic or hypnotic		119 291 (8.86)		108 950 (8.89)
Dispensed antipsychotic		45 779 (3.40)		42 154 (3.44)
Dispensed dementia drugs		9 234 (0.69)		8 554 (0.70)
Dispensed mood stabilisers		26 627 (1.98)		24 261 (1.98)
Care home resident		46 095 (3.42)		45 925 (3.75)
SIMD missing		120 706 (8.96)		0
Died		363 743 (27.01)		336 244 (27.43)
Age at death (years)	80.29 (10.24)		80.23 (10.27)	
Age at death (years) - women	81.98 (10.19)		81.94 (10.23)	
Age at death (years) - men	78.26 (9.92)		78.18 (9.93)	
Died with mental disorder as primary cause		35 543 (9.77)		32 737 (9.74)
Died with mental disorder as any cause		69 569 (19.13)		63 974 (19.03)
Admitted to psychiatric hospital		26 688 (1.98)		23 747 (1.94)
Age at admission (years)	72.97 (11.24)		72.92 (11.28)	

Figure 6-3 shows the distribution of age by gender of the whole sample of people aged ≥50 years as at 1st January 2009 (n=1 346 714). The peak at aged around 62 years reflects people born immediately after the Second World War in 1946-7. There is another marked step in both genders around age 89 years, showing fewer people alive who were born before 1920. This may reflect either high maternal and infant mortality or miscarriage rate in 1918-20 due to the Spanish influenza pandemic, a peak in births after the end the First World War, or a combination of the two.[431]

Figure 6-3: Population pyramid showing age (in whole-month intervals) in January 2009, by gender



The mean number of medications dispensed within one quarter in the analytic sample (who all received at least one drug) was 4.99 (SD=3.65). The median number of drugs was 4, and interquartile range 2-7. Table 6-5 shows the breakdown of the drugs dispensed according to the groups used for survival analyses.

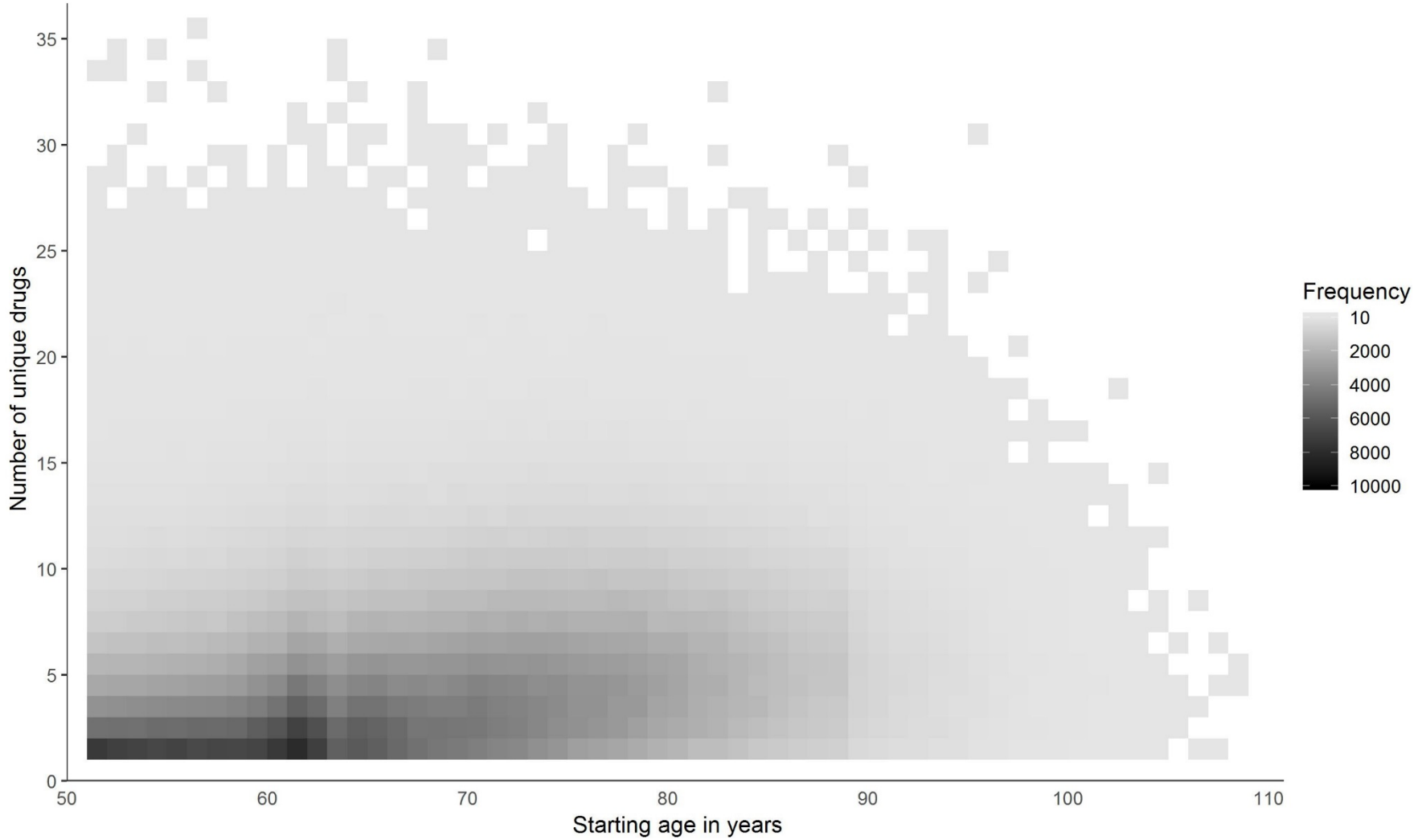
Table 6-5: Number of unique drugs dispensed in analytic sample

Total number of unique drugs	N (%)	N (%) of grouped number of drugs
1	196 313 (16.01)	661 030 (53.92)
2	171 951 (14.03)	
3	156 431 (12.76)	
4	136 335 (11.12)	
5	119 136 (9.72)	421 000 (34.34)
6	101 776 (8.30)	
7	82 825 (6.76)	
8	65 581 (5.35)	
9	51 682 (4.22)	
10	39 484 (3.22)	143 864 (11.74)
11	29 490 (2.41)	
12	22 008 (1.80)	
13	15 939 (1.30)	
14	11 150 (0.91)	
15	8 019 (0.65)	
16	5 526 (0.45)	
17	3 890 (0.32)	
18	2 716 (0.22)	
19	1 796 (0.15)	
≥20	3 846 (0.31)	

I used linear regression for a cross-sectional analysis of age and number of medications in the first quarter of 2009. In an unadjusted model, increase in age by one year was associated with an increase in total drugs by 0.090 (95% CI 0.090 to 0.091, $P<0.001$).[20] When adjusted for gender, SIMD and care home status, this reduced to 0.087 (95% CI 0.087 to 0.088, $P<0.001$). The distribution of continuous unique drugs dispensed by patient age in January 2009 is shown as a heat map in Figure 6-4.

[20] Throughout this chapter, I give regression results to three decimal places to provide a level of detail suitable to the size of the dataset.

Figure 6-4: Heat map showing distribution of unique drugs by age (outliers at extreme old age removed to avoid identification)



The mean age for patients taking each number of unique drugs is displayed in Figure 6-5. This shows that although mean age increases steeply for people receiving 1-5 drugs, the increase does not remain linear. The mean age peaks at 71.9 (SD=10.6) years for people taking 11 drugs, then decreases to 68.4 (SD=10.1) years for people receiving ≥20 drugs.

Figure 6-5: Mean age in January 2009 according to number of unique drugs dispensed

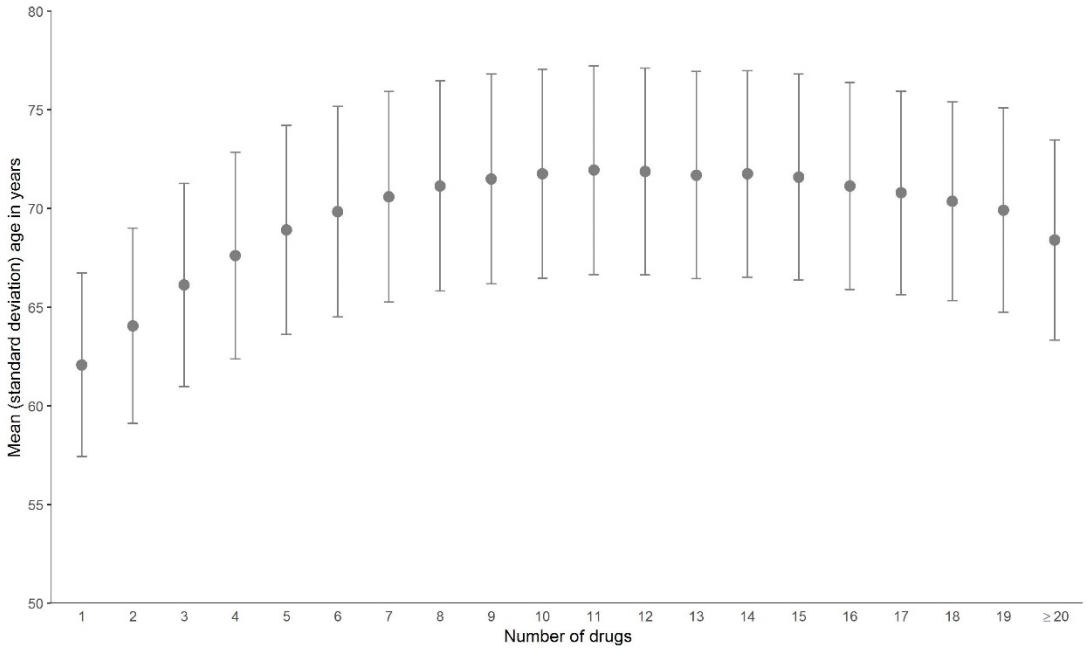
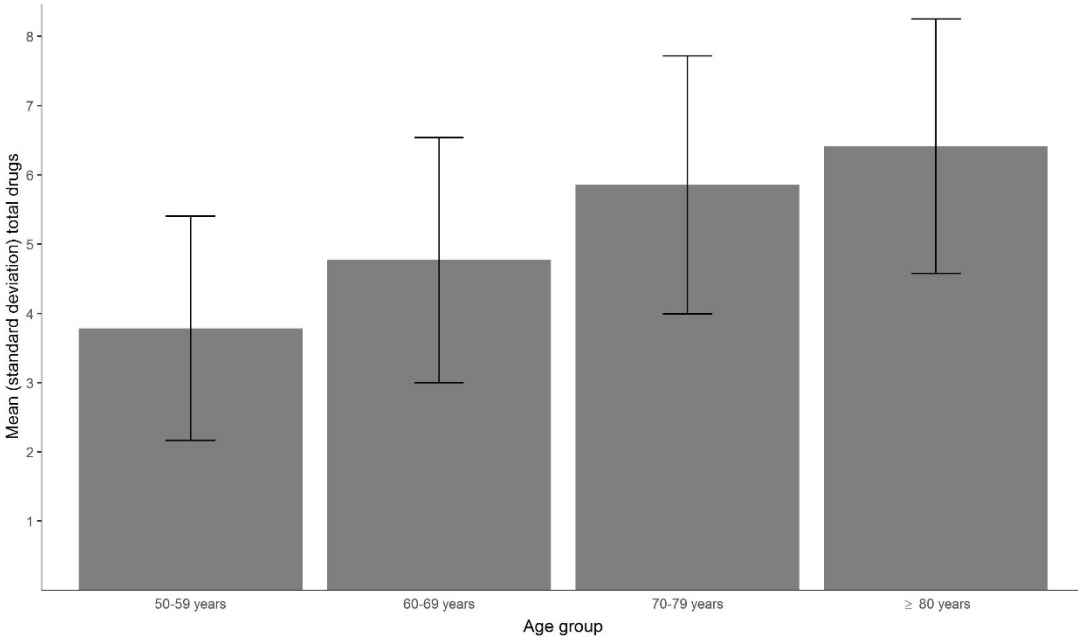


Figure 6-6 is a bar chart of the mean unique drugs dispensed according to ten-year age bands, showing an increase in mean number of drugs with age.

Figure 6-6: Mean unique drugs dispensed according to age in January 2009, in 10-year bands



For stratified analyses using both Cox regression and Kaplan-Meier analyses, I split the sample into age groups and bands by number of medications. Table 6-6 shows the characteristics of the analytic sample as divided by age group.

Table 6-6: Characteristics of analytic sample by age group

	N (%) or mean (SD)		
	50-64 years	**65-79 years**	**≥80 years**
All	562 889 (45.92)	484 311 (39.51)	178 694 (14.58)
Female gender	302 401 (53.72)	267 101 (55.15)	117 929 (65.99)
Care home resident	2 223 (0.39)	13 411 (2.77)	30 291 (16.95)
Mean number of medications (SD)	4.04 (3.33)	5.58 (3.70)	6.41 (3.67)
1-4 medications	377 071 (66.99)	222 728 (45.99)	61 231 (34.27)
5-9 medications	144 681 (25.70)	192 634 (39.77)	83 685 (46.83)
≥10 medications	41 137 (7.31)	68 949 (14.24)	33 778 (18.90)
Dispensed any psychotropic medication	143 107 (25.42)	107 929 (22.29)	52 707 (29.50)
Dispensed antidepressant	104 369 (18.54)	65 891 (13.61)	27 953 (15.64)
Dispensed anxiolytic or hypnotic	44 247 (7.86)	42 219 (8.72)	22 484 (12.58)
Dispensed antipsychotic	17 155 (3.05)	15 106 (3.12)	9 893 (5.54)
Dispensed dementia drugs	340 (0.06)	3 528 (0.73)	4 686 (2.62)
Dispensed mood stabilisers	12 933 (2.30)	8 477 (1.75)	2 851 (1.60)
Died	54 478 (9.68)	149 514 (30.87)	132 252 (74.01)
Died with mental disorder as primary cause	1 306 (2.40)	10 751 (7.19)	20 680 (15.64)
Died with mental disorder as any cause	4 155 (7.63)	22 912 (15.32)	36 907 (27.91)
Admitted to psychiatric hospital	8 618 (1.53)	10 384 (2.14)	4 745 (2.66)

6.4.1.1 Psychotropic drug use

Characteristics of the analytic sample according to psychotropic drug use status are in Table 6-7. People receiving psychotropic drugs were older, more likely to be female and be resident in a care home. They were more likely to die, especially with psychiatric causes, at younger ages than people not receiving psychotropic drugs. A higher proportion of them were admitted to psychiatric hospital, at younger ages, than those not receiving psychotropic drugs.

Table 6-7: Characteristics of analytic sample by psychotropic drug status

	N (%) or mean (SD)		
	No psychotropic drug	**Receiving ≥1 psychotropic drug**	***P* for difference**
All	922 151	303 743	
Starting age in years	67.31 (10.55)	67.55 (11.53)	**<0.001** (t=10.15)
50-64 years	419 782 (45.52)	143 107 (47.11)	
65-79 years	376 382 (40.82)	107 929 (35.53)	
≥80 years	125 987 (13.66)	52 707 (17.35)	
Female gender	484 207 (52.51)	203 224 (66.91)	**<0.001** (χ^2= 19 230)
Care home resident	20 700 (2.24)	25 225 (8.30)	**<0.001** (χ^2= 23 268)
Number of medications	4.31 (3.11)	7.07 (4.32)	**<0.001** (t=326.39)
Died	227 675 (24.69)	108 569 (35.74)	**<0.001** (χ^2= 14 026)
Died with mental disorder as primary cause	17 571 (1.91)	15 166 (4.99)	**<0.001** (χ^2= 8 379.3)
Died with mental disorder as any cause	35 252 (3.82)	28 722 (9.46)	**<0.001** (χ^2= 14 658)
Admitted to psychiatric hospital	10 322 (1.12)	13 425 (4.42)	**<0.001** (χ^2= 13 101)
Age at death in years	80.53 (10.00)	79.59 (10.78)	**<0.001** (t=24.3)
Age at admission in years	76.23 (10.47)	70.38 (11.22)	**<0.001** (t=41.32)

Figure 6-7 is a bar graph representing the proportion of each age group receiving psychotropic medication, with a breakdown of medication types as listed in Table 6-3 (page 210). Antidepressants were the most commonly received psychotropic drug in all age groups.

Figure 6-7: Proportion of each age group dispensed psychotropic drugs

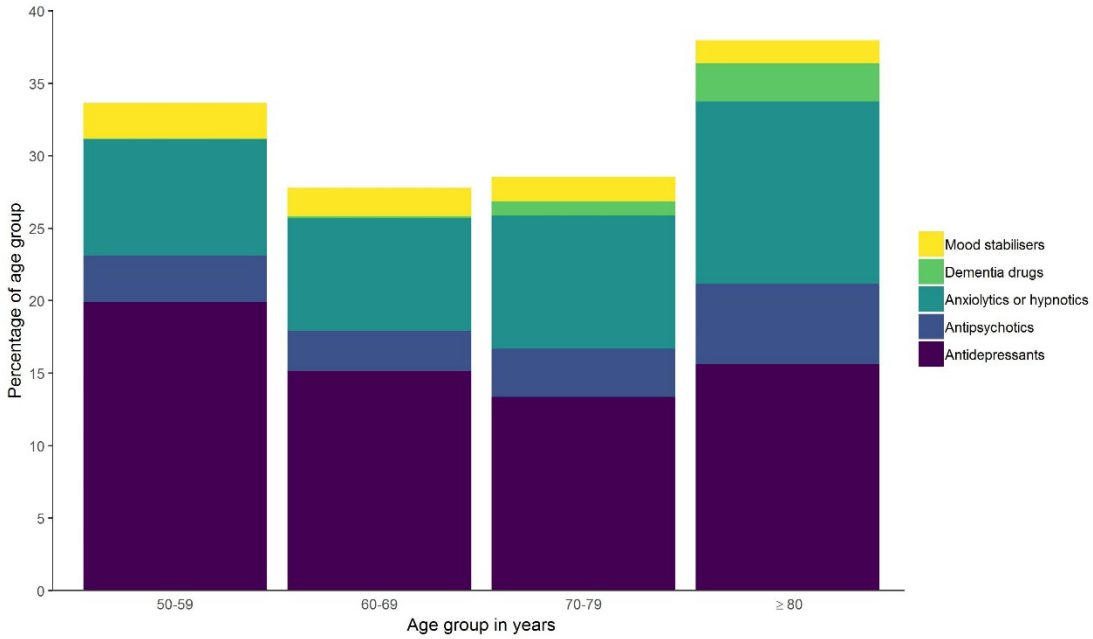
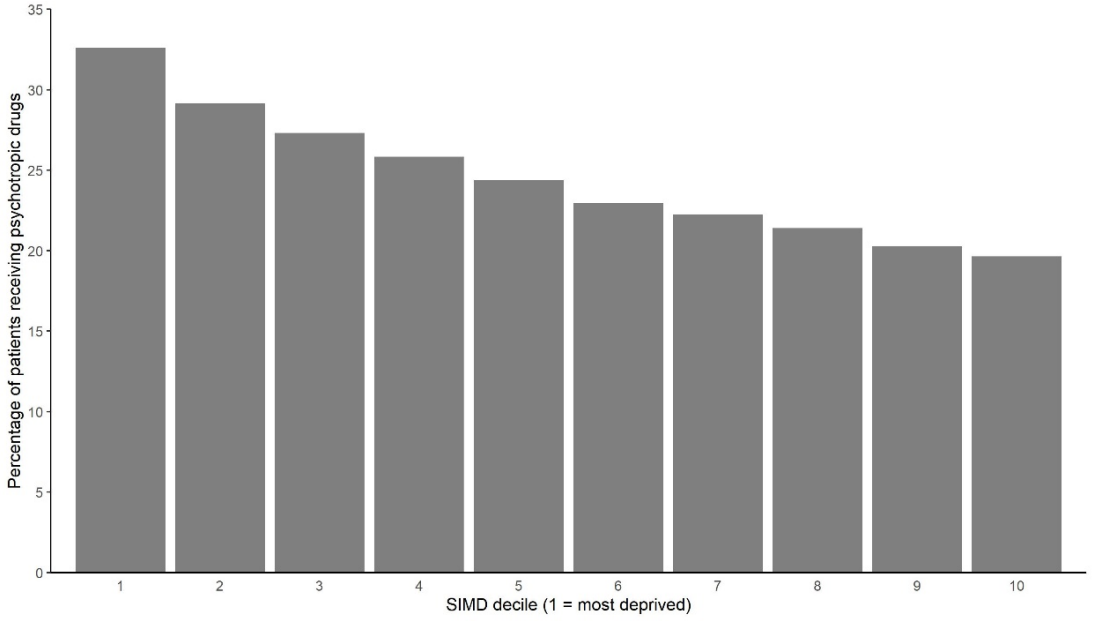


Figure 6-8 shows the proportion of patients in each SIMD decile that received at least one psychotropic drug, suggesting decreasing use of psychotropic drugs with decreasing deprivation.

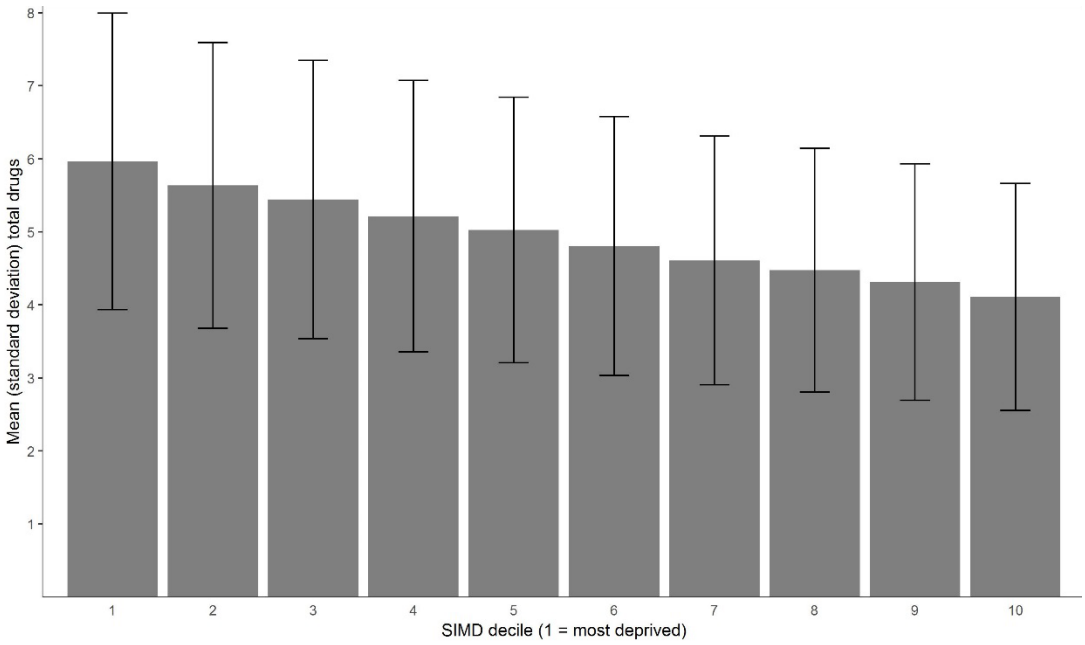
Figure 6-8: Psychotropic drug use by deprivation decile



Because previous research has found an association between increasing deprivation and increasing levels of polypharmacy, I used linear regression to explore the association between increasing SIMD decile at 1st January 2009 and unique drugs dispensed in that quarter. In an unadjusted model, increasing SIMD decile by one (that is, decreasing deprivation) had an associated decrease in total number of drugs (β= -0.200, 95% CI -0.202 to -0.197, *P*<0.001). In a model adjusted for age, gender and care home status, this reduced further to -0.203 (95% CI -0.205 to -0.201, *P*<0.001).

I plotted the mean number of dispensed drugs according to SIMD decile, where 1 is the most and 10 the least deprived decile, in Figure 6-9. This shows a decrease in the mean number of drugs as deprivation decreases. The mean number of drugs for people in SIMD decile 1 was 5.96 (SD=4.06) and in decile 10, 4.11 (SD=3.11). On Student's t-test, there was a difference between these two deciles, with t=124.21 and *P*<0.001.

Figure 6-9: Mean drugs dispensed according to deprivation decile



Dementia was the most common mental or behavioural disorder listed on death certificates, with alcohol and substance use second. Table 6-8 lists the breakdown of the types of mental disorders listed on death certificates. The definitions of each group of disorders are in Table 6-2 on page 207.

Table 6-8: Deaths with mental disorder on the death certificate

Group of disorders	Primary cause of death (% of all deaths)	In any cause of death field (including primary) (% of all deaths)
Dementia or mild cognitive impairment	31 503 (9.37)	57 241 (17.02)
Delirium	118 (0.04)	689 (0.20)
Other organic disorders	<10	27 (0.01)
Mental and behavioural disorders due to use of alcohol	908 (0.27)	3 156 (0.94)
Other psychoactive substance use	32 (0.01)	1 974 (0.59)
Schizophrenia and other non-organic psychotic disorders	33 (0.01)	529 (0.16)
Depression and other mood (affective) disorders	106 (0.03)	792 (0.24)
Bipolar affective disorder and mania	21 (0.01)	239 (0.07)
Anxiety and adjustment disorders	<10	114 (0.03)
Somatoform, dissociative and other neurotic disorders	0	<10
Eating disorders	<10	15 (0.00)
Other disorders	0	<10

6.4.2 Survival analysis: all-cause mortality

6.4.2.1 Cox proportional hazards models

To contextualise explorations of mental disorders as causes of death, the first analyses were of mortality with any cause. Preliminary graphical analysis of Schoenfeld residuals for mortality confirmed that the proportional hazards assumption had not been violated. On Cox regression, the hazard ratio (HR) for mortality with medications increasing by one was 1.089 (95% CI 1.088 to 1.090, $P<0.001$), adjusted for starting age, gender, SIMD and care home status. With psychotropic drug use as an additional covariate, the HR was 1.080 (95% CI 1.079 to 1.081, $P<0.001$). In a subsample excluding patients receiving psychotropic drugs (n=922 151), the HR for mortality with each additional medication was 1.087 (95% CI 1.086 to 1.088, $P<0.001$), adjusted for starting age, gender, SIMD and care home status. Receiving a larger number of dispensed drugs was associated with all-cause mortality in all these tests.

I also conducted Cox regression models with each number of medications used as a categorical exposure, collapsing this at ≥20 drugs. The results of these analyses are listed in Table 6-9 and displayed in Figure 6-10.

Table 6-9: Cox proportional hazards ratios for all-cause mortality with number of unique drugs

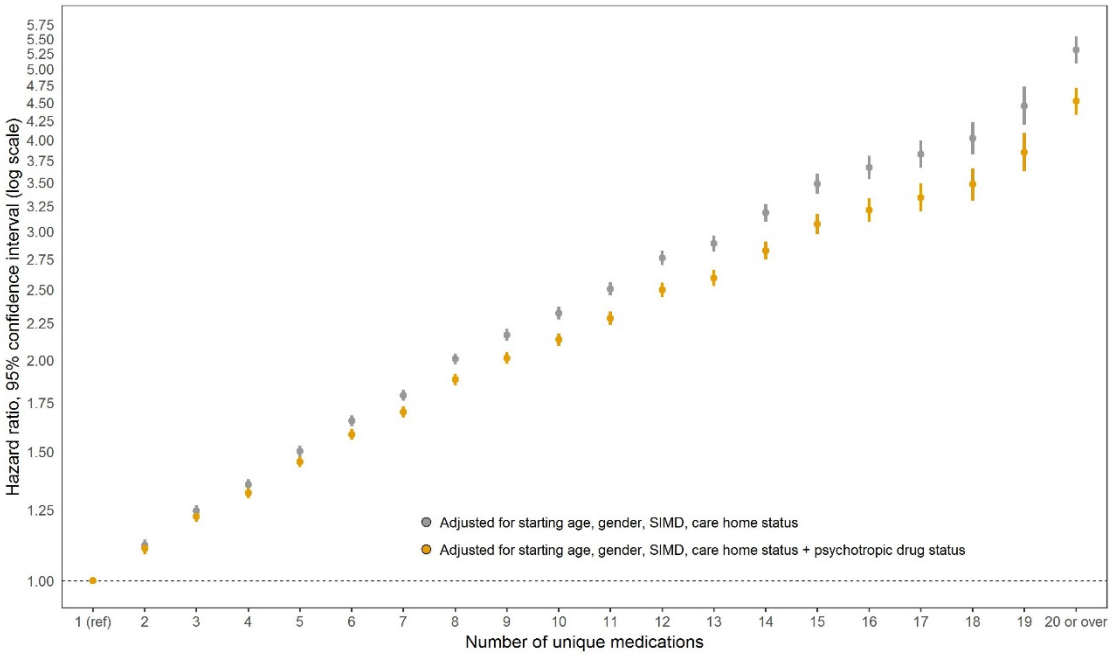
Number of unique drugs	Model 1: HR (95% CI)	Model 2: HR (95% CI)
1	Reference	Reference
2	1.118 (1.098 to 1.137) *	1.106 (1.087 to 0.126) *
3	1.246 (1.225 to 1.267) *	1.224 (1.203 to 1.245) *
4	1.352 (1.330 to 1.375) *	1.317 (1.295 to 1.339) *
5	1.503 (1.478 to 1.528) *	1.452 (1.428 to 1.477) *
6	1.652 (1.624 to 1.680) *	1.584 (1.557 to 1.611) *
7	1.791 (1.760 to 1.822) *	1.699 (1.670 to 1.729) *
8	2.007 (1.972 to 2.043) *	1.883 (1.850 to 1.918) *
9	2.166 (2.216 to 2.206) *	2.013 (1.976 to 2.051) *
10	2.318 (2.273 to 2.364) *	2.133 (2.091 to 2.176) *
11	2.502 (2.450 to 2.555) *	2.282 (2.234 to 2.331) *
12	2.759 (2.697 to 2.822) *	2.495 (2.439 to 2.553) *
13	2.887 (2.815 to 2.960) *	2.591 (2.526 to 2.658) *
14	3.180 (3.092 to 3.271) *	2.824 (2.744 to 2.905) *
15	3.484 (3.375 to 3.596) *	3.069 (2.972 to 3.168) *
16	3.666 (3.532 to 3.804) *	3.207 (3.089 to 3.329) *
17	3.822 (3.661 to 3.990) *	3.338 (3.196 to 3.485) *
18	4.020 (3.822 to 4.229) *	3.477 (3.305 to 3.658) *
19	4.452 (4.192 to 4.727) *	3.846 (3.621 to 4.085) *
≥20	5.308 (5.088 to 5.536) *	4.516 (4.328 to 4.713) *

* $P<0.001$ in all analyses

Model 1: Adjusted for starting age, gender, SIMD, care home status

Model 2: Adjusted for starting age, gender, SIMD, care home status and psychotropic medication use

Figure 6-10: Forest plot of hazard ratios for mortality with medication use in adults aged ≥50 years

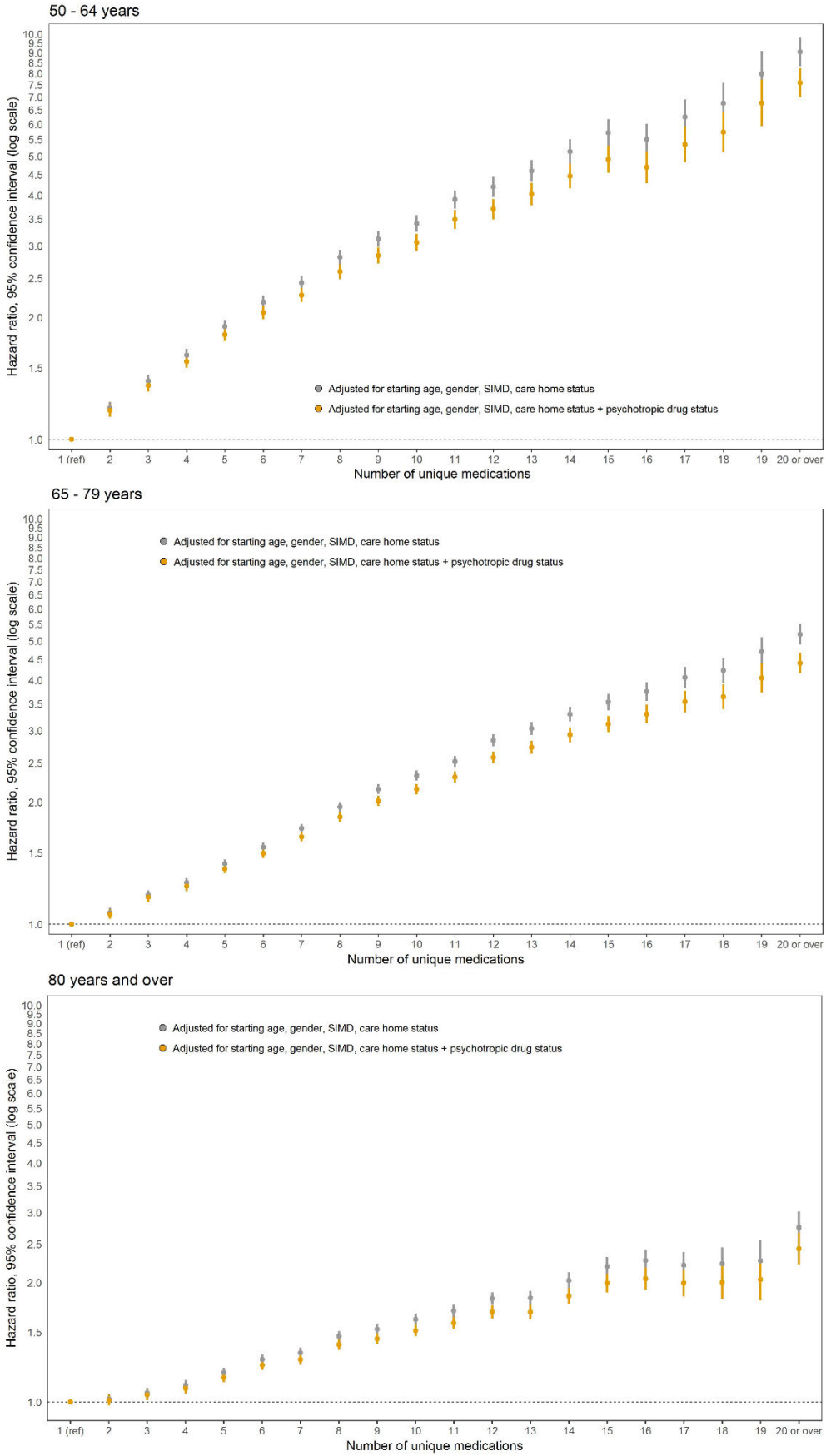


Although these analyses were adjusted for starting age, to further investigate the importance of age in these associations, I conducted stratified analyses in three age groups, 50-64, 65-79 and ≥80 years. The results for an increase in drugs by one are listed in Table 6-10 and with specific medication numbers shown in Figure 6-11.

Table 6-10: Hazard ratios for all-cause mortality with increase in drugs by one, stratified by age

Age group	Covariates	HR (95% CI)	*P*-value
50-64 years	Starting age, gender, care home status, SIMD	1.123 (1.121 to 1.125)	<0.001
	Starting age, gender, care home status, SIMD, psychotropic drug use	1.111 (1.109 to 1.113)	<0.001
65-79 years	Starting age, gender, care home status, SIMD	1.095 (1.094 to 1.096)	<0.001
	Starting age, gender, care home status, SIMD, psychotropic drug use	1.085 (1.084 to 1.087)	<0.001
≥80 years	Starting age, gender, care home status, SIMD	1.058 (1.056 to 1.059)	<0.001
	Starting age, gender, care home status, SIMD, psychotropic drug use	1.051 (1.049 to 1.052)	<0.001

Figure 6-11: Hazard ratios for all-cause mortality with medication use by age group



These age-stratified analyses demonstrate that the association between increasing medication use and mortality was present at all ages, but was less pronounced as age increased.

