Exploration of the comorbidity of chronic pain, cardiometabolic disease and depression

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Abstract

Background and aims:

Comorbidity is usually defined as the presence of one or more long-term conditions (LTCs) co-occurring with an index condition, while it can also be used to refer to a particular combination of multiple LTCs. In this thesis, the focus was on the comorbidity of chronic pain, cardiometabolic disease and depression. Chronic pain commonly co-occurs with other long-term conditions, particularly cardiometabolic disease and depression. Yet little is known about this comorbidity and its implications. This thesis aims to identify the existing knowledge of the comorbidity of chronic pain, cardiometabolic disease and depression; to examine the prevalence of the comorbidity in UK Biobank and investigate the sociodemographic and lifestyle factors associated with the comorbidity; to examine the effect of the comorbidity on health outcomes, and to describe the lived experience and insight of people living with this comorbidity.

Methods:

This was a multimethod study with four phases of research. 1) A narrative systematic review and synthesis of current literature relating to the comorbidity of chronic pain, cardiometabolic disease and depression. 2) A cross-sectional study of UK Biobank, a large dataset of over 500,000 adults aged 38-73 in the UK, in which the prevalence of the comorbidity was examined. Logistic regression was used to analyse associations between sociodemographic and lifestyle factors and the comorbidity, and the relationship between the three conditions. 3) An observational study of baseline data linked with routine health data, including hospital admission and mortality using UK Biobank. Incidence of death and Major Adverse Cardiovascular Events (MACE) in participants with and without the comorbidity were examined in the total study sample (N = 500,313). Survival analysis of a subsample (N = 128,066) was used to analyse the effect of the comorbidity on mortality and MACE, presented using hazard ratios (HR) with 95% confidence interval (CI). 4) A qualitative study involving secondary analysis of ten interviews from participants with the comorbidity. Thematic analysis was conducted to explore the everyday experience of living with the comorbidity

alongside the participants' insights into the comorbidity and interacting with health care professionals.

Results:

Phase 1) The systematic review identified 15 relevant publications (13 studies). one study showed that chronic pain, angina, and depression co-occurred in 1.8% of the general population study sample. Key evidence gaps were identified regarding the prevalence, health effects and patient experience of the comorbidity. Phase 2) Among 500,313 eligible UK Biobank participants, 8,640 (1.73%) had the comorbidity, which was associated with being aged 45 years and older (particularly aged 55-59 years), being female, being from an ethnic group other than white, living in more deprived areas, current or past smoking, being overweight or obese as classified by Body Mass Index (BMI). While drinking alcohol (all categories compared to non-drinkers) and doing any physical activity were associated with a lower risk of the comorbidity. Phase 3) In the sub-sample (N = 128,066), participants with only the three conditions of interest had an increased risk of death presented (HR 2.10, 95% CI: 1.84, 2.41) and MACE (HR 2.13, 95% CI: 1.79, 2.52) compared with healthy participants after adjusting for covariates of sociodemographic and lifestyle factors. Phase 4) Chronic pain was described by the participants as the condition that has the most impact on their daily lives. Some participants considered chronic pain as a complication of their cardiometabolic disease. Others felt that depression was a result of their pain due to the impact it had on their life, particularly in terms of their independence, which has been considered in terms of biographical disruption. Nevertheless, participants felt that considering the combined conditions collectively was more important than focusing on the condition with the most impact. The importance of holism was emphasised, and participants reported a desire for health services to be holistic.

Conclusion:

Findings from each phase were integrated to address the overall research aim. There is a lack of existing literature on the comorbidity of chronic pain, cardiometabolic disease and depression, this combination of conditions was prevalent, associated with adverse health outcomes, and impacted the everyday

lives of people. This thesis has important implications for health service provision suggesting a holistic approach to managing people with the comorbidity and has implications for wider multimorbidity research in general.

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Author's Declaration

I, Simin Wu, declare that, except where explicit reference is made to the contribution of others, that this dissertation is the result of my own work and has not been submitted for any other degree at the University of Glasgow or any other institution.

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Presentations

Selected presentations arising from this research

1. What are the effects of the comorbidity of chronic pain, cardiometabolic disease and depression on health outcomes? A UK Biobank cohort study. The Society for Academic Primary Care (SAPC) Annual Scientific Meeting, 2021.

2. Comorbidity of chronic pain, cardiometabolic disease, and depression: a cohort study in UK Biobank. Aberdeen, Dundee, Edinburgh, Glasgow and St Andrews (ADEGS), 2021.

3. Comorbidity of chronic pain, cardiometabolic diseases and depression: a systematic review. Scottish Pain Research Committee (SPaRC) Annual Scientific Meeting, 2020.

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Abbreviations

Abbreviation	Full text
ACG	Ambulatory Care Groups
ADL	Activities of Daily Living
AF	Atrial fibrillation
BDI	Beck Depression Inventory
BMI	Body Mass Index
CAQDAS	Computer-assisted qualitative data analysis software
CCDSS	Canadian Chronic Disease Surveillance System
CCI	Charlson Comorbidity Index
CDS	Chronic Disease Score
CDSR	Cochrane Database of Systematic Reviews
CES-D	Centre for Epidemiologic Studies Depression Scale
CHD	Coronary heart disease
CI	Confidence interval
CINAHL	Cumulative Index to Nursing and Allied Health Literature
CIRS	Cumulative Illness Rating Scale
CMD	Cardiometabolic disease
COPD	Chronic obstructive pulmonary disease
CPSP	Central post-stroke pain
CVD	Cardiovascular disease
CWP	Chronic widespread pain
DLA	Disability Living Allowance
DPN	Diabetic painful neuropathy
DPNP	Diabetic peripheral neuropathic pain
DSM	Diagnostic and Statistical Manual of Mental Disorders
DSM-IV	4^{th} version of Diagnostic and Statistical Manual of Mental Disorders
DUSOI	Duke Severity of Illness Checklist
EDS	Ehlers-Danlos syndromes
ESA	Employment and Support Allowance
GMS	General Medical Services
GS:SFHS	General Scotland: Scottish Family Health Study
H_0	Null-hypothesis
HADS	Hospital Anxiety and Depression Scale
HES	Hospital episodes statistics