6.4.2.2 Sensitivity analyses

To account for the missing data in SIMD, I performed sensitivity analyses with two methods: including all patients but not using SIMD as a covariate, and imputing SIMD and including it as a covariate. The results, in Table 6-11, show minimal change in effect size compared to analyses in the sample excluding those with missing SIMD. These results are of Cox regression models for all-cause mortality with a continuous increase in unique drugs.

Table 6-11: Sensitivity analyses for continuous increase in drug use with all-cause mortality

Sample	Covariates	HR (95% CI)	*P*-value
All receiving ≥1 drug, including those with missing SIMD (n=1 346 714)	Starting age, gender, care home status	1.094 (1.093 to 1.095)	<0.001
	Starting age, gender, care home status, psychotropic drug use	1.085 (1.084 to 1.086)	<0.001
All receiving ≥1 drug, with imputed SIMD (n=1 346 714)	Starting age, gender, care home status, SIMD	1.089 (1.088 to 1.089)	<0.001
	Starting age, gender, care home status, psychotropic drug use, SIMD	1.079 (1.078 to 1.080)	<0.001

6.4.2.3 Cox proportional hazards models with psychotropic medication as the exposure

Following the confirmation that psychotropic drug use did attenuate the associations between overall drug use and mortality, I conducted secondary analyses of psychotropic drug use as the exposure variable in the sample of complete cases (n=1 225 894). The hazard ratio for mortality in those taking any psychotropic drug compared to those who did not was 1.262 (1.252 to 1.271, *P*<0.001), adjusted for total number of drugs, starting age, gender, care home status and SIMD.

6.4.2.4 Kaplan-Meier curves

Using the survival models in the Cox models above, I plotted Kaplan-Meier curves for all-cause mortality with medication use categorised into 1-4, 5-9 and ≥10 concurrent drugs. In order to account for age, I analysed the three age groups separately, with age at death as the outcome, as shown in Figure 6-12. Within these age groups, there is a 15-year range in the starting age, so I also plotted these curves with time to death as the time variable, out of the maximum 102 months (Figure 6-13). In both these sets of plots and in all age groups, increasing categories of medication were associated with earlier age at or faster time to death. The differences between drug groupings became less marked in older age groups.

Figure 6-12: Kaplan-Meier plots of survival probability and age at death by number of medications dispensed

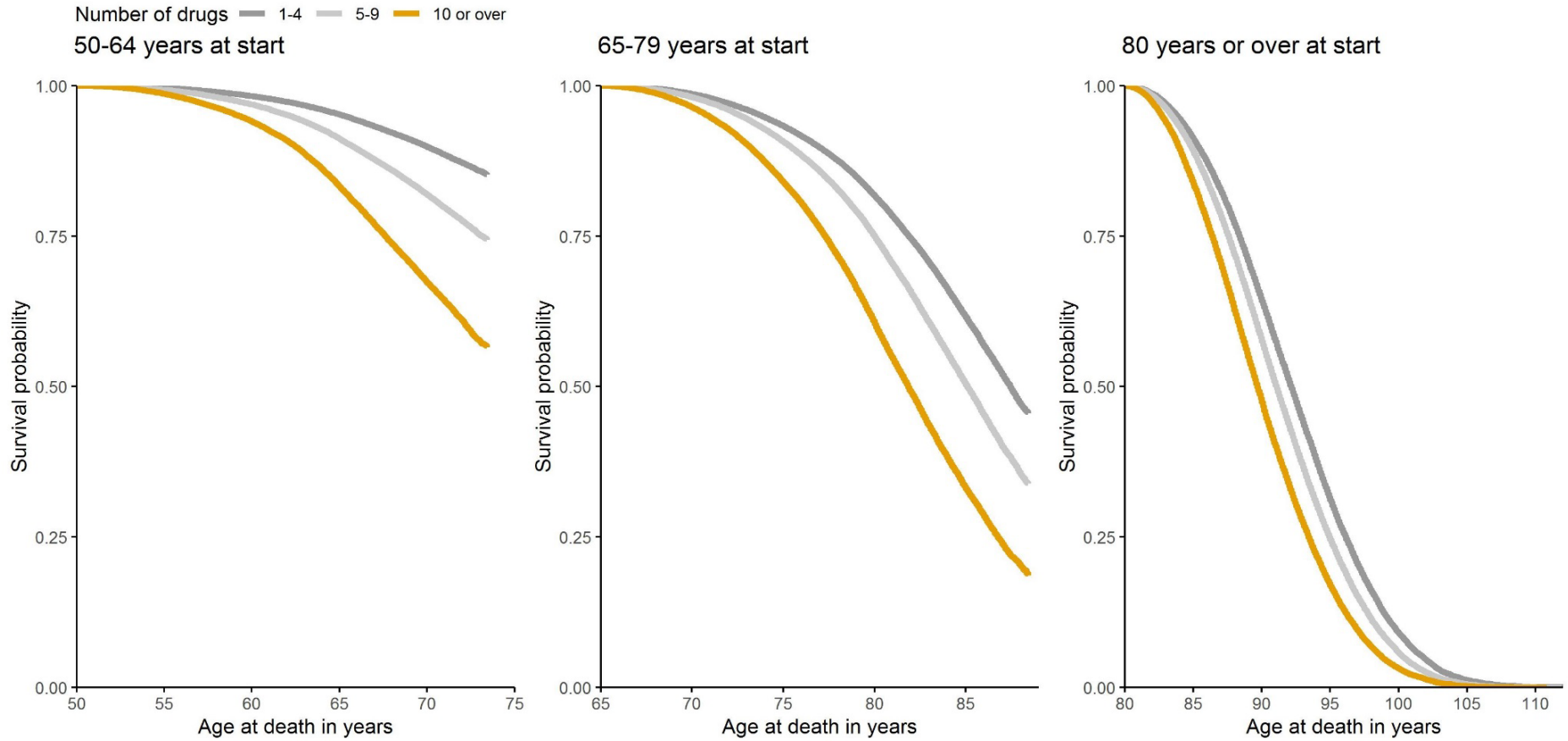
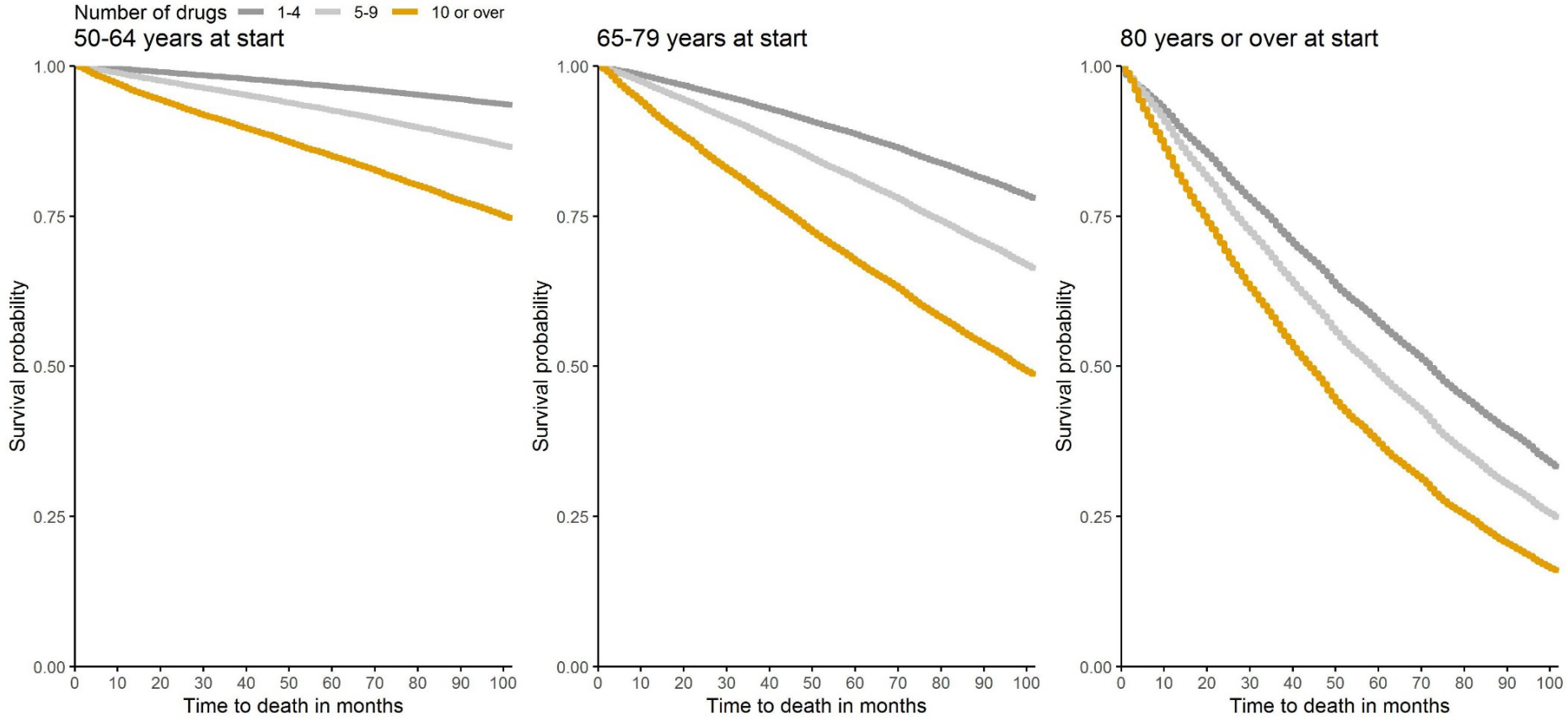


Figure 6-13: Kaplan-Meier plots of survival probability and time to death by number of medications dispensed



6.4.3 Survival analysis: mortality with mental or behavioural disorder as primary cause of death

6.4.3.1 Cox proportional hazards models

The hazard ratio for mortality with a mental disorder as the primary cause of death with continuous drug count increasing by one was 1.011 (95% CI 1.008 to 1.014, P<0.001), adjusted for starting age, gender, SIMD and care home status. When psychotropic medication use was an additional covariate, the association's direction reversed, with HR=0.979 (95% CI 0.976 to 0.982, P<0.001). In the subsample of only patients not receiving psychotropic drugs (n=922 151), the HR for primary psychiatric cause of death with each additional medication was 0.993 (95% CI 0.988 to 0.998, P=0.004), adjusted for starting age, gender, SIMD and care home status. Table 6-12 lists the results of analyses treating each number of drugs separately and they are represented in Figure 6-14 on page 239. These show that when adjusting for psychotropic drug use, increases in medication use were not statistically significantly associated with a primary psychiatric cause of death from 2 to 6 medications, and for ≥7 medications, higher levels of medication use were inversely associated with dying and having a mental disorder as primary cause of death.

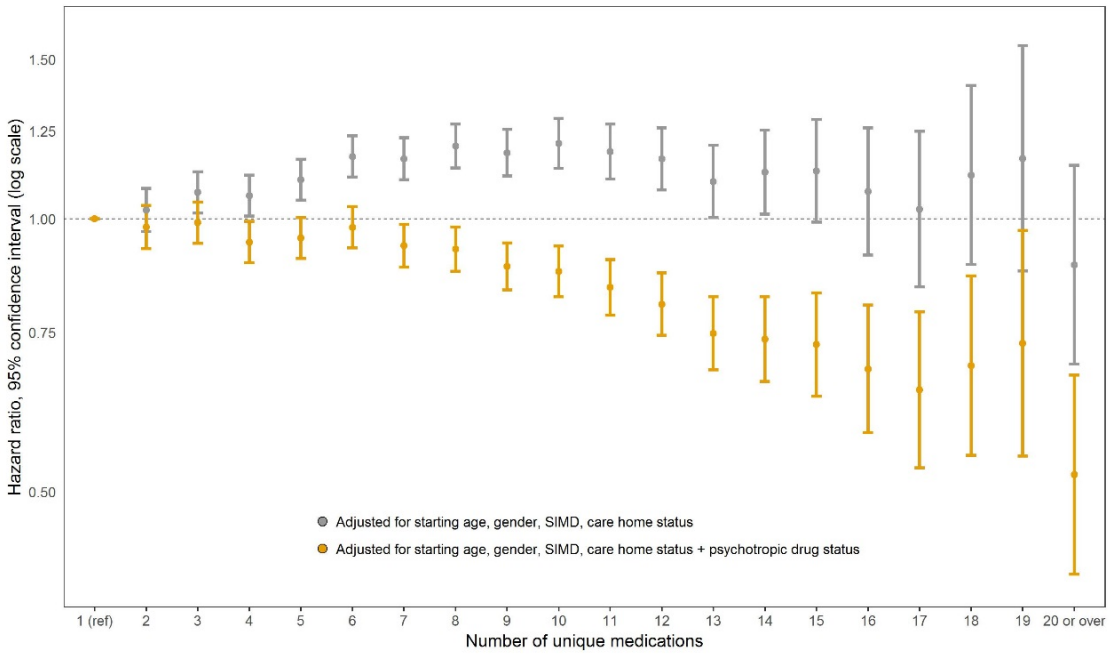
Table 6-12: Cox proportional hazards ratios for mortality with primary psychiatric cause of death with number of unique drugs

Number of unique drugs	Model 1		Model 2	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
1	Reference		Reference	
2	1.023 (0.968 to 1.080)	0.422	0.980 (0.928 to 1.035)	0.464
3	1.070 (1.015 to 1.127)	0.012	0.991 (0.940 to 1.044)	0.722
4	1.061 (1.007 to 1.118)	0.026	0.943 (0.894 to 0.993)	0.027
5	1.105 (1.049 to 1.164)	<0.001	0.953 (0.904 to 1.004)	0.069
6	1.172 (1.112 to 1.234)	<0.001	0.979 (0.929 to 1.032)	0.424
7	1.165 (1.104 to 1.229)	<0.001	0.934 (0.885 to 0.986)	0.014
8	1.203 (1.137 to 1.272)	<0.001	0.926 (0.875 to 0.980)	0.008
9	1.183 (1.115 to 1.255)	<0.001	0.886 (0.835 to 0.941)	<0.001
10	1.211 (1.137 to 1.291)	<0.001	0.875 (0.821 to 0.934)	<0.001
11	1.186 (1.107 to 1.272)	<0.001	0.840 (0.783 to 0.902)	<0.001
12	1.164 (1.076 to 1.259)	<0.001	0.805 (0.744 to 0.872)	<0.001
13	1.100 (1.003 to 1.205)	0.043	0.748 (0.682 to 0.821)	<0.001
14	1.126 (1.012 to 1.253)	0.029	0.737 (0.661 to 0.820)	<0.001
15	1.130 (0.992 to 1.287)	0.066	0.727 (0.638 to 0.828)	<0.001
16	1.072 (0.913 to 1.260)	0.397	0.683 (0.581 to 0.790)	<0.001
17	1.025 (0.841 to 1.249)	0.806	0.648 (0.531 to 0.790)	<0.001
18	1.118 (0.891 to 1.403)	0.337	0.689 (0.549 to 0.865)	0.001
19	1.166 (0.876 to 1.552)	0.293	0.729 (0.548 to 0.971)	0.031
≥20	0.890 (0.691 to 1.145)	0.364	0.522 (0.406 to 0.673)	<0.001

Model 1: Adjusted for starting age, gender, SIMD, care home status

Model 2: Adjusted for starting age, gender, SIMD, care home status and psychotropic medication use

Figure 6-14: Forest plot of hazard ratios for mental disorder as primary cause of death with increasing medications in adults aged ≥50 years

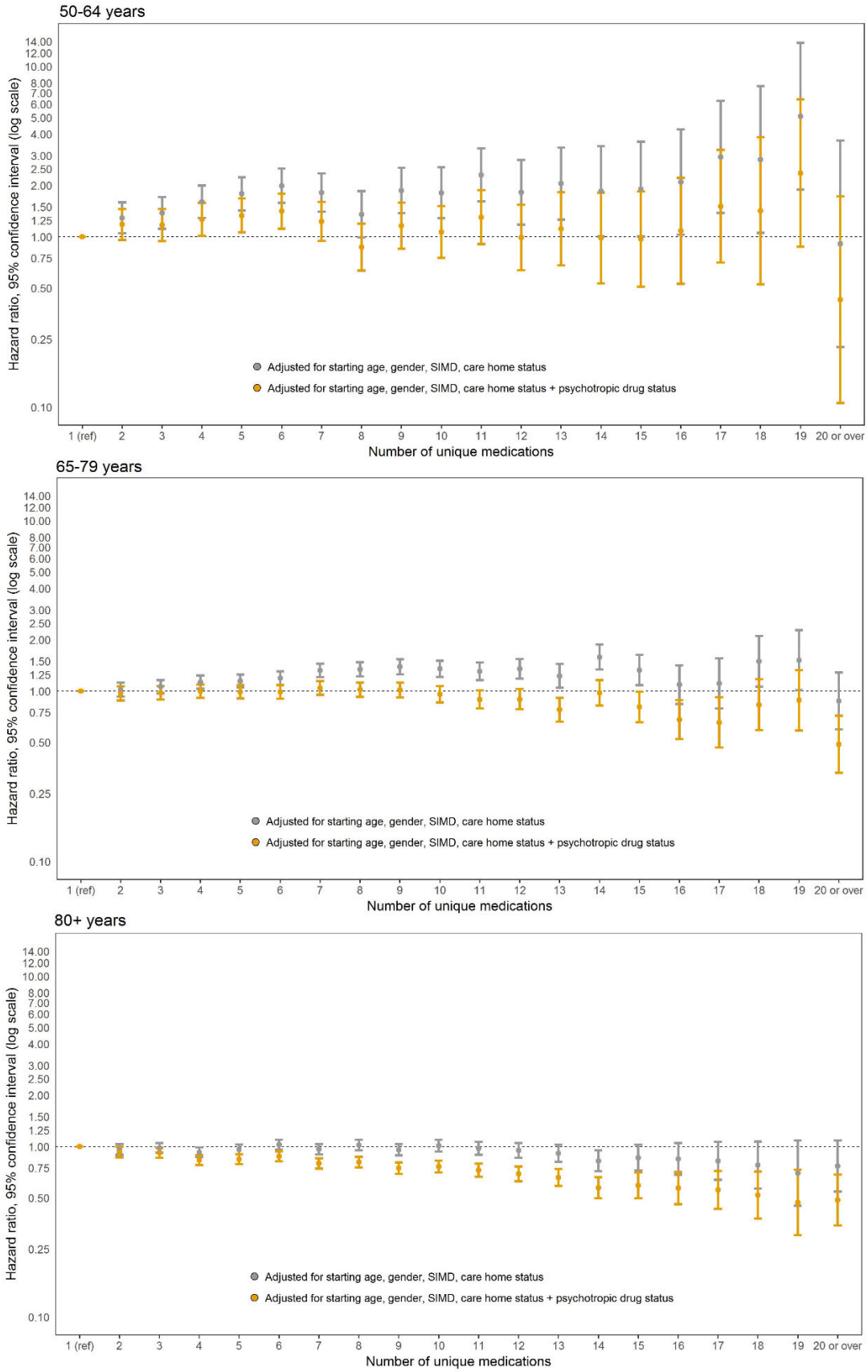


I then carried out stratified analyses by age group. The results are listed in Table 6-13 and displayed in Figure 6-15 on page 240.

Table 6-13: Hazard ratios for mental disorder as primary cause of death with increase in drugs by one, stratified by age

Age group	Covariates	HR (95% CI)	*P*-value
50-64 years	Starting age, gender, care home status, SIMD	1.048 (1.033 to 1.063)	<0.001
	Starting age, gender, care home status, SIMD, psychotropic drug use	0.998 (0.983 to 1.014)	0.809
65-79 years	Starting age, gender, care home status, SIMD	1.024 (1.019 to 1.029)	<0.001
	Starting age, gender, care home status, SIMD, psychotropic drug use	0.988 (0.983 to 0.994)	<0.001
≥80 years	Starting age, gender, care home status, SIMD	0.996 (0.992 to 1.000)	0.051
	Starting age, gender, care home status, SIMD, psychotropic drug use	0.974 (0.968 to 0.980)	<0.001

Figure 6-15: Forest plot of hazard ratios for mortality with mental disorder as primary cause by medication use, by age group



In people aged 50-79 years, increasing medication use was associated with an increase in mortality with a mental disorder as the primary cause, but adding psychotropic medication as a covariate removed the association's statistical significance. In people aged ≥80 years, increasing medication use was inversely associated with mortality where a mental disorder was the primary cause of death, when adjusting for psychotropic medication use only.

6.4.3.2 Sensitivity analysis

To account for the missing SIMD values, I performed sensitivity analyses with the same methods as for all-cause mortality. Table 6-14 shows the hazard ratios for primary psychiatric mortality with an increase in drug use by one. The results were robust to the sensitivity analyses.

Table 6-14: Sensitivity analyses for continuous increase in drug use for mortality with a mental disorder as the primary cause

Sample	Covariates	HR (95% CI)	*P*-value
All receiving ≥1 drug, including those with missing SIMD (n=1 346 714)	Starting age, gender, care home status	1.014 (1.011 to 1.017)	<0.001
	Starting age, gender, care home status, psychotropic drug use	0.982 (0.979 to 0.985)	<0.001
All receiving ≥1 drug, with imputed SIMD (n=1 346 714)	Starting age, gender, care home status, SIMD	1.012 (1.009 to 1.015)	<0.001
	Starting age, gender, care home status, psychotropic drug use, SIMD	0.980 (0.977 to 0.983)	<0.001

6.4.3.3 Cox proportional hazards models with psychotropic medication as the exposure

In the sample of complete cases (n=1 225 894), the hazard ratio for mortality where there was a mental disorder as primary cause of death in those taking any psychotropic drug compared to those who did not was 2.182 (95% CI 2.130 to 2.235, *P*<0.001), adjusted for total number of drugs, starting age, gender, care home status and SIMD.

6.4.3.4 Kaplan-Meier curves

I plotted Kaplan-Meier curves for mortality with a mental disorder as the primary cause of death, in three age groups, with time to death and age at death as the time variables. These are shown in Figure 6-16 on page 243 and Figure 6-17 on page 244. There was little difference in mortality rates between drug groups in the 50-64 years age group with either time metric. People taking 5-9 drugs had the highest increased probability of mortality with mental disorders as a primary cause where time to death was the time metric, followed by those on ≥10 and 1-4 medications. Regarding age at death, the same pattern is seen in those aged 65-79 years and in those aged ≥80 years and there is little difference between the groups with some overlap at extreme old age.

Figure 6-16: Kaplan-Meier curves for mortality with mental disorder as a primary cause of death and age at death

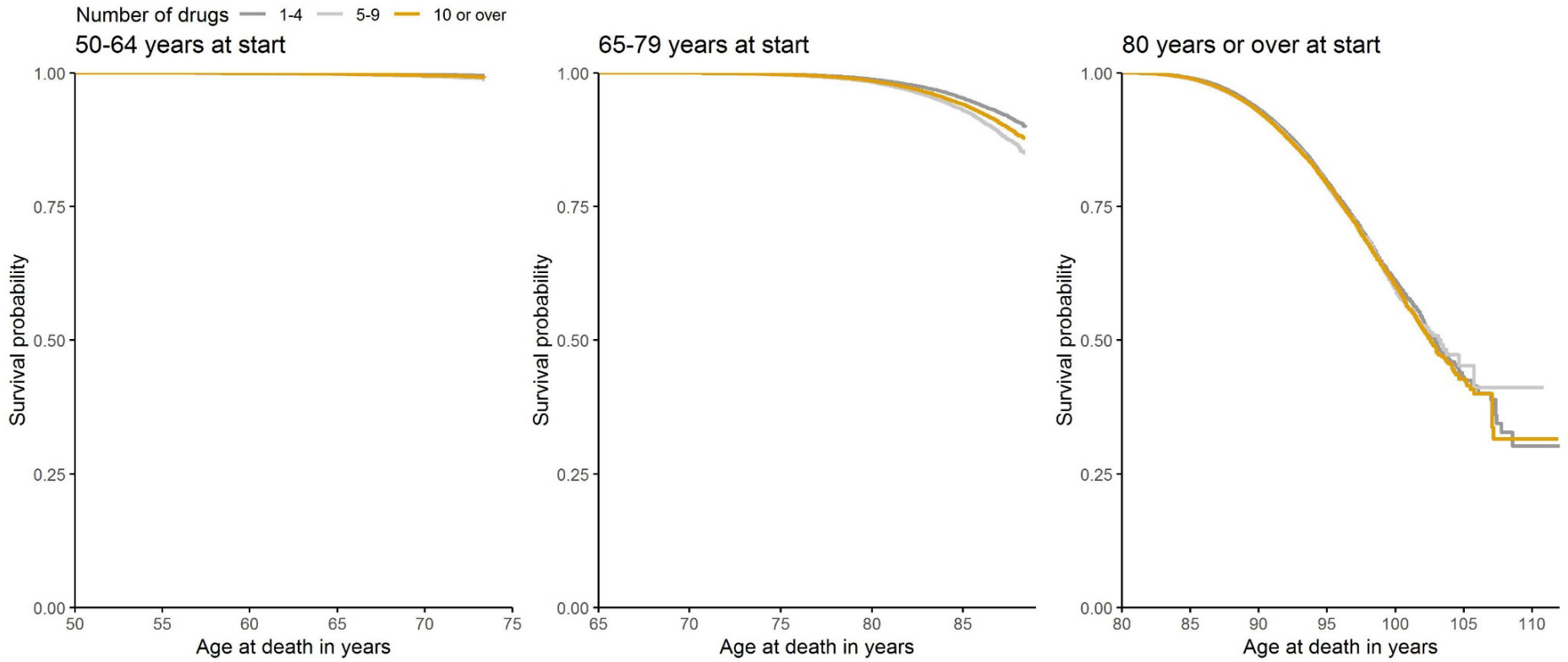
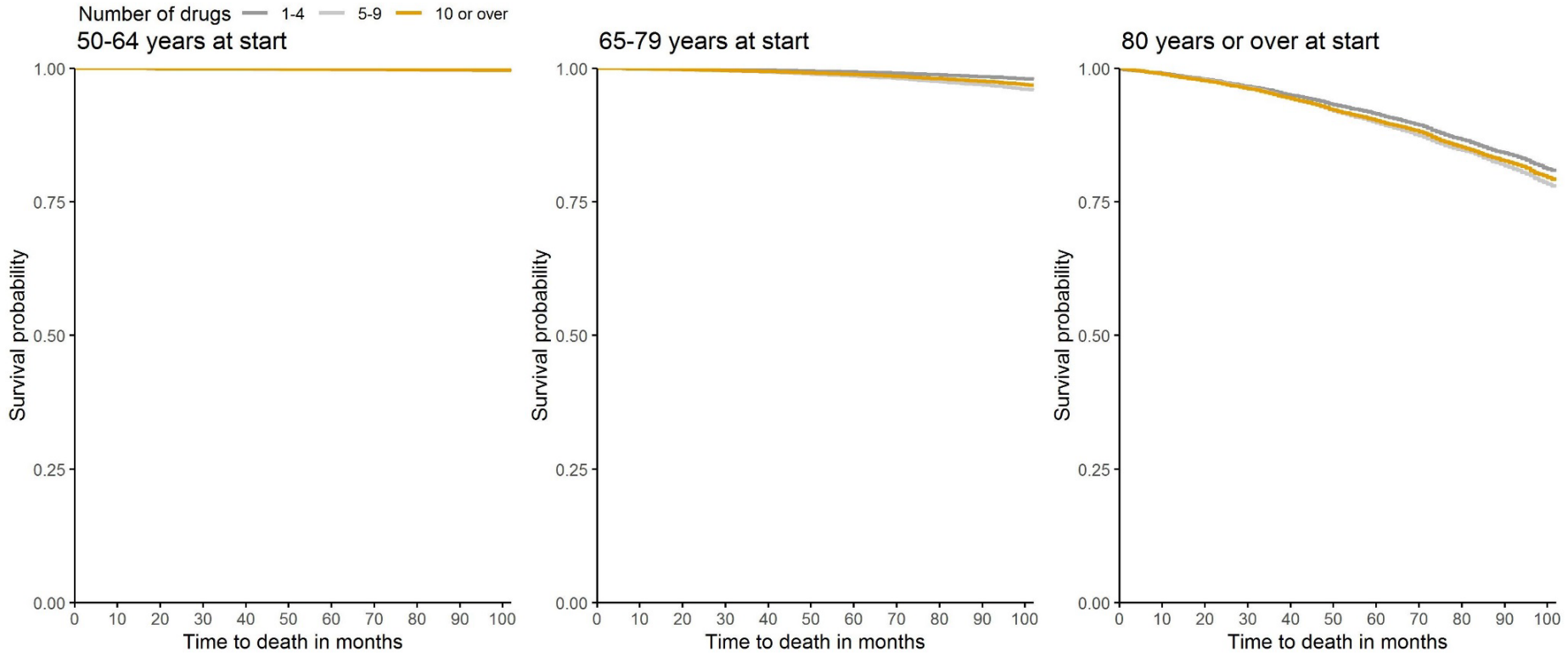


Figure 6-17: Kaplan-Meier curves for mortality with mental disorder as a primary cause of death and time to death



6.4.4 Survival analysis: mortality with mental or behavioural disorder in any field on death certificate

6.4.4.1 Cox proportional hazards models

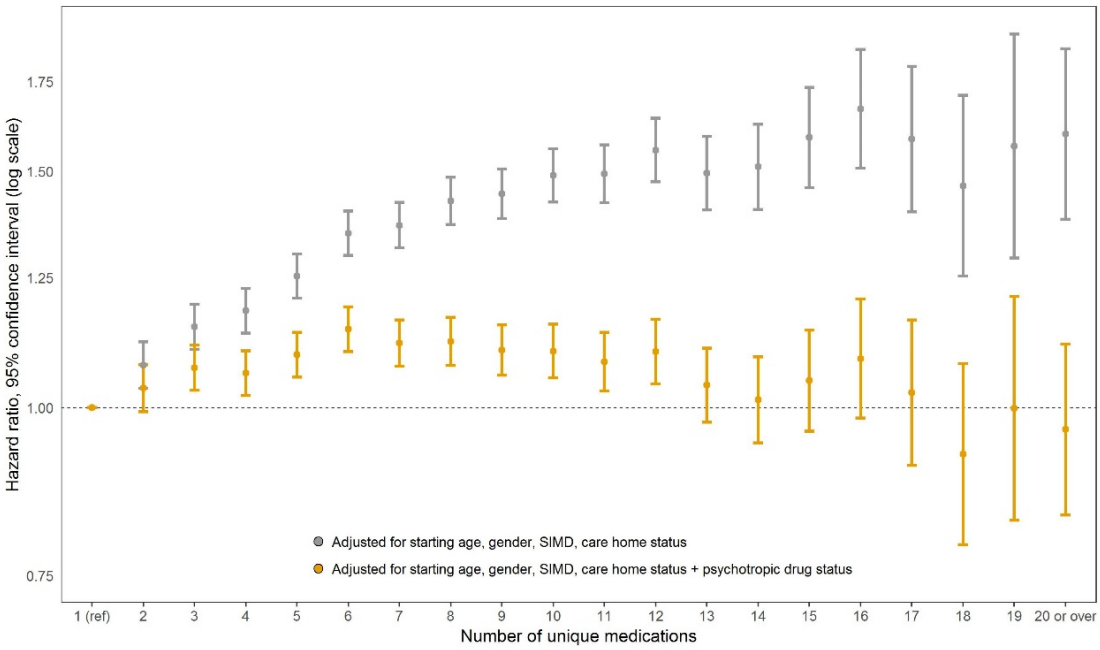
Using Cox regression models for mortality with a mental disorder in any field on the death certificate (including as the primary cause), each additional medication had an HR of 1.033 (95% CI 1.031 to 1.035, *P*<0.001) when adjusting for age, gender, SIMD and care home status. With psychotropic medication as an additional covariate, the HR reduced to 1.002 (95% CI 1.000 to 1.005, *P*=0.033). When excluding those receiving psychotropic medication, the HR was 1.016 (1.013 to 1.020, *P*<0.001). The HRs for each number of medications are listed in Table 6-15 and displayed in Figure 6-18. They show only slight cumulative increases in HR with increasing medication, with smaller effect sizes (and results not meeting conventional statistical significance) with higher numbers of drugs received.

Table 6-15: Cox proportional hazards ratios for mortality with any psychiatric cause of death with number of unique drugs

Number of unique drugs	Model 1		Model 2	
	HR (95% CI)	***P*-value**	**HR (95% CI)**	***P*-value**
1	Reference		Reference	
2	1.076 (1.033 to 1.120)	<0.001	1.034 (0.993 to 1.077)	0.102
3	1.149 (1.105 to 1.194)	<0.001	1.071 (1.030 to 1.113)	0.001
4	1.181 (1.137 to 1.227)	<0.001	1.061 (1.021 to 1.103)	0.002
5	1.253 (1.206 to 1.302)	<0.001	1.095 (1.054 to 1.138)	<0.001
6	1.349 (1.298 to 1.401)	<0.001	1.144 (1.101 to 1.189)	<0.001
7	1.368 (1.315 to 1.422)	<0.001	1.117 (1.074 to 1.162)	<0.001
8	1.426 (1.369 to 1.485)	<0.001	1.120 (1.075 to 1.167)	<0.001
9	1.443 (1.383 to 1.506)	<0.001	1.104 (1.057 to 1.153)	<0.001
10	1.490 (1.423 to 1.559)	<0.001	1.102 (1.052 to 1.154)	<0.001
11	1.494 (1.421 to 1.570)	<0.001	1.082 (1.029 to 1.138)	0.002
12	1.556 (1.473 to 1.643)	<0.001	1.101 (1.042 to 1.164)	0.001
13	1.495 (1.404 to 1.593)	<0.001	1.039 (0.975 to 1.108)	0.234
14	1.512 (1.405 to 1.626)	<0.001	1.014 (0.942 to 1.091)	0.720
15	1.590 (1.458 to 1.733)	<0.001	1.047 (0.960 to 1.142)	0.295
16	1.670 (1.508 to 1.848)	<0.001	1.088 (0.982 to 1.205)	0.106
17	1.585 (1.400 to 1.795)	<0.001	1.026 (0.906 to 1.162)	0.687
18	1.463 (1.253 to 1.709)	<0.001	0.923 (0.790 to 1.079)	0.315
19	1.567 (1.293 to 1.898)	<0.001	0.999 (0.824 to 1.211)	0.991
≥20	1.599 (1.382 to 1.851)	<0.001	0.963 (0.832 to 1.116)	0.618

Model 1: Adjusted for starting age, gender, SIMD, care home status
Model 2: Adjusted for starting age, gender, SIMD, care home status and psychotropic medication use

Figure 6-18: Forest plot of hazard ratios for mortality with mental disorder as any cause of death by medication use, adults aged ≥50 years



Results of the Cox regression stratified by age group for an increase in medication by one are shown in Table 6-16.