HES	Hospital episodes statistics
HF	Heart failure
HICs	High-income countries
HR	Hazard ratio
HS	Hidradenitis suppurativa
IASP	The International Association for the Study of Pain
IBS	Irritable bowel syndrome
ICD-10	10th version of the International Statistical Classification of Diseases
IQR	Interquartile Range
IRAS	Integrated Research Application System
Kg/m2	kilogram/(metre^2)
KM	Kaplan-Meier
LTC	Long-term condition
MACE	Major adverse cardiovascular events
MAP	Multimorbidity in Arthritis and persistent musculoskeletal Pain
MDD	Major depressive disorder
ME	Myalgic encephalomyelitis
MeSH	Medical Subject Headings
MI	Myocardial infarction
MRC	Medical Research Council
MSK	Musculoskeletal
N/R	Not Reported
NA	Not applicable
NAPCRG	North American Primary Care Research Group
NHANES	National Health and Nutrition Examination Survey
NHIS	National Health Interview Survey
NHS	National Health Service
NMR	National mortality registry
OR	Odds Ratio
OSOP	One sheet of paper
PCC	Patient-centred care
PECOS	Population, Exposure, Comparators, Outcomes and Study Designs
PHQ	Patient Health Questionnaire
PIP	Personal Independence Payment
PNPD	Painful Diabetic Peripheral Neuropathy

PoTS	Postural tachycardia syndrome
PRISMA	The Preferred Reporting Items for Systematic reviews and Meta-Analyses
PROSPERO	International Prospective Register of Systematic Reviews
PVD	Peripheral vascular disease
QOF	Quality and Outcomes Framework
QoL	Quality of life
RA	Rheumatoid arthritis
RCT	Randomised controlled trials
SD	Standard deviation
SIMD	Scottish Index of Multiple Deprivation
SSRI	Selective Serotonin Reuptake Inhibitors
TIA	Transient ischaemic attack
UK	United Kingdom
US	United States
WBI	World Health Organization Well Being Index
WHO	World Health Organization

Chapter 1 Introduction

This chapter provides an overview of the thesis and details of the key concepts underpinning comorbidity research. At the end of this chapter a summary of the structure of the thesis is provided.

1.1 Concepts of comorbidity and multimorbidity

Although chronic conditions commonly occur together (Barnett et al., 2012), comorbidity and multimorbidity are relatively new concepts. Moreover, it is mainly a phenomenon of interest in public health and is often neglected in practice. The definition of comorbidity and multimorbidity continues to develop. This section introduced the concepts of comorbidity and multimorbidity.

1.1.1 Comorbidity

Comorbidity is usually defined as the presence of one or more long-term conditions (LTCs) co-occurring with a specified index condition (Harrison et al., 2021). Using this definition, comorbidity involves a specific condition as the main or index condition, and other conditions co-exist alongside this disease. The index condition and the comorbid conditions can be selected in various ways according to the research questions being addressed (Valderas et al., 2009). For example, the chosen index condition can often be decided upon based on its utility in helping to provide information that has the potential to influence clinical management of patients (Valderas et al., 2009). For example, cardiometabolic diseases like diabetes, heart disease and hypertension are commonly considered as index condition due to their high prevalence and major adverse impacts on health (Schellevis et al., 1993). The comorbid conditions chosen can be complications of the index conditions, conditions developed from the pre-existing condition, or conditions with no obvious relationship (Jones, 2010).

Multiple co-occurring LTCs were noticed as early as the 1960s (Wilson et al., 1962). The concept of comorbidity was first introduced by Feinstein in 1970 as “any distinct additional clinical entity that has existed or may occur during the clinical

course of a patient who has the index disease under study" (Feinstein, 1970). With the growing prevalence of co-occurrence of LTCs in clinical practice, the concept has been increasingly used, and various definitions have been offered to interpret this phenomenon (de Rooij et al., 2014). In 1996, a literature review was conducted to examine the concepts of comorbidity and suggested the original definition with an index condition (van den Akker et al., 1996). Nevertheless, except for the 'classical' definition implying an index condition, the review also identified several studies referring to comorbidity as the co-occurrence of several diseases (Verbrugge et al., 1989, Seeman et al., 1989, Cornoni-Huntley et al., 1991). So, there is not complete consensus on the definition of comorbidity.

Several tools for measuring comorbidities have been created and modified (Huntley et al., 2012). Commonly used tools include Chronic Disease Score (CDS) (Von Korff et al., 1992, Iommi et al., 2020), the Charlson Comorbidity Index (CCI) (Drosdowsky and Gough, 2022, Charlson et al., 1987), the Duke Severity of Illness Checklist (DUSOI) (Parkerson et al., 1993, Navarro-Cano et al., 2003), Elixhauser Index (Elixhauser et al., 1998), Ambulatory Care Groups (ACG) System (Starfield et al., 1991) and the Cumulative Illness Rating Scale (CIRS) (Linn et al., 1968, Hudon et al., 2005). The use of the concept of comorbidity in these measurement tools was focused on the 'co-morbid' and not distinct from multimorbidity (described below).

1.1.2 Multimorbidity

Multimorbidity is different and distinct from comorbidity (Harrison et al., 2021). Multimorbidity refers to the presence of two or more LTCs *without* reference to a particular index condition (Boyd and Fortin, 2010). The concept of "multimorbidity" has been used by academics referring to multiple LTCs since 1976 (Harrison et al., 2021). Multimorbidity, although still referring to the co-occurrence of two or more chronic conditions, is different as it can refer to any combination of chronic conditions, and no single condition is more central than the others i.e. no index condition is considered (Harrison et al., 2021).

1.1.3 Definition of comorbidity in this thesis

The definition of comorbidity with an index condition or the definition of multimorbidity does not cover all the circumstances of the co-occurrence of LTCs. For example, a specific combination of multiple equally important LTCs would be inapplicable to either definition. Examining specific co-occurring LTCs instead of any combination of LTCs is of interest because different combinations involve different parts of health services and produce different types of challenges for treating and managing the diseases and a different experience for people living with the conditions. In a certain combination of LTCs, the index condition could differ when considered from different perspectives. The doctors and specialists would see the conditions in their speciality as the index condition (Harrison et al., 2021), but people living with the LTCs may consider the importance of each condition in different ways, depending on how the different conditions affect their lives, and expect to receive person-centred clinical diagnosis and treatment (Bonavita and De Simone, 2008) that meets their expectations. The significance of the role of the index condition is under discussion and examined in this thesis.