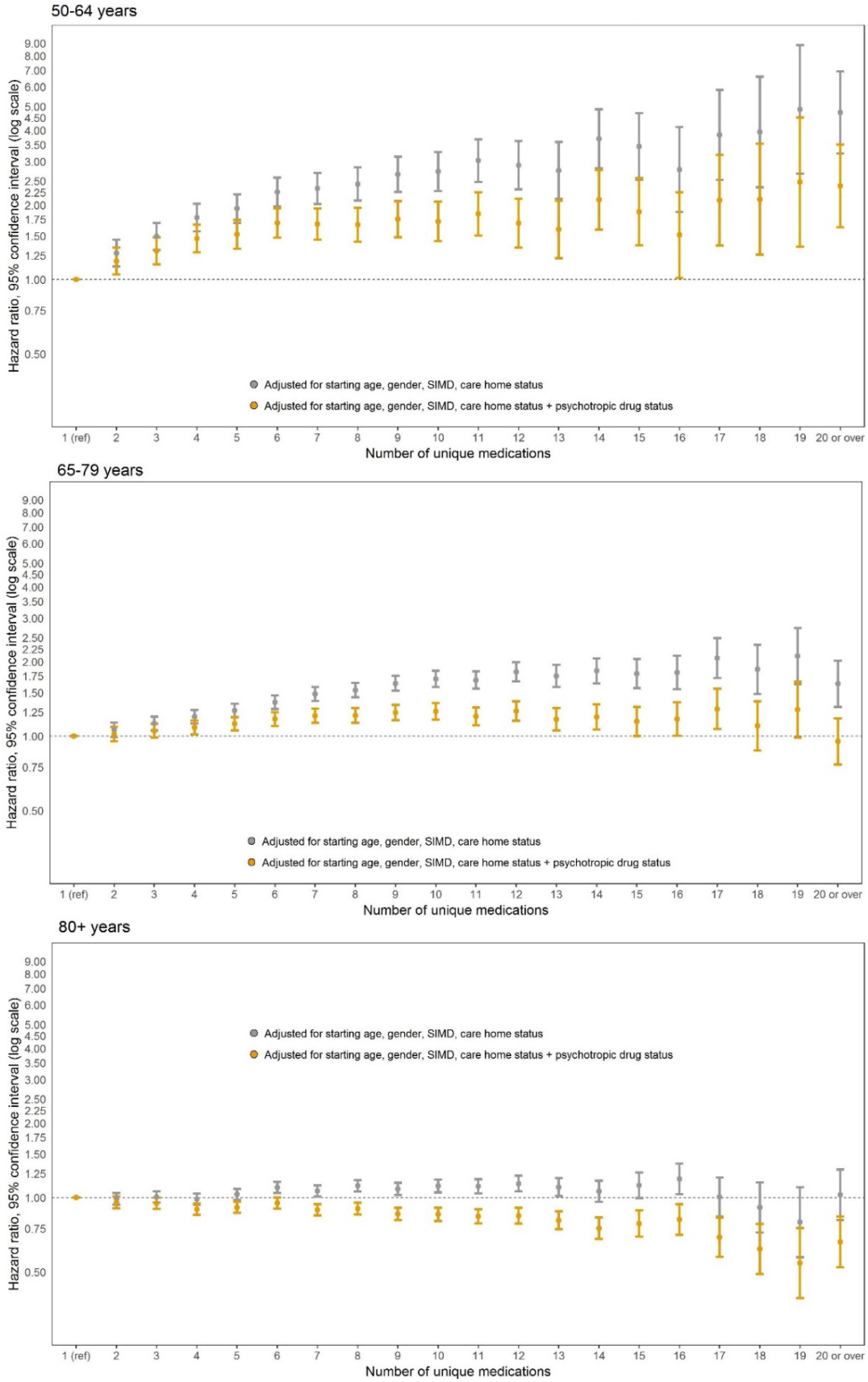
Table 6-16: Hazard ratios for mental disorder as any cause of death with increase in drugs by one, stratified by age

Age group	Covariates	HR (95% CI)	*P*-value
50-64 years	Starting age, gender, care home status, SIMD	1.086 (1.078 to 1.094)	<0.001
	Starting age, gender, care home status, SIMD, psychotropic drug use	1.042 (1.033 to 1.050)	<0.001
65-79 years	Starting age, gender, care home status, SIMD	1.047 (1.043 to 1.050)	<0.001
	Starting age, gender, care home status, SIMD, psychotropic drug use	1.014 (1.011 to 1.018)	<0.001
≥80 years	Starting age, gender, care home status, SIMD	1.010 (1.007 to 1.013)	<0.001
	Starting age, gender, care home status, SIMD, psychotropic drug use	0.984 (0.981 to 0.987)	<0.001

In people aged 50-79 years, there was a positive association between increasing number of drugs and increased mortality with any mental disorder. This association persisted when adjusting for psychotropic medication use. The associations were

weaker in the 65-79 year age group than 50-64 years. Plots of individual drug numbers show that the association is not significant with all numbers of drugs (see Figure 6-19). In people aged ≥80 years, there was a positive association between increasing number of drugs and mortality but this became an inverse relationship when adjusting for psychotropic medication use. Figure 6-19 shows the hazard ratios for individual drug numbers in this age group and shows that this inverse association only meets conventional statistical significance at ≥4 drugs.

Figure 6-19: Forest plot of hazard ratios for mortality with mental disorder as any cause of death by medication use, by age group



6.4.4.2 Sensitivity analysis

Sensitivity analyses accounting for the missing data in the SIMD variable generated similar results to the main analyses, as shown in Table 6-17, suggesting that conducting the main analysis in complete cases only was reasonable.

Table 6-17: Sensitivity analyses for continuous increase in drug use for mortality with a mental disorder as any cause

Sample	Covariates	HR (95% CI)	*P*-value
All receiving ≥1 drug, including those with missing SIMD (n=1 346 714)	Starting age, gender, care home status	1.037 (1.035 to 1.039)	<0.001
	Starting age, gender, care home status, psychotropic drug use	1.007 (1.004 to 1.009)	<0.001
All receiving ≥1 drug, with imputed SIMD (n=1 346 714)	Starting age, gender, care home status, SIMD	1.033 (1.031 to 1.035)	<0.001
	Starting age, gender, care home status, psychotropic drug use, SIMD	1.003 (1.001 to 1.005)	0.007

6.4.4.3 Cox proportional hazards models with psychotropic medication as the exposure

I conducted secondary analyses of psychotropic drug use as the exposure variable in the sample of complete cases (n=1 225 894). On Cox regression, the hazard ratio for mortality where there was a mental disorder as any cause of death in those taking any psychotropic drug compared to those who did not was 2.099 (95% CI 2.063 to 2.136, *P*<0.001), adjusted for total number of drugs, starting age, gender, care home status and SIMD.

6.4.4.4 Kaplan-Meier curves

Using the Cox regression models above, I generated Kaplan-Meier curves for survival probability where there was a mental or behavioural disorder in any field on the death certificate, as shown in Figure 6-20 and Figure 6-21. I again conducted separate analyses stratified by age group. Similarly to the analyses looking at primary cause of death, these show that the 5-9 drugs group had the lowest survival probability in people aged 50-79 years, with the greatest difference between drug groups visible in the 65-79 year age group. For people aged over 100 years, where age at death was the time variable, the drug group curves cross over which may reflect the smaller sample size in this demographic.

Figure 6-20: Kaplan-Meier curves for mortality with mental disorder as any cause of death and age at death

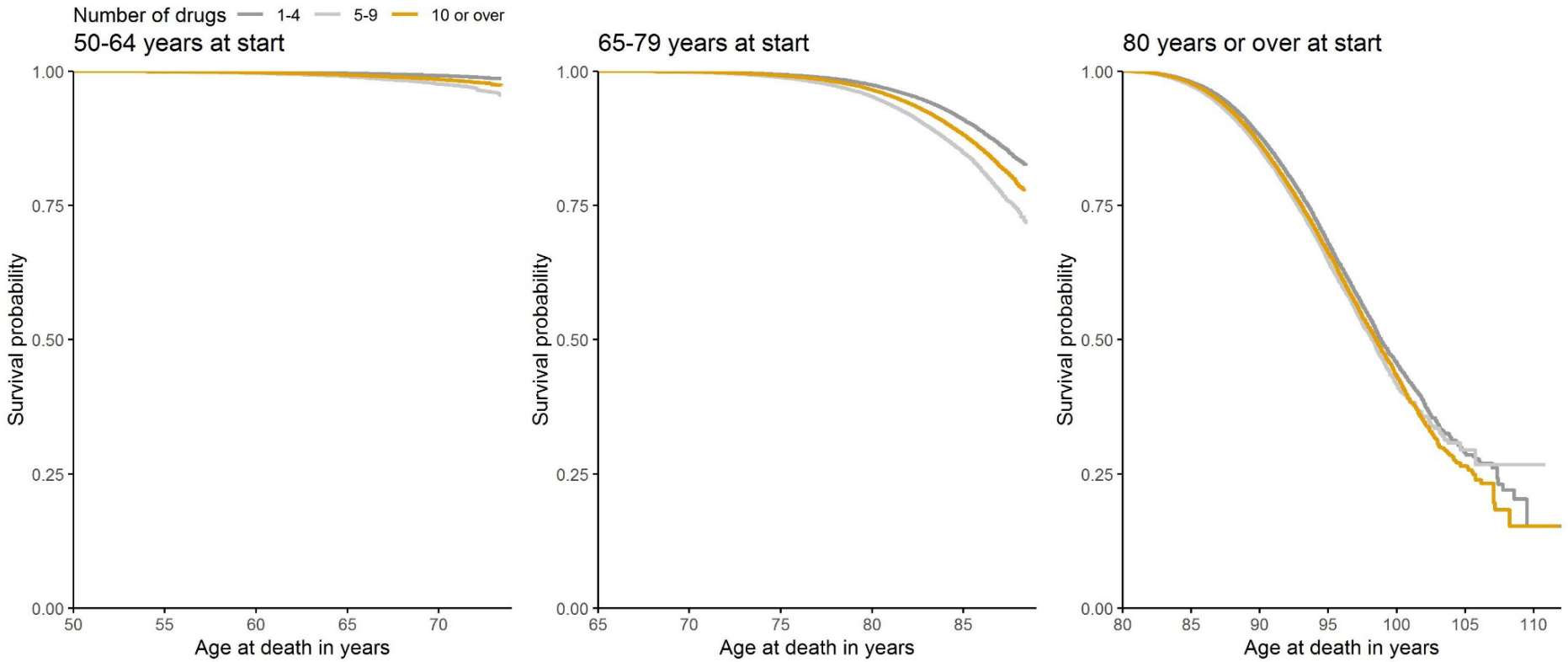
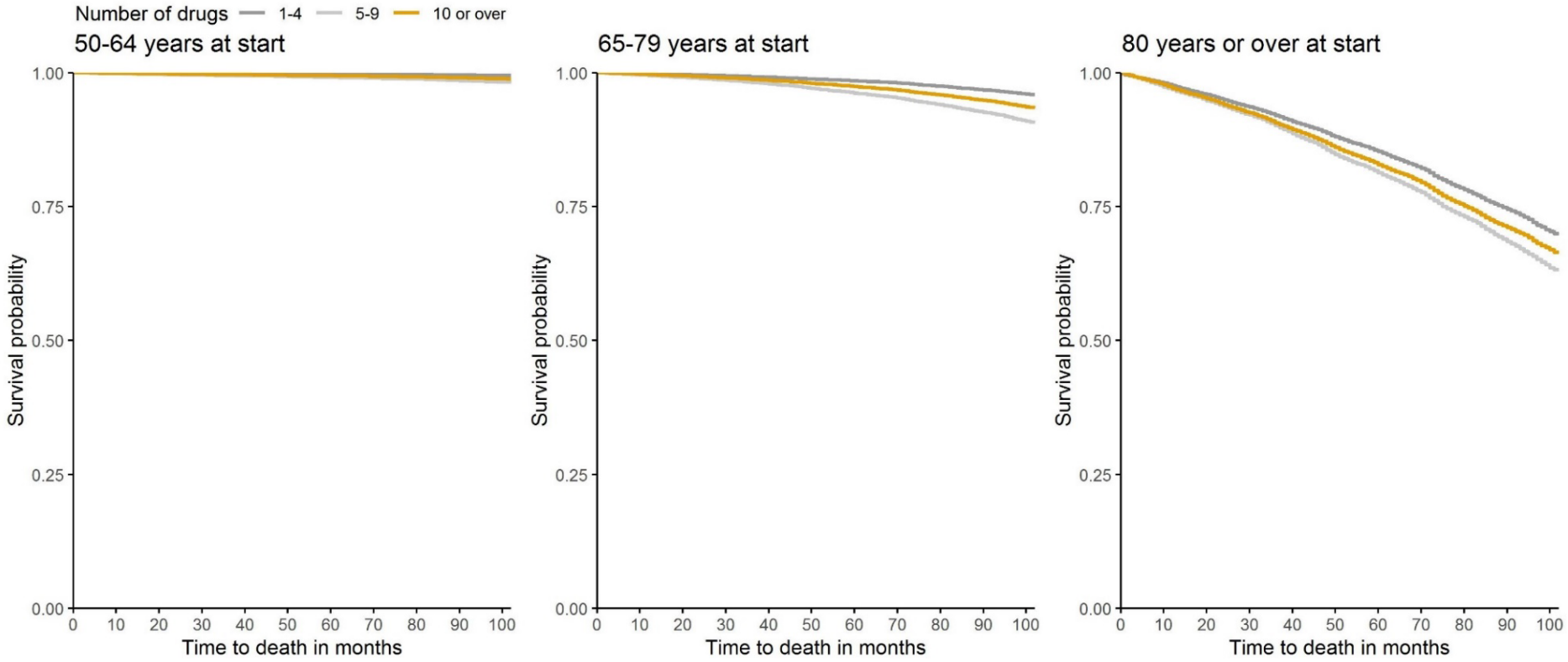


Figure 6-21: Kaplan-Meier curves for mortality with mental disorder as any cause of death and time to death



6.4.5 Survival analysis: psychiatric admission

6.4.5.1 Cox proportional hazards models

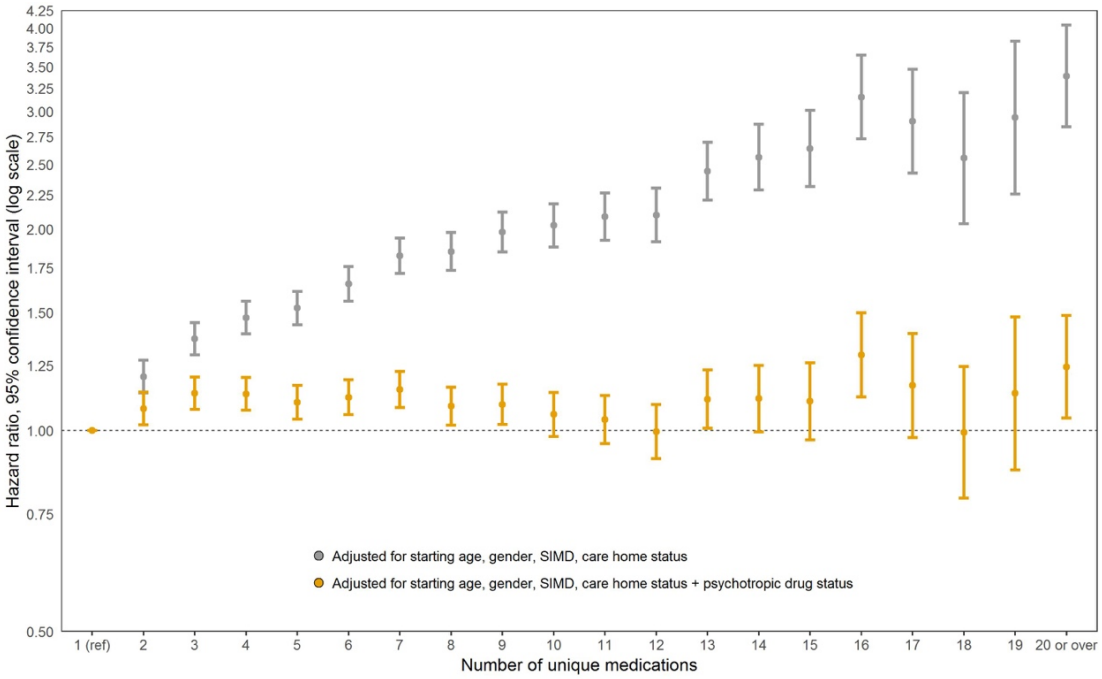
The final survival analyses in this cohort explored first episode of psychiatric admission as the outcome, with age at admission as the time variable. On preliminary graphical analysis of Schoenfeld residuals for psychiatric admission, I determined that the proportional hazards assumption had not been violated. On Cox regression, the hazard ratio for psychiatric admission with each additional continuous medication was 1.064 (95% CI 1.061 to 1.068, *P*<0.001), adjusted for starting age, gender, SIMD and care home status. When psychotropic drugs were an additional covariate, the hazard ratio reduced to 1.002 (95% CI 0.999 to 1.006, *P*=0.246). In a subsample of patients not taking psychotropic drugs (among which there were 10 322 admissions to psychiatric hospital), the hazard ratio per additional drug was 1.002 (95% CI 0.995 to 1.008, *P*=0.623). The results for individual drugs between 1 and ≥20 are shown in Table 6-18 and plotted in Figure 6-22.

Table 6-18: Cox proportional hazards ratios for first admission to psychiatric hospital with number of unique drugs

Number of unique drugs	Model 1		Model 2	
	HR (95% CI)	***P*-value**	**HR (95% CI)**	***P*-value**
1	Reference		Reference	
2	1.203 (1.137 to 1.273)	<0.001	1.078 (1.019 to 1.140)	0.009
3	1.370 (1.296 to 1.449)	<0.001	1.136 (1.074 to 1.201)	<0.001
4	1.475 (1.394 to 1.561)	<0.001	1.134 (1.071 to 1.200)	<0.001
5	1.524 (1.438 to 1.615)	<0.001	1.101 (1.039 to 1.168)	0.001
6	1.656 (1.561 to 1.757)	<0.001	1.121 (1.056 to 1.190)	<0.001
7	1.825 (1.717 to 1.939)	<0.001	1.151 (1.082 to 1.224)	<0.001
8	1.852 (1.736 to 1.977)	<0.001	1.087 (1.017 to 1.161)	0.014
9	1.980 (1.849 to 2.120)	<0.001	1.093 (1.020 to 1.172)	0.012
10	2.026 (1.880 to 2.182)	<0.001	1.056 (0.979 to 1.140)	0.155
11	2.089 (1.925 to 2.267)	<0.001	1.037 (0.955 to 1.127)	0.389
12	2.100 (1.915 to 2.303)	<0.001	0.995 (0.907 to 1.093)	0.924
13	2.443 (2.212 to 2.697)	<0.001	1.113 (1.007 to 1.231)	0.036
14	2.564 (2.289 to 2.872)	<0.001	1.115 (0.994 to 1.251)	0.063
15	2.640 (2.315 to 3.011)	<0.001	1.105 (0.968 to 1.262)	0.139
16	3.154 (2.730 to 3.643)	<0.001	1.296 (1.121 to 1.498)	<0.001
17	2.901 (2.425 to 3.470)	<0.001	1.167 (0.975 to 1.397)	0.093
18	2.555 (2.038 to 3.203)	<0.001	0.993 (0.792 to 1.246)	0.951
19	2.938 (2.258 to 3.823)	<0.001	1.136 (0.873 to 1.479)	0.344
≥20	3.391 (2.844 to 4.043)	<0.001	1.245 (1.043 to 1.485)	0.015

Model 1: Adjusted for starting age, gender, SIMD, care home status
Model 2: Adjusted for starting age, gender, SIMD, care home status and psychotropic medication use

Figure 6-22: Forest plot of hazard ratios for first psychiatric admission with increasing medications in adults aged ≥50 years



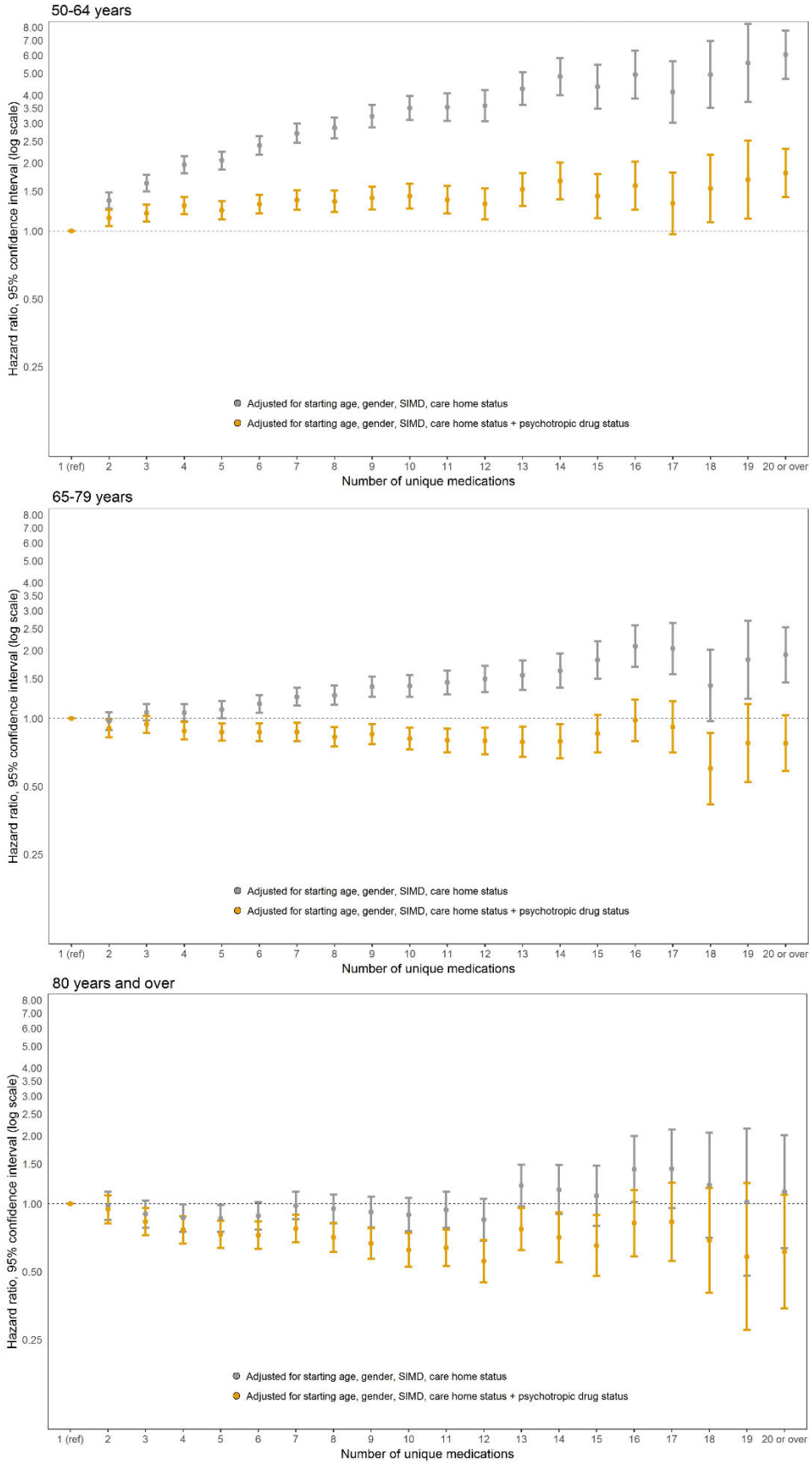
As there was a relatively high mean age of those admitted to psychiatric hospital, I analysed the sample stratified by age group, with the results for increasing drugs by one listed in Table 6-19.

Table 6-19: Hazard ratios for admission to psychiatric hospital with increase in drugs by one, stratified by age

Age group	Covariates	HR (95% CI)	*P*-value
50-64 years	Starting age, gender, care home status, SIMD	1.104 (1.098 to 1.109)	<0.001
	Starting age, gender, care home status, SIMD, psychotropic drug use	1.025 (1.020 to 1.031)	<0.001
65-79 years	Starting age, gender, care home status, SIMD	1.041 (1.036 to 1.047)	<0.001
	Starting age, gender, care home status, SIMD, psychotropic drug use	0.987 (0.982 to 0.993)	<0.001
≥80 years	Starting age, gender, care home status, SIMD	1.009 (1.001 to 1.018)	0.022
	Starting age, gender, care home status, SIMD, psychotropic drug use	0.973 (0.965 to 0.981)	<0.001

Plots of the hazard ratios for individual drugs are shown in Figure 6-23. In the youngest group, increasing medications were associated with higher risk of psychiatric admission regardless of covariates and only at 17 medications did the association not meet conventional statistical significance. Adjusting for psychotropic drug use in this group reduced the association. When adjusting for psychotropic drug use in the older age groups, taking 4-14 (for 65-79 years) or 3-15 (for ≥80 years) medications was inversely associated with being admitted to psychiatric hospital. Psychotropic drug use therefore appears to be a particularly important factor when assessing this outcome, perhaps because it represents that patients taking psychotropic drugs had a pre-existing psychiatric diagnosis.

Figure 6-23: Forest plot of hazard ratios for first psychiatric admission with increasing medications, by age group



6.4.5.2 Sensitivity analysis

To explore if removing or imputing SIMD changed the strength of association, I performed sensitivity analyses as for the other outcomes. The results, in Table 6-20, show little difference from the hazard ratios of analyses in the sample of complete cases.

Table 6-20: Sensitivity analyses for first psychiatric admission with continuous increase in drug use

Sample	Covariates	HR (95% CI)	*P*-value
All receiving ≥1 drug, including those with missing SIMD (n=1 346 714)	Starting age, gender, care home status	1.071 (1.067 to 1.074)	<0.001
	Starting age, gender, care home status, psychotropic drug use	1.007 (1.004 to 1.010)	<0.001
All receiving ≥1 drug, with imputed SIMD (n=1 346 714)	Starting age, gender, care home status, SIMD	1.064 (1.061 to 1.067)	<0.001
	Starting age, gender, care home status, psychotropic drug use, SIMD	1.002 (0.999 to 1.005)	0.272

6.4.5.3 Cox proportional hazards models with psychotropic medication as the exposure

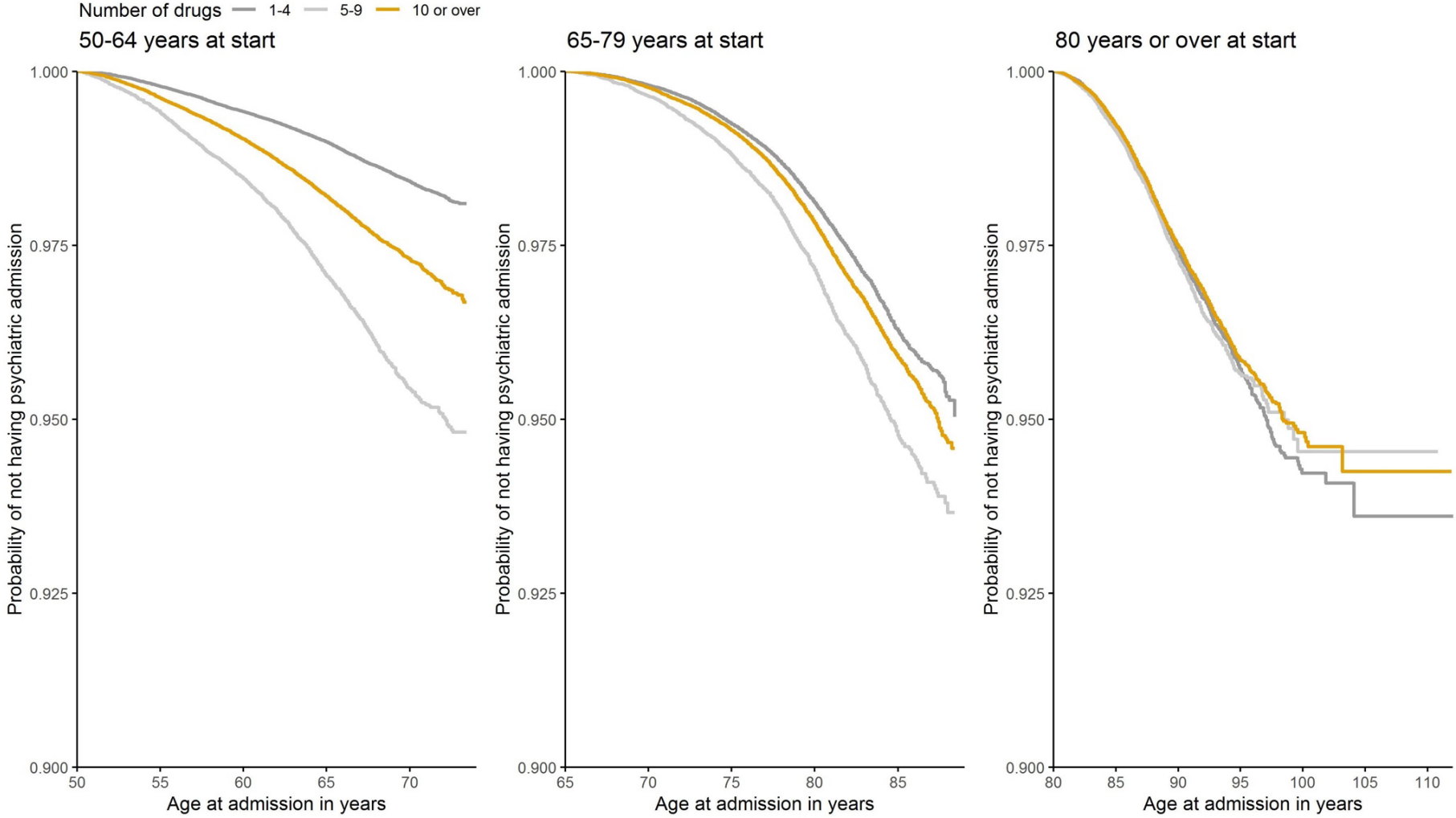
I conducted secondary analyses of psychotropic drug use as the exposure variable in the sample of complete cases (n=1 225 894). On Cox regression, the hazard ratio for psychiatric admission in those taking any psychotropic drug compared to those who did not was 4.217 (95% CI 4.100 to 4.337, *P*<0.001), adjusted for total number of drugs, starting age, gender, care home status and SIMD.

6.4.5.4 Kaplan-Meier curves

Using the same Cox models as above, I plotted Kaplan-Meier curves of survival probability, where survival meant not being admitted to psychiatric hospital in the study period. I compared age groups, and performed separate analyses for age at admission and time to admission as the time variable, in Figure 6-24 on page 258 and Figure 6-25 on page 259. In all patients, those taking 5-9 medications had the highest survival probability followed by those on ≥10 and 1-4 medications, although the overall differences in probability were small. The difference between drug use groups was

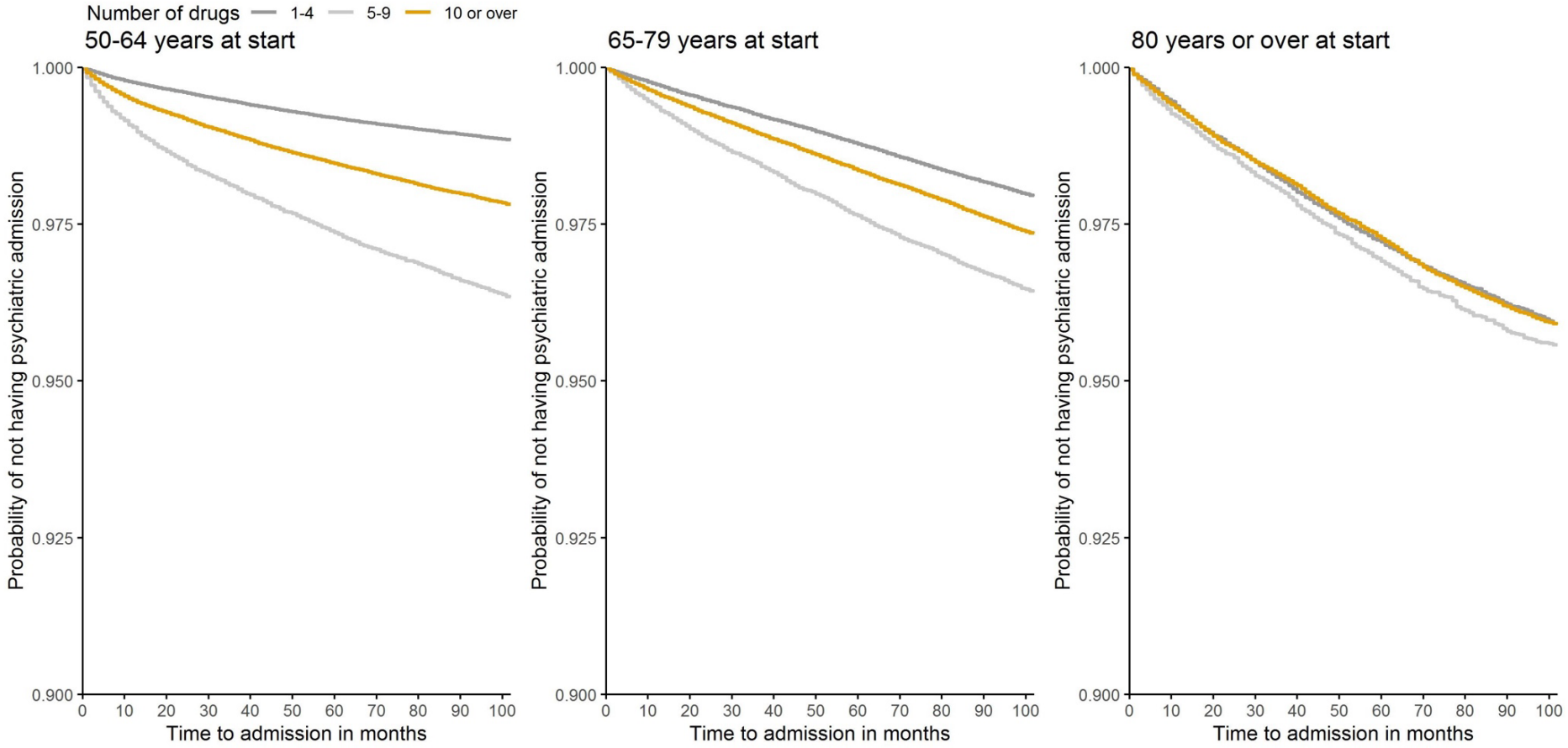
more defined in the youngest group. These graphs are limited by not accounting for covariates; this is particularly important here where psychotropic drug use is an important factor. Of note, in these graphs only, I truncated the y-axis to show clearer visual definition between the groups; the main point here is that the differences between groups are small.

Figure 6-24:Kaplan-Meier curves for admission to psychiatric hospital and age at admission



NB. Y-axis truncated to allow clearer differentiation between groups.

Figure 6-25: Kaplan-Meier curves for admission to psychiatric hospital and time to admission



NB. Y-axis truncated to allow clearer differentiation between groups for ease of visual interpretation

6.5 DISCUSSION

6.5.1 Summary of main findings

Polypharmacy is common in Scotland, with 46% of this sample of adults aged 50 years and over receiving five or more different medications during a three-month period in 2009. In keeping with previous research, I found that increasing medication use correlated with older age and increasing levels of socioeconomic deprivation.[37] Receiving more medication was associated with all-cause mortality and remained significant when adjusting for all covariates, but the association was less pronounced with increasing age.

Increasing medication count was marginally associated with mortality where there was a mental disorder anywhere on the death certificate, and was strongly associated at the highest levels of medication use, especially in the youngest age group. The association persisted but was attenuated when psychotropic drug use was added as a covariate, except in those aged ≥80 years where adding psychotropic drugs as a covariate reversed the direction of association. Total medication count was associated with mortality where a mental disorder was the primary cause of death when adjusted for age, gender, care home status and SIMD but inversely so when psychotropic drug use was added as a covariate.

The association between larger numbers of medication and mortality with mental disorders was weaker than that with all-cause mortality, especially when adjusting for psychotropic drug use.

Receiving larger numbers of medication did increase the risk of admission to psychiatric hospital, but when adjusting for psychotropic drug use, the association was attenuated. Given that psychotropic drug use is very relevant in people admitted to psychiatric hospital, it should be accounted for and the null hypothesis cannot be rejected in this case.

These findings suggest that polypharmacy is likely to be less negatively associated with the measured mental health outcomes than it is to overall mortality rates. Along with the noticeable difference made by adjusting for psychotropic medication, I surmise that the medication taken by people with psychiatric conditions (that become evident in the data either at death or by psychiatric admission) are of overall benefit. The findings may also be explained by the mental health outcomes being relatively crude. Future work could explore a more clinically precise outcome such as diagnosis on psychiatric outpatient contact.

6.5.2 Hypotheses addressed

1. Using larger numbers of medications, accounting for psychotropic prescriptions, was:
    a. Not convincingly associated with presence of a mental disorder anywhere on death certificates (fully adjusted HR=1.002 (95% CI 1.000 to 1.005, *P*=0.033)
    b. Not associated with admission to psychiatric hospital (adjusted HR with each additional medication=1.002 (95% CI 0.999 to 1.006, *P*=0.246).
2. Using larger numbers of medications was associated with increased all-cause mortality, with HR for increase in medication by one of 1.080 (95% CI 1.079 to 1.081, *P*<0.001), adjusted for age, gender, SIMD, care home status and psychotropic drug use.

The positive association between psychotropic drug use and all the outcomes is of interest, particularly that being dispensed a psychotropic drug carried a 26% increased risk of dying from any cause. I included these analyses for completeness when its relevance as a covariate was clear. It would be worthwhile exploring this further, perhaps examining each psychotropic drug group separately. However, this would mean using psychiatric conditions as exposures and would move away from the principal goal of this thesis, which is to explore broadly physical risk factors with psychiatric outcomes.

6.5.3 Comparison with other literature

In my analyses, 7.3% of the population aged ≥50 years and 18.9% of those aged ≥80 years received ≥10 unique drugs. This is lower than that reported by the Scottish Government using 2014 figures, which showed that 13.3% of over 50 year-olds and 26% of over 80 year-olds took ≥10 drugs.[25] Differences between this report and my results could be explained by the fact their data included all the population, whereas my analytic sample was only of those receiving at least one medication. However, if I had been able to include those taking no medication, my estimate would be smaller as the total sample size would increase. In addition, where I looked at individual drugs, they used BNF paragraphs (approximately equating to drug class) over six months instead of my three, and included a criterion specifying that at least one drug they had defined as 'high risk'. They did not specify whether this included all prescribable items or only chemically active drugs. My prescribing data are from 2009 so there may have been an increase between then and 2014, which would be supported from other evidence suggesting an increase in polypharmacy, perhaps related to population ageing.[37,377] A cross-sectional Scottish study of over 1.4m adults reported that 1.75% of the population were taking eleven or more repeat medications in 2007, but this figure is for all adults aged 18 years and over.[394] Similarly, a separate Scottish study using 2006 primary care data found that 4.6% of 180 815 patients aged ≥20 years were prescribed ≥10 medications on repeat prescription.[393] As my data were from all patients aged ≥50 years in Scotland, they are more representative of this age group.

Previous population-based research from Sweden, retrospectively assessing the records of deceased people, has found an increase in polypharmacy in the last year of life.[414] The proportion of people exposed to ≥10 medications increased from 30.3% to 47.2% in that year. This was due not only to symptomatic treatments but also long-term preventive medication. The reasons for this may be that people nearing the end of life had more symptoms or new conditions requiring treatment, whether or not it was expected that they would die. In any case, this increase in the last year of life may partly explain my finding that polypharmacy is associated with increased mortality.

Psychotropic drug use, particularly of antipsychotics, has been extensively investigated in relation to adverse outcomes. A population-based study from Finland that adjusted for relevant comorbidities gives a hazard ratio for nine-year mortality of 2.07 (95% 1.73 to 2.47) for people taking any antipsychotics compared to those taking none.[432] A Swedish register study of 1 288 875 people aged ≥65 years found that people taking one psychotropic drug were at increased risk of death in one year compared to those on none (adjusted HR=1.42 (95% CI 1.39 to 1.45)), and that this increased with the number of concurrently prescribed psychotropic medicines.[433] These results are in line with my results in section 6.4.2.3, where the HR for all-cause mortality for patients taking any psychotropic drug compared to those not taking a psychotropic drug was 1.262 (95% CI 1.252 to 1.271, P<0.001), albeit with a smaller estimate. This may be due to the younger age of my sample.

A 2016 systematic review of the use of mental health diagnoses from administrative data explored 39 studies on this topic, with a wide variety in the quality of publications.[434] The authors concluded that psychotic disorders were more accurately recorded than anxiety disorders. Although the outcome of psychiatric admission in my analyses was broad, it is robust; details on admission dates are subject to less error than those of diagnoses.[395]

6.5.4 Strengths

This is the largest UK-based longitudinal study of polypharmacy to date and the first to consider psychiatric outcomes at such scale. Using routine data in a universal healthcare system offers insights into the outcomes and experiences of real patients, rather than volunteers in cohort studies. For example, cross-sectional work exploring polypharmacy and multimorbidity in people with chronic obstructive pulmonary disease has been undertaken in the UK Biobank cohort,[254] but the response rate to UK Biobank invitations was 5.5%.[435] The dataset used in this chapter uses population-level data from everyone who uses the NHS.

6.5.5 Limitations

It was not possible to control for multimorbidity in this dataset, as the main exposure variable was routinely collected prescription information. This is not currently linked to primary care diagnosis lists in this cohort. In some recent polypharmacy studies, there has been a move towards accounting for number of diagnoses to address confounding by indication.[377,379] However, a systematic review of polypharmacy outcome studies found this was done in only 20 out of 58 included studies (receiving 'good' or 'fair' rating).[291] Other work using NHS Scotland prescribing data has inferred multimorbidity from the number of body systems addressed by prescriptions; cautiously used, this could be an approach for future research.[436]

Previous research found that the strength of association between the number of drugs prescribed and potentially avoidable hospitalisation was reduced when the number of conditions was added as a covariate.[437] Another study reported that the main factor associated with polypharmacy in Scotland is multimorbidity, although the impact of increasing conditions is less when they are concordant comorbidities (conditions within a disease group, such as cardiovascular, that require similar pharmacological treatment).[393] However, when choosing between counting diagnoses and medications to measure burden of disease, an advantage of medication use is that it may better represent the patient's overall severity. For example, a severe form of one illness such as chronic obstructive pulmonary disease would require multiple medications but only count as one diagnosis.

6.5.5.1 Medication appropriateness

It was not possible with the data available to measure whether medication was prescribed appropriately. There are two widely used methods of assessing potential medication appropriateness in older people, the American Geriatrics Society's Beers Criteria for Potentially Inappropriate Medication Use in Older Adults [438] and the Screening Tool of Older People's Prescriptions and Screening Tool to Alert to Right Treatment (STOPP/START) criteria.[439,440] These tools were developed for clinical use, on the premise that adverse drug reactions in older people are common and avoidable. They both require information beyond medication prescribed, such as drug indication, comorbid conditions or physiological parameters such as blood test results.

The availability of a large quantity of data that lacks in detail is a recognised limitation of this sort of 'big data' research.[441] One study of over 38 000 primary care patients examined prescriptions using only applicable elements of the STOPP/START criteria.[442] This would be a possible way to address inappropriateness in future work using my prescribing data. In addition, current Scottish Government polypharmacy guidance specifies that patients' preferences and priorities should be considered.[27] This emphasises that for clinical application, decisions should be taken at an individual patient level, which again cannot be accounted for in population-based studies.

Many of the people receiving multiple medications in my sample probably had several conditions, for which multiple medications managed their symptoms or disease progression or were appropriate secondary prevention. Reviews and consensus statements on polypharmacy in recent years have advised against assuming that all polypharmacy is negative and unnecessary, and instead treating it as *"potentially problematic rather than always inappropriate"*.[37,443,444] Furthermore, it can be simultaneously appropriate and problematic even within one individual.[445] In this chapter I have therefore reported only the total medication use per person in relation to the outcomes of interest, rather than assuming polypharmacy is inherently negative. In fact, my results show that receiving larger numbers of medication decreased the likelihood of psychiatric admission.

The PIS extract did not include dosage or frequency regimens, so I could not establish indication for medications where there are more than one possible indication. This is particularly relevant when I generated my psychotropic drug variable, for example, low-dose tricyclic antidepressants are used for pain or night-time sedation; levomepromazine for nausea and carbamazepine or valproate for epilepsy. The inclusion of these drugs is a limitation, but it could be argued that, if given at a therapeutic dose, their psychotropic action persists regardless of their indication.

6.5.5.2 Prescribing Information System extract limitations

Examining unique drugs from one quarter in 2009 means that patients may have received a high number within that quarter because of an acute process. For example, in an acute exacerbation of COPD, numerous drugs are required and several antibiotics may be tried. This capture of drugs may reflect more acute scenarios than the chronic ones that are intended to fit in with my overall perspective on polypharmacy. In addition, looking at an isolated quarter does not allow the elucidation of whether or not drugs are prescribed for long-term use.

Using the CHI system to identify people on no medications for whole population estimates misses people who do not have a CHI number, such as recent migrants, and may include also people who have migrated out of Scotland. Among people without a CHI number, people from disadvantaged and vulnerable groups such as homeless people or prisoners (who did not have CHI numbers prior to 2012) are likely to be over-represented.[446]

Due to the nature of data availability and access through eDRIS, I did not have sufficient information on people who were not prescribed any medication to include them in survival analyses. According to the CHI system, there were 661 109 people who received no medications during the quarter in question. These people did not appear in the PIS extract from which starting age was taken, so I had to exclude them from survival analyses. Using one as the reference number of drugs for regression models may have led to under-estimates of the effect size, if we are to extrapolate results and assume that people on no medication have an even smaller likelihood of the relevant outcomes than those on one medication. However, it is possible that some people taking no medication are less healthy than those on a small number; they may have chronic undiagnosed and untreated illnesses and do not seek medical care. They could also have been hospital inpatients for the whole initial study period in 2009. I plan to obtain comparable data on people taking no medication, so I can revisit my analyses and test whether the associations remain.

PIS does not record over-the-counter medication or those dispensed by hospitals. Hospitals dispense medication to inpatients (who are arguably the most unwell people in a community) during an admission or for short-term use after discharge. They also provide specialist medication such as biologics, clozapine and some long-acting injectable antipsychotics.[53] These are important, but probably relatively rarely prescribed treatments. In early 2009, drugs for dementia would have been initiated by specialists (usually psychiatrists). It is impossible to know how many of these were prescribed on community prescription pads and processed by community pharmacies, and therefore appear in this dataset, and how many were dispensed by hospital pharmacies. In future work I could combine medication over a longer initial period or compare changes over time, which would account for some of the hospital dispensing issues.

Continuous Positive Airways Pressure (CPAP) is the mainstay of treatment for one particular chronic condition, obstructive sleep apnoea. The supply of these machines is also not captured in PIS. This is one disease area where medication does not act as a marker for the condition and where using a list of diagnoses seems preferable.

Adherence to prescribed medication or treatment is recognised as a problematic area, with estimates for treatment adherence stable around 50%.[30,447,448] However, these estimates in large-scale health records are calculated by comparing prescribed with dispensed medications. At such a scale, it would be impossible to know the true adherence to prescribed medication once it has been dispensed. A small study of 84 patients with multimorbidity using self-reported actual adherence found rates of 94.7%, but this was likely affected by recall and self-presentation biases.[449] A study of the Generation Scotland cohort found an adherence rate of 84.9% to antidepressants, as measured by the more reliable Proportion of Days Covered method.[450] My data are therefore conservative estimates of the total medication actually consumed by each person. However, using dispensed, rather than prescribed, medication is a strength over some previous similar studies.[378,393,394]

Memantine was first approved by the European Medicines Agency in 2002, Galantamine in 2000, Rivastigmine in 1998 and Donepezil in 1997.[451] They are therefore relatively new drugs and are restricted to specialist use.[100] In addition, National Institute for Health and Clinical Excellence (NICE) guidance in 2005 changed the criteria for which patients would be eligible, with this later revised in 2011.[452,453] This may explain the relatively low numbers of dementia drugs dispensed in 2009 (2.6% of people aged ≥80 years) and more recent data would better reflect current usage.

My psychotropic medication covariate was a simple binary variable in these analyses; future work could explore types of medication, combinations and the number of psychotropic medications taken. The differences in hazard ratios when including psychotropic drug use as a covariate are probably due to it being a marker of pre-existing psychiatric diagnosis. This could explain the disparities in hazard ratios for psychiatric hospital admission, for example.

There is an increasing body of evidence that anti-hypertensive medication is associated with a decreased risk of developing dementia. A German primary care study of 12 400 people with dementia and 12 400 matched controls found a decrease in dementia incidence with most antihypertensive medication subtypes (excluding diuretics).[89] This could be one explanation for the lower rates of mental disorders than overall mortality in people with polypharmacy. Investigating individual drugs or using a trial emulation design is a potential avenue for further exploration.

6.5.5.3 Confounding factors

There are likely to be numerous confounding factors that may explain the associations found between polypharmacy, death and psychiatric admission. These include lifestyle factors such as smoking status and alcohol or substance intake, other physical issues such as underweight or obesity and environmental issues. This information is not available from the routinely collected data process, such as when generating a prescription or recording a death. These are accepted limitations that

must be considered when balancing the benefits of a very large dataset such as this.[109,110] In addition, I did not account for the month or year of death, therefore neglecting any seasonal influences on mortality rates. It is possible, therefore, that residual confounding exists and my results over-estimate the associations found.

Owing to variation in multimorbidity prevalence by ethnic group, I had originally intended to include ethnicity as a covariate in my analyses.[278] However, ethnicity is not recorded on prescriptions or death certificates and is only available from hospital admission or outpatient records. Even in people who did have a linked hospital record, the majority had 'not known' or 'not provided' codes, meaning this became uninformative. The 2011 census found that in Scotland, 4% of people reported non-white ethnicity.[454] The poor quality of ethnicity recording in health records is a recognised problem, and the Scottish Health and Ethnicity Linkage Study was set up to address this, linking census information to health records.[455] This information was also linked to psychiatric admissions and Mental Welfare Commission for Scotland's records on detentions under the Mental Health (Care and Treatment) (Scotland) Act 2003. The study found that people from all ethnic minorities were at increased risk of being detained and that there were significant variations in the rates of psychiatric disorders and admissions between groups, that remained when adjusting for socioeconomic markers.[456] A representative population survey, the Health Survey for England, found that although ethnic minority respondents were not less likely to use primary care than white participants, there were inequalities in their access to hospital services.[457] This suggests that ethnicity is important when exploring mental health outcomes and that this is a limitation of my analyses.

6.5.5.4 Accuracy of death records

The death record is complete for all deaths registered in Scotland for the study period. However, it does not capture deaths that occurred outside of Scotland, meaning that an individual appearing in the study sample in 2009 who later moved away from Scotland and died elsewhere would not be recorded as having died. The assumption that these people survived the study period could lead to an under-estimation of the probability of dying. The NRS official estimates for migration, broken down by age, are only publicly available for 2015-17.[458] In this example period, 20 637 people

aged 57 and over (who would have been aged ≥50 years at the start of my study period) emigrated from Scotland, either elsewhere in the UK or the world. During the same time, 21 699 people migrated into Scotland, raising the possibility that perhaps some of the emigrants had previously moved into Scotland and would not have appeared in my 2009 prescribing sample. My linked dataset did not allow for tracking of individuals' migration.

The software used to code causes of death in Scotland was updated in 2011 and replaced in 2017.[459,460] These changes implemented updates to the WHO ICD-10 rules and resulted in increased prevalence of dementia as a primary cause of death. For example, the 2017 change increased the number of deaths where dementia was the primary cause by 7.5%, because people who died with respiratory infections and dementia were now classified as having died primarily of dementia in most cases.[460] In addition, the Certification of Death (Scotland) Act 2011 was implemented in 2015, mandating accuracy checks on at least 10% of Medical Certifications of Cause of Death.[461] The changes may mean that my survival analyses for mental disorders as causes of death may be less comparable between individuals, depending on when they died. However, the relevance is limited, as I did not track trends in specific diagnoses as causes of death over time. My analyses with the outcome of a mental and behavioural disorder as any cause of death, rather than the primary one, would capture dementia in scenarios both before and after the change.

The way the death certificate is completed is open to some subjectivity on the part of the completing doctor as to which conditions are relevant to the death. This is a particular issue for many mental disorders and means it is likely the prevalence on death certificates is much lower than in the general population. Although it would be very unusual to list a depressive disorder as a primary cause of death, it was only listed anywhere on 792 (0.24%) death certificates in my dataset. This is lower than the estimated population lifetime prevalence, which has been calculated as 6.4%,[462] although this figure varies depending on how depression is screened for or measured.[463] This would suggest it is either considered irrelevant to death even as a contributory factor or is underreported on death certificates.

I may have over-estimated the extent of psychiatric disorders on death certificates by including alcohol and substance use disorders, as at death these may have primarily physical consequences. However, I used only the codes from Chapter V of ICD-10, and cirrhosis, for example, would be recorded under liver diseases in Chapter XI as K70.3. This area may be one example of where creating a dichotomy between mental and physical disorders is artificial and does not fit with patient experience.

6.5.5.5 Dementia on death certificates

Dementia was by far the most prevalent mental disorder coded on death certificates, contributing 88.4% of all mentions of mental disorders in any field. For practical reasons, I did not include analyses with each mental disorder as an outcome in this chapter, but aim to do this, specifically for dementia and depression, in future work. This will have the benefit of informing policy more specifically, with reference to individual outcomes. It is likely that dementia accounted for most of the associations found in the included analyses, and separating the other conditions would have reduced the statistical power of those observations.

The recording of dementia has come under scrutiny on death certificate diagnoses elsewhere. A recent cohort study of 7 115 people with clinically diagnosed dementia in London aged ≥65 years found that frequency of dementia recording increased from 39.9% in 2006 to 63.0% in 2013.[464] The rates in the Edinburgh area were higher, with a study using 2010 data from 502 deceased individuals with dementia finding 71.5% had dementia listed on their death certificate.[465] The prevalence of dementia or mild cognitive impairment on death certificates in my sample of adults aged ≥50 years was 17%. This compares to UK-wide prevalence figures published by Alzheimer's Research UK of 16.3% for women and 8.7% for men, with a significant increase in prevalence on death certificates from around 2011 onwards.[466] Using data from 24 506 deceased participants of the Cognitive Function and Ageing Study (CFAS) in England and Wales, the proportion of death certificates including a diagnosis of dementia rose from 11.6% in 1990-2008 to 20.3% in 2008-2018.[467] This study also compared death certificates with study visit diagnoses and found an

increase in sensitivity of death certificates from 21.0% in the earlier period to 45.2% latterly.

6.5.6 Implications

The presence of polypharmacy implies that an individual is in poor health and, as has been demonstrated in this chapter and in previous research, at increased risk of death from any cause. This chapter has explored mental health outcomes linked to polypharmacy. The findings do not convincingly support the overall hypotheses of this thesis that multimorbidity and polypharmacy are associated with mental disorders.

6.6 CONCLUSIONS

In this large population-based cohort, receiving a larger number of medications was associated with mortality, even after adjusting for starting age and other relevant demographics. There was a weaker association between polypharmacy and death with psychiatric diagnoses and psychiatric admissions, and adjustment for psychotropic drug use further attenuated these associations. It is likely that polypharmacy acted here as a marker for multimorbidity or overall poor health, but may also have contributed independently to mortality. My analyses are observational and cannot infer causality or temporality.

Chapter 7 presents an overview of all the findings in this thesis and their relevance to existing research. It also considers future directions possible using this dataset, for example using a medication-based index of multimorbidity such as the Chronic Disease Score or Medication-Based Disease Burden Index, as identified in my systematic review.[147,148]

Chapter 7 Discussion

7.1 INTRODUCTION

In this thesis, I have explored in detail the measurement of multimorbidity and the relationship between multimorbidity and polypharmacy with mental disorders and brain health outcomes. In this chapter, I summarise my main findings and discuss their limitations, application and the conclusions I have drawn.

7.2 SUMMARY OF FINDINGS

7.2.1 Measurement and methodology

I conducted a systematic search of the literature on multimorbidity measures for use in the community or population, and a detailed review of the resulting 35 articles. The main conclusions from this work were that it is important to understand the original design of a multimorbidity index before applying it. The development and publication of new indices since my search suggests that there continues to be appetite for novel measurement tools despite there already being an abundance of them available.[217,218,468] In Chapter 3, I explored the overall limitations of indices and the process of measuring multimorbidity using robust disease counts instead of an index. This method is especially relevant where the outcomes examined in a study do not clearly match an existing index design. For the data analysis chapters, I therefore used the commonest method of measuring multimorbidity and polypharmacy, namely counts of diseases or medication.[112]

7.2.2 Hypotheses addressed using data analysis

The main question posed by this thesis was whether physical multimorbidity and polypharmacy are associated with an increased risk of mental disorders or markers of poor brain health. I addressed the hypotheses as stated below.

7.2.2.1 Hypothesis 1

Physical multimorbidity (or having a larger number of chronic conditions) will be associated with an increased risk of mental

disorders. The greater the burden of multimorbidity, the higher the individual's risk of developing a mental disorder.

In cross-sectional analyses of data from the PREVENT Dementia study (Chapter 4), I found that having a larger number of chronic conditions was associated with self-reported depression and anxiety disorder and increasing Center for Epidemiologic Studies Depression (CES-D) scores but not increasing Spielberger State-Trait Anxiety Inventory (STAI) scores. Antidepressant use was an important covariate in these analyses. Multimorbidity as a binary measure was only associated with self-reported anxiety and not self-reported depression, continuous CES-D or STAI scores. There were no associations between increasing chronic conditions and scores on COGNITO cognitive tests.

7.2.2.2 Hypothesis 2

Polypharmacy, or using larger numbers of medications (adjusting for antidepressant or psychotropic drugs), will be associated with poorer mental health, and the greater the burden of polypharmacy, the higher a person's risk of developing a mental disorder.

In Chapter 4, analysing cross-sectional data from the PREVENT Dementia study showed that higher use of medications was associated with self-reported depression and increasing CES-D scores, although antidepressant use attenuated these associations. Increasing medication use was not associated with self-reported anxiety, STAI scores or COGNITO subtests. Dichotomous measures of polypharmacy were only associated with self-reported anxiety (with wide confidence intervals) and not with any other mental disorder outcomes.

Chapter 6 included longitudinal analyses of routinely collected NHS data. When adjusting for psychotropic drug use, I found no convincing association between higher medication use and mental disorders on death certificates. In this case, there was also an inverse association between increasing drug use and mortality where there was a mental disorder anywhere on the death certificate in people aged over 80 years.

There was no association between increasing medication use and admission to psychiatric hospital when adjusting for psychotropic drug use.

7.2.2.3 Hypothesis 3

> Physical multimorbidity or greater number of conditions, and polypharmacy or greater number of medications, will be associated with outcomes linked to dementia on structural MRI neuroimaging.

In the PREVENT Dementia study explored in Chapter 4, I found no significant associations between having a larger number of chronic conditions or using more medications with hippocampal volume, cerebral microhaemorrhages or either deep white matter or periventricular Fazekas scores.

7.2.2.4 Hypothesis 4

> Multimorbidity, or having a larger number of chronic conditions, will be associated with lower concentrations of cerebrospinal fluid (CSF) amyloid-β, as a marker of Alzheimer's disease.

In Chapter 5, when analysing data from the EPAD longitudinal cohort study I found that multimorbidity, or an increased number of chronic conditions, was inversely associated with lower concentrations of CSF amyloid-β, as a marker of Alzheimer's disease. This directly opposed the stated hypothesis.

7.2.3 Comparison between results across datasets

Overall, I did not observe the expected associations between multimorbidity or polypharmacy and mental disorders or brain health. I conducted complementary analyses in diverse datasets and interrogated each in an approach tailored to its components and study design. It is therefore not possible to compare the outcomes from each chapter directly.

However, in general, having multiple chronic physical conditions was associated with depression and anxiety, was inversely associated with CSF amyloid positivity and was not associated with any cognitive or imaging measures of neurodegeneration. It is notable that associations existed between multimorbidity or polypharmacy and the clinical or patient-reported outcomes such as depression but not with the biomarkers. Age is an important contributor, as many of the biomarkers were taken from middle-aged study participants. These findings could suggest that multimorbidity is more important to mental health outcomes as experienced by individuals, rather than in specific biological pathways. This may be explained by psychological or personality factors related to having multiple physical symptoms.

Using a larger number of medications was associated with having a self-reported diagnosis of depression. It was not associated with anxiety disorders, and when adjusting for psychotropic drug use was not associated with psychiatric admissions or mental disorders listed on death certificates. This was unexpected, especially in the context of a clear relationship between polypharmacy and increased mortality. The lack of association may reflect the fact that the count of medications and method for adjusting for psychotropic drug use were relatively crude. Polypharmacy where the patient is taking several psychotropic medications, for example, is likely to represent more severe mental illness, in comparison to a patient taking the same number of drugs which comprise numerous treatments for physical conditions and one antidepressant. This limitation can be addressed in future research using the NHS prescribing dataset.

7.3 LIMITATIONS

7.3.1 Study design

Chapters 4 and 5 used cross-sectional designs in cohort studies of healthy mid-life volunteers. Both studies were designed to investigate factors contributing to neurodegeneration. While multimorbidity and polypharmacy are relevant to neurodegenerative diseases, the populations are not best designed to explore other mental health outcomes. For example, they were not powered to identify a proportion

of people with a diagnosis of depression. However, multimorbidity and polypharmacy in mid-life are under-researched and as they are emerging as important risk factors for neurodegeneration, my work provides valuable insights in this area.

7.3.2 Causal inference in observational studies

Observational studies of this type cannot infer causality, regardless of whether they are longitudinal or cross-sectional.[469] Causality implies that a specific state or risk factor is truly significant and becomes important when considering public health or policy interventions. In 1965, Sir Austin Bradford Hill listed his suggestions for additional evidence needed to interpret association as causation, in the historical context of the recently established association between smoking and lung cancer.[470] His viewpoints were that the following characteristics of an association should be considered:

a. Strength
b. Consistency (or replicability),
c. Specificity
d. Biological gradient (or dose-response)
e. Plausibility
f. Coherence (that the findings fit with other known facts about the disease)
g. Experiment (i.e. translation into a randomised trial)
h. Analogy (for example, pre-existing evidence of an association in a similar condition)
i. Temporality.[470]

Hill's original paper listed these as general viewpoints and did not propose they were criteria or provide methods for testing each one. Nor did he suggest that all his viewpoints must be met; temporality is the only requisite criterion.[471] My analyses in Chapters 4 and 5 were cross-sectional, so cannot provide evidence of temporality. My longitudinal analyses in Chapter 6 did not produce convincing results of any new associations (except for the established link between polypharmacy and mortality). Overall, I do not consider that any of my results can suggest causality based on this list.

7.3.3 Temporality

Cross-sectional analyses cannot explore the order in which events occur, or in this case, diseases accumulate. Temporality is a relevant consideration in multimorbidity research, particularly when studying physical and mental disorders together. For example, in a cross-sectional study, a patient diagnosed with diabetes who later developed depression and one with chronic depression who later developed diabetes would both be counted as having two conditions.[20] There may be shared predisposing or aetiological factors for these conditions.

People with chronic mental disorders are known to have poor physical health, and relevant research and interventions usually assume that the mental disorder came first. Analysis of data from 47 609 participants in the World Mental Health Surveys between 2001-2011 revealed strong associations between the onset of mental disorders with later physical conditions and that having multiple mental disorders increased the risk of physical conditions.[286] An American study of 664 838 patients' records found that mental disorders preceded cancer diagnoses in both sexes and in all age groups.[472] These associations may be explained by confounding factors such as smoking. The temporality of physical-mental multimorbidity onset in general may also be important. A Danish population study of 27 262 people who had died by suicide with 468 007 matched controls found that physical and mental illnesses both increased the risk of suicide independently.[473] The adjusted incident rate ratio for suicide in patients with a mental disorder diagnosed after a physical illness was 1.54 (95% CI 1.46 to 1.63) and mental disorder diagnosed before physical illness was 0.90 (0.85 to 0.95), both compared to those with only a psychiatric diagnosis. Mental illness occurring after the onset of physical illness increased the risk of suicide beyond that of physical or mental illness alone. My analyses in Chapters 4 and 5 therefore cannot show which comes first of multimorbidity and mental health symptoms or diagnoses.

7.3.4 Dynamicity

As discussed in Chapter 3, multimorbidity is usually treated as a one-dimensional construct although it is constantly changing within an individual. There is evidence from repeated survey data that changes in an individual's number of conditions have varying associations with depressive symptoms, for example.[474] Even within one

chronic condition, intensity and severity can fluctuate depending on whether it is currently active or causing symptoms.[114] A limitation of all my analyses is that I did not measure trajectories of multimorbidity or polypharmacy, although this is in keeping with most similar research.[114]

7.3.5 Sample size and statistical power

The sample size used in Chapter 4 (n=210) is relatively small for some of the questions examined. For example, a 2017 systematic review of observational studies exploring the association of multimorbidity with depression found 40 papers, of which 6 (15%) had a sample size of less than 210.[288] Using this dataset did have the benefit of allowing the inclusion of detailed measures of symptoms and markers of neurodegeneration. The EPAD dataset used in Chapter 5 is of a reasonable size compared to similar studies (n=447). A systematic review of dementia biomarkers found that of 37 studies examining amyloid-β in CSF or plasma, 29 (92%) had a sample size of less than 500.[106]

Because I used existing datasets, the sample size was fixed. The PREVENT Dementia study's initial planned sample size was 150, based on genetic and biomarker studies, with development of dementia as the primary outcome, so the sample I used exceeded this.[51] EPAD aims to have several thousand participants in readiness for clinical trials of disease-modifying drugs for dementia that will require stratification by amyloid status. The number in the first data release (n=500) was powered to contain sufficient amyloid positive participants for this purpose.[52,475]

There is potential for some overlap between participants in EPAD (Chapter 5) and the NHS cohort (Chapter 6). Among my EPAD sample, 65 of the 447 eligible participants (14.5%) were recruited from study sites in Scotland. These individuals would have to have been aged 50 years or over on 1st January 2009 in order to also appear in the NHS sample. EPAD started recruiting people aged 50 years and over in 2016. Even if all 65 EPAD participants were aged at least 50 years in January 2009, this is 0.005% of the overall NHS sample size. In addition, the exposure and outcome variables were

different between Chapters 5 and 6 so any overlap is unlikely to have affected the results.

7.3.6 Measurement of chronic conditions and medications

The comparability between chapters is further limited because I used different measures of multimorbidity in Chapters 4 and 5 depending on the data available and on the research questions. For example, in Chapter 4 I excluded psychiatric diagnoses from the condition count as I used specific mental disorder outcomes, whereas the list of conditions used in Chapter 5 included mental disorders (except dementia) as the outcome was a biomarker of Alzheimer's disease. Clinical mental disorders were less relevant to this biological outcome. Despite Chapter 2 revealing numerous potential multimorbidity indices, I used disease counts in my analyses. This was for pragmatic reasons and I clearly justified my choices of candidate condition lists in Chapters 4 and 5. In order to strengthen my results and allow comparability with other studies, I also included dichotomous measures of multimorbidity. Using counts of conditions has advantages, such as practicality and preventing the possible bias associated with using an index weighted on a particular outcome. However, as discussed in Chapters 2 and 3, counts are limited by assuming the same importance for each condition and not representing patients' burden of disease well.[118]

I was unable to harmonise the lists of conditions between Chapters 4 and 5 because the medical history in PREVENT Dementia was taken from a set list of conditions within the Case Report Form. These conditions did not provide the requisite information to either map onto the list of conditions from Barnett and colleagues [39] or onto the free-text style medical history collected in the EPAD study. In order to maximise the sensitivity of each list at detecting meaningful conditions and burden of disease, I aimed to include between 25 and 75 conditions per list as recommended by previous research.[260] If I had used one list of only the conditions that could be definitely identified in both samples, this would have been much shorter and less sensitive.

In Chapter 6, I used counts of simultaneous drugs received from among all prescribable active substances. This, along with categorising the number of medications, is the most frequent method of measuring polypharmacy.[32] My systematic review in Chapter 2 revealed that there are at least four weighted drug indices, designed to measure multimorbidity through medication use rather than to measure polypharmacy itself.[145–148] In the NHS dataset where diagnoses were not available, I chose to refer to medication counts rather than attempt to infer multimorbidity from them. In PREVENT Dementia, where both diagnoses and medications were available, I handled each separately.

Simple drug counts have limitations similar to disease counts. In clinical practice, they have limited significance when treated without consideration of the individual's level of multimorbidity.[32] Drug counts do not account for differences between medications, such as in side effects or interactions.[37] Measuring medication use at one time point does not reflect the patient's true intake of drugs over time.[476] In contrast with the lists of eligible conditions available for measuring multimorbidity, drugs are usually counted from any prescriptions the patient receives.[260] A 2017 systematic review of polypharmacy definitions did not comment on whether medications were counted from lists, implying that they included all possible medication.[32] It was also not possible to assess concordance with prescriptions using any of the included datasets, in keeping with most other polypharmacy research.[30,447] There are overall limitations inherent in counting diseases or drugs throughout this thesis, which are common to other studies with similar methods.[11,114]

7.3.7 Generalisability of results

Chapters 4 and 5 included relatively healthy volunteers and are therefore not generalisable to the whole population or clinical practice due to selection bias. In addition, they relied upon self-reported medical and medication history which were both subject to recall bias and are likely to over-estimate the level of multimorbidity. A Dutch study found that the prevalence of multimorbidity (≥2 conditions) in 2011 was 16.2% according to the GP records of 359 682 people and 17.5% on health survey self-reports from around 15 000 community inhabitants.[63] This discrepancy was

present despite the list of conditions being longer (28 conditions) in the GP sample than the survey (11 conditions). Another study of 1 625 people aged over 65 years in Québec found poor agreement between self-report and health records for a list of 17 conditions.[477] Hyperlipidaemia and gastrointestinal diseases had the lowest agreement between the two sources (Kappa 0.05 and 0.11 respectively). One approach which aims to improve the accuracy of self-reports, particularly in people with low health literacy, is a new multimorbidity questionnaire developed in 2017.[223] It asks patients about conditions including clear diagnoses such as diabetes but also groups of symptoms, such as 'musculoskeletal conditions causing pain or limitation'.

I chose the PREVENT Dementia and EPAD datasets for their depth of phenotyping, and complemented them with a population-based study in Chapter 6. A limitation of most multimorbidity studies that use survey data is that they miss the population of younger, more deprived people whose multimorbidity often includes substance use and associated conditions.[39,478] These patients would only have appeared in my NHS dataset if they were aged 50 years or over and engaging with primary care sufficiently to receive prescribed drugs. They would be unlikely to participate in voluntary cohort studies either, so my work has limited generalisability to this group.

7.3.8 Sociocultural homogeneity

The populations studied in this thesis were all from high-income countries in Europe. Multimorbidity is increasing in prevalence worldwide, and in low and middle income countries (LMICs) there is disparity between patients' burden of disease and available treatments.[89] Data from the 2003 World Health Surveys showed that the prevalence of multimorbidity (the co-existence of two chronic diseases from a list of six, including depression and psychotic illness) in people aged over 65 years was 30.2% in Nepal and 27.1% in Georgia.[479] Further work from the same World Health Surveys found increased odds of multimorbidity (≥2 of a possible nine conditions) in people with any depressive episode, with a pooled OR of 3.26 (95% CI 2.98 to 3.57).[480] This was the case in 42 out of the 43 LMICs included and confirms that physical-mental multimorbidity is also prevalent in these countries.

My systematic review included relevant papers from any country, but of 35 original papers, only one came from an LMIC, India.[139] Our search strategy was limited to English language, which may have reinforced this restriction. Within Europe, there are varying figures for estimates of multimorbidity prevalence.[59] In the Survey of Health, Ageing and Retirement in Europe (a study of people aged ≥50 years in 14 European countries and Israel), multimorbidity was defined as the co-existence of ≥2 self-reported conditions from a possible list of 12.[66] This study showed that the prevalence of multimorbidity, adjusted for age and gender, was 26.2% in northern Europe compared to 35.2% in Eastern European countries. This may be due to socioeconomic and cultural differences, for example relating to access to and use of healthcare.