To avoid ambiguity, in this thesis, the concept of comorbidity followed a wider interpretation and was defined as the specific combination of co-occurring LTCs (chronic pain, cardiometabolic disease and depression) with or without a clear index condition.

1.1.4 Prevalence of co-occurring LTCs

The issue of comorbidity and multimorbidity is of concern because it is prevalent, especially in older people (Jakovljević and Ostojić, 2013). As many countries have ageing populations, the phenomenon of co-occurring LTCs has become a major global health issue (Mezzich and Salloum, 2008). Across the world, approximately one-third of adults have multimorbidity (Nguyen et al., 2019).

In an early study of 1,217,103 Medicare beneficiaries aged 65 years and older living in the United States in 1999, 82% of them had one or more chronic conditions, and 65% had multiple chronic conditions (Wolff et al., 2002). From a patient survey in

2010 of the general adult population in Canada, 19.0% (95% CI 18.0-20.0) of the study sample reported having two or more chronic conditions (Agborsangaya et al., 2012). The Canadian Chronic Disease Surveillance System (CCDSS) reported that the overall prevalence of multimorbidity, having two or more chronic conditions, was 26.5% in 2011/12 (Feely et al., 2017).

In a UK study using data from 182 general practices, a total of 16% of the 100,000 participants from the general population reported more than one LTC included in the Quality and Outcomes Framework (QOF), and 58% reported more than one LTC from a wider list (Salisbury et al., 2011). The QOF is part of the payment system for general practice and is part of the General Medical Services (GMS) contract introduced in 2004. It remunerates practices based on the achievement of indicators of quality of care for a range of chronic conditions (e.g. diabetes and hypertension) (Roland and Guthrie, 2016). It is becoming more common for people to have multiple co-existing chronic conditions (Valderas et al., 2009), especially in countries with an ageing population (Feely et al., 2017). The US National Comorbidity Survey found the comorbidity prevalence of 79% in patients with lifetime disorders (Kessler et al., 1994).

A cross-sectional study of all patients in Scotland found the prevalence of multimorbidity was 23.2% (95% CI: 23.08-23.21); multimorbidity was not only increasingly prevalent with age, but also found to begin earlier in those from more socioeconomically deprived areas, with mental health disorders being particularly common (Barnett et al., 2012). People with intellectual disabilities also have an extremely high prevalence (98.7%) of multimorbidity across their entire adult life course (Kinnear et al., 2018).

1.1.5 Impact of co-occurring LTCs

Comorbidity and multimorbidity are important issues because of their adverse impact on health and health services. There is a growing interest in examining the impact of multiple LTCs on health outcomes (Landwehr et al., 2000). The co-occurrence of LTCs is not simply the sum of individual diseases (Starfield, 2011). Instead, comorbidity and multimorbidity are associated with more complex and

expensive treatment, healthcare and management, yet with worse health outcomes (Valderas et al., 2009).

The association between multimorbidity and health-related quality of life (QoL) has been examined and has found that multimorbidity negatively affects health-related QoL in the adult population (Fortin et al., 2006, Makovski et al., 2019). The consultation rates of those with multimorbidity were higher in a study of people registered with 182 general practices (Salisbury et al., 2011). Treating multiple LTCs in one person in isolation would potentially lack holism (Salisbury et al., 2011). Patients with comorbidity or multimorbidity tend to receive multiple medications, and polypharmacy increases the risk of drug interactions and adverse events (Guthrie et al., 2012). In the US, approximately 80% of Medicare spending is devoted to patients with four or more chronic illnesses, with costs increasing exponentially with higher multimorbidity (Wolf et al. 2002).

1.2 structure of thesis

The Background (Chapter 2) lays the foundation of the whole study. It identifies the existing knowledge of the three conditions of interest and the evidence gaps, along with the overall aims and objectives. The different approaches used in the study are described in the Methodology (Chapter 3). The study used a multimethod approach involving a systematic review, statistical data analysis of a large research cohort and secondary analysis of qualitative data. Chapter 3 is a theoretical chapter about the background of the methods and concepts underpinning the use of a multimethod approach and related methods.

Following the methodology chapter, four results chapters (Chapters 4-7) describe the study findings. Chapter 4 is a narrative systematic review which identified the key evidence gaps and provided the rationale for the important research questions needing addressed in the further studies. Chapter 5 is a cross-sectional study which describes the baseline data of UK Biobank and the prevalence of the three conditions, along with prevalent combinations. It also provides information on the sociodemographic and lifestyle factors associated with the comorbidity, and the relationship between the three conditions. Chapter 6 introduces a follow-up of

the cohort of UK Biobank and provides information about the linkage of the baseline data with health outcome data. There are two parts of this study: a descriptive analysis measuring the incidence of the health outcomes with the comorbidity in the total study sample; and a survival analysis of the relationship between the comorbidity and health outcomes in a subsample. Chapter 7 presents the final study of this thesis, a secondary qualitative analysis of the Multimorbidity in Arthritis and persistent musculoskeletal Pain (MAP) Study. This chapter illustrates the experience of living with the comorbidity and provides the patient's insights and completes the multimethod approach to understanding the impact of the comorbidity at the individual level.

The overall findings of this multimethod PhD are summarized in the Discussion (Chapter 8). It synthesises the research findings about the comorbidity of chronic pain, cardiometabolic disease and depression from the different perspectives.

In addition to this introductory chapter, the seven chapters of the main body of the thesis relate to each other and provide a detailed exploration of the comorbidity of chronic pain, cardiometabolic disease and depression.

Chapter 2 Background

2.1 Introduction

2.1.1 Overview of this chapter

This thesis presents an investigation into the current knowledge of the impact of the comorbidity of chronic pain, cardiometabolic disease and depression on health outcomes and experiences. This chapter reviews the existing knowledge on these individual conditions and the comorbidity and lays the foundation for the whole thesis. The three health conditions of interest are introduced in terms of the definitions, disease types, prevalence, impact, and management. Secondly, a review of the existing literature that involves the combination of two diseases of chronic pain, cardiometabolic disease and depression is described. It highlights the gaps in evidence and explains why it is important to examine the comorbidity

of chronic pain, cardiometabolic disease and depression. Finally, the aims and objectives of this thesis are outlined.

2.2 Health conditions of interest

In this thesis, the co-occurrence of chronic pain, cardiometabolic disease and depression were explicitly of interest because they are common conditions with major adverse impacts on health and wellbeing. This section introduces the three health conditions of interest individually.

2.2.1 Chronic pain

2.2.1.1 Defining pain

The feeling of pain is a common experience that almost everyone encounters at some point. Pain is described as an unpleasant personal experience and is subjective in nature. The International Association for the Study of Pain (IASP) revised the definition of pain as "an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage" (Raja et al., 2020).

Pain is categorised as acute or chronic pain based on the duration and mechanism characteristics of different clinical entitles (Grichnik and Ferrante, 1991). With a short duration, acute pain can be relieved by curing the damaged tissue. Acute pain is protective of the body by impacting the behaviour to prevent further damage (Treede et al., 2015b). In contrast, chronic pain is long-term and considered harmful (Ligon et al., 2016). Clinical interview or questionnaires about pain are mainly used for assessing pain.

In our study, chronic pain (or persistent pain) is defined as pain that lasts for more than three months /12 weeks as has been defined by IASP as being clear and measurable (Treede et al., 2019).

2.2.1.2 Classifications of chronic pain

Chronic pain is classified as chronic primary pain (in single or multiple sites, significant emotional distress or significant disability in functioning and daily life), chronic cancer pain (caused by cancer itself or cancer treatment), chronic postsurgical and posttraumatic pain (after surgery or from injuries), chronic neuropathic pain (caused by the damage of the nervous system), chronic headache and orofacial pain (occurring on at least half of the days for at least three months), chronic visceral pain, and chronic musculoskeletal (MSK) pain (directly affecting bones, joints, muscles, or related soft tissues) (Treede et al., 2015b).

Neuropathic pain is cause by a lesion or disease involving the peripheral or central nervous system from a stroke, diabetic neuropathy and other injuries of the nervous system (Dworkin et al., 2003).

Chronic widespread pain (CWP) has been included in the definition of chronic primary pain. CWP as defined by the American College of Rheumatology 1990 (ACR-1990) as chronic pain (pain lasting longer than three months) "being on the left and right sides of the body, above and below the waist, and on the axial skeleton (Wolfe et al., 1990)." The definition of CWP has been further developed and in 2010, ACR-2010 defined CWP as chronic pain in multiple sites of the body with additional physical symptoms (Wolfe et al., 2010).

There are also different locations of bodily chronic pain: head pain, face pain, neck pain, shoulder pain, back pain, low back pain, abdominal pain, hip pain, knee pain, joint pain, arm or leg pain (Bair et al., 2003).

2.2.1.3 Prevalence of chronic pain

Chronic pain is a significant public health concern in developed (Tunks et al., 2008) and developing countries (Sá et al., 2019).

The prevalence of chronic pain estimates varies across studies, in different research settings and definitions of chronic pain. Chronic pain affects approximately 20% of the population (Treede et al., 2015b). The prevalence of

chronic pain lasting for more than six months was measured at 19% in 15 European countries and Israel (Breivik et al., 2006). The pooled prevalence from a systematic review and meta-analysis was 43.5% (95% CI: 38.4%-48.6%) from 19 studies of the population in the UK (Fayaz et al., 2016). The prevalence of chronic pain from a telephone survey was 18.9% of a representative sample of adults in Canada (Schopflocher et al., 2011). Pain for three months was self-reported by 17.1% of males and 20.0% of females in a randomly selected sample of 17,543 people from the Australian population (Blyth et al., 2001). In 2016, 20.4% of U.S. adults (50.0 million) reported chronic pain from National Health Interview Survey (NHIS) data (Dahlhamer et al., 2018). The pooled prevalence from a systematic review and meta-analysis of studies in South America, Asia and Africa was 18% (95% CI: 10%-28%) after adjusting for publication bias (Sá et al., 2019).

Regarding CWP, a systematic review and meta-analysis show prevalence estimates for CWP ranged between 10% and 15% (Mansfield et al., 2016). A cross-sectional study of adults in the general population in the North of England reported that the prevalence of CWP was 11.2% (Croft et al., 1993).

2.2.1.4 Impact of chronic pain

The QoL of individuals is significantly impacted by chronic pain. QoL for people with chronic pain was reported to be significantly reduced relating to psychological diseases like depression and anxiety (Inoue et al., 2015, Kalia and OConnor, 2005, Reid et al., 2011). Depression was a major challenge for chronic pain relief and thus highly related to QoL in people with chronic pain (Elliott et al., 2003), which is discussed in detail in the next section.

Life expectancy for people with chronic pain is reduced mainly due to cardiovascular disease (Okifuji and Hare, 2015). A survival analysis of a cohort of 6,940 individuals followed for ten years found that chronic pain was significantly associated with all-cause mortality (HR 1.32, 99% CI, 1.14-1.54) (HR, hazard ratio; CI, confidence interval) (Torrance et al., 2010). After adjusting for the covariates of sociodemographic factors and other LTCs, the association between chronic pain and death was no longer significant. However, the association between severe

chronic pain (severity assessed by Chronic Pain Grade questionnaire) and death was significant (HR 1.49, 99% CI 1.21-1.84) as was death due to circulatory system diseases (HR 1.68, 99% CI 1.20-2.35). After adjusting for sociodemographic factors (age, gender, ethnicity, and Townsend score), participants with CWP were 30% more at risk of death than pain-free participants, specifically associated with death due to cancer and cardiometabolic disease (McBeth et al., 2009). Other studies also found that participants with CWP had an increased risk of excessive mortality (Macfarlane et al., 2017) and death due to cardiovascular disease after adjusting for the confounders of lifestyle factors (Croft et al., 1993).

Chronic pain has been shown to be associated with a higher risk of suicide (Hooley et al., 2014, Hassett et al., 2014) and related to negative feelings like depression and hopelessness and higher overdose deaths (Bohnert et al., 2016, Dunn et al., 2010).

2.2.1.5 Management of chronic pain

Chronic pain is a personal experience that people may not be able to accurately describe to others (Vetter, 2007). It can only be described and expressed by people who experienced an unpleasant experience and could not be confirmed by visible tissue damage or confirmed by investigation data (Kleinman, 2020). It does not necessarily have a specific cause. The clear mechanisms of chronic pain can be unknown and with multiple mechanisms proposed (Dobecki et al., 2006).