The imbalance in multimorbidity studies in LMICs compared to high-income countries has been recognised before, and is also reflected in the fact that integration of care interventions have only been implemented in high-income countries.[481,482] This is pertinent when LMICs have comparatively little mental health policy and legislation, in addition to their funding being even more limited for mental than physical healthcare.[481,483] Studying only high-income countries could therefore perpetuate the inequalities in research.

7.3.9 Confounding factors

As in other observational studies, confounding is a potential explanation for the results found in my analyses. I adjusted for variables that were clinically relevant, available, and which emerged as statistically significant in preliminary analyses. However, there is likely to be residual confounding.[484] This could be from relevant known factors such as alcohol use and smoking history which were either not available in the NHS data or did not emerge as significant in PREVENT Dementia and EPAD. There could also be unknown confounders. For example, a study on 2 002 individuals from Canada, Albania, Brazil and Colombia explored multimorbidity and depression.[485] The authors found no association between the two, but the incidence of depression varied across study regions, suggesting that geographical factors may play an important role.

Chapter 5 used EPAD data from 12 sites across Europe, where the prevalence of each chronic disease could vary. The variation could relate not only to the aetiology of conditions but also their likelihood of being diagnosed. CSF amyloid positivity may also differ due to environmental factors. In addition, the sites used different recruitment methods, for example from memory clinics or population-based studies.[52] Owing to the varied number of participants between sites, where some had small numbers, I did not adjust for site in my analyses, but this could be seen as a limitation. People with multimorbidity have complex clinical presentations and social circumstances, which were not captured by my methods of quantifying chronic conditions. There may be relevant, more nuanced, factors here that are difficult to measure.

7.3.10 Accounting for pre-existing psychotropic drug use

In Chapters 4 and 6, it was challenging to account for pre-existing psychiatric diagnoses when mental disorders were the outcome of interest. As an attempt to do so, I included antidepressant use as a covariate in relevant analyses in Chapter 4, and any psychotropic drug use in Chapter 6. In Chapter 6, where the sample size was large enough, I additionally conducted sensitivity analyses excluding those patients taking psychotropic drugs. The two main areas of uncertainty are temporality (whether the mental disorder pre-dated the multimorbidity or polypharmacy) and partial treatment (patients or participants taking psychotropic drugs might be expected to have treated or resolved mental disorders).

The main findings of this thesis depend on whether psychotropic drug use was included as a covariate. Any associations found were attenuated when it was, suggesting that these factors (as markers for pre-existing mental disorders) explain the associations found. Previous research has already established that physical multimorbidity is common in people with chronic mental disorders but there is still limited evidence on whether multimorbidity increases the risk of mental disorders.[486] Future work could address this by exploring temporality in more detail.

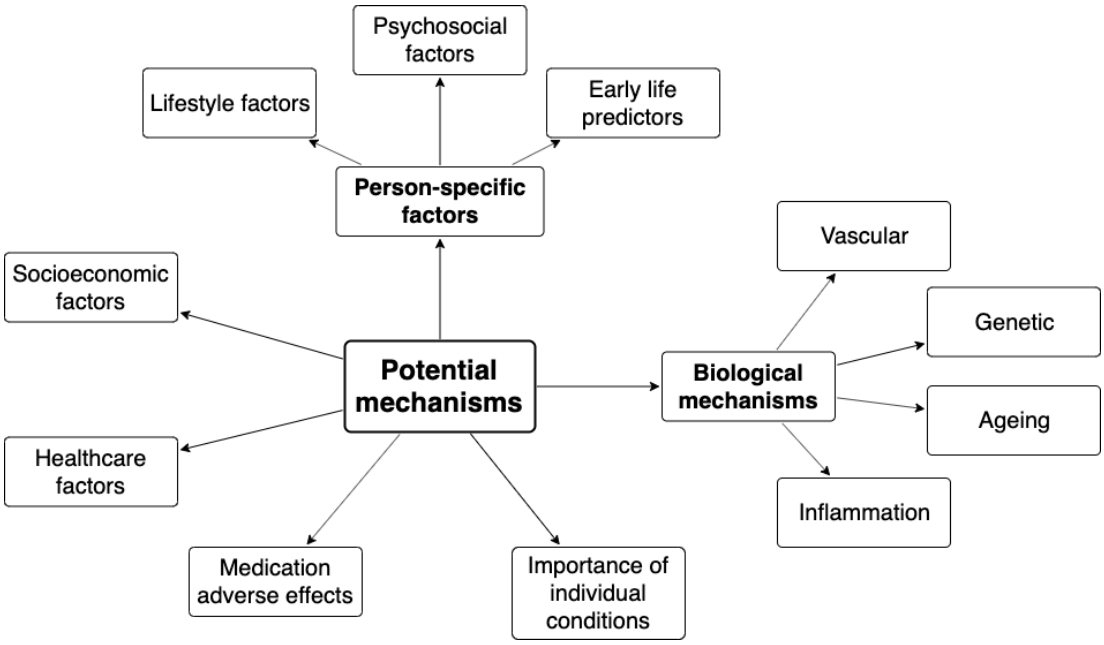
7.3.11 Mind-body dualism

The broad research question of physical conditions as the exposure and mental disorders as outcomes creates a dichotomy between physical and mental health. For example, in Chapter 4, I excluded psychiatric conditions from counts of conditions when depression was the outcome. This separation has been used in clinical medicine for centuries and remains evident in the organisation of most health services. However, humans are embodied beings; this dichotomy has no scientific basis.[487] In addition, multimorbidity in its truest sense includes both physical and mental disorders.[7] By disentangling them and specifying physical multimorbidity in Chapter 4, perhaps I was not studying true multimorbidity. However, only by separating physical and mental illnesses can we understand the links between the two and strengthen the case for integration and parity.[488]

7.4 POTENTIAL MECHANISMS

Interactions between physical multimorbidity and poor mental or brain health may be due to a range of biological, psychological and social mechanisms. There are multiple factors at play and any causality is likely to be bi-directional.[489] Conditions could have common predisposing and perpetuating factors. In clinical practice, the symptoms of physical and mental disorders often overlap. It can be difficult to disentangle their chronology and attribute symptoms to conditions.[490] Longitudinal approaches allow the exploration of whether physical multimorbidity or mental disorders precede the other. Figure 7-1 shows the possible explanatory mechanisms which are explored in this chapter.

Figure 7-1: Spider diagram of potential mechanisms for associations between multimorbidity and mental illness or neurodegeneration



7.4.1 Importance of individual conditions

It may be that individual conditions are more important than overall multimorbidity at influencing mental health. It is known that stroke and myocardial infarction, for example, are commonly followed by depressive episodes [491,492] and that depression commonly co-exists with each of diabetes, hypertension and arthritis.[271] Some physical and mental disorders have risk factors in common, for example hypertension and hypercholesterolaemia being linked with both cardiovascular disease and Alzheimer's dementia.[493]

There is a complex relationship between blood pressure, depression, and cognitive impairment or dementia, the direction of which is uncertain.[494] Hypertension in mid-life is an established risk factor for both vascular and Alzheimer subtypes of dementia.[40] Hypotension, particularly low diastolic blood pressure, in later life may also be associated with increased rates of dementia.[495] Other vascular risk factors, particularly those related to lifestyle, commonly co-exist with depression. Some evidence suggests that depressive symptoms may be a prodromal feature of dementia, with another explanation being that depression and dementia share common aetiology.[496] It is also useful here to examine these interactions across age groups. Changes in blood pressure over time may lead to different trajectories,

particularly of cognitive profile.[497] It is therefore worthwhile considering this risk factor in the overall context of physical health relating to various mental health outcomes. These contributions of specific conditions or risk factors may explain why my broader approach to multimorbidity did not capture convincing associations with mental disorders; perhaps certain conditions are more relevant than overall disease burden.

7.4.2 Early life predictors

This thesis has taken a life-course approach to multimorbidity, including mid-life, ageing and later life samples. There is some evidence to suggest that early life factors are also associated with later multimorbidity. A longitudinal study of children born in Hertfordshire, England between 1931 and 1939 found that, among the 2 299 who survived to follow-up in 2007-8, higher rates of childhood illnesses were associated with multimorbidity (from a list of 11 conditions and free-text) at age 69-76 years.[498] These associations persisted when adjusting for childhood factors including socioeconomic status. A similar study of 10 584 participants of the US Health and Retirement Study also found that poor childhood health was associated with adult multimorbidity, even when adjusted for adult socioeconomic status.[499] The Hertfordshire study captured information from the participants' child health records and found no significant associations with other childhood factors such as birth weight and method of feeding.[498] It did not include adverse childhood experiences. A recent review suggested that the established link between childhood adversity and schizophrenia may be explained by the increased inflammation that appears after childhood adversity; neuroinflammation has been associated with psychosis.[500] Peripheral inflammation is also associated with a number of physical conditions including cardiovascular disease and type II diabetes.[500] Therefore, both physical and mental illnesses could share life-course aetiology whatever the mechanism, and this association warrants further exploration.

7.4.3 Psychosocial explanations

For individual people, there may be psychological or social explanations for the co-existence of their physical multimorbidity and mental illness. For example, someone who is aware of having multiple conditions and the burden of managing them may

identify that this makes them more anxious or depressed.[478,501] Polypharmacy, as a consequence and daily reminder of multimorbidity, can reinforce this phenomenon, and patients may worry about making mistakes with their medication.[502] Furthermore, the symptoms of chronic conditions often include pain and fatigue, which can contribute to low mood and anxiety.[503] Chronic physical conditions can be linked to functional impairment and social isolation;[504] these too are risk factors for anxiety and depression [505] and cognitive impairment.[47] They may also limit patients' ability to seek or access mental health care or treatment when required, or in some cases impede the recognition of depression.[486,506]

Research has been conducted on the relationship between health perceptions and multimorbidity in a Swedish population-based longitudinal study of 2 293 people aged 60 years and over.[507] Health perceptions and life satisfaction were measured using self-report questionnaires, and participants were followed up for a mean of nine years, reporting new diagnoses from a list of 60 possible conditions.[255] Regardless of whether or not participants had multimorbidity at baseline, high life satisfaction and positive health outlook were associated with a lower rate of accumulating conditions.[507] Personality factors may therefore influence people's likelihood of reporting symptoms and their threshold for impacting on daily life. Again, there may be common underlying factors acting as residual confounders, such as early life experience, that lead to low life satisfaction and multimorbidity, but objective research in this area is limited. I discussed these psychosocial issues with my Lay Contributor, as summarised in Chapter 8 (8.3.1, page 311).

7.4.4 Socioeconomic factors

Previous research has found that the prevalence of multimorbidity increases with socioeconomic deprivation.[39,504] A systematic review of 24 cross-sectional studies on this topic confirmed the association, and found that low, compared to high educational attainment was associated with increased odds of multimorbidity (OR=1.64, 95% CI 1.41 to 1.91).[508] Barnett and colleagues' Scottish primary care epidemiology study of all ages found that multimorbidity including both physical and mental illnesses was almost twice as prevalent in the most, versus the least deprived areas (11.0% versus 5.9% respectively).[39] In addition, patients in the most deprived

decile were over twice as likely to have any mental disorder. Socioeconomic status is therefore highly relevant and should always be considered when exploring physical-mental multimorbidity. It is also potentially important in polypharmacy, particularly where patients have to pay for prescriptions. I adjusted for deprivation index in Chapter 6, and used educational level as a covariate in Chapters 4 and 5 as it is both a marker of socioeconomic status and relevant to brain health.[40] In future studies using NHS data, it could be useful to stratify by deprivation decile to explore this issue further.

7.4.5 Lifestyle factors

People with chronic mental disorders may have poorer physical health due to difficulties accessing healthcare, side effects of medication and lifestyle factors such as higher rates of smoking and physical inactivity.[489] These factors may contribute to the life expectancy of people with serious mental illness being 12-13 years shorter at birth than that of those without.[509] Lifestyle factors may also partly explain the relevance of socioeconomic status to the associations between chronic physical and mental conditions. A mediation analysis of 10 693 participants aged 50 years and over across six waves of the English Longitudinal Study of Ageing explored physical health (as measured by the six-item Katz Activities of Daily Living (ADL) score) and mental health (CES-D score) separately as both exposures and outcomes.[510] The authors suggested that there may be both direct and indirect effects of physical health on mental health and vice versa. They found that the indirect effects of past mental health on current physical health included social interactions, lifestyle choices including physical activity and smoking, socioeconomic status and biological factors. However, the relationship between past physical health and current mental health was mediated only by physical activity. This paper studied mediating factors in depth, but is limited by extrapolating functional ability (Katz ADL score) to represent overall physical health and CES-D, a specific depression scale, to general mental health. However, other studies have confirmed this association between physical inactivity and multimorbidity.[511]

A report on multimorbidity from the Global Alliance for Chronic Disease has stated that public health interventions to address lifestyle factors such as diet and exercise

should be prioritised to address multimorbidity.[512] The intervention of the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER) trial included advice on diet, exercise, cognitive training and optimising vascular risk factors.[513] Its primary aim was to prevent cognitive decline but secondary analyses showed a reduction in participants developing new chronic diseases after two years.[514] This suggests that holistic interventions focusing on lifestyle factors could improve both cognitive outcomes and the prevalence of multimorbidity.

7.4.6 Biological mechanisms

7.4.6.1 Vascular mechanisms

The co-existence of physical multimorbidity and mental disorders may be due to common aetiological or predisposing factors. This is clearer in some conditions than others. As introduced in section 7.4.1 on page 286, there is robust evidence that vascular pathology is present in the brains of people with dementia, both of vascular and Alzheimer's subtypes.[343] In addition, according to Alexopolous:

> *"cerebrovascular disease may predispose, precipitate or perpetuate some geriatric depressive syndromes."*[515]

This is known as the vascular hypothesis of depression. Current theories are that this may be due to focal vascular damage and white matter lesions disrupting neural connectivity or causing hypoperfusion and inflammation.[516]

A cross-sectional study within the Irish Longitudinal Study on Ageing examined 2 616 participants' frontal lobe perfusion, orthostatic blood pressure and depressive symptoms according to the eight-item CES-D.[517] Participants with significant depressive symptoms had significantly lower frontal perfusion but this was likely mediated by having lower blood pressure. A systematic review of mortality in late-life depression meta-analysed longitudinal data from nearly 200 000 individuals across 61 studies.[518] Depression was associated with an increased risk of cardiovascular mortality (risk ratio 1.31, 95% CI 1.20 to 1.43) but this was not different from its association with all-cause mortality (risk ratio 1.34, 95% CI 1.27 to 1.42). Like most mental disorders, depression is a multifactorial condition with relevant biological,

psychological and social factors.[290] Its causes and manifestations are heterogeneous and research is underway exploring whether it in fact represents several conditions.[519] In addition to vascular contributions, other mechanisms that may co-exist with physical conditions include monoamine neurotransmitter disturbance and hypothalamic-pituitary-adrenal axis dysregulation.[490]

7.4.6.2 Genetic components

There may be some common genetic aetiology between physical and mental disorders. For example, there are known shared single nucleotide polymorphisms for schizophrenia and cardiovascular disease.[520] This could be applicable to the co-existence of multimorbidity and mental disorders, although there is little research into the genetics of multimorbidity. A 2018 paper aiming to create an atlas of multimorbidity genetics listed disease phenotypes linked by findings from Genome-Wide Association Studies (GWAS).[521] The authors reported the existence of clusters of conditions with related underlying pathology, such as fat metabolism. A limitation of this paper is that the disease traits they included are not compatible with the lists of conditions in clinical multimorbidity research. For example, they included Crohn's disease and colorectal cancer alongside measurements such as muscle strength and body height. It is therefore not applicable to the clinically orientated understanding of multimorbidity. A more relevant study conducted a network analysis of chronic conditions among 1 749 722 people with at least two chronic conditions in Catalonia, using primary care records.[522] Diseases were listed from the clinical chapters of ICD-10. Using the emergent patterns in this network analysis as a guide, the authors then explored genetic associations in a different cohort, identifying that the most common diseases shared 20 associated variants with each other. Smoking was also associated with the conditions in question, which the authors remarked was likely an important causal factor.

A Swedish study examining the associations between subjective cognitive impairment or Cognitive Impairment No Dementia (CIND) and multimorbidity investigated 11 379 twin individuals without dementia.[523] The authors found a stronger relationship between chronic diseases and both types of cognitive impairment when there was multimorbidity. Including familial confounders attenuated the association between

most disease clusters and CIND, suggesting genetic and early life environmental factors are important in this relationship. However, the association between chronic diseases and subjective cognitive impairment was not attenuated by these familial factors. It may be that subjective cognitive impairment is more related to issues at the time of testing, such as mood symptoms, rather than genetic or early life factors.[105] In addition, these findings have some parallels with my results in Chapter 4, that condition and medication counts were more strongly associated with self-reported depression and anxiety disorders than with scores on symptom scales.

Two studies have examined associations between specific psychological traits and genetic predisposition to physical and mental illness in the UK Biobank cohort, even among participants with no physical or mental diagnoses.[524,525] One study of 108 038 participants explored associations between neuroticism and polygenic risk scores from GWAS consortia.[524] The authors reported associations between neuroticism and the polygenic risk scores for coronary artery disease and several mental disorders including major depressive disorder. However, the analysis also showed significant associations with physical risk factors for coronary artery disease, namely body mass index and smoking status. A further study of 112 151 UK Biobank participants revealed an association between scores on specific cognitive tests (verbal-numerical reasoning) with the polygenic risk scores for ischaemic stroke and coronary artery disease, as well as Alzheimer's disease and schizophrenia.[525] There has been no research conducted into associations between each of these psychological traits and multimorbidity. It could be argued that rather than relying on polygenic risk scores, epidemiological research examining these traits in people with extant diagnoses would be just as valuable, although would not elucidate causal factors.

Genomic instability, including defective DNA repair and accumulation of mutations, is a hallmark of ageing.[526] It is also associated with multimorbidity and inflammation.[504] Telomeres are sequences of nucleotides at the end of chromosomes. They protect the genome from damage and are shortened by cell division; short telomeres induce cell senescence.[527] Shorter telomeres are associated with both physical and mental chronic conditions.[528,529] Recent

research explored whether telomere length could be a biomarker for multimorbidity but found it was not clearly related to multimorbidity and was therefore unsuitable.[530] Ageing is also associated with epigenetic alterations, for example changes in DNA methylation, which may play a role in the development of multimorbidity as additional conditions accumulate.[526,531] Overall, there has been a range of genetics research relevant to interactions between physical and mental health, but none has found a convincing genetic signature of multimorbidity. With the increasing interest in epigenetics in relation to brain health, this is likely to become an important area of future study.[532]

7.4.6.3 Ageing and inflammation

The prevalence of both multimorbidity and mental disorders (including dementia and depression) increases with age.[39,59,533–535] This can be understood at a cellular level. Hallmarks of cellular ageing not yet discussed include deregulated nutrient sensing, mitochondrial dysfunction, cellular senescence and stem cell exhaustion.[526] Inflammation increases with age, probably partly due to the accumulation of tissue damage and senescent cells releasing pro-inflammatory cytokines, both of which perpetuate the inflammatory process. Over time, the immune system also becomes less adept at clearing pathogens and dysfunctional host cells.[526] As discussed in section 7.4.2 (page 287), inflammation is implicated in the pathogenesis of type II diabetes, one of the commonest conditions contributing to multimorbidity,[536] and atherosclerosis, a cause of vascular conditions.[537]

The link between inflammation and multimorbidity has been specifically examined in a longitudinal study of 1 018 people aged 60 years and over, with a list of 15 candidate conditions.[538] This study identified that higher baseline levels and steeper increase of the inflammatory cytokine interleukin-6 was associated with an increased rate of developing multimorbidity, adjusted for age, sex and education. The authors also discovered that this link was not associated with individual conditions. Inflammation has established links with schizophrenia, depression and Alzheimer's disease,[539,540] so inflammation could explain the co-existence of physical multimorbidity and mental disorders. It is being investigated as a potential treatment target in depression.[541] Potential aetiological overlap could inform future treatment

and preventative interventions for multimorbidity, both regarding lifestyle factors and pharmacological management.[542]

More clinically apparent age-related changes, such as differing length and depth of sleep, may predispose to or perpetuate mental disorders in older people.[490] Multimorbidity does not appear exclusively in older people, and the majority of people with multimorbidity are aged under 65 years.[39] It may therefore be more representative of biological, rather than chronological age, although its presence in younger adults can display a different combination of diseases, for example including those related to substance use disorders. In summary, as discussed in section 7.2.3 (page 275), my findings suggest that multimorbidity and polypharmacy are more connected with clinical mental disorders than the biological processes linked to dementia.

7.4.7 Healthcare factors

People with one condition are more likely to acquire another by virtue of the fact that they attend healthcare.[20] For example, when consulting a GP about one condition they may have their blood pressure checked and gain a diagnosis of hypertension. This can introduce a form of selection bias, even to population studies.

A systematic review of polypharmacy in multimorbidity found five studies that reported low recognition and suboptimal treatment of depression in people with chronic conditions.[29] Mental disorders in people with multimorbidity may therefore be under-treated. In contrast, there is some evidence that people with multimorbidity experience better overall healthcare than those without,[543] and for example their attendance at healthcare means their vaccine uptake is higher.[544] A systematic review on depression recognition in primary care found that among 13 studies, only four found that higher physical multimorbidity burden reduced rates of depression recognition, two papers found physical multimorbidity increased recognition and the remaining seven were equivocal.[506] The review found that the quality of treatment for depression was not convincingly different between people with and without physical

multimorbidity. Conversely, a systematic review of the literature on the medical care received by people with comorbid mental and substance use disorders found that they had more contacts with physical healthcare services than people with no mental disorders, but that these contacts were of lower quality.[545]

People with more conditions perhaps have more insight into their physical symptoms compared to those with fewer diagnosed conditions who may not have sought healthcare. A patient with well-managed hypertension and COPD, for example, might have better overall health than someone who has symptoms of both conditions but has not been diagnosed; the patient with diagnoses would score higher on a disease count than the one with none. This phenomenon is particularly relevant in studies of volunteers, given that likely participants have been shown to be more health conscious than non-responders.[546] It reduces the generalisability of these results as people with higher disease counts in cohort studies may actually be healthier than non-responders. It seems unlikely to explain the inverse relationship between multimorbidity and amyloid positivity presented in Chapter 5, as this was measured by biomarkers which are not influenced by personality or self-report. However, there has been some research suggesting that personality factors may play an indirect role in the development of clinical dementia, probably through lifestyle and social engagement factors.[547]

There may be a tendency against intervention, for example prescribing, in people with pre-existing multimorbidity and polypharmacy. For example, Soysal and colleagues found that, among 12 148 patients with dementia, those taking ≥10 medications were less likely to be prescribed an acetylcholinesterase inhibitor for dementia symptoms (20.5% of this group) than people on 0-4 (25.8%) or 5-9 (27.5%) medications (P<0.001 for both comparisons).[380] This may reflect clinicians' judgement, tailored to each individual, that people with multimorbidity and polypharmacy are likely to be more frail and gain less benefit from adding another medication. They may also have lower tolerance for medication adverse effects. However, there is evidence that acetylcholinesterase inhibitors are effective at managing cognitive symptoms in people with dementia.[548] This could mean that clinicians do not initiate psychotropic

medication in people with multimorbidity even when it might benefit their mental health.[380]

7.4.7.1 Medication adverse effects

Most people with multimorbidity take multiple medications.[379] As well as the conditions themselves contributing to mental disorders, the medications, both individually and as components of polypharmacy, have psychiatric symptoms as adverse effects.[101] Interactions between medicines may also contribute to this burden, for example causing delirium.[389] In future work it would be ideal to explore each of multimorbidity and polypharmacy while adjusting for the other, to address this issue.[379]

7.5 IMPORTANCE AND RELEVANCE

7.5.1 Contribution to existing evidence

In this thesis, I have explored the latest methodology of measuring multimorbidity and conducted novel analyses of its association with mental and brain health outcomes. My systematic review in Chapter 2 provided an updated overview of all available multimorbidity indices, along with comprehensive critique of their methods and application. This was the first review of its kind since 2012, with an up-to-date search, and I expect will be used by multimorbidity researchers from both epidemiological and clinical backgrounds.[112] I summarised other methods of measuring multimorbidity, and important considerations, in Chapter 3.

In Chapter 4, I corroborated previous findings of associations between the number of conditions and clinical depression, and its less often studied relationship with anxiety disorder, in a deeply phenotyped mid-life cohort. There has been less research on polypharmacy than multimorbidity in relation to mental health, with no existing evidence linking medication use and anxiety. My analyses in this area are therefore novel. In all of these analyses I complemented self-report with symptom scale scores, which is a strength over previous research.

In Chapters 4 and 5, I explored multimorbidity and medication use in relation to biomarkers linked to cognitive impairment and Alzheimer's disease. There is limited existing research in this area, although some studies found associations between multimorbidity and markers of neurodegeneration.[98] My work in Chapter 5 is the first to examine multimorbidity and CSF amyloid. The negative findings in Chapter 4, as well as the robust inverse association between multimorbidity and CSF amyloid, build on other research to suggest that multimorbidity is not linked to known biomarkers for neurodegeneration. They challenge previous hypotheses and may pose new questions about mechanisms. For example, the co-existence of multimorbidity and dementia, which is a multifactorial clinical condition, is likely due to other biological or psychosocial pathways.

Previous population-level research has described cross-sectional associations between physical multimorbidity and mental disorders.[39] My work on NHS Scotland data in Chapter 6 is the largest UK study of polypharmacy to date and the first to consider psychiatric outcomes. I found no convincing associations between increasing medication use and the psychiatric outcomes, although they had limited sensitivity. The fact that psychotropic medication use attenuates associations is important, suggesting that pre-existing psychiatric diagnoses are relevant to any overlap. This could inform the design of future work, aiming to ensure that temporality is considered where possible.

7.5.2 Policy applications

The part of this thesis with the biggest potential impact on policy is likely to be the systematic review of multimorbidity indices in Chapter 2. It will be of practical use when choosing between methods of quantifying multimorbidity or illness burden for a variety of purposes. It has already been consulted in an ongoing re-evaluation of the boundary between general adult and older people's mental health services in NHS Lothian. As well as the direct application of my systematic review, epidemiological research provides context for policy interventions.[549]

7.5.2.1 Public mental health

A 2016 King's Fund report highlighted the importance of integrating physical and mental healthcare for people with multimorbidity, suggesting as its top priority that mental health should be incorporated into public health programmes.[550] In 2018, the Scottish Government published six public health priorities, one of which was *"A Scotland where we have good mental wellbeing".*[551] My finding that multimorbidity is linked to mental health diagnoses and symptoms is relevant to patients. It could be used when disseminating related public mental health information, for example that people with multiple conditions are at risk of depression and should seek medical help early.

Public Health Scotland, the new body sponsored by the Scottish Government and the Convention of Scottish Local Authorities, oversees a national set of adult mental health indicators.[552] The aim is to use them to monitor public mental health, associated risk and protective factors and related inequalities to inform resource allocation. The indicators include 'general health', disability and chronic conditions as contextual factors for mental health and wellbeing. The latest data available for these indicators come from the Scottish Health Surveys, a repeated representative sample of adults living in private households in Scotland.[553] The response rate has been decreasing since the survey's inception, with the 2018 survey including 4 810 adults, with a response rate of 57%.[554] The surveys allow linkage to health records with participant consent, but do not include residents of institutions such as care homes, and the response rate suggests probable selection bias. In contrast, my results from routinely collected data include almost the whole older adult population who use healthcare. My findings could therefore beneficially complement these survey data when monitoring mental health indicators. Using routinely collected data also minimises waste, in line with the former Chief Medical Officer for Scotland's Realistic Medicine agenda.[555]

The findings of no associations between multimorbidity or polypharmacy and biomarkers of neurodegeneration in this thesis are also informative. They add evidence that multimorbidity and polypharmacy are unlikely to be modifiable targets in interventions to prevent dementia.

7.5.2.2 Healthcare integration

Regardless of causality, my cross-sectional results in Chapter 4 showed a co-existence of multimorbidity, polypharmacy and depression. In the NHS data analysed in Chapter 6, the use of psychotropic drugs emerged as important in associations between medication use and mental health outcomes. These findings highlight the fact that physical-mental multimorbidity is common and involves the careful balancing of medication. It has previously been acknowledged that managing co-existing physical and mental illnesses poses particular challenges in healthcare.[556,557] My findings of associations between multimorbidity, polypharmacy and self-reported mental illnesses support previous policies and reports on this topic. For example, the Royal College of General Practitioners has recognised the potential for improved primary mental healthcare for people with multimorbidity.[558] My research could be used to support these calls for healthcare integration, including liaison psychiatry in primary care, where patients with multimorbidity receive most of their care.[559]

7.5.3 Multimorbidity interventions

There are several existing interventions to promote the physical health of people with mental disorders. These often involve training for clinical staff and could be applied in the other direction, for example integrating geriatric medicine and old age psychiatry services [560,561] or increasing mental health nursing input to general practices.[562] *The Lancet Psychiatry* has recently published a Commission emphasising the importance of optimising physical healthcare for people with severe mental illnesses.[563] This also recommends that physical and mental healthcare be integrated, especially in primary care, and suggests multidisciplinary approaches to multimorbidity, particularly in addressing potentially modifiable risk factors common to poor physical and mental health.[481,563]

There has been recent research interest into interventions for physical-mental multimorbidity. For example, a large cluster-randomised trial of the 3D (Dimensions of care, Depression and Drugs) approach to integrated care for multimorbidity compared 797 patients in an intervention group with 749 patients receiving usual care

in GP practices in England and Scotland.[564] The intervention consisted of six-monthly reviews with a nurse, doctor and pharmacist, as well as training and organisational changes at practice level. There was no significant difference in the primary outcome of quality of life scores between groups or a secondary outcome of Hospital Anxiety and Depression Scale (HADS) scores. However, patients in the intervention group rated their care as more patient-centred and reported greater satisfaction with their care.[564]

There have been few trials among people with multimorbidity that have mental health as a primary outcome. The COINCIDE trial featured input from Psychological Wellbeing Practitioners among people with both depression and either diabetes or coronary heart disease and included around 190 participants in each arm.[565] The results showed an improvement in depression scale scores and quality of life and the intervention was found to be cost-effective. The IMPACT randomised controlled trial focused on 1 801 adults with depression in the USA.[566] The intervention was a depression care manager and outcomes were depression and health-related quality of life. The presence of multimorbidity alongside depression did not affect response to the intervention.

There have been trials of several interventions which aimed to identify and limit polypharmacy where appropriate. A 2016 systematic review of interventions by pharmacists found four studies, all of which had a reduction in inappropriate prescribing as their outcome. None specifically referred to mental disorders or dementia.[567] There is some work into improving care for people with dementia that includes both psychological intervention and medication review as part of collaborative care.[568] A broader literature exists exploring methods of reducing prescribing errors in people with multimorbidity.[569] As polypharmacy most often occurs in people with multimorbidity, any interventions improving care for people with multimorbidity usually comprise medication considerations.[570]

7.5.4 Clinical applications

The Academy of Medical Sciences' 2018 report on multimorbidity research asked how mental health conditions might be prevented among those with chronic physical conditions.[7] My results cannot directly answer this question, but may suggest that preventing or managing multimorbidity could promote better mental health. It would seem intuitive that people with multimorbidity could benefit from early detection and treatment of mental illnesses. The 3D trial's intervention included screening for depression and dementia and did not improve overall mental health symptoms.[564] However, the results did not include rates of diagnosis or treatment of these conditions; identifying them could have led to benefits to patients that were not measured in the trial.

Multimorbidity is known to co-exist with dementia but my results cannot confirm that multimorbidity increases the risk of neurodegeneration as measured by biomarkers.[39] It may be more important to gain evidence on what constitutes quality care for people with dementia that acknowledges their comorbidities than to try to aim to reduce dementia incidence by preventing multimorbidity.

Clinical trials have yet to find an intervention that is effective at reducing depressive symptoms in people with multimorbidity or polypharmacy. Therefore, at present, it is perhaps more pertinent to identify that people with multimorbidity are at higher risk of developing mental disorders to allow early diagnosis and support. Epidemiological work, especially from population-based studies such as that presented in Chapter 6, remains valuable in informing this area.

7.5.5 Application to future research

The systematic review in Chapter 2 will have direct relevance to forthcoming studies, both for choosing a measure of multimorbidity to use as an exposure or covariate and when considering designing new indices. The previous major similar reviews have been cited over 400 times each, suggesting they are widely used.[112,113,116] Given

the continued publication of new multimorbidity indices, the review is also likely to be updated in future.

The analyses and results from PREVENT Dementia presented in Chapter 4 provide some information on the co-existence of chronic conditions, polypharmacy and granular depression and anxiety outcomes. The cross-sectional analyses in a small dataset did not permit me to draw firm conclusions, but did allow preliminary explorations to prepare future work, particularly gaining experience with analysing cohort study data.

The inverse association found between multimorbidity and amyloid in the EPAD cohort in Chapter 5 did not provide evidence of a lack of causality. However, it may steer future research into the explanatory mechanisms between multimorbidity and dementia away from the amyloid pathway, if the findings are confirmed on replication in a larger or longitudinal study.

Working with these smaller datasets has carried its own lessons for designing my future research, acknowledging the limited ability to rely upon results with limited statistical power and the understandable difficulty publishing them. These experiences emphasised to me the importance of exploiting the opportunities afforded by large datasets.

The analyses in NHS Scotland routinely collected data confirm the previously reported association between polypharmacy and mortality, in a longitudinal Scottish cohort, for the first time. This will inform future research with a specific focus on Scotland. In the analyses with mental disorders as outcomes, there was no overt association with increasing numbers of medication. The questions the results raised were about the importance of the constituents of polypharmacy. This highlights that future large-scale pharmaco-epidemiological studies should consider including markers for specific drug groups. Assumptions cannot be made about causality or the order of events,

diagnoses or prescriptions, even in longitudinal research, and I aim to address this in future analyses. This issue of temporality is pertinent to all multimorbidity research, especially focusing on physical-mental multimorbidity, as the timing of a specific diagnosis may influence its contribution to an individual's overall disease burden.

If my results were to be included in the evidence review for public health policy changes as mentioned above, any intervention using associations between multimorbidity and depression or other mental disorders should be tested in a research setting first.

7.6 PLANNED FUTURE WORK

This thesis has addressed important research questions but also opened up further topics and avenues for exploration within the same datasets and in others. With the increasing attention on multimorbidity, there have been several consensus statements developed on priorities for research in this area, namely by the James Lind Alliance, Academy of Medical Sciences and The National Institute for Health and Care Excellence (NICE).[89–91] When designing future analyses, I will consult this guidance and a Lay Contributor or Patient and Public Involvement (PPI) group, building on the work presented in Chapter 8.

7.6.1 Further analyses using NHS data

The considerable size of this dataset is a major strength and its breadth will allow several future research questions to be answered. These include:

1. Additional diagnosis data
    a. Adding diagnoses from both general and psychiatric hospital admissions (SMR01 and SMR04) to ask more detailed questions about specific mental health outcomes, such as delirium
    b. Using psychiatric outpatient diagnoses (from SMR00) as outcomes as these are likely to represent clearer clinical assessment and diagnosis than death certificates. For example, dementia diagnoses made in old

age psychiatry clinics should be relatively robust, assuming they are accurately recorded.

2. Interrogating the impact of specific classes of drug on mental health outcomes, or exploring possible rare but important side effects of common drugs, for example:
    a. Anticholinergics
    b. Benzodiazepines
    c. Alpha-blockers
    d. Carbonic anhydrase inhibitors
    e. Anti-convulsants
3. Calculating a weighted index such as the Chronic Disease Score [148] or Medication-based Disease Burden Index [147] to infer multimorbidity burden from medication data
4. Tracking the effects on mortality or mental health outcomes of changes in medication use over time, for example the addition of specific medication, using multi-level modelling
5. Using clustering or dendrogram techniques to explore the outcomes relating to different combinations of drugs.

In the longitudinal analyses in Chapter 6, I took the exposure variable and covariates from baseline only. While most of the demographic covariates used (gender, deprivation) are unlikely to change over time, patients probably moved between groups in the others (care home residence and psychotropic medication use). Therefore, using time-varying covariates would be an improvement for future work.