Accompanying psychological and functioning problems, the disease burden of pain itself is only one of the challenges for people living with chronic pain. An early study concluded that chronic pain could not be entirely cured for most patients (Ashburn and Staats, 1999). In a survey study in 2005, moderate to severe chronic non-cancer pain was reported by 40% of the participants as not being adequately controlled by prescription pain medication (Breivik et al., 2006). The healthcare of chronic pain aims to control the pain and make the patient function as well as possible (Ashburn and Staats, 1999).

2.2.2 Cardiometabolic disease

2.2.2.1 Types of Cardiometabolic disease

Cardiometabolic diseases are a group of chronic conditions of cardiovascular disease (CVD) and metabolic health issues (Ndisang and Rastogi, 2013).

Cardiovascular diseases are conditions related to the heart or blood vessels, including heart diseases and stroke (Nabel, 2003). Coronary heart disease (CHD), or coronary artery disease, develops from limited blood flow or damage to blood vessels supplying the heart (Torpy et al., 2009). Angina is one of the important symptoms of CHD, which is pain or discomfort in the chest that occurs when the heart muscle is short of supply of oxygen from the blood (Cubrilo-Turek, 2003). Myocardial infarction (MI), also known as a heart attack, is another clinical presentation of CHD that occurs when the supply of oxygen from the blood is completely blocked, and heart muscle may be damaged (Henderson, 1996). Heart failure (HF) is a complex of symptoms, including fatigue, breathlessness, and congestion, that occurs when the heart muscle is damaged and inadequately pumps blood over the body (Cohn, 1996). Atrial fibrillation (AF) is the random but not rhythmic contraction of atria which causes irregular and rapid heart rate with reduced efficiency and performance of the heart (Nattel, 2002). AF is commonly associated with CHD and HF (Lip and Tse, 2007). Peripheral vascular disease (PVD), also named peripheral arterial disease, is a circulation disorder caused by narrowing of blood vessels outside the heart or supplying other organs like the brain and lower limb (Baumgartner et al., 2005). Stroke (cerebrovascular disease) is a condition that occurs when blood flow is disrupted by the blockage or haemorrhage of blood vessels supplying the brain, causing death and dysfunction of brain cells (Lo et al., 2003). When the disruption and damage are temporary with a short duration, a transient ischaemic attack (TIA) occurs (Daffertshofer et al., 2004).

Metabolic disease is a cluster of conditions of the abnormal or disrupted metabolism process closely related to obesity, insulin resistance, and dyslipidemia (Eckel et al., 2005). Obesity, measured by the body mass index (BMI, kg/m^2), can

exacerbate insulin resistance and contribute to developing CVD (Guo et al., 2014). Diabetes mellitus is a chronic condition affected by glucose metabolism, including type I diabetes and type II diabetes (Forouhi and Wareham, 2010). The glucose level in the blood is higher than normal in patients with type I diabetes. Type II diabetes is caused by problems with abnormal insulin in the body. Hypertension refers to lasting high blood pressure (Staessen et al., 2003). Problems with metabolism are also risk factors for CVD (Cornier et al., 2008).

These conditions are highly related to each other and combined as cardiometabolic disease, the concept of overlap between metabolic health issues and CVD (Saxon et al., 2020).

2.2.2.2 Prevalence of cardiometabolic disease

Cardiometabolic disease has become a growing burden globally (Sattar et al., 2020).

From 2009-2012, 15.5 million people in the United States over 20 years were estimated to have CHD, with the prevalence of CHD of 7.6% and 5.0% for males and females; the estimated prevalence of stroke was 2.6% (Balakumar et al., 2016). In a systematic review of 53 studies, the prevalence of CVD was 32.2% in people with diabetes (N = 4,289,140) (Einarson et al., 2018). Diabetes prevalence has increased rapidly in recent years (Zimmet et al., 2014). In a study of around 30,000 participants with cancer in the US, the most common conditions were hypertension and diabetes (Piccirillo et al., 2008). Hypertension (Staessen et al., 2003) is one of the most common diseases in developed countries, with a prevalence of more than 20% in the general population (Nabel, 2003). In a large cohort in the US that was followed for ten years, the crude cumulative incidence of newly diagnosed diabetes was 6.1% (Guo et al., 2014).

2.2.2.3 Impact of cardiometabolic disease

Cardiometabolic disease has severe consequences and is one of the leading causes of death globally.

The mortality from CVD has been found to decrease over the past few decades due to improvements in prevention and treatment, but meanwhile, metabolic disease has increased globally and is occurring in the younger population due to lifestyle changes (Sattar et al., 2020).

During 1997-2007, the incidence of age-adjusted mortality rates (per 100 000 population) in the general population in the United States were 165.0 from heart disease, 37.6 from stroke, 21.5 from diabetes, and 9.0 from hypertension (Shah et al., 2019). Whilst a second study reported that over one-third of all deaths in the United States were attributable to CVD in the United States in 2000 (Nabel, 2003). CVD was reported as one of the leading causes of death, followed by cancer in high-income countries (HICs) (Dagenais et al., 2020, Guo et al., 2014, Baron-Franco et al., 2017). Type II diabetes is associated with rising morbidity and mortality risk and a high financial burden as an epidemic in HICs and globally (Guo et al., 2014).

Cardiometabolic disease not only impacts mortality but also health service utilisation like hospital admissions and is associated with a high economic burden (Kurlander et al., 2009, Liu et al., 2002). National Health Service records of the UK show that the in-patient episodes for all CVD increased by 46,300 from 2010-2014 (Bhatnagar et al., 2016).

2.2.2.4 Management of cardiometabolic disease

Cardiometabolic disease is often comorbid with other LTCs; thus, the patients should be comprehensively treated (Saxon et al., 2020).

Cardiometabolic diseases share risk factors and management in common, and there is an increasing prevalence of cardiometabolic diseases occurring together (Reiter-Brennan et al., 2021). The combination of MI, stroke and diabetes is reported to be associated with excess mortality from a study using routine primary care data via the Clinical Practice Research Datalink, covering 7% of the UK population and linked with Hospital Episode Statistics (HES) (Canoy et al., 2021). Comorbidities in HF are associated with a higher death rate and health utilisation, and worse self-care (Baron-Franco et al., 2017).