An approach to addressing causation (as discussed in section 7.3.2) would be to use target trial emulation, a technique for scrutinising observational data in respect to a specific treatment.[471,571] This entails setting eligibility criteria and including the participants who meet them, then matching those who received a specific treatment with those who did not and comparing their outcomes. The matching can be undertaken using propensity scores.[572] However, the quality of outcome and covariate data in the NHS dataset, for example the lack of cognitive test scores and information on ethnic group, would limit the value of these results.

The datasets held by ISD Scotland do not currently capture primary care medical records, but collecting data at GP practice level is being piloted in the Scottish Primary Care Information Resource (SPIRE), with rollout ongoing.[573] This will generate reports for practices on levels of multimorbidity in their patients but will also be open to applications from researchers for anonymised data.[574] When its database has grown, this could be a potential source of more detailed population-level data on chronic conditions to complement my polypharmacy analyses.

7.6.2 PREVENT Dementia

My analyses were of the pilot phase of PREVENT Dementia, including 210 participants at one site. Cross-sectional data for 700 participants across five sites will become available soon, which would allow replication of my analyses this larger cohort. This will address the main limitation of a small sample size. Data from follow-up visits will also permit longitudinal analyses, for example to investigate whether changes in the number of conditions or medications are associated with changes in scores on CES-D. Given that the pilot phase contains mid-life participants, changes during ageing are of particular note.

7.6.3 EPAD

I analysed the first 500 EPAD participants; initial data from 1 500 participants has recently been released and two-year follow-up of the original ones will soon follow.[475] I plan to replicate my analyses both in the larger cohort and on follow-up. As highlighted by a peer reviewer of the paper presented in Chapter 5, the observed inverse association between multimorbidity and amyloid positivity may disappear as these participants age. Longitudinal data will also allow analysis of multimorbidity as a dynamic, rather than static, concept, as recommended by a consensus of multimorbidity experts.[114] Another strength of future research using this dataset would be the addition of cognitive function outcomes, allowing complementary analysis of both biomarker status and clinical phenotype.

7.6.4 Additional analyses in UK Biobank

UK Biobank is an ongoing prospective cohort study of over 500 000 volunteers in Great Britain. The participants give detailed medical histories and undergo numerous biometric measurements.[575] Multimorbidity research within UK Biobank is already taking place, for example regarding its prevalence, clusters and associations with medication adverse events.[254,278] Physical-mental multimorbidity has been explored in UK Biobank in specific, rather than general, contexts, such as chronic pain, depression and bipolar affective disorder.[576] Existing research has used computational techniques to identify interactions between depression and specific diseases (all by self-report).[577] These approaches need to include pragmatic clinical oversight, for example identifying that there are apparent comorbidities between depression and other psychiatric disorders, whereas these may represent aspects of the same underlying diagnosis. Potential future areas of multimorbidity research in UK Biobank would be to examine clustering of conditions and whether participants move between them. This would fit with the Academy of Medical Sciences' stance on multimorbidity which emphasises that it is not the co-existence of a discordant collection of conditions, but that there are meaningful clusters.[7] Repeated medical histories and linkage to medical records would allow multimorbidity to be treated as dynamic in this cohort. Its large size, both in terms of number of participants and data items collected, would mean that analyses where participants could move between clusters may require the adoption of machine learning techniques, a newer approach to large-scale data analysis.[578]

7.6.5 Multimorbidity measurement

In my systematic review in Chapter 2, I found and summarised 35 multimorbidity indices. With the publication of this paper, I hope to provide guidance for other researchers choosing how to measure multimorbidity. One limitation of my work was that I did not compare the predictive ability of indices with each other. There has been one systematic review that aimed do this, with a search in March 2011 and restricted to those that included either the Charlson or Elixhauser indices in the comparison.[233] There is scope to update this review, with more specific search terms but broader inclusion criteria, and compare the indices in a suitable dataset.

7.6.6 Alternative directions

This thesis has laid the foundations for future epidemiological work but may also inform research using alternative methods, such as trials of interventions for identifying and improving mental health symptoms in people with multimorbidity. The results are also informative to dementia trials, both those of drugs and of preventative interventions, suggesting that multimorbidity should be included as a covariate.

7.7 CONCLUSIONS

Multimorbidity is a multi-faceted and multi-factorial clinical state. It often includes both physical and mental illness. There are numerous difficulties to face when attempting to measure it and in designing clinically relevant research that addresses unanswered questions. These challenges include the specific measurement of multimorbidity itself and attention to the dataset's design and size. My research corroborated previous evidence of associations between physical multimorbidity and clinically relevant mental illness diagnoses and symptoms. There was no positive relationship between multimorbidity and biomarkers of Alzheimer's disease risk in cross-sectional analyses. Population-level data did not support the hypothesis that polypharmacy, accounting for psychotropic drug use, would be associated with psychiatric outcomes. Accounting for pre-existing mental disorders was a methodological challenge in these analyses. My overall findings pose further questions, such as the importance of the order of conditions' development, and will inform future research.

> *"All scientific work is incomplete – whether it be observational or experimental. All scientific work is liable to be upset or modified by advancing knowledge. That does not confer upon us a freedom to ignore the knowledge we already have, or to postpone the action that it appears to demand at a given time."*
>
> Sir Austin Bradford Hill, 1965 [470]

Chapter 8 A patient's perspective on living with multiple chronic conditions: reflections on involving a lay contributor in this PhD

8.1 BACKGROUND

Patient and public involvement (PPI) is increasingly recognised as important for improving the quality of research and its relevance to patients.[579] Many large trials now involve lay representatives, but there is less emphasis on PPI for researchers with smaller projects. I enjoyed presenting my proposal for the work presented in Chapter 6 to the Farr Institute Scotland Public Panel, both in making the material accessible to a lay audience and having the opportunity to discuss it. I was struck that the participants identified limitations I had not considered, for example noting that continuous positive airways pressure (CPAP) machines, a sign that a patient has a serious chronic condition, would not be included in prescribing records. They approached my research questions from a different angle, without the preconceptions that often accompany a clinical or research background.

I have been supported throughout this PhD by charitable and public funding and analysed routinely collected NHS data. It therefore seemed appropriate to consult a member of the public with personal experience of the conditions I was researching. I aimed to involve a lay contributor in my PhD to relate my epidemiological findings to the context of an individual person living with multimorbidity.

8.2 METHODS

8.2.1 Planning and preparation

The Alzheimer's Society and other major charitable research funders have been promoting PPI for over 20 years.[580] They require evidence of PPI in grant and PhD fellowship applications, and the diversity of PPI research projects is expanding. When starting to plan this collaboration, I conducted an online search and found no evidence of other students recruiting patients to be involved for the duration of their PhD.

I therefore met the University of Edinburgh's PPI Adviser and together we designed a proposal. I initially wrote a short description of my research and the lay involvement I envisaged. I found potential contributors through a local ageing research network; ethical approval was not required. I approached Mrs Mary Nisbet, who agreed to be involved.[21] In her initial response, she said she had:

> *"no degrees or special qualifications, just the experience of everything that has come my way over the last 80 years".*

She has several chronic conditions and takes multiple medications. At our preliminary meeting, we discussed her role together and she suggested the title of Lay Contributor.

8.2.2 Meetings

Mary agreed to meet me for about two hours approximately every two months for the remainder of my PhD, in a café that was convenient to her (see Figure 8-1). At most of our meetings, I summarised my recent work and results and Mary offered feedback including possible explanations and application to her daily life. I prepared relevant discussion questions not only on my research but also on recent multimorbidity publications or other topical issues. Mary gave her perspectives from her own experience both as a patient and as a carer to her two late husbands. She offered specific insights into my systematic review (Chapter 2) that I incorporated into the manuscript, and helped prepare a lay summary of it.

[21] Mrs Nisbet has given written consent to be named, for details of our discussions to be summarised, and for her photograph to be used. She has a copy of the original submission of this chapter and has approved its contents.

Figure 8-1: Discussing topical issues around multimorbidity and healthcare, September 2018

8.3 RESULTS

8.3.1 Perspectives on multimorbidity and polypharmacy

We discussed the difficulties of defining multimorbidity; that counting conditions does not reflect each one's severity or contribution to a person's overall health and daily independence. Mary used the phrase *"old age doesn't come alone"*, meaning that as she has aged, several health problems have occurred simultaneously and one seemed to lead to another. She pointed out that people with an existing health condition are more likely to visit their GP and perhaps consequently attract more diagnoses. I elaborated on this idea in section 7.4.7 and explained during our discussions that epidemiology is in general limited to observing population outcomes rather than individual behaviour.

Mobility and memory were two key areas that Mary mentioned were concerns for her and her peers. These are reflected in an ethnographic study of people with multiple conditions, highlighting the fact that symptoms or independence can be more important to individuals than firm clinical diagnoses.[501] This report also identified that the biggest impact for a patient is not the number of conditions they have, but how they are supported and cared for. This moderates the impact of having

multimorbidity. As well as promoting mobility, the report recommends that patients be encouraged to take an active role in their care and to identify achievable goals. I described the dementia prevention studies analysed in this thesis and that their aims were to identify modifiable causes of cognitive decline to prevent it occurring. Mobility was not included in my work but I appreciated its importance and links with functioning and independence.

Mary observed that when defining conditions as chronic, this can negate important illnesses that are considered to be resolved or acute. For example, cancer that has been treated and is in remission might be a source of worry for patients, and a major life event for older people, such as a hip fracture requiring surgical repair, would not be counted in many multimorbidity measures. We also discussed the limitations of observational studies and epidemiology. Mary thought my findings from large-scale data analysis would be less applicable to GPs, as their clinical decisions had to account for all the factors relating to the individual patient in front of them. My response was that looking at patterns in data from large numbers of people helped inform guidelines under which individuals would be treated.

The term ‘multimorbidity’ did not appeal to Mary; she said she associated ‘morbid’ with death and that it sounded bleak. This is in keeping with a 2018 commentary written by a multimorbidity researcher who highlighted patients’ discomfort with the term. He and his PPI group advised either avoiding the term or reserving its use for communicating with clinicians or researchers.[21] As outlined in section 1.2.3, I chose to use the term multimorbidity in this thesis as a technical shorthand but was careful not to conflate it with chronic condition count. I also avoid using it in lay communications where possible.

Mary said that taking multiple medications made her feel she *“didn’t have long left”.* When discussing my investigations into polypharmacy and mental health, she suggested a causative explanation – that people might feel depressed or disheartened by the notion of needing to take numerous medicines as it implies

"you're serious". She also raised the possibility that people worry about the medications themselves, and whether they *"mix"*. I explained the self-report symptom scales CES-D and STAI and that these capture individuals' experience of mental health symptoms but not their explanations for or understanding of them.

8.3.2 Attitudes and communication

Our discussions often turned to the difference in attitudes to health and fitness among Mary's peers. For example, she believes that staying active is the best way to avoid physical decline and *"getting stuck in your armchair"*. Despite feeling tired, she practises yoga, walks uphill most days and swims once a week. She tries to encourage her friends to do the same but some say, *"I can't"*. She also reflected on a family member who had frequently complained about her health, whether or not she seemed to be ill. Relating these issues to specific aspects of my research, we agreed that personality and experiences significantly affect people's perceptions of illness burden. This could influence their responses to self-report surveys (both when reporting diseases and answering symptom scales) and their approaches to engaging with medical care.

Qualitative research has explored perceptions of living with multimorbidity, both from patients' and doctors' perspectives. A meta-synthesis of studies on this topic found that both patients and doctors had feelings of vulnerability and uncertainty when managing multiple chronic conditions, but that there was little evidence that parties discussed these shared challenges.[581] There is research interest in interventions to improve patients' involvement in decision-making about their care. A 2019 Cochrane review of trials of these interventions found three studies with a cumulative total of 1 879 participants.[582] The interventions included coaching, workshops and goal-focused nurse reviews aiming to empower patients to express what was important to them at healthcare appointments. The systematic review concluded that specific interventions may help patients receive care tailored to their own priorities, but it found limited evidence on other outcomes and suggested that more attention was needed to this topic.

Communication was another recurring topic of our PPI discussions. Mary values healthcare professionals being clear and honest, and prefers direct contact such as receiving copies of relevant letters. She loses faith in doctors when she hears different advice from specialists and her GP, and said, *"you wonder who's wrong"*. She believes that NHS care could be better integrated. I drew on my clinical experience to share practical limitations, for example that in our area, GPs and hospitals have different computer systems. I suggested that teams being able to access each other's health records more easily could improve continuity of care.

8.3.3 Priorities for research

The James Lind Alliance is an organisation that aims to bring patients and clinicians together to identify priorities for research.[583] During our collaboration, they held an online survey for their Priority Setting Partnership for Multiple Conditions in Later Life. Mary and I both participated in the survey and discussed this process. The partnership published its top ten priorities for research in May 2018, as shown in Box 8-8-1.[90] The Academy of Medical Sciences and National Institute for Health and Care Excellence (NICE) have also published research priorities for multimorbidity.[7,91] A recent publication summarising the James Lind Alliance findings compares the three sets of recommendations according to categories.[584] Each of the organisations has a different background and priorities. Mary and I read this overview paper together and reflected that the psychosocial category contained only James Lind Alliance recommendations and that NICE was interested in life expectancy as well as clinical care issues.[91] Mortality was not mentioned in the James Lind Alliance recommendations. Mary assigns more importance to quality of life than predicting death, and this is reflected in the more patient-focused nature of the James Lind Alliance's work.

Box 8-8-1: Top Ten priorities for research from the James Lind Alliance Priority Setting Partnership for Multiple Conditions in Later Life [90]

1. How can current health, social care and voluntary sectors in the UK be optimised to more effectively meet the needs of older people living with multiple conditions?
2. What are the most effective, cost effective and acceptable ways to reduce social isolation in older people with multiple conditions?
3. What are the most effective, cost effective and acceptable strategies for the prevention of multiple conditions in later life?
4. In what ways can carers of older people with multiple conditions be supported to maintain their own physical and psychological wellbeing?
5. What is the most effective, cost effective and acceptable form of exercise therapy in different health and social care settings with older people with multiple conditions? How does exercise therapy affect outcomes in this population?
6. How can the recognition and management of frailty be improved in older people with multiple conditions? Would this lead to an increase in perceived quality of life?
7. How can Comprehensive Geriatric Assessment be optimally delivered in different patient populations experiencing multiple conditions in older age?
8. What are the most effective, cost effective and acceptable interventions to improve the psychological wellbeing of older people with multiple conditions?
9. How can independent living be most effectively and acceptably enabled in older people with multiple conditions in the UK?
10. How do older people with multiple conditions perceive and manage their risk of falls? How can fear of falling be effectively addressed?

8.3.4 PPI in other PhDs

Since my collaboration with Mary began, other examples of PPI in PhDs have emerged. For example, a 'patient buddy' system has been established for non-clinical PhD students in rheumatoid arthritis research at the University of Birmingham.[585] Basic science dementia researchers, including PhD students, at the University of Edinburgh have met people with dementia and their carers for tours of the laboratories

and to share experiences.[586] A PhD student at Keele University studied self-harm in older adults in a project designed with patient input from the outset.[587] Three PPI participants met for four workshops to discuss plans for a systematic review and qualitative study. This approach was more formal and thorough than mine, but having a single contributor for the duration of my PhD had its own advantages, in that I was able to develop a working relationship with Mary and she felt personally invested in my work.

A researcher from the University of Bristol included two PPI contributors throughout her PhD, the topic of which was lay people's attitudes to PPI in research.[588] A 2019 paper from researchers at the University of Bradford outlined diverse PPI methods within four doctoral research projects, with most recruiting groups of participants and one using online engagement.[589] A paper published in 2020 by two researchers at the University of Manchester described their experiences of incorporating PPI into their doctoral research.[590] One of these included involving two 'research buddies' throughout the duration of the project. The paper also highlighted that although PPI in PhD projects does take place, it is rarely reported in the literature. It provides recommendations for PPI at various stages of the PhD process. These recent developments suggest an increasing interest and use of PPI in doctoral research, even since the beginning of my PhD.

8.4 LIMITATIONS AND CHALLENGES

Patients and lay representatives should ideally be involved from the start of a research project. I was unaware that this was possible when preparing my PhD proposal. However, when I did hear about opportunities for PPI, I designed the role at the beginning of the second year of my PhD. This has motivated me to involve patients early in future research planning.

As there was no evidence of best practice for involving a lay contributor in a PhD, I had to consult generic PPI guidance and develop my own style and plan for meetings. Mary and I had a relatively informal style for our meetings. This suited our one-to-one

approach and my aim to hear Mary's general views and experiences, but a more structured meeting with an agenda could be more tangibly productive, particularly in a group of PPI participants.

A limitation of PPI is that the views of the contributor do not represent those of all patients. However, this is not qualitative research, rather the aim is to include the perspectives of one patient, acknowledging that they, like all other patients, bring their own history and complex background.

8.5 REFLECTIONS AND CONCLUSION

Mary reported enjoying her involvement in research. Although she sometimes found it difficult to see the overall goal of her contribution, she was pleased that a researcher was interested in a patient's experience, and felt she was doing something worthwhile to repay many years of healthcare she has received.

It was not expensive or difficult to involve Mary in my work; she volunteered her time and costs were limited to refreshments and a round trip in a taxi to meet my supervisors. I have valued Mary's input. I was able to see my research through the eyes of a potential study participant and possible future beneficiary. She has helped me clarify my research findings as I prepared to explain them to her. This was useful not only for consolidating my ideas but in planning for future public engagement. Perhaps most importantly, she has reminded me that research is only clinically meaningful when applied to an individual, with all the complexities they bring.

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Appendix 1: Center for Epidemiologic Studies Depression Scale

Radloff 1977 [300][22]

The following items refer to how you felt last week
Scores: Rarely or none of the time (<1 day) = 0
Some or a little of the time (1-2 days) = 1
Occasionally (3-4 days) = 2
Most of the time (5-7 days) = 3

I was bothered by things that don't usually bother me	
I did not feel like eating; my appetite was poor	
I felt that I could not shake off the blues even with the help of my family or friends	
I felt that I was just as good as other people	Scoring inverted
I had trouble keeping my mind on what I was doing	
I felt depressed	
I felt everything I did was an effort	
I felt hopeful about the future	Scoring inverted
I thought my life had been a failure	
I felt fearful	
My sleep was restless	
I was happy	Scoring inverted
I talked less than usual	
I felt lonely	
People were unfriendly	
I enjoyed life	Scoring inverted
I had crying spells	
I felt sad	
I felt that people disliked me	
I could not get "going"	

[22] Adapted with wording as written in PREVENT case report form. Permission granted by SAGE Publications for gratis reuse in doctoral thesis, 27 July 2018.

Appendix 2: Paper published in *Journal of Comorbidity*

Article

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Associations between midlife chronic conditions and medication use with anxiety and depression: A cross-sectional analysis of the PREVENT Dementia study

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Abstract

Background: Multimorbidity including physical and mental illness is increasing in prevalence. We aimed to investigate the associations between physical conditions and medication use with anxiety and depression in midlife.

Methods: We conducted an observational cross-sectional study of volunteers in the PREVENT Dementia study. Using logistic and linear regression, we investigated the association between increasing numbers of self-reported chronic physical conditions and medications with self-reported depression and anxiety disorder, and scores on the Center for Epidemiologic Studies Depression (CES-D) scale and Spielberger State-Trait Anxiety Inventory (STAI) state subtest.

Results: Of the 210 participants, 148 (71%) were women and 188 (90%) Caucasian. The mean age was 52 (standard deviation (SD) 5.5) years. The mean number of physical conditions was 2.2 (SD 1.9) and medications 1.7 (SD 2.2). Each additional physical condition was associated with increased odds of self-reported depression (odds ratio (OR) 1.41, 95% confidence interval (CI) 1.11 1.80; p 0.004, adjusted for age and gender) and anxiety disorder (OR 1.70, 95% CI 1.30 2.37; $p < 0.001$). Increasing medication use was associated with self-reported depression (adjusted OR per additional medication 1.35, 95% CI 1.08 1.71; p 0.008) but not anxiety disorder. For each additional condition, CES-D scores increased by 0.72 (95% CI 0.11 1.33; p 0.020) and for each extra medication, by 0.88 (95% CI 0.32 1.44; p 0.002). There was no significant association between increasing conditions and medications with STAI scores. In models accounting for antidepressant use, all associations were attenuated.

Conclusions: Having more physical conditions is associated with anxiety and depression in midlife, and taking more medications is associated with depression but not anxiety.

Keywords
Multimorbidity, polypharmacy, depression, middle-aged, anxiety disorders

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Introduction

Multimorbidity (the coexistence of multiple chronic dis eases) and polypharmacy (taking many different medica tions) are complex areas attracting increasing research and policy attention.[1] Although often linked with older age, multimorbidity and polypharmacy are becoming more pre valent in midlife.[2,3] Existing research shows that multimor bidity including both physical and mental illness is common and associations between physical and mental health are likely to be bidirectional.[2,4]

The evidence regarding the interplay between multimor bidity and depression or anxiety in midlife is limited. For example, regarding depression, a recent systematic review revealed that adults with multimorbidity had a three times greater risk of depression than people with no chronic phys ical conditions.[5] However, only one of the 40 studies included in that review investigated a midlife cohort (aged 45 64 years), with 26 studies on older people and 13 on adults of all ages, reflecting the fact that research on multi morbidity and polypharmacy tends to focus on older age groups.[6] With regard to anxiety, cross sectional studies have shown that multimorbidity and anxiety coexist.[7,8] There is some evidence that increasing numbers of medication are associated with more depressive symptoms, but this area is less well understood.[9] Furthermore, there is little research into associations between polypharmacy and anxiety.

Midlife cohorts are increasingly studied in relation to the early manifestations of neurodegenerative diseases that may later lead to dementia. Identifying risk disease inter actions may contribute to reducing incidence via risk mod ification strategies.[10] Depression and anxiety in midlife have been identified as risk factors for dementia,[11,12] although the direction of the association remains uncer tain.[13] Therefore, understanding the interplay between mul timorbidity and polypharmacy with depression and anxiety is crucial, given the fact that all four have been associated with poor brain health and dementia.

PREVENT Dementia is an ongoing cohort study designed to investigate midlife risk factors for neurodegen erative diseases.[14] It offers opportunities to explore the associations between multimorbidity, polypharmacy, depression and anxiety in midlife and to allow better under standing both of this age group and of future brain health.

Objective

We aimed to investigate whether increasing numbers of chronic conditions and medications were associated with depression and anxiety in this cross sectional midlife cohort.

Methods

Participants

This is an observational cross sectional study of a conve nience sample of volunteers in the first phase of PREVENT Dementia (a dementia prevention study) in London, UK. Volunteers were eligible to participate in PREVENT Dementia if they were aged 40 59 years at baseline and were fluent in English. Potential participants who reported having cognitive impairment or dementia were excluded, as were those with known contraindication to magnetic resonance imaging (MRI). Recruitment took place through a local database (DemReg),[15] the UK wide Join Dementia Research database (JDR),[16] via publicity online and at pub lic presentations. The DemReg and JDR databases are both open to anyone aged 18 years and over who consent to be contacted about research. Recruitment to DemReg was facilitated via memory clinics, meaning those in the age group of interest for this study were likely attending the clinic as a family member of a patient. JDR is an online database and, therefore, is available to anyone with Inter net access. These databases were selected as the major recruitment tools for the study as they contained contact details of volunteers meeting inclusion criteria who were motivated to participate in research studies. The study team aimed to recruit half of the participants with a family history of dementia and half without. All participants gave written informed consent and approval for the study was given by the NHS Research Ethics Committee, Camber well St Giles. Participants underwent in depth physical and cognitive testing, comprehensive medical, lifestyle and mental health questionnaires, brain MRI and fMRI and provided neurodegenerative disease biomarkers.[17] The study protocol is published in detail elsewhere, including justification of the predefined minimum sample size of 150 participants.[14]

Depression measures

Depressive symptoms were measured using the Center for Epidemiologic Studies Depression (CES D) scale.[18] The CES D is a validated self administered scale containing 20 questions about depressive symptoms and scored out of 60. The questions cover mood, cognitive and somatic symptoms of depressive disorder, and participants rate how often they have experienced them in the past week (0 *less than 1 day*, 1 *1 2 days*, 2 *3 4 days* and 3 *5 7 days*). Although a cut off of $\geq$16 is generally used to identify people with depression, the participant's rating for each item measures frequency of each reported symptom, so any increase may be of clinical interest.[19] In addition, even low levels of psychological distress have been associated with negative outcomes including mortality.[20] We anticipated that only a small proportion of this cohort of volunteers would be classified as depressed so chose to analyse raw scores as a pseudo continuous variable. Participants' self report of an active, current diagnosis of depression came from the medical history, which was taken at interview by a qualified doctor.

Anxiety measures

Anxiety symptoms were measured using the Spielberger State and Trait Anxiety Inventory (STAI) state subtest.[21] It consists of 20 questions on symptoms of anxiety, scored from one to four based on participants' reported severity (*not at all*, *somewhat*, *moderately so* and *very much so*) resulting in a score between 20 and 80. A cut off of $\geq$40 for clinically significant anxiety is frequently used, although higher cut offs have been shown to have higher accuracy at detecting clinical anxiety disorders in older people.[22] As the STAI was originally designed as a contin uous scale and we were interested in symptoms, we again used the overall score as a pseudo continuous variable. Participants' self report of current anxiety disorder was taken from the medical history.

Chronic conditions

The PREVENT Dementia case report medical history includes a list of medical conditions. Participants were asked whether they had ever had each condition and whether it was currently active. They also had the oppor tunity to report other conditions, which were recorded as free text by the interviewing doctor. We reviewed all poten tial conditions and defined them as chronic if they were likely to be present for at least six months, have an impact on quality of life and have a pattern of recurrence or dete rioration. This definition was based on a combination of definitions from the International Classification of Primary Care, version 2 and from the NHS National Services Scot land Information Services Division.[23,24] Depending on the nature of each condition, some were included if they had ever been diagnosed and others only if they were active. We excluded psychiatric disorders due to their overlap with our outcomes. This left 55 possible chronic physical con ditions, which are listed, with their duration definitions, in Appendix 1. Multimorbidity is commonly defined as the coexistence of two or more conditions and many studies use dichotomous variables (e.g. 0 1 versus 2 conditions). However, this approach does not capture the full distribu tion of conditions, particularly at the higher extremes.[25] We, therefore, used continuous counts of conditions as exposure variables for analyses.

Medication history

At the research interview, study doctors collected informa tion on current medication use according to participant self report. This included drug name, dose, frequency and indication. The reported medications were then coded according to the World Health Organization's (WHO) Ana tomical Therapeutic Chemical (ATC) classification sys tem.[26] Over the counter vitamins or health supplements were excluded, as were entries with insufficient informa tion to generate an ATC code. Due to the likely effect of antidepressant use on both depression and anxiety out comes, we excluded antidepressants from the total count of medications. We aimed to account for anxiolytic medi cations but included them in the overall count. We used this adjusted medication count as an exposure variable in regression models.

Additional variables

Participants reported their age and gender, which we included in all regression models as these are clinically relevant factors influencing depression and anxiety symp toms. Use of antidepressants was both clinically relevant and statistically significant in preparatory analyses. Con sidering that antidepressants are used for several indica tions, we reviewed the free text records on medication indication and generated a variable for antidepressant use for any psychiatric indication. We included this variable in a separate adjusted model and tested for interaction effects between chronic conditions and antidepressant use. We conducted sensitivity analyses in a sample excluding parti cipants who took antidepressants for psychiatric indica tions. We also created a variable for using ATC coded anxiolytic medications.

Statistical analysis

All analyses were run in R version 3.4.3.[27] We used Stu dent's *t* test to compare the mean age, chronic conditions and medications between people with and without self reported depression and anxiety disorder. Linear regres sion models were used for the continuous outcome variables (CES D and STAI scores) and logistic regres sion for binary outcomes, namely, the presence of self reported depression and anxiety disorder. Owing to the disproportionate gender split, we performed additional analyses stratified by gender.

Results

Description of the sample

The sample, from the pilot phase of PREVENT Dementia in London, UK, consisted of 210 individuals, 148 (70.5%) of whom were women. The mean age was 52.0 (SD 5.5) years and median 53 years. Self reported race was Cauca sian for 89.5% of participants with the next largest groups being Black (*n* 7, 3.3%) and Indian subcontinent (*n* 7, 3.3%). Almost half (103, 49.0%) of the participants had a first degree relative with dementia; 10 (4.8%) were current smokers, 80 (38.1%) were ex smokers and 120 (57.1%) had never smoked. The mean weekly alcohol intake was 11.5 units (SD 12.4), and the mean body mass index was 27.7 kg/m^2 (SD 5.3). The principal demographic details are listed in Table 1. The mean number of chronic physical conditions was 2.2 (SD 1.9), with a range of 0 9. The mean number of medications reported was 1.7 (SD 2.2)

Table 1. Sample characteristics in whole sample ($n = 210$).

Variable	*n* (%)	Mean (SD)
Gender (female)	148 (70.5)	
Race (Caucasian)	188 (89.5)	
Current depression (self-report)	16 (7.6)	
Current anxiety disorder (self-report)	21 (10.0)	
Taking antidepressant for any indication	26 (12.4)	
Taking anxiolytic medication	1 (0.5)	
Age (years)		52.0 (5.5)
Education (years)		15.9 (3.4)
CES-D Total (possible range 0 60)		9.2 (8.2)
STAI Total (possible range 20 80)		30.4 (9.4)
Number of chronic physical conditions		2.2 (1.9)
Number of current medications including antidepressants		1.7 (2.2)
Number of current medications excluding antidepressants		1.5 (2.0)

SD: standard deviation; CES-D: Center for Epidemiologic Studies Depression; STAI: State-Trait Anxiety Inventory.

Table 2. Characteristics of participants reporting depression or anxiety disorder.

	No depression	Self-reported depression	*p* for difference (Student's *t*-test)	No anxiety disorder	Self-reported anxiety disorder	*p* for difference (Student's *t*-test)
Mean age in years (SD)	52.0 (5.4)	51.3 (6.3)	0.642	52.0 (5.4)	51.4 (6.3)	0.656
Mean number of chronic physical conditions (SD)	2.1 (1.8)	3.6 (2.5)	0.025	2.0 (1.6)	4.2 (2.4)	<0.001
Mean number of medications taken (excluding antidepressants) (SD)	1.4 (1.8)	2.7 (3.2)	0.140	1.4 (1.9)	2.2 (2.5)	0.174

SD: standard deviation; CES-D: Center for Epidemiologic Studies Depression; STAI: State-Trait Anxiety Inventory.

and range 0 12. After excluding antidepressants, the mean number of medications was 1.5 (SD 2.0). Only one participant (0.5%) was taking an anxiolytic medica tion so due to low prevalence, this variable was not included in further analyses. Appendix 1 lists all the included conditions with their prevalence in this sample. There were no missing data for any of the variables included.

For participants with at least one chronic condition, the mean number of medications per condition was 0.7 (SD 0.9). Among all participants, 119 (56.7%) had two or more conditions and 48 (22.9%) people took three or more med ications (39 (18.6%) excluding antidepressants). There was a statistically significant difference between the mean number of chronic physical conditions among people with and without self reported depression (μ_1 3.6, μ_2 2.1; p 0.025) but not number of medications or age (Table 2). For people with and without self reported anxiety disor der, there was a difference in the mean number of chronic conditions (μ_1 4.2, μ_2 2.0; $p < 0.001$) but not the number of medications or age. Figure 1 shows box plots of these distributions.

We found that 26 (12.4%) participants were taking anti depressants, of whom 18 (8.6%) were doing so for psychia tric indications. Within this group, 13 (72.2%) participants reported a diagnosis of depression and 12 (66.7%) reported anxiety disorder. We tested for interaction effects between chronic conditions and antidepressant use and found no statistically significant interaction. Table 3 presents the characteristics of participants according to their antidepres sant status; there was a significantly higher rate of self reported depression and anxiety disorder among those taking antidepressants for a psychiatric indication. People taking antidepressants also had significantly higher mean CES D scores (μ_1 14.3, μ_2 8.7; p 0.021) and mean chronic conditions (μ_1 3.7, μ_2 1.4; p 0.006).

Depression outcomes

On the CES D, 35 (16.7%) participants scored 16 or over, which is the accepted cut off for depression. The mean CES D score was 9.2 (SD 8.1). Sixteen people (7.6%) reported a diagnosis of depression in their medical history, and of these, seven (44.0%) scored above the 16 cut off point on the CES D. Nine (4.3%) participants reported both depression and an anxiety disorder.

With each additional physical condition, the CES D score increased by 0.72 units (95% CI 0.11 1.33; p 0.020) after adjustment for age and gender. However, the estimate dropped below conventional significance levels when we additionally adjusted for antidepressant use (β 0.56, 95% CI 0.06 1.18; p 0.078) and in a

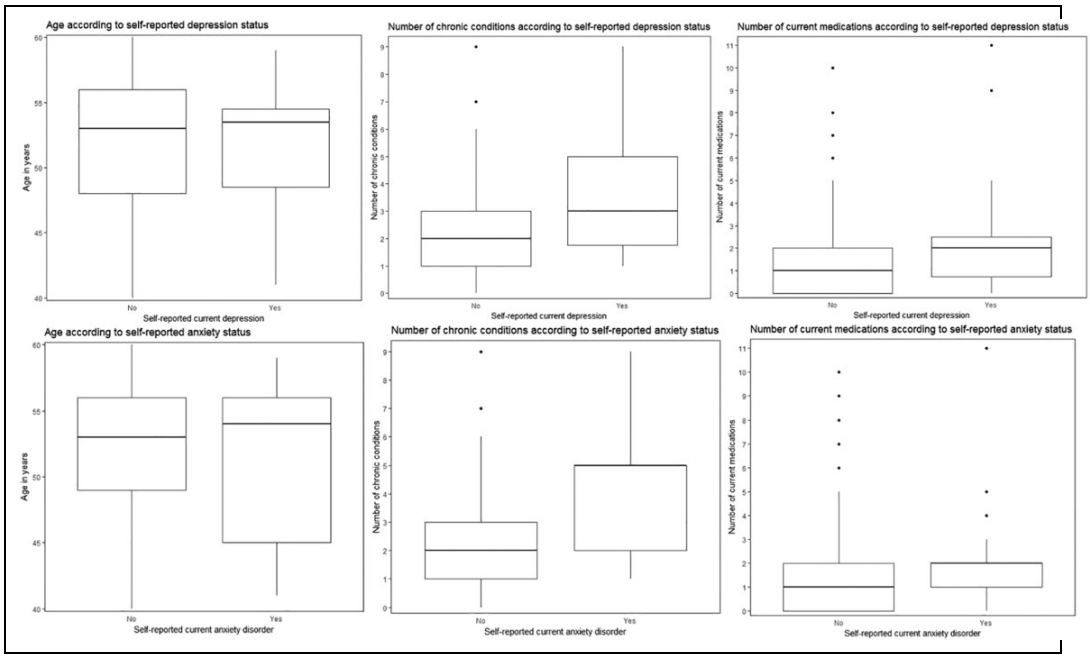

Figure 1. Box plots of age, chronic conditions and medication for self-reported outcomes in whole sample ($n = 210$).

Table 3. Characteristics of sample based on antidepressant status.

	Not taking antidepressant for psychiatric indication ($n = 192$)		Taking antidepressant for psychiatric indication ($n = 18$)		
Variable	*n* (%)	Mean (SD)	*n* (%)	Mean (SD)	*p* for difference (Student's *t*-test or χ^2 test)
Gender (female)	132 (68.8)		16 (88.9)		0.128
Race (Caucasian)	172 (89.6)		16 (88.9)		1
Current depression (self-report)	3 (1.6)		13 (72.2)		**<0.001**
Current anxiety disorder (self-report)	9 (4.7)		12 (66.7)		**<0.001**
Age (years)		51.9 (5.5)		52.1 (5.8)	0.907
Education (years)		15.9 (3.3)		16.5 (4.6)	0.575
CES-D Total (possible range 0 60)		8.7 (7.9)		14.3 (9.1)	**0.021**
STAI Total (possible range 20 80)		30.0 (9.4)		34.0 (9.1)	0.090
Number of chronic physical conditions		2.0 (1.8)		3.7 (2.2)	**0.006**
Number of current medications excluding antidepressants		1.4 (1.8)		2.9 (3.)	0.052

SD: standard deviation; CES-D: Center for Epidemiologic Studies Depression; STAI: State-Trait Anxiety Inventory.
Bold figure indicates $p < 0.05$.

subsample of participants who did not take antidepressants for psychiatric indications (β 0.43, 95% CI 0.23 1.08; p 0.199).

Similarly, although each additional medication emerged as associated with higher CES D scores (β 0.88, 95% CI 0.32 1.44; p 0.002, adjusted for age and gender), even when including antidepressant use as a covariate (β 0.74, 95% CI 0.18 1.31; p 0.011), testing the association in a subsample of those not taking antidepressants rendered it non significant (β 0.53, 95% CI 0.09 1.16; p 0.094).

The odds ratio (OR) for self reported depression with the number of chronic physical conditions, adjusted for age and gender, was 1.41 (95% CI 1.11 1.80; p 0.004). Additionally adjusting for antidepressant use reduced the OR to 1.26 (0.83 1.90; p 0.273). The OR adjusted for age and gender per unit increase in number of medications

Table 4. Summary of regression analysis results.

		Exposure					
		Chronic physical conditions			Medications excluding antidepressants		
Outcome	Model	Coefficient (95% CI)	OR[a] (95% CI)	*p* Value	Coefficient (95% CI)	OR[a] (95% CI)	*p* Value
Depression							
CES-D	Model 1	**0.72 (0.11, 1.33)**		**0.020**	**0.88 (0.32, 1.44)**		**0.002**
	Model 2	0.56 (0.06, 1.18)		0.078	**0.74 (0.18, 1.31)**		**0.011**
	Model 3[b]	0.43 (0.23, 1.08)		0.199	0.53 (0.09, 1.16)		0.094
Self-reported depression	Model 1		**1.41 (1.11, 1.80)**	**0.004**		**1.35 (1.08, 1.71)**	**0.008**
	Model 2		1.26 (0.83, 1.90)	0.273		1.13 (0.79, 1.70)	0.545
	Model 3[b]		NA			NA	
Anxiety							
STAI	Model 1	0.14 (0.57, 0.85)		0.704	0.27 (0.39, 0.92)		0.425
	Model 2	0.01 (0.72, 0.73)		0.986	0.16 (0.51, 0.83)		0.637
	Model 3[b]	0.06 (0.71, 0.84)		0.871	0.20 (0.54, 0.95)		0.588
Self-reported anxiety disorder	Model 1		**1.70 (1.35, 2.19)**	**<0.001**		1.23 (0.99, 1.51)	0.045
	Model 2		**1.73 (1.30, 2.37)**	**<0.001**		1.04 (0.78, 1.36)	0.800
	Model 3[b]		NA			NA	

OR: odds ratio; CI: confidence interval; CES-D: Center for Epidemiologic Studies Depression; STAI: State-Trait Anxiety Inventory.
[a]OR per unit increase in number of chronic conditions or medications.
[b]N.B. smaller sample size, as below: model 1: whole sample (*n* 210), adjusted for age and gender; model 2: whole sample (*n* 210), adjusted for age, gender and use of antidepressants for psychiatric indication; model 3: sample excluding participants taking antidepressants for psychiatric indication (*n* 192), adjusted for age and gender (not calculated for self-reported diagnoses of depression and anxiety disorder due to high proportion of people with diagnoses taking medication).
Bold figure indicates $p < 0.05$.

for self reported depression was 1.35 (1.08 1.71; *p* 0.008). This OR reduced to 1.13 (0.79 1.70; *p* 0.545) when additionally adjusting for antidepressant use with psychiatric indication.

Both increasing number of medications and increasing chronic conditions were associated with increasing CES D score and self reported depression. These associations were attenuated when accounting for antidepressant use for psy chiatric indications and became no longer statistically sig nificant at conventional levels. All regression analysis results are summarized in Table 4.

Anxiety outcomes

The mean score on the STAI was 30.4 (SD 9.4). Twenty one participants (10%) reported a diagnosis of anxiety dis order in their medical history; of these, 7 (33.3%) scored above the cut off of 40 on the STAI and 18 had ≥2 physical conditions.

There were no significant associations between an increasing number of chronic conditions and the STAI state score in a model adjusted for age and gender (β 0.14, 95% CI 0.57 0.85; *p* 0.704). This remained non significant when additionally adjusting for antidepressant use (β 0.01, 95% CI 0.72 0.73; *p* 0.986). The regres sion coefficient for the effect of each additional medication on the STAI score was β 0.27 (95% CI 0.39 0.92; *p* 0.425) and this remained non significant when adding antidepressant use as a covariate (β 0.16, 95% CI 0.51 0.83; *p* 0.637). In the subsample of participants who did not take antidepressants for a psychiatric indication, the associations between both chronic conditions and medica tion with STAI did not meet conventional significance lev els (presented as model 3 in Table 4).

The OR (95% CI) adjusted for age and gender for self reported anxiety disorder with number of chronic condi tions was 1.70 (1.35 2.19; $p < 0.001$). Additionally adjusting for antidepressant use increased the OR to 1.73 (1.30 2.37; $p < 0.001$). The OR (95% CI) adjusted for age and gender per unit increase in number of medications for self reported anxiety disorder was 1.23 (0.99 1.51; *p* 0.045). This OR remained non significant at 1.04 (0.78 1.36; *p* 0.800) when additionally adjusting for antidepressant use.

Analyses stratified by gender

The results of regression analyses stratified by gender are presented in Appendix 2. Table 2A shows that in women, there were associations between chronic physical condi tions and medications with CES D scores and self reported depression. There were also associations between conditions, but not medications, and self reported anxiety disorder. Additionally adjusting for antidepressant use ren dered the associations non significant, apart from the model including chronic conditions and self reported anxi ety disorder. By contrast, in men, the only significant asso ciation was between increasing medication use and increasing CES D scores. Depression was reported by one

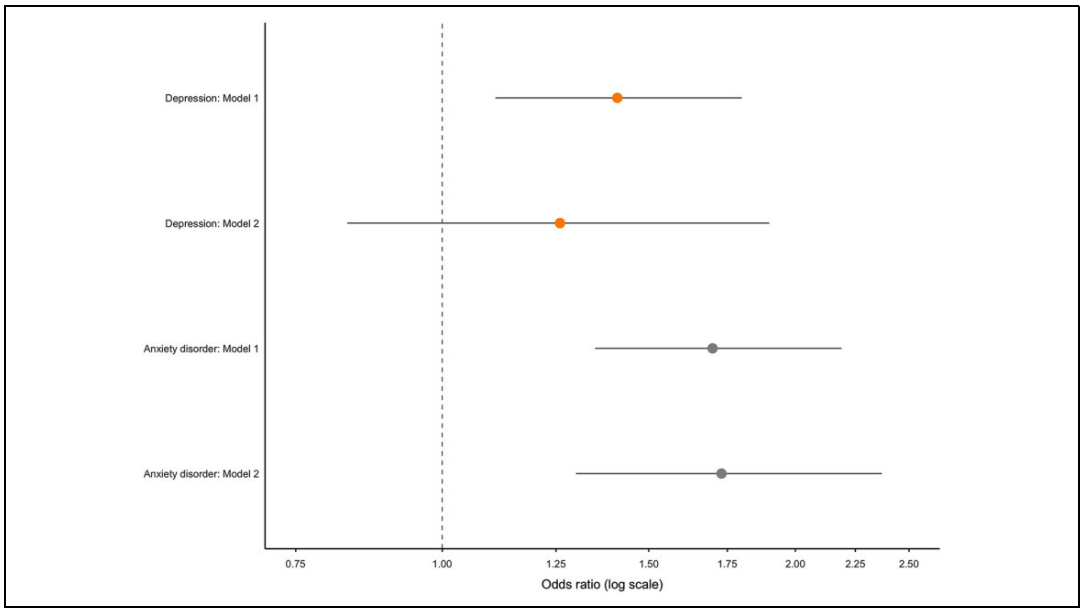

Figure 2. OR (95% CI) of self-reported outcomes with each additional chronic physical condition: whole sample ($n = 210$). OR: odds ratio; CI: confidence interval.

(1.6%) male participant and anxiety disorder by two (3.2%) male participants, so we did not conduct analyses with self reported depression or anxiety disorder as out comes in men.

Figures 2 and 3 show the OR and 95% CI for self reported depression and anxiety per unit increase in chronic conditions and medications, respectively.

In summary, no clear association between increasing medication use and anxiety measures emerged. Chronic conditions were associated with self reported anxiety dis order but not increasing STAI scores.

Discussion

Key results

We found associations between increasing chronic condi tions and self reported depression, increasing CES D scores and self reported anxiety disorder, but not STAI score. There were associations between increasing numbers of medication with both self reported depression and increasing CES D scores. There was no association between increasing medication count and anxiety, either self reported or according to the STAI. The findings no longer met conventional significance levels when adjusting for antidepressant use, suggesting that a preexisting diag nosis with partial treatment may explain the observed associations.

Comparison to existing literature

Participants in the initial wave of the PREVENT Dementia study had a mean of 2.2 chronic physical conditions. Recent publications in similar age groups found figures of 0.8 chronic conditions in an English primary care cohort and 1.2 chronic conditions in Scottish data.[2,28] The appar ently above average prevalence of multimorbidity in PRE VENT Dementia participants may reflect the self report method of gathering medical history.

The majority of PREVENT Dementia participants were taking at least one medication and among those, the mean number of medications taken was 2.6 (SD 2.2). In contrast, a population level analysis in one region of Scotland found that among adults (mean age 50.1 years) prescribed any medication, the mean was 4.4 prescribed medications.[29] The PREVENT Dementia cohort reported more than would be expected in terms of medical conditions but were receiv ing less than would be expected in terms of medication. This could imply a population that is very observant of their own health but reporting conditions not severe enough to require treatment. This discrepancy is, therefore, likely due to the use of volunteers in PREVENT Dementia.

It is difficult to compare multimorbidity studies when there is disparity between the number of possible condi tions listed in each of them. Previous studies reviewing prevalence estimates of multimorbidity using disease counts have recommended using a list of at least 12

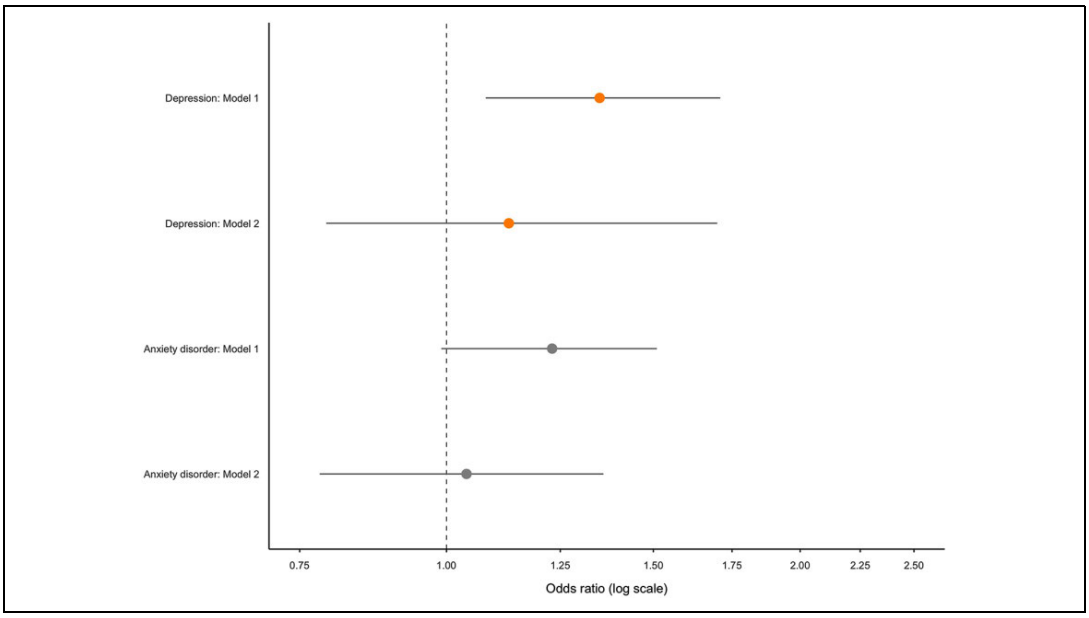

Figure 3. OR (95% CI) of self-reported outcomes with each additional medication: whole sample ($n = 210$). OR: odds ratio; CI: confidence interval.

conditions[30] and between 25 and 75 conditions.[31] Our list of 55 conditions is likely to have been more sensitive than those in previous similar studies, with the consequent risk of over estimation of multimorbidity.

We found an association between increasing number of medications (excluding antidepressants) and scores on the CES D and self reported depression. The only similar study using this measure was published in 1989 and found a similar association but did not account for antidepressant use.[9] There has also been an increase in the prevalence of polypharmacy since then.[3] There is little in the literature about medication use and specific anxiety outcomes, so our analyses are novel in this area.

A systematic review and meta analysis of 40 articles found an OR of 1.45 (95% CI 1.28 1.64; $p < 0.001$) for depression with each additional condition, which our analyses of self reported depression support. All of the articles reviewed used either a depression rating scale or clinical diagnosis; none considered both.[5] A very large cross sectional study of primary care patients with depression and controls found that people with depres sion were more likely to have multimorbidity and that this association was stronger in people with socioeco nomic deprivation.[32] This was a representative sample from primary care, but used routinely collected diagnos tic information from health records and symptom mea sures were not available. Our research builds on this evidence by assessing both self reported diagnoses and symptom scales as outcomes.

There have been two cross sectional studies specifically exploring the link between multimorbidity and anxiety, both of which found statistically significant associations. One was a large international study of adults aged over 18 years, which measured multimorbidity from a list of nine conditions and anxiety with a single question answered on a 5 point scale.[7] The other measured anxiety according to the Beck Anxiety Inventory and multimorbidity from a list of seven conditions, in participants aged over 65 years.[8] Again, there is strength in our research using both self reported diagnosis and symptom scales; we found a similar association between increasing chronic conditions and anxiety disorder but not symptoms as reported on STAI. This difference between reported diagnosis and objective measurement may reflect the fact that those who report a diagnosis are likely to be receiving treatment and, there fore, report fewer active symptoms.

Strengths and limitations of this study

The complementary outcomes we examined include not only validated rating scales but also participant reported clinical diagnoses. This selection of measures, therefore, adds breadth compared to previous research in this area. Furthermore, there is limited published work on multimor bidity and polypharmacy in midlife, so this work fills an important gap.

The data available were collected in the baseline pilot phase of PREVENT Dementia, only permitting exploratory

cross sectional analyses of 210 participants. The cohort was designed as a longitudinal study and follow up data collections are ongoing. Cross sectional analysis leaves questions about direction of causality unclear. It is known, for example, that all mental disorders are associated with later physical health consequences, so the findings from this study may reflect reverse causality in that people who were originally depressed experienced physical health deterioration.[33] The recruitment of volunteers who are likely to have an interest in dementia research limits the generalizability of our results. The sample is 89.5% Cau casian which is close to the UK proportion of 87.2% but less diverse than the population of London where 59.8% of people are white.[34]

Although the STAI and CES D feature some questions on somatic symptoms of anxiety and depression, the major ity are cognitive symptoms so this is unlikely to capture physical symptoms of physical conditions. However, peo ple with anxiety and depression, particularly older people, can report physical symptoms as the primary com plaint.[35,36] This may lead to seeking medical attention and, therefore, receiving more diagnoses of physical conditions. The self report nature of the PREVENT Dementia medical history and the overlap between the clinical presentations of depression and anxiety disorder meant that a number of participants reported both conditions. The questions in the screening tests mean that CES D includes symptoms of generalized anxiety disorder and STAI, symptoms of depression.[22,37] In addition, there is an overlap between multimorbidity and polypharmacy and we did not adjust for either when assessing each exposure.[38]

With such a sample size, groups within the data set can be small, for example, only 26 participants reported current use of antidepressant medication. There are also more women (148, 70.5%) than men in the sample, so when groups are subdivided by gender, they can become very small for example, only seven men took antidepressants. It is important to recognize the role of chance in analyses on these numbers, and effect size could be over estimated. In addition, we adjusted for covariates that were clinically relevant and statistically significant in preparatory analyses but there may be residual confounding from unmeasured factors. These exploratory analyses will inform future research in a larger sample from this cohort.

The nature of the PREVENT Dementia initial visit is that all the medical history and medications are self reported. This can lead to several types of bias including recall bias and social desirability bias.[39] Self reported depression may be more sensitive than CES D for identi fying people with a clinical diagnosis who have received treatment and, therefore, perform better on testing than they might have done untreated. However, participants may also report depression that has not been clinically diagnosed, more so perhaps than a physical condition. Previous studies comparing self report with diagnostic or screening tests for depression have remarked upon this complex relationship.[40] Self reported antidepressant use in cohort studies, however, has been found to correlate strongly with prescription records.[41]

In all but one analysis, an apparent association between exposure and outcomes ceased when including antidepres sant use as a covariate. This implies that taking antidepres sants, perhaps as a marker for mental disorders (fully or partially treated), is an important explanation in the path way between chronic conditions, medication use and anxi ety and depression. The overlap between physical and mental illness is complex and difficult to capture but we attempted to understand it by approaching it from several different angles. This is a strength over previous research, which has not attempted to account for the treatment of depression or anxiety.[5,7 9] In addition, antidepressant use suggests a preexisting diagnosis of mental illness, but detailed temporality of mental and physical diagnoses can not be ascertained in cross sectional data. Future waves of the PREVENT Dementia study will allow longitudinal exploration of this issue.

Implications

The presence of associations between increasing chronic conditions, medications and depression supports the important interaction of physical health and resulting medication burden with mental health, even in midlife. The modest nature of these results in a small sample size limits the certainty with which conclusions can be drawn but reinforces the need to corroborate them in larger data sets. A particular strength of completing this work in a pilot wave of an ongoing longitudinal study is the oppor tunity to revisit the analyses when data from future waves are available. In these cross sectional analyses, we were unable to evaluate the implications for participants' future development of dementia, but follow up may allow this. The focus on midlife individuals may also inform strate gies to improve health in later life. For example, if midlife physical health can be optimized, this may reduce later anxiety and depression.

Conclusions

In this cross sectional study of a middle aged cohort of volunteers, we found associations between increasing chronic conditions and self reported depression, depressive symptoms and self reported anxiety disorder but not anxi ety symptoms. In addition, there were associations between increasing number of medications and depression (both self reported and according to a screening scale) but not anxiety. The use of antidepressants, as a marker for preex isting mental illness, attenuated the associations found. This work adds to understanding of physical and mental health multimorbidity.

Acknowledgements

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Data availability

The data sets analysed during this study are available from PREVENT Dementia and can be accessed by application via the following URL: https://preventdementia.co.uk/for-researchers/

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Supplemental material

Supplemental material for this article is available online.

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Appendix 1

Table 1A. List of included chronic physical conditions with prevalence in PREVENT Dementia baseline phase.

Condition	Definition	Prevalence, *n* (%)
Eye disease	Currently active	113 (53.8)
Asthma	Currently active	28 (13.3)
Migraine	Currently active	27 (12.9)
Sleep disorder	Currently active	25 (11.9)
Gastro-oesophageal reflux disease	Currently active	23 (11.0)
Hypertension	Currently active	22 (10.5)
Irritable bowel syndrome	Currently active	17 (8.1)
Other musculoskeletal condition (each free text entry checked for relevance)	Currently active or ever recorded	17 (8.1)
Cardiac arrhythmia	Currently active	14 (6.7)
Cancer	Ever diagnosed	14 (6.7)
Osteoarthritis	Currently active	26 (12.4)

(continued)

Table 1A. (continued)

Condition	Definition	Prevalence, *n* (%)
Degenerative disc disease	Currently active	13 (6.2)
Anaemia	Currently active	12 (5.7)
Chronic constipation	Currently active	12 (5.7)
Hypothyroidism	Currently active	11 (5.2)
Diabetes	Currently active	7 (3.3)
Peripheral vascular disease venous	Currently active	6 (2.9)
Other gastrointestinal disorder (each free text entry checked for relevance)	Currently active or ever recorded	5 (2.4)
Inflammatory bowel disease	Ever recorded	4 (1.9)
Other genitourinary/reproductive disorder (each free text entry checked for relevance)	Currently active or ever recorded	4 (1.9)
Other haematological disorder (each free text entry checked for relevance)	Currently active or ever recorded	3 (1.4)
Cholelithiasis	Currently active	3 (1.4)
Diverticulitis	Currently active	3 (1.4)
Peripheral nerve disorder	Currently active	3 (1.4)
Angina	Currently active	2 (1.0)
Other cardiovascular disease (each free text entry checked for relevance)	Currently active or ever recorded	2 (1.0)
Peptic ulcer disease	Currently active	2 (1.0)
Liver disease (excluding hepatitis)	Currently active	2 (1.0)
Other eye disease (each free text entry checked for relevance)	Currently active or ever recorded	2 (1.0)
Gout	Currently active	2 (1.0)
Stroke	Ever diagnosed	2 (1.0)
Other neurological disorder (each free text entry checked for relevance)	Currently active or ever recorded	2 (1.0)
Valvular heart disease	Currently active	1 (0.5)
Coronary artery disease	Ever diagnosed	1 (0.5)
Gastrointestinal bleed	Currently active	1 (0.5)
Benign prostatic hyperplasia	Currently active	1 (0.5)
Nephrolithiasis	Currently active	1 (0.5)
Hyperthyroidism	Currently active	1 (0.5)
Other metabolic (each free text entry checked for relevance)	Currently active or ever recorded	1 (0.5)
Immune deficiency	Currently active	1 (0.5)
Other immunological condition (each free text entry checked for relevance)	Currently active or ever recorded	1 (0.5)
Aortic aneurysm	Ever diagnosed	0
Cholecystitis	Currently active	0
Chronic obstructive pulmonary disease	Ever diagnosed	0
Collagen vascular disease	Currently active	0
Congenital heart disease	Currently active	0
Congestive heart failure	Ever diagnosed	0
Hepatitis	Currently active	0
Kidney disorder	Currently active	0
Pacemaker	Ever reported	0
Pancreatitis	Currently active	0
Parkinson's disease	Ever diagnosed	0
Peripheral vascular disease arterial	Currently active	0
Seizure/convulsion disorder	Currently active	0
Tuberculosis	Currently active	0

Appendix 2

Results of supplementary analyses stratified by gender

Table 2A. Women only.

		Exposure					
		Chronic physical conditions			Medications excluding antidepressants		
Outcome	**Model**	Coefficient (95% CI)	OR[a] (95% CI)	*p* Value	Coefficient (95% CI)	OR[a] (95% CI)	*p* Value
Depression							
CES-D	Model 1	**0.81 (0.12, 1.51)**		**0.021**	**0.74 (0.01, 1.48)**		**0.048**
	Model 2	0.62 (0.09, 1.32)		0.085	0.50 (0.25, 1.25)		0.190
Self-reported depression	Model 1		**1.43 (1.12, 1.84)**	**0.005**		**1.44 (1.12, 1.90)**	**0.005**
	Model 2		1.33 (0.88, 2.05)	0.177		1.25 (0.84, 2.06)	0.329
Anxiety							
STAI	Model 1	0.33 (0.50, 1.16)		0.436	0.10 (0.79, 0.98)		0.828
	Model 2	0.16 (0.69, 1.02)		0.707	0.12 (1.03, 0.79)		0.795
Self-reported anxiety disorder	Model 1		**1.71 (1.34, 2.25)**	**<0.001**		1.25 (0.98, 1.58)	0.061
	Model 2		**1.72 (1.29, 2.40)**	**<0.001**		1.05 (0.79, 1.42)	0.732

OR: odds ratio; CI: confidence interval; CES-D: Center for Epidemiologic Studies Depression; STAI: State-Trait Anxiety Inventory.
[a]OR per unit increase in number of chronic conditions or medications: model 1: women only (*n* 148), adjusted for age; model 2: women only (*n* 148), adjusted for age and use of antidepressants for psychiatric indication.

Table 2B. Men only.[a]

		Exposure			
		Chronic physical conditions		Medications excluding antidepressants	
Outcome	Model	Coefficient (95% CI)	*p* Value	Coefficient (95% CI)	*p* Value
Depression					
CES-D	Model 1	0.37 (1.01, 1.75)	0.592	**1.10 0.22, 1.97)**	**0.015**
	Model 2	0.36 (1.09, 1.80)	0.622	**1.10 (0.21, 2.00)**	**0.016**
Anxiety					
STAI	Model 1	0.59 2.03, 0.84)	0.412	0.55 (0.41, 1.50)	0.256
	Model 2	0.52 (2.02, 0.99)	0.492	0.60 (0.37, 1.57)	0.221

CI: confidence interval; CES-D: Centre for Epidemiologic Studies Depression; STAI: State-Trait Anxiety Inventory; model 1: men only (*n* 62), adjusted for age; model 2: men only (*n* 62), adjusted for age and use of antidepressants for psychiatric indication.
[a]Self-reported depression and anxiety disorder not included owing to small number of male participants reporting these diagnoses.

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Appendix 3: Public Benefit and Privacy Panel for Health and Social Care (PBPP) Application Form

Application Control *Applicants should not fill out this section*			
Application Coordinator	Lizzie Nicholson		
Application Number	1516-0552	Submitted Date	26 May 2017
Applicant Name	Lucy Stirland		
Proposal Name	Associations between polypharmacy and mental health outcomes in older adults: an epidemiological approach		

NOTE TO APPLICANTS

Prior to completing your application form you should:

- Contact the eDRIS Team, who will assist you - Nss.edris@nhs.net or by phone on 0131 275 7333
- Read and understand the separate Guidance for Applicants

Your application should be typed, not handwritten. Your eDRIS application coordinator will inform you how to submit your application form and any supporting evidence. Before submitting your completed application, you should ensure that:

- All relevant sections of the application are complete
- Relevant supporting evidence is attached
- Individuals named on the form have read and approved its submission

Please note that submitted applications may be circulated to panel members, administrative colleagues, NHSScotland information governance and information security colleagues, Caldicott Guardians, the CHI Advisory Group and, where appropriate, non-NHS Scotland colleagues from a variety of participating partner bodies, in the course of processing. You must make your eDRIS application coordinator aware of any confidential or sensitive information contained in your

application which you would consider inappropriate for circulation in such a manner. Your application could be subject to disclosure or partial disclosure under the Freedom of Information (Scotland) Act, and will be retained in line with NHSScotland information policy.

Section 1 - People

1.1	**Applicant** *Please read section 1.1 of the guidance*	
1.1.01	Full Name:	Lucy Stirland
1.1.02	Title:	Dr
1.1.03	Position:	Clinical Research Fellow
1.1.04	Professional Registration No.:	GMC 7070540
1.1.05	Organisation Name:	The University of Edinburgh, Centre for Dementia Prevention
1.1.06	Address:	5th Floor, Kennedy Tower, Royal Edinburgh Hospital, Morningside Terrace, Edinburgh
1.1.07	Postcode:	EH10 5HF
1.1.08	Telephone Number:	0131 537 6257
1.1.09	Email:	l.stirland@ed.ac.uk
1.1.10	Do you have an NHS contract/honorary contract?	Yes (Honorary Specialty Registrar in Old Age Psychiatry, NHS Lothian)
1.1.11	Provide details of the most recent information governance training undertaken - a list of training courses is included at Appendix A, and you should particularly indicate if you have undertaken any of those listed	
	Name of course:	MRC Data Confidentiality
	Link to course content:	http://byglearning.co.uk/mrcrsc-lms/course/category.php?id=1
	Institution:	MRC
	Date completed:	04/06/16

1.2	**Clinical Sponsor/Lead** *Please read section 1.2 of the guidance*	
1.2.01	Full Name:	Tom Russ
1.2.02	Title:	Dr
1.2.03	Position:	Intermediate Clinical Fellow
1.2.04	Professional Registration No.:	GMC 6097438

1.2.05	Organisation Name:	The University of Edinburgh, Centre for Dementia Prevention
1.2.06	Address:	5th Floor, Kennedy Tower, Royal Edinburgh Hospital, Morningside Terrace, Edinburgh
1.2.07	Postcode:	EH10 5HF
1.2.08	Telephone Number:	0131 537 6672
1.2.09	Email:	t.c.russ@ed.ac.uk
1.2.10	Does this person have an NHS contract/honorary contract?	Yes (Honorary Consultant Psychiatrist, NHS Lothian)
1.2.11	Provide details of the most recent information governance training undertaken - a list of training courses is included at Appendix A, and you should particularly indicate if this person has undertaken any of those listed	
	Name of course:	MRC Data Confidentiality
	Link to course content:	http://byglearning.co.uk/mrcrsc-lms/course/category.php?id=1
	Institution:	MRC
	Date completed:	26/01/15

1.3	**Information/Data Custodian** *Please read section 1.3 of the guidance*
Same as Clinical Sponsor/Lead	

1.4	**Others with access to identifiable or potentially identifiable data** *Please read section 1.4 of the guidance*
Not applicable	

1.5	**Others** *Please read section 1.5 of the guidance*		
Complete this section if applicable – for each additional person			
Full Name:	Dr Graciela Muniz Terrera	Involvement in Proposal:	Primary PhD Supervisor
Organisation:	Centre for Dementia Prevention, University of Edinburgh	Position:	Senior Lecturer in Biostatistics and Epidemiology
Full Name:	Prof Craig Ritchie	Involvement in Proposal:	Assistant PhD Supervisor
Organisation:	Centre for Dementia Prevention, University of Edinburgh	Position:	Professor of Psychiatry of Ageing

Section 2 – Organisations & Bodies

2.1	**Organisation or Body Leading Proposal** *Please read section 2.1 of the guidance*	
2.1.01	Organisation or Body Name:	The University of Edinburgh
2.1.02	Is this organisation or body a registered data controller? If 'Yes', provide Data Protection Registration Number:	Yes Z6426984
2.1.03	Is this a commercial organisation or body?	No
2.1.03a	If 'Yes', please provide a full explanation of the organisation or body's activity and industry sector, including any previous experience of using NHSScotland data - append supporting documentation as appropriate	*If applicable*
2.1.04	Is this organisation or body wholly funding or paying for the costs of conducting the proposal?	Yes

2.2	**Organisation or Body Funding Proposal** *Please read section 2.2 of the guidance*
Not applicable	

Section 3 – Overview

3.1	**Proposal Essentials** *Please read section 3.1 of the guidance*	
3.1.01	Proposal title/name:	Associations between polypharmacy and mental health outcomes in older adults: an epidemiological approach
3.1.02	Is this proposal an extension or renewal of an existing approval (for example to conduct a study over a wider geographic area or for a longer period of time)? Please provide details, include the reference number of the original approval, and summarise the changes requested	No
3.1.03	Is this new proposal related to a previous application (approved or not)? Please give details, indicate if this is a resubmission, including the reference number of the original submission	No
3.1.04	What is (are) the substantive purpose(s) of the proposal? (tick all that apply)	

	☐ Patient Care ☐ Audit ☐ Service Planning/Improvement ☐ Systems Implementation/Testing ☐ Quality (Clinical, Educational, etc)	☒ Research ☐ Performance Monitoring/Management ☐ Health/Social Care Administration ☐ Training/Education
	If other clearly defined purpose, please give details:	
3.1.05	Does the proposal require the use of information which can identify or potentially identify individuals?	For linkage only – researchers will not have access to this.
3.1.06	Access is being requested to data from which sources? (tick as many as are relevant) ☐ A single NHS Scotland Board (excluding NSS) ☒ NHS National Services Scotland ☐ More than one NHS Scotland Board ☐ A national NHS Scotland system/database ☐ More than one NHS Scotland system/database ☒ Community Health Index (CHI) database ☐ NHS Central Registry	
	If other, please give details:	
3.1.07	Provide a full, clear concise outline of the proposal background – describe why it is needed, aims and objectives and envisaged benefits to the public and/or patients: It is common for people to have more than one health problem at a time, particularly as they get older. Recent research in Scotland has shown that people with multiple physical conditions are more likely to have mental health problems. In addition, older people are more likely to be prescribed multiple medications (known as polypharmacy). I aim to find out if there are links between polypharmacy and mental ill health in older age. Information about prescriptions in Scotland is routinely recorded. Every person registered with a GP in Scotland has a unique number, the Community Health Index (CHI) which appears on all their prescriptions and	

	contacts with health services. I will request anonymised prescription data for all Scottish residents who were aged over 50 in 2009, namely the number and types of medication they were given. Using the CHI, this information can be matched to any subsequent mental health diagnoses recorded in psychiatric or general hospital contacts and on death certificates. I will look at the commonest and most important mental health problems that can arise in older people, including depression, dementia and delirium (a temporary state of confusion that can occur at times of physical illness). I will group people by the number of medications they receive (for example, no medication, less than three medications, four or more medications) and compare the subsequent mental health diagnoses of these groups. I will ensure that I match the groups for other relevant factors such as age and socioeconomic status. I expect to be able to calculate the risk of developing certain mental health problems in relation to the number of medications people take. I will also examine whether the breakdown of these medications into different types of drugs affects the association between numerous prescriptions and mental health. I will also look at particular combinations of certain individual medications (for example, the inclusion of antihistamines or sedatives such as diazepam) to see if these are linked to mental health problems. Using people's anonymised routinely collected data offers a unique opportunity to examine an important question at a population level and produce findings that will be relevant for these same people's future healthcare. My research will deepen our understanding of links between physical and mental health, for example, helping to answer questions about who is most likely to develop mental health problems. If I find a link between polypharmacy and mental illness, this may be useful for doctors to identify people at higher risk of developing mental health problems early. It may also influence prescribing decisions for people who are already taking multiple medications, for example encouraging doctors to prescribe the minimum number of medications necessary. I will publish my findings in academic journals and will present at conferences. I will give public talks where the opportunity arises and will be active on social media. My aim is to share my results with a wide audience so that clinicians can apply my findings when caring for their patients and ultimately the public will benefit from my use of these data.
3.1.08	Provide a full, clear and concise outline of the proposal design, listing: data sources; sample size; inclusion/exclusion criteria (eg involvement in trial/survey; health event, etc); relevant date range; need for identifiable or potentially identifiable data; requirement for a matched control cohort etc. My proposed project will examine the links between the number of prescriptions a person receives and their subsequent mental health diagnoses. My principal data sources for this project are held by the Information Services Division of NHS National Services Scotland (ISD).

	They will be: prescription details from the Prescribing Information System (PIS), outpatient hospital data (SMR00), general inpatient hospital data (SMR01), mental health inpatient hospital data (SMR04), and National Records of Scotland (NRS) death certificate data. From 2009 onwards, the PIS is linked to the other databases using the Community Health Index (CHI) number. Therefore my date range will be from the date in 2009 when linkage was first available to the most recent data available at the time of extraction. I will also request information from the CHI database, including postcodes to allow the eDRIS analyst to determine Scottish Index of Multiple Deprivation (SIMD) deciles (researchers will not receive the full postcode) and a flag for care home residency. I will include all people living in Scotland who were aged 50 or over on the date that PIS linkage first began in 2009. From National Records of Scotland population estimates for 2009 I calculate this to include approximately 1.87 million people. The age cut-off of 50 will allow me to focus my research on the older and ageing population in whom I am most interested due to their increased likelihood of having multiple physical conditions, subsequent polypharmacy, and concurrent mental health disorders. I will request prescribing information on all people in my age range in Scotland, regardless of the number of medications they receive. I will then group people by the number of medications they receive (including those on no medication) and compare the mental health outcomes of these groups. In addition to overall numbers of prescriptions, I will request a breakdown of these prescriptions by British National Formulary (BNF) chapter to examine whether different classes of medication carry different associations. I will also request information on individual medications in order to further analyse these links. Most research into polypharmacy focuses on counts of medication alone, so including classes of drug and specific medications in such a large cohort will produce novel and enlightening results. Due to the large size of my proposed sample, I will request quarterly extracts from 2009 onwards, which will allow me to follow people's medication history, including seasonal trends, across a period long enough that means my outcomes of interest are likely to occur. Please see the appended data flow diagram for the steps which will require linkage and anonymization. I will not require access to any identifiable patient data; these data will already have been anonymised by the eDRIS analyst by the time I receive them. I will not share the data I receive with any other researchers except for the data custodian named above. When I have generated findings from my research I will publish these in scientific journals but due to the large population-level numbers involved, and the fact I will have been dealing with anonymised data, I consider the risk of inadvertent identification to be negligible.