In addition to the co-occurrence of different types of cardiometabolic disease, cardiometabolic disease is commonly co-occurring with other health conditions. The examination of 17 non-communicable diseases in Dutch adults found the three most prevalent clusters were the combinations of two diseases of musculoskeletal pain, cardiometabolic diseases, and psychological distress (depression and anxiety), and were related to lower self-rated health (Slagboom et al., 2021).

With the complexity of comorbidity and multimorbidity, patients especially require comprehensive treatment caring not only for the cardiometabolic disease itself, but also the diets, physical activity, rehabilitation, self-management and psychological issues (Reiter-Brennan et al., 2021). Awareness and education of holistically managing cardiometabolic disease with co-occurrence of LTCs is essential.

2.2.3 Depression

2.2.3.1 Defining depression

Depression is a medical illness with persistent feelings of sadness that cannot remit even after the external cause of the emotions are resolved (Belmaker and Agam, 2008). Major depressive disorder (MDD) involves depressed moods, decreased interests, reduced cognitive function, and disturbed sleep and appetite (Otte et al., 2016).

There are various tools to measure depression: the questionnaire of Hospital Anxiety and Depression Scale (HADS) (Bjelland et al., 2002), the World Health Organization Well Being Index (WBI) (Topp et al., 2015), the Patient Health Questionnaire (PHQ) (Kroenke et al., 2003) and Diagnostic and Statistical Manual of Mental Disorders (DSM) (Löwe et al., 2004), and Beck Depression Inventory (BDI) (Beck et al., 1996). According to the DSM, fourth edition, Text Revision, MDD is distinguished from other depressive disorders with less symptoms, that warrants further in-depth consideration with clinicians (Soleimani et al., 2011).

2.2.3.2 Prevalence of depression

Depression has an estimated prevalence of 5% in the general population of adults globally from the World Health Organization (WHO) that varies in different countries (Reiter-Brennan et al., 2021). In a meta-analysis of a total of 68 studies, the cross-sectional prevalence of depression was reported as 12.9% (Lim et al., 2018).

Depression is widely undetected, especially in less developed countries, and the actual prevalence is underestimated because of stigma and inadequate resources for mental health (Summergrad, 2016, Löwe et al., 2004). Cross-sectional studies show the prevalence of 50-70% of undetected depression in patients in primary care (Timonen and Liukkonen, 2008).

2.2.3.3 Impact of depression

Unlike cardiometabolic disease, which is a leading cause of death, depression is rarely fatal; nevertheless, it has a significant adverse impacts on those living with the condition (Holden, 2000).

With its high prevalence and recurrent nature, depression is a major cause of functional disability globally and produces significant social and economic burdens (Gelenberg, 2010, Otte et al., 2016, Tse and Bond, 2004). It has additional adverse effects on functioning when co-occurring with other chronic conditions (Katon and Ciechanowski, 2002). The WHO of 245,404 participants from 60 countries worldwide found the one-year prevalence of depression was 3.2% (95% CI: 3.0-3.5), and depression has the greatest adverse impact on health among LTCs after controlling for confounding factors of socioeconomics and health conditions. In this World Health Survey study, participants with depression comprised 9.3% and 23.0% of those with comorbid chronic physical conditions.

Furthermore, depression is the most important psychiatric disorder for increasing the risk of suicide, and the association was found to relate to comorbid disorders (i.e. substance misuse and anxiety) (Hawton et al., 2013). Furthermore, these

comorbid disorders were associated with treating chronic pain (Wiedemer et al., 2007) and cardiometabolic disease (Casey, 2005).

2.2.3.4 Management of depression

Depression commonly occurs with physical conditions, and its management should be comprehensive and consider the combination of mental and physical conditions (Doherty and Gaughran, 2014).

Managing a mental health disorder like depression has different challenges from managing physical conditions, and there are additional challenges in managing combinations of physical and mental conditions (Jones, 2010, Doherty and Gaughran, 2014). A higher prevalence of chronic physical conditions was reported in 6,510 adults who had a mental disorder in Korea between 2006 and 2007 (Chang et al., 2016b). General adult population surveys collected in 17 countries show a significant association between physical conditions and depressive and/or anxiety disorders (Scott et al., 2007).

In addition, depression is frequently undetected and patients' unwillingness to seek help hampers the treatment and management of depression (Health, 2010).

2.3 Co-occurrence of two diseases

This section shows that the cooccurrence of two diseases from chronic pain, cardiometabolic disease and depression, are well recognised and extensively researched.

2.3.1 Pain & cardiometabolic disease

Existing literature shows the association between chronic pain and CVD (Bahramali, 2016). In a retrospective chart review in the US, 56.4% of patients admitted to the cardiology service were on pain medication (Kabbara et al., 2018). As outlined above, PVD is a circulation disorder in blood vessels outside the heart or other organs and is common in lower limb pain (Balakumar et al., 2016). In a report

from the American Heart Association, approximately 60% of people with PVD had various leg symptoms of pain and claudication (Mozaffarian et al., 2016).

Central post-stroke pain (CPSP) is a common complication of stroke (Harrison and Field, 2015, Naija et al., 2013). In a prospective hospital-based multicentre study in Italy, the prevalence of pain was 31.90% in the chronic post-stroke stage (Paolucci et al., 2016). A meta-analysis of 69 studies estimated the pooled prevalence of CPSP in patients with stroke at 11% (95% CI: 7-18%) (Liampas et al., 2020).

Diabetic painful neuropathy (DPN) is one of the most common chronic complications of diabetes (Gianarkis and Fusco, 2010), and many studies have examined the combination of neuropathic pain and diabetes (Cortez et al., 2014). The prevalence of diabetic peripheral neuropathic pain (DPNP) was 30.3% (N = 1,046) in patients with diabetes examined in a cross-sectional study in South Africa (Jacovides et al., 2014). Patients with painful DPN were found to have a lower QoL than DPN patients without pain in a Croatia study (Dobrota et al., 2014). A study of 993 participants with diabetes from Veterans Affairs medical centres in the US shows that those with chronic pain comprised around 60% of respondents and had poorer self-management of diabetes (Krein et al., 2005). After adjusting for risk factors, Participants with diabetes had a statistically significant higher prevalence of chronic low back pain from the National Health and Nutrition Examination Survey (NHANES) in 2009-2010 (Hassoon et al., 2016). Chronic pain was significantly associated with a decreased health-related QoL in participants with diabetes in a German study of around 500 multimorbid patients with type II diabetes (Kamradt et al., 2017).