3.1.09	Does the proposal have implications for, or target, sensitive groups or vulnerable populations? Please give details
	Mental health is an integral part of my research question and as such I will be requesting data regarding psychiatric hospital admissions, mental health diagnoses in other hospital records and on death certificates. My aim is to produce research that will eventually lead to better healthcare for people with complex health problems, particularly those with mental ill health. I would also need access to ethnicity information in order to properly account for the impact of this on outcomes. I will ask for information on broad categories of ethnic group only (for example, white, white European and non-white). In addition, because I am requesting data for a very large number of people, it is very unlikely that a particular ethnicity category will make an individual identifiable. I will also take other steps to minimise the risk of inadvertent identification, for example, requesting Scottish Index of Multiple Deprivation (SIMD) deciles derived by eDRIS analysts instead of personally accessing postcodes.
3.1.10	Does the proposal seek to use information exclusively about deceased persons? Please give details
	No
3.1.11	Have any members of the public/lay representatives been involved in the proposal design? Please give details
	A summary of the proposal was reviewed by the Farr Institute Scotland's Public Panel and written feedback received on 3rd February 2017. Comments included: *"The study design's good – the researcher has avoided trying to prove too many aspects relating to the hypothesis"*; *"This type of study is long overdue"*; *"From life-experience with 'the elderly', 'Polypharmacy' does require proper study for, all too often, it is chance encounter with a third party that discovers 'innocent errors'."*
3.1.12	Has any peer review of the proposal been undertaken? Please give details (for example formal review by a peer organisation or funding body, informal internal review, review by a third party)
	This project formed part of my proposal to study for a PhD in the PsySTAR (Psychiatry: Scottish Training in Academic Research) programme, funded by the Medical Research Foundation and MRC. I had to defend my proposal at an interview with Professors of Psychiatry who make up the PsySTAR board, and have made approved amendments following this. In addition, my three PhD supervisors Dr Graciela Muniz Terrera, Prof Craig Ritchie and Dr Tom Russ have ongoing contributions to my project and have reviewed this application.
3.1.13	Is there *any* commercial aspect or dimension to the proposal or its outcomes? Please give details

	No

3.2	**Proposal Geography** *Please read section 3.2 of the guidance*
☐ Local/Regional (relating to one or more specific areas within Scotland)	
☒ National (relating to the whole of Scotland)	
☐ UK-wide (relating to the whole of the UK, or to UK regions outside Scotland)	
☐ International (relating to areas within the EEA)	
☐ International (relating to areas beyond the EEA)	

3.3	**Proposal Duration and Frequency** *Please read section 3.3 of the guidance*	
3.3.01	What is the proposed duration of the proposal?	5 years
3.3.02	Does the proposal require updates of information at regular intervals? Please give details	No
3.3.03	Are you seeking approval to iterate the proposal (ie the *whole* project, audit or study) at regular intervals? Please give details	No

3.4	**Statutory and Regulatory Context** *Please read section 3.4 of the guidance*	
3.4.01	Does your proposal have a statutory or regulatory justification - is the proposal responding to a statutory or regulatory instruction, duty or order? Please give details	No
3.4.02	Which Data Protection Act schedule 2 and schedule 3 conditions are relevant? (a list of conditions can be found at Appendix B)	Schedule 2.5d: This medical research will be conducted in the public interest because I aim to investigate combinations of illnesses, our understanding of which will improve healthcare provision. Schedule 3.8: I am a doctor conducting medical research and am used to exercising confidentiality in my clinical practice.
3.4.03	Are there any relevant information sharing agreements, protocols or contracts in place which support your proposal? Please give details	No

	and attach as supporting documentation if available	
3.4.04	Has a Privacy Impact Assessment been carried out which supports your proposal? Please give details and attach as supporting documentation if available	No. I have considered the Information Commissioner's Office PIA Code of Practice screening questions. All data that is disclosed to people who would not have had routine access will be anonymised. The NSS data is already being used for research via ISD. I asked the Farr Institute Scotland Public Panel their views on the use of anonymised routinely collected data from patients who had not directly consented to this. Comments included: *"I have no problem with anonymised data being used for this purpose."* *"I have no issue with the use of anonymised healthcare records in the proposed study"* *"The researcher's 'target' is inanimate properly anonymised data – not any 'person/s' for the linking of one with the other is severed – by an approved independent agency."*
3.4.05	Has local Caldicott approval been given for your proposal at a local level? Please give details	No
3.4.06	Are approvals from Caldicott Guardians outside Scotland pending or received? Please give details	Not applicable

3.5	**Research and Ethics Governance** *Please read section 3.5 of the guidance*	
3.5.01	Has your proposal sought research/ethics approval?	No
3.5.01a	If yes, please provide committee details and status of approval (ie pending, approved, etc). Please attach as supporting documentation if available	*If applicable*

3.5.01b	If no, please explain why research/ethics approval is not sought:	I have liaised with my eDRIS research coordinator and with Jo-Anne Robertson at the Academic and Clinical Central Office for Research and Development (ACCORD), a partnership between NHS Lothian and the University of Edinburgh. I was advised that existing eDRIS ethics approvals would apply to my research and therefore a new application was not necessary. I will continue to update ACCORD with my progress on this research.

3.6	**Safe Havens** *Please read section 3.6 of the guidance*	
3.6.01	Do you intend to access the data requested exclusively through a safe haven listed at Appendix A? Please provide details of which safe haven/s	Yes - NHS NSS ISD Electronic Data Research Innovation Service (at Farr Institute)
3.6.02	If you applying to use NHS NSS data and you do not intend to do this through the National Safe Haven, please explain why	*Not applicable*

Section 4 – Data & Data Subjects

4.1	**Data yet to be collected** *Please read section 4.1 of the guidance*
Not applicable	

4.2 All Other Datasets / sources *Please read section 4.2 of the guidance*		
Dataset/source Name	Data Controller (Organisation)	Original purpose compatible with proposal?
SMR00 – Outpatient attendance	NHS National Services Scotland	SMR is widely used for research in epidemiology and public health
SMR01 – General/ Acute Inpatient and Day Case		

SMR04 – Mental Health Inpatient and Day Case		
Prescribing Information System (PIS)	NHS National Services Scotland	PIS is routinely used for research into the safety, efficacy and efficiency of medicine use in Scotland
CHI database	NHS National Services Scotland	The CHI database exists to ensure patients can be identified and to track individual patients across healthcare episodes. The CHI database will be needed to create the cohort for my research, which focuses on linking prescription data with subsequent diagnoses in health records.
Death registrations	National Records of Scotland (NRS)	NRS death records data are used to produce health statistics for research and for informing policy. They are linked to the Scottish Morbidity Database (SMR) and these linked records have been used in published health research.

How were individuals originally informed of the use of their data? (if known)
I am requesting access to anonymised routinely collected data. The individuals in question are users of the NHS and protected by The Charter of Patient Rights and Responsibilities under the Patient Rights (Scotland) Act 2011. This Charter specifies that patients have the right to know how their personal health information is used. Clear information on confidentiality is distributed in the public domain in various formats, including the NHS Scotland factsheet "Your Health, Your Rights" and a NHS National Services Scotland leaflet "Safe and Secure Use of Personal Health Information". See Section 7 for URLs to these documents.
For existing dataset/sources for which the data controller is not an NHSScotland board, please append evidence of the data controllers permission to use the data

4.3 Data Variables *Please read section 4.3 of the guidance*			
Dataset/source Name	Variable	Time Period/Range	Processing only?
Please see attached spreadsheet			Choose an item.

Please justify your need for identifiable or potentially identifiable variables:
I will only request CHI numbers for linkage and will not have access to any identifiable data once they have been anonymised. I am requesting SIMD deciles (derived from postcodes before I receive the data) to minimise the risk of geographical identification. I am requesting age in months in order to allow a chronological examination of the patient's clinical course. I am requesting hospital admission durations rather than specific admission dates.

4.4	**NRS/NHSCR Data Sources** *Please read section 4.4 of the guidance*	
Complete this section if access to NHSCR is required, or if there is any National Records of Scotland involvement		
4.4.01	Does the proposal require access to NHS Central Registry as a sampling frame for cohorts?	No
4.4.02	Does the proposal involve flagging of individuals on the NHSCR for long term follow up?	No
4.4.03	If yes, is flagging necessary: ☐ To trace and contact individuals throughout the UK? ☐ To be informed of fact and cause of death? ☐ To be informed of the incidence of on-going cancers? ☐ To be informed of emigrations prospectively and retrospectively?	
4.4.04	Is any other NRS involvement required? Please provide details	No

4.5	**Making Contact with Individuals** *Please read section 4.5 of the guidance*	
4.5.01	Is any direct contact with any group of individuals required? If Yes, please provide details below	No

4.6	**Community Health Index (CHI) Database** *Please read section 4.6 of the guidance*	
Complete this section if access to CHI Database is required		
4.6.01	What monitoring and audit of the use of CHI is planned? Please provide details	Access to the CHI database will be required to create my cohort. Access will be sought by the NSS indexing team who follow established audit and monitoring procedures.
4.6.02	What technical method will be used to access CHI (online read-only, download, other extract,	The NSS indexing team will access the CHI database to create my cohort. The cohort will then be anonymised before I have access to it.

	anonymised extract, etc)? Please provide details	
4.6.03	Have any risks been identified in the proposal which relate specifically to CHI?	I will not personally have access to CHI data as this will be used by the NSS indexing team to create a cohort. CHI numbers will have been removed when I receive the information.

Section 5 – Methodology & Data Processing

5.1	**Methodology** *Please read section 5.1 of the guidance*	
5.1.01	Does the proposal require any of the following: ☒ Data matching/linking ☐ Single anonymised data extract ☐ Use of matched controls Other (please specify):	
5.1.02	Who is carrying out any indexing/ linkage/anonymisation, and where?	NSS
5.1.03	Which data sources listed at section 4.1 and 4.2 will NSS/NRS receive identifiers for linkage purposes?	All sources are within NSS/NRS. All datasets listed in 4.2 will be linked together.
5.1.04	What variables will be provided for linkage? ☒ CHI Number ☐ Forename ☐ Surname ☐ Date of Birth ☐ Address or Postcode ☐ NHS Number Other Please Specify:	

5.2	**Access** *Please read section 5.2 of the guidance*
Complete the following section if you answered 'No' to question 3.6.1	
Not applicable	

5.3	**Store & Use** *Please read section 5.3 of the guidance*
Complete the following section if you answered 'No' to question 3.6.1	

Not applicable

5.4	**Transfer** *Please read section 5.4 of the guidance*	
5.4.01	Please provide details of security policy/procedure to ensure that data will be transferred in such a way that it is protected from inappropriate or unauthorised access (mention email encryption, secure file transfer protocols SFTP, device encryption, physical controls, etc, as appropriate) - append supporting documentation	I will access data via the NSS Safe Haven and will not transfer it elsewhere (see Data Flow Diagram). If I am granted remote access to the Safe Haven, I will do so through University of Edinburgh computers (PC with encrypted hard drive and encrypted laptop; both of which require secure log-in). I will comply with the University's Information Security Policy (see appended document, section 4.2 Information Handling).
5.4.02	At what intervals/ trigger points will data transfer take place?	Only when eDRIS analyst makes data available via NSS Safe Haven. I will access data through the Safe Haven.
5.4.03	Will any identifiable or potentially identifiable data be transferred outside of the UK?	No
5.4.03 b	If yes, please provide details of the country of destination, the method of transfer, the proposed location and method of storage outside of the UK, and details of any further onward transfer	*Not applicable*
5.4.04	Other than initial transfers from source systems, is there any copying of data required within the proposal? Please give details	No

5.5	**Dissemination** *Please read section 5.5 of the guidance*	
5.5.01	Will proposal findings be published or disseminated beyond the proposal team?	Yes
5.5.01a	If yes, how will proposal findings be published or disseminated, to	I will submit my findings for publication in academic journals

	what audience and in what format? Please give details	and presentation at conferences. They will also form part of my PhD thesis which will be published online. I will participate in public engagement through the Centre for Dementia Prevention and Edinburgh Neuroscience, both of which have research engagement specialist advisors and are active on social media. My aim is to disseminate my results to the widest audience possible so that clinicians, and ultimately the public, benefit from my use of this data.
5.5.01b	If yes, what steps will be taken to ensure that persons cannot be identified in published findings (eg disclosure control procedures (safe haven), use of aliases, numbers, avoidance of small geographical areas, avoidance of small numbers, etc)? Please give details	I will not publish or disseminate the raw data I work with as this will be kept secure in the NSS Safe Haven. I will only have access to anonymised data so the results of my analysis will not be identifiable. I will be working with data from very large numbers of prescriptions and hospital contacts from across Scotland to look at population trends. I am requesting variables that limit the risk of inadvertent identification (such as SIMD decile and broad ethnicity categories).
5.5.01c	If yes, are there any circumstances where a living or dead individual would be cited? (eg where a person consented to their data being used as a case study)? Please give details	No
5.5.01d	If yes, were any permissions to publish data required or sought (for example from data controllers)? Please provide details	*Not applicable*

5.6	**Retain/Dispose** *Please read section 5.6 of the guidance*	
5.6.01	Which information/data/records retention policy will you be applying to the proposal data (details of the policy and the organisation to which it belongs)?	Charter for Safe Havens in Scotland, Technical Annex points 14 and 15 (Scottish Government). I will also comply with the University of Edinburgh's Research Data Management

		Policy (URL listed in Section 7).
5.6.02	How long do you intend to retain identifiable or potentially identifiable data after the conclusion of the proposal (including archive/backup copies)?	5 years
5.6.03	Who will retain the data and where?	eDRIS at NSS Safe Haven
5.6.04	What is the purpose for retaining the data for the specified time?	For academic accountability purposes regarding my publications including PhD thesis
5.6.05	What method of disposal or destruction will be used when this period has expired (including archive/backup copies)?	This will occur in accordance with the NSS Safe Haven Charter, Technical Annex points 14 and 15.
5.6.06	What evidence will be obtained that destruction has occurred (eg IT supplier certificate of destruction, etc)?	This will be conducted by eDRIS at NSS Safe Haven.

5.7	**Review** *Please read section 5.7 of the guidance*	
5.7.01	Describe how the mechanisms which safeguard data security will be audited and reviewed at regular intervals to ensure their continued efficacy	The Safe Haven conducts penetration testing every two years in accordance with the Charter for Safe Havens in Scotland, Technical Annex point 8. The current version of the University of Edinburgh's Information Security Policy (v2.1, October 2014) had a suggested revision date of 2016. The University's Computing Regulations are updated annually.
5.7.02	Describe any resource implications to any of the proposed measures for the protection of physical or technical security of information which are unresolved at the time of this application? (for example encryption of devices is an intention not yet fulfilled, training is not yet undertaken, etc)	None
5.7.03	Describe the breach reporting mechanisms to be invoked in the event of any inappropriate access to data or other information security incident	I will report any breach to my research coordinator at eDRIS and to the University of Edinburgh Incident Response Team as part of their Information Security Incident Response Policy.

Section 6 – Declaration

- I DECLARE THAT this application is accurate, and that, should it be successful, any health data made accessible will be used for no other purpose, and in no other way, than as described above.
- I UNDERTAKE TO notify the Public Benefit and Privacy Panel of any future changes to the purpose or manner in which data is processed in accordance with this application.
- I UNDERSTAND THAT any future applications by me, or my employing or sponsoring organisation, may be refused should any health data made accessible be used for any other purpose or in any other way than that described above.
- I CERTIFY THAT all those who have access to health data in this proposal are aware of the requirements of confidentiality and understand that any breach (eg disclosure of confidential information to a person not authorised to receive it) will be reported to the data controller, and in the case of NHS Scotland originated data to Scottish Government eHealth division.
- I GUARANTEE THAT no publication will appear in any form in which an individual may be identified without the written permission of that individual, and that I will apply appropriate disclosure control when planning publications involving the data requested.
- I UNDERSTAND THAT the Data Controller, and agents acting on its behalf, reserves the right to inspect the data on the sites where it is being processed.

To be signified by the APPLICANT

Name (in Capitals): LUCY STIRLAND	Date: 11/05/2017

- I DECLARE THAT (the applicant named above) is a *bona fide* worker engaged in a reputable project and that the data she asks for can be entrusted to her in the knowledge that she will conscientiously discharge her obligations, including in regard to confidentiality of the data, as stated in the declaration above.

To be signified by the INFORMATION CUSTODIAN named in Section 1.3 above (where the Information Custodian is not the applicant).

Name (in Capitals): TOM RUSS	Date: 11/05/2017

Section 7 - Supporting Evidence

Supporting Evidence *Please read section 7 of the guidance*
Please list each piece of supporting evidence which you have included with your application in the box below – the name of each should clearly indicate what the document/file/reference is about
Appended: 1. Data Flow Diagram 2. Variables spreadsheet 3. University of Edinburgh Information Security Policy 4. The Scottish Government, A Charter for Safe Havens in Scotland, November 2015 - University of Edinburgh Computing Regulations 2016-17 is available at: http://www.ed.ac.uk/files/atoms/files/golden_computing_regulations_-_ay16-17.pdf - University of Edinburgh Research Data Management Policy is available at: http://www.ed.ac.uk/information-services/about/policies-and-regulations/research-data-policy - The Charter of Patient Rights and Responsibilities is available at: https://www.nhsinform.scot/care-support-and-rights/health-rights/patients-charter/the-charter-of-patient-rights-and-responsibilities - NHS Scotland Factsheet "Your Health, Your Rights" is available at: https://www.nhsinform.scot/media/1233/confidentiality-english.pdf - NHS National Services Scotland leaflet "Safe and Secure Use of Personal Health Information" is available at: http://www.isdscotland.org/About-ISD/Confidentiality/20150910-SafeSecureInfo-web.pdf

Appendix A – Reference lists for applicants

1. Examples of Existing Datasets and Data Sources	
SMR 00 Outpatients	SMR 04 Mental Health

SMR 01 Inpatients and Day Cases	SMR 06 Cancer Registration
SMR 02 Maternity	SMR 11/SBR Neonatal/Scottish Birth Records
Scottish Drugs Misuse Database (SDMD)	Birth Registrations
A&E – Accident & Emergency	Stillbirth Registrations
PIS Prescribing Information	Death Registrations
CHSP-PS/CHSP-S/SIRS – Child Health Surveillance and Immunisation	SCI-DC
NHS National Service Scotland's Information Services Division (ISD) maintains a National Dataset Catalogue (NDC) containing details of all health and health related datasets that are held by ISD. The Administrative Data Liaison Service (ADLS) publishes further information on key NHSScotland datasets	

2. Common Identifiable Variables		
Forename	Middle Name	Surname
CHI Number	Date of Birth	UK NHS Birth Registration Number
Gender	Postcode	

3. Recognised Safe Havens
NHS NSS ISD Electronic Data Research Innovation Service (@Farr Institute)
NHS Research Scotland South East (ACCORD)
NHS Research Scotland East (TASC)
NHS Research Scotland North (DaSH)
NHS Research Scotland West
University of Dundee Health Informatics Centre (HIC)
National Records Scotland Scottish Longitudinal Study (SLS)
Robertson Centre @ Glasgow University

4. Research and Information Governance Training
MRC Research Data and Confidentiality online module
University of Edinburgh SHIP Information Governance training

NHS Health and Social Care Information Centre On-line Information Governance training
NHSScotland Information Governance eLearning: • Safe Information Handling (Foundation Level) • Information Handling in Practice (Intermediate Level)

5. Sensitive Data Categories		
Abortion	Mental health	Contraception
Pregnancy in age < 16 years	Drugs and alcohol misuse	Crime related statistics
Sexually transmitted disease	Suicide	Ethnicity
Assisted conception		

6. Vulnerable Populations	
Adults with Incapacity	Drugs users
Minority ethnic groups	Specific religious affiliation

Appendix B –The Caldicott Principles & the Data Protection Principles (& Schedules)

1. Caldicott Principles
1. **Justify the purpose(s)** Every single proposed use or transfer of patient identifiable information within or from an organization should be clearly defined and scrutinized, with continuing uses regularly reviewed, by an appropriate guardian.
2. **Don't use patient identifiable information unless it is necessary** Patient identifiable information items should not be included unless it is essential for the specified purpose(s) of that flow. The need for patients to be identified should be considered at each stage of satisfying the purpose(s).
3. **Use the minimum necessary patient-identifiable information** Where use of patient identifiable information is considered to be essential, the inclusion of each individual item of information should be considered and justified so that the minimum amount of identifiable information is transferred or accessible as is necessary for a given function to be carried out.
4. **Access to patient identifiable information should be on a strict need-to-know basis** Only those individuals who need access to patient identifiable information should have access to it, and they should only have access to the information items that they need to see. This may mean introducing access controls or splitting information flows where one information flow is used for several purposes.

5.	**Everyone with access to patient identifiable information should be aware of their responsibilities** Action should be taken to ensure that those handling patient identifiable information - both clinical and non-clinical staff - are made fully aware of their responsibilities and obligations to respect patient confidentiality.
6.	**Understand and comply with the law** Every use of patient identifiable information must be lawful. Someone in each organization handling patient information should be responsible for ensuring that the organization complies with legal requirements.
7.	**The duty to share information can be as important as the duty to protect patient confidentiality** Health and social care professionals should have the confidence to share information in the best interests of their patients within the framework set out by these principles. They should be supported by the policies of their employers, regulators and professional bodies.

2. Data Protection Principles	
1.	Personal data shall be processed fairly and lawfully and, in particular, shall not be processed unless – (a) at least one of the conditions in Schedule 2 is met, and (b) in the case of sensitive personal data, at least one of the conditions in Schedule 3 is also met
2.	Personal data shall be obtained only for one or more specified and lawful purposes, and shall not be further processed in any manner incompatible with that purpose or those purposes
3.	Personal data shall be adequate, relevant and not excessive in relation to the purpose or purposes for which they are processed
4.	Personal data shall be accurate and, where necessary, kept up to date
5.	Personal data processed for any purpose or purposes shall not be kept for longer than is necessary for that purpose or those purposes
6.	Personal data shall be processed in accordance with the rights of data subjects under this Act
7.	Appropriate technical and organizational measures shall be taken against unauthorized or unlawful processing of personal data and against accidental loss or destruction of, or damage to, personal data
8.	Personal data shall not be transferred to a country or territory outside the European Economic Area unless that country or territory ensures an adequate level of protection for the rights and freedoms of data subjects in relation to the processing of personal data

3. Data Protection Schedule 2 & 3 Conditions
Schedule 2 – Conditions for Processing any Personal Data

1. The data subject has given his **consent** to the processing
2. The processing is necessary— (a) for the **performance of a contract** to which the data subject is a party, or (b) for the taking of steps at the request of the data subject with a view to entering into a contract
3. The processing is necessary for compliance with any **legal obligation** to which the data controller is subject, other than an obligation imposed by contract
4. The processing is necessary in order to protect the **vital interests** of the data subject
5. The processing is necessary— (a) for the administration of **justice**, (aa) for the exercise of any functions of either **House of Parliament**, (b) for the exercise of any functions conferred on any person by or under any **enactment**, (c) for the exercise of any functions of the **Crown, a Minister of the Crown or a government department**, or (d) for the exercise of any other functions of a **public nature exercised in the public interest** by any person
6. (1) The processing is necessary for the purposes of **legitimate interests** pursued by the data controller or by the third party or parties to whom the data are disclosed, except where the processing is unwarranted in any particular case by reason of prejudice to the rights and freedoms or legitimate interests of the data subject. (2) The Secretary of State may by order specify particular circumstances in which this condition is, or is not, to be taken to be satisfied
Schedule 3 – Conditions for Processing any Sensitive Personal Data
1. The data subject has given his **explicit consent** to the processing of the personal data
2. (1) The processing is necessary for the purposes of exercising or performing any right or obligation which is conferred or imposed by law on the data controller in connection with **employment**
3. The processing is necessary— (a) in order to protect the **vital interests** of the data subject or another person, in a case where— (i) **consent cannot be given** by or on behalf of the data subject, or

(ii) the data controller **cannot reasonably be expected to obtain the consent** of the data subject, or

(b) in order to protect the **vital interests** of another person, in a case where **consent** by or on behalf of the data subject has been **unreasonably withheld**

4. The processing—

(a) is carried out in the course of its **legitimate activities** by any body or association which—

(i) is **not established or conducted for profit**, and

(ii) exists for political, philosophical, religious or trade-union purposes,

(b) is carried out with appropriate safeguards for the rights and freedoms of data subjects,

(c) relates only to individuals who either are members of the body or association or have regular contact with it in connection with its purposes, and

(d) does not involve disclosure of the personal data to a third party without the consent of the data subject

5. The information contained in the personal data has been **made public** as a result of steps deliberately taken **by the data subject**

6. The processing—

(a) is necessary for the purpose of, or in connection with, any **legal proceedings** (including prospective legal proceedings),

(b) is necessary for the purpose of obtaining **legal advice**, or

(c) is otherwise necessary for the purposes of establishing, exercising or defending **legal rights**

7. (1) The processing is necessary—

(a) for the **administration of justice**,

(aa) for the exercise of any functions of either **House of Parliament**,

(b) for the exercise of any functions conferred on any person by or under an **enactment**, or

(c) for the exercise of any functions of the **Crown, a Minister of the Crown or a government department**

(2)The Secretary of State may by order—

(a) exclude the application of sub-paragraph (1) in such cases as may be specified, or

(b) provide that, in such cases as may be specified, the condition in sub-paragraph (1) is not to be regarded as satisfied unless such further conditions as may be specified in the order are also satisfied

7A. (1) The processing—

(a) is either—

(i) the disclosure of sensitive personal data by a person as a member of an **anti-fraud** organisation or otherwise in accordance with any arrangements made by such an organisation; or

(ii) any other processing by that person or another person of sensitive personal data so disclosed; and

(b) is necessary for the purposes of preventing fraud or a particular kind of fraud

(2) In this paragraph "an anti-fraud organisation" means any unincorporated association, body corporate or other person which enables or facilitates any sharing of information to prevent fraud or a particular kind of fraud or which has any of these functions as its purpose or one of its purposes

8. (1) The processing is necessary for **medical purposes** and is undertaken by—

(a) a health professional, or

(b) a person who in the circumstances owes a duty of confidentiality which is equivalent to that which would arise if that person were a health professional

(2) In this paragraph "medical purposes" includes the purposes of preventative medicine, medical diagnosis, medical research, the provision of care and treatment and the management of healthcare services

9. (1) The processing—

(a) is of sensitive personal data consisting of information as to **racial or ethnic origin**,

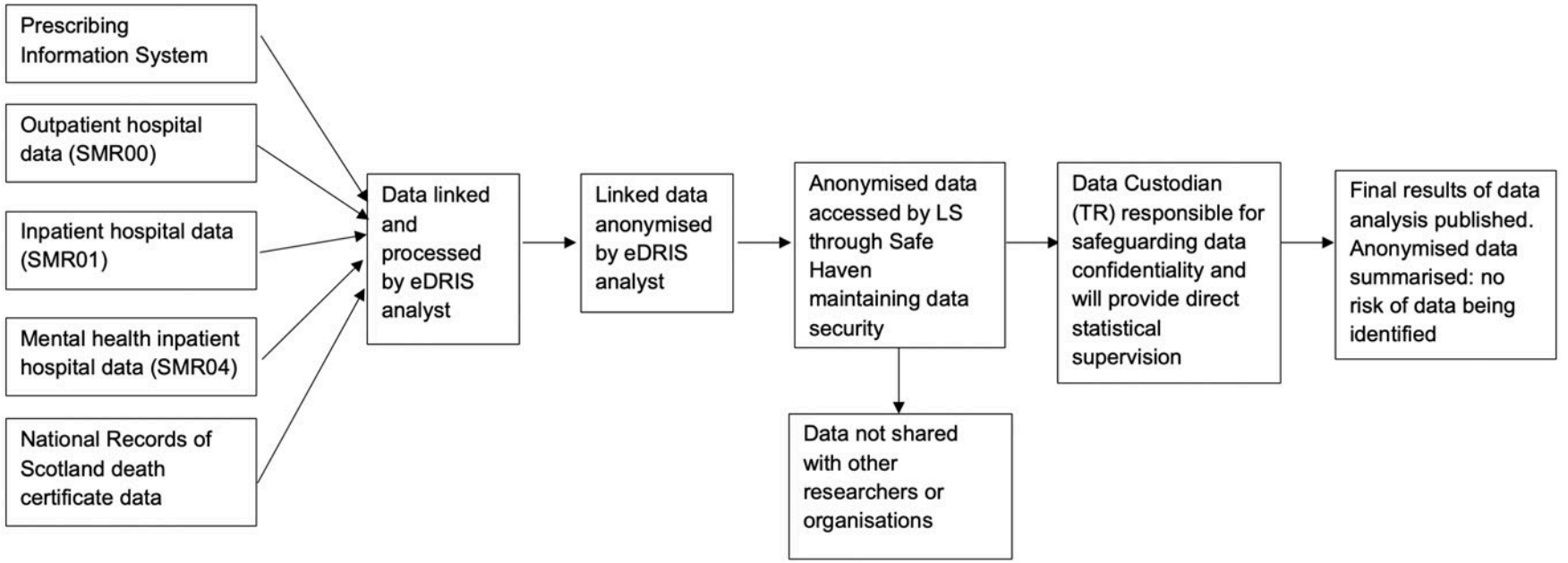
(b) is necessary for the purpose of identifying or keeping under review the existence or absence of **equality of opportunity** or treatment between persons of different racial or ethnic origins, with a view to enabling such equality to be promoted or maintained, and

(c) is carried out with appropriate safeguards for the rights and freedoms of data subjects

(2) The Secretary of State may by order specify circumstances in which processing falling within sub-paragraph (1)(a) and (b) is, or is not, to be taken for the purposes of sub-paragraph (1)(c) to be carried out with appropriate safeguards for the rights and freedoms of data subjects

10. The personal data are processed in circumstances specified in an order made by the Secretary of State for the purposes of this paragraph

Data Flow Diagram



4.3 Data variables spreadsheet

Dataset/source	Variable name	Time Period/Range	Processing only?	Outcomes of interest
Prescribing information system (PIS)	Unique study ID (anonymous)		No	
	Patient age in months at beginning of each quarter	2009 to most recent available, age at beginning of each quarter	No	Age ≥50 at date PIS first linked to SMR in 2009
	CHI number	2009 to most recent available	Yes	
	Pat gender code	2009 to most recent available	No	
	Count of unique drugs dispensed	2009 to most recent available, quarterly extracts	No	
	Unique drugs dispensed, subdivided by PI BNF Chapter code	2009 to most recent available, quarterly extracts	No	
	Concatenated variable of all drugs dispensed, by PI Approved name	2009 to most recent available, quarterly extracts	No	
	PI Prescribable item type	2009 to most recent available, quarterly extracts	Yes - exclude appliances/devices from extract	
Outpatient (SMR00)	Unique study ID (anonymous)		No	
	CHI number	2009 to most recent available	Yes	
	Ethnic group	2009 to most recent available	No	Group A breakdown, Group B-H as single variable
	Specialty	2009 to most recent available	No	
	Main condition	2009 to most recent available	No	ICD-10 Codes F00-F99 inclusive

Dataset/source	Variable name	Time Period/Range	Processing only?	Outcomes of interest
	Other condition 1	2009 to most recent available	No	ICD-10 Codes F00-F99 inclusive
	Other condition 2	2009 to most recent available	No	ICD-10 Codes F00-F99 inclusive
	Other condition 3	2009 to most recent available	No	ICD-10 Codes F00-F99 inclusive
	Other condition 4	2009 to most recent available	No	ICD-10 Codes F00-F99 inclusive
	Other condition 5	2009 to most recent available	No	ICD-10 Codes F00-F99 inclusive
	Age in months	2009 to most recent available	No	
Inpatient (SMR01)	Unique study ID (anonymous)		No	
	CHI number	2009 to most recent available	Yes	
	Length of hospital stay in days	2009 to most recent available	No	
	Main condition	2009 to most recent available	No	ICD-10 Codes F00-F99 inclusive
	Other condition 1	2009 to most recent available	No	ICD-10 Codes F00-F99 inclusive
	Other condition 2	2009 to most recent available	No	ICD-10 Codes F00-F99 inclusive
	Other condition 3	2009 to most recent available	No	ICD-10 Codes F00-F99 inclusive
	Other condition 4	2009 to most recent available	No	ICD-10 Codes F00-F99 inclusive
	Other condition 5	2009 to most recent available	No	ICD-10 Codes F00-F99 inclusive
	Age on admission in months	2009 to most recent available	No	

Dataset/source	Variable name	Time Period/Range	Processing only?	Outcomes of interest
	Ethnic group	2009 to most recent available	No	Group A breakdown, Group B-H as single variable
Mental Health Inpatient (SMR04)	Unique study ID (anonymous)		No	
	CHI number	2009 to most recent available	Yes	
	Ethnic group	2009 to most recent available	No	Group A breakdown, Group B-H as single variable
	Length of stay in days	2009 to most recent available	No	
	Age on admission in months	2009 to most recent available	No	
	Discharge - main condition	2009 to most recent available	No	
	Discharge - other condition 1	2009 to most recent available	No	
	Discharge - other condition 2	2009 to most recent available	No	
	Discharge - other condition 3	2009 to most recent available	No	
	Discharge - other condition 4	2009 to most recent available	No	
	Discharge - other condition 5	2009 to most recent available	No	
National Records of Scotland: Deaths	Unique study ID (anonymous)		No	
	CHI number	2009 to most recent available	Yes	
	Age at death in months	2009 to most recent available	No	
	Primary cause of death	2009 to most recent available	No	ICD-10 Codes F00-F99 inclusive

Dataset/source	Variable name	Time Period/Range	Processing only?	Outcomes of interest
	Secondary cause 0	2009 to most recent available	No	ICD-10 Codes F00-F99 inclusive
	Secondary cause 1	2009 to most recent available	No	ICD-10 Codes F00-F99 inclusive
	Secondary cause 2	2009 to most recent available	No	ICD-10 Codes F00-F99 inclusive
	Secondary cause 3	2009 to most recent available	No	ICD-10 Codes F00-F99 inclusive
	Secondary cause 4	2009 to most recent available	No	ICD-10 Codes F00-F99 inclusive
	Secondary cause 5	2009 to most recent available	No	ICD-10 Codes F00-F99 inclusive
	Secondary cause 6	2009 to most recent available	No	ICD-10 Codes F00-F99 inclusive
	Secondary cause 7	2009 to most recent available	No	ICD-10 Codes F00-F99 inclusive
	Secondary cause 8	2009 to most recent available	No	ICD-10 Codes F00-F99 inclusive
	Secondary cause 9	2009 to most recent available	No	ICD-10 Codes F00-F99 inclusive
CHI Database	CHI number	2009 to most recent available	Yes	
	Unique study ID (anonymous)		No	
	SIMD decile (2016 version)	2009 to most recent available, SIMD at beginning of each quarter	No	
	Pat care home residency flag	2009 to most recent available, taken at beginning of each quarter	No	