2.3.2 Pain & Depression

Although chronic pain and depression are independent and distinct, their association is well-recognised, and antidepressants are widely used to treat chronic pain conditions (Saravanan and Krishnaraju, 2013).

People living with chronic pain are reported to have a co-occurrence of psychological problems (Ashburn and Staats, 1999), and depression is the most common mental health disorder in people with chronic pain (Birket – Smith, 2001). As well as producing physical symptoms, chronic pain can lead to anxiety and depression (Niikura et al., 2010) and affect health by causing sleep disturbance and substance-related disorders (Katzman et al., 2014). Neural mechanisms of pain-induced depression have been examined (Humo et al., 2019, Sheng et al., 2017). The combination of pain and depression is associated with more medical visits and higher costs in healthcare (Bair et al., 2003).

In a review, the prevalence of pain varies from 15% to 100%, with an average of 65%, in patients with depression, due to different settings of the study and different ways of measuring pain and depression (Bair et al., 2003). Another literature review found that people with depression are more likely to have pain symptoms than those without depression (Katona et al., 2005). 21% of participants were diagnosed with depression because of their pain in a study of 46,394 participants from 15 European countries and Israel (Breivik et al., 2006).

People with chronic pain and depression reported more severe pain, and the severity is positively associated with the degree of depression, as discussed in a review article (Birket – Smith, 2001). CWP was found to be strongly associated with depression and anxiety in a cross-sectional study of 2,034 participants in the UK (Croft et al., 1993). In term of the link of depression and pain, the definite timeline of which comes first is unknown, as there is evidence to support both timelines (Linton and Bergbom, 2011).

2.3.3 Cardiometabolic disease & depression

Cardiometabolic disease is associated with depression through potential biological mechanisms of altered sympathetic stimulation and lipid metabolism related to depression, lifestyle factors like physical inactivity influenced by depression, and negative mood from depression (Balakumar et al., 2016). In addition to psychological causes, several metabolic conditions, such as insulin resistance, and high blood pressure, may be the causal pathways of depression (Plante, 2005).

Depression is associated with various medical problems, including heart disease (Holden, 2000). The prevalence of depression in patients with HF ranges from 13% to 77% (Lang and Mancini, 2007), and the authors observed potential interactions between antidepressant medications and those medications commonly used in the treatment of HF (Sherwood et al., 2007). Depression is one of the important consequences of stroke, and post-stroke depression affects functional recovery (Qin et al., 2018). Post-stroke depression is associated with higher levels of impaired cognition and higher mortality rates (Kotila et al., 1999). Patients with diabetes are approximately three times more likely to have depression than those without diabetes, as discussed in a review article (Balakumar et al., 2016).

2.4 Co-occurrence of all three conditions

The comorbidity of chronic pain, cardiometabolic disease and depression was chosen as an exemplar of commonly occurring conditions, in order to consider impacts and outcomes of such a combination of conditions. This section underpins why these conditions were chosen and outlines what is known about this comorbidity of interest.

2.4.1 Justification of this specific combination

The examination of the specific combination of chronic pain, cardiometabolic disease, and depression is of significant importance due to the high prevalence of these conditions individually in the population and their significant impact on health outcomes, as outlined in section 2.2. The three conditions are closely related with each other and very likely to co-occur in terms of shared mechanisms and shared risk factors. The presence of one condition may increase the risk of developing or exacerbating the other two conditions, creating a complex interplay between the conditions.

2.4.1.1 Shared mechanisms

Existing evidence has suggests that depression, cardiometabolic conditions, and musculoskeletal pain are interconnected (Slagboom et al., 2021). Pain and depression are both subjective experiences that are influenced by various factors

such as experiences, cognitive processes, and emotional states (Nekovarova et al., 2014). Research suggests that the combination of chronic pain and depression may relate to neural substrates, and there is growing evidence that neuroimmune and neuroinflammatory mechanisms play a significant role in the association between chronic pain and depression (Burke et al., 2015). Psychological factors of maladaptive coping responses from an individual's chronic pain experience, such as increased negative thinking, perceived helplessness, and low self-efficacy, may lead to depression (Campbell et al., 2003).

The association of chronic pain and depression is not only related to psychiatric aspects, but also related to cardiometabolic conditions (Scherer et al., 2016). Dysregulated homeostatic biological pathways in depressed patients, such as increased inflammation and disrupted leptin and insulin, may explain the common phenomenon of the combination of depression and cardiometabolic conditions (Milaneschi et al., 2020). A study examined comorbidity of MDD and cardiometabolic conditions and found that certain deficiencies in brain activity within the stress circuitry can lead to a loss of parasympathetic control, and parasympathetic motor nuclei in the brainstem can have negative impacts on overall cardiovascular function (Goldstein et al., 2019).

However, the relationship between the three conditions is complex and bidirectional. It's important to address the three conditions in a comprehensive manner to improve overall well-being.

2.4.1.2 Shared risk factors

These conditions share several risk factors, such as socioeconomic status, obesity and physical activity, that may contribute to the development and exacerbation of the three conditions (Guo et al., 2014). Poor access to healthcare for individuals from areas of low socioeconomic status may contribute to the development of these three conditions. Obesity is an important risk factor of cardiometabolic disease (Cornier et al., 2008), while it also has a strong independent association with pain that is not fully explained by markers of insulin resistance, inflammation, osteoarthritis, or neuropathy (Ray et al., 2011). Low physical activity is another

important risk factor of chronic pain (particularly back pain), cardiometabolic disease and depression (Andreae, 2016, Cassidy et al., 2016). Noncompliance with medical recommendations and smoking cessation, which are strongly associated with depression, could lead to the development of cardiovascular disease (Joynt et al., 2003).

The examination of the specific combination of these conditions can provide valuable insight that may inform the development of more effective interventions and management.

2.4.2 Existing evidence

Several studies have involved the examination of chronic pain, cardiometabolic disease, and depression, but did not touch on the combination of these three conditions and thus provided very little information about the prevalence, associated factors and the impact of the comorbidity, as detailed below.

A large population-based cohort of 453,648 participants in Denmark evaluated the effect of perceived stress on the survival of people with multimorbidity (Prior et al., 2016). The three conditions of interest (chronic pain, cardiometabolic disease and depression) were examined in this cohort study, but the particular combination of these three conditions was not examined specifically. A study that examined systematic reviews reporting sex effects of chronic pain, cardiometabolic disease and depression (Duan-Porter et al., 2016) focused on evaluating sex effects rather than investigating the combination of the three conditions. The effects of post-stroke pain on QoL and depression in stroke were examined in 24 patients with post-stroke pain (Mishchenko et al., 2017). However, the pain was assessed by asking if the participant had pain over the last week. The average duration of included participants was 2.3 ± 0.9 months (mean ± SD, standard deviation). The findings could not show the long-term effect of pain with stroke and depression. In addition, the sample size is relatively small, thus weak to reflect the overall pattern of the comorbidity in the general population. A qualitative study interviewed 13 patients with post-stroke shoulder pain. It found a negative influence of chronic pain on self-management and that the pain could

lead to negative mental health experiences like depressive feelings (Lindgren et al., 2018). However, depressive and other psychiatric symptoms were mixed together and not examined in the sample of participants with chronic pain and cardiometabolic disease.

Given that very limited literature was identified from a brief scoping review, a more comprehensive systematic review was needed to identify the existing evidence on the comorbidity of chronic pain, cardiometabolic disease and depression.

Overall, the examination of chronic pain, cardiometabolic disease and depression is of significant importance due to the high prevalence of these conditions in the population and their significant impact on individual and societal well-being. Furthermore, the presence of one condition may increase the risk of developing the other conditions, creating a complex interplay between the conditions. The examination of the specific combination of these conditions can provide valuable insight into shared mechanisms and aetiologies that may inform the development of more effective interventions and treatments.

2.4.3 Lack of evidence

2.4.3.1 Measurement of the comorbidity

The evidence outlined above shows that chronic pain, cardiometabolic disease and depression are prevalent individually and in combination with two diseases. Thus, the co-occurrence of all three conditions would not be expected to be unusual. However, limited population-based information is available on the comorbidity of chronic pain, cardiometabolic disease and depression, and the prevalence of this pattern of comorbidity is uncertain.

Moreover, the characteristics of people with chronic pain, cardiometabolic disease and depression is not known. The distribution of sociodemographic (age, gender, ethnicity, economic status, education level, income, marital status) and lifestyle

factors (smoking, alcohol intake, dietary patterns, caffeine intake, physical activity) in the population with chronic pain, cardiometabolic disease and depression has not been examined. This combination of diseases with different characteristics may have a complex pattern of risk factors. For example, stronger associations between depression and pain was found at a younger age (Schaakxs et al., 2017), but cardiometabolic disease was found associated with advancing age (Sniderman and Furberg, 2008). In a population study in Scotland, it was found that the absolute number of participants with multimorbidity was higher in participants younger than 65 years, which could result from the combination of physical and mental conditions (Barnett et al., 2012).

As summarised in the previous sections, the adverse health effects of chronic pain, cardiometabolic disease and depression individually are well recognised, and the more severe effects of the combination of two diseases from these three conditions are somewhat known. However, little existing literature has focused on the health effects of the combination of all these three conditions.

It is important to know whether the combination of these three prevalent conditions with significant negative impacts on health outcomes is a common phenomenon and to know the characteristics of the population with this comorbidity and the factors associated with the comorbidity, along with the impact on health outcomes.

2.4.3.2 Patients' perspectives

Chronic illnesses like chronic pain, cardiometabolic disease and depression impact people's daily life and cause significant disease burden (Kowal et al., 2012, Greden, 2001, Tandon et al., 2018) and treatment burden (Gallacher et al., 2018). Treatment burden describes the work a person does to manage their illness(es), including scheduling and attending appointments, accessing clinics, obtaining prescriptions, self-monitoring (i.e. checking blood pressure and blood sugar), enacting self-management routines, and improving diet and lifestyles (i.e. physical activity, smoking and drinking alcohol) (Katon and Ciechanowski, 2002). Existing

literature has discussed key core components of treatment burden (Mair and May, 2014).

It is known, therefore, that living with chronic illness is challenging and one might reasonably suppose that living with multiple chronic diseases can be more challenging than with single conditions (Hughes et al., 2013). With both physical and mental health symptoms, the comorbidity of chronic pain, cardiometabolic disease and depression may be complex to manage. Thus, living with the comorbidity of the three conditions together could be a complex cumulative burden. Comorbidity could potentially lead to reduced adherence to treatment and medication due to negative feelings from the depression or the level of the treatment burden, growing healthcare costs and indirect costs, and more health service utilisation. However, little research on patients' perspectives of living with chronic pain, cardiometabolic disease and depression individually has been done, as discussed in a previous study (Katona et al., 2005). Moreover, patients' descriptions of living with the comorbidity of these three conditions together, their insights into this specific combination, and their experience with health care is unknown.

2.5 Aims and objectives

This thesis aims to examine the prevalence of the comorbidity of chronic pain, cardiometabolic disease and depression and its effects on health outcomes and to explore the lived experiences and insights of people with this combination of conditions. More specifically, this thesis aimed to answer the following research questions:

1. What do we know about the comorbidity of chronic pain, cardiometabolic disease and depression?

2. How common is it to have this comorbidity and what sociodemographic and lifestyle factors are associated with the comorbidity?

3. What are the effects on health outcomes of this comorbidity?

4. What is the lived experience and insight of people living with this comorbidity?

A Multimethod approach was used to answer the research questions, and involved four distinct phases of work:

1. Systematic review and synthesis of current literature relating to individuals with the comorbidity of chronic pain, cardiometabolic disease and depression;

2. Cross-sectional study of the prevalence and association of sociodemographic and lifestyle factors with the comorbidity reporting in UK Biobank, a large dataset of over 500,000 adults aged 38-73 in the UK;

3. A cohort study examining the relationship between the comorbidity and health outcomes from data linkage of baseline and routine health data, including hospital admission and mortality (using UK Biobank);

4. Secondary analysis of a qualitative study of participants' perspectives on the daily life of living with the comorbidity, to describe the everyday experience and understand the participants' insights.

2.6 Conclusion

The exploration of the comorbidity of chronic pain, cardiometabolic disease and depression could potentially inform the development of interventions that could optimise management of the comorbidity and improve the care of people living with this comorbidity.

In this chapter, the background knowledge on the comorbidity of chronic pain, cardiometabolic disease and depression was presented. A clear evidence gap was identified and informed the aims and research questions for the thesis. The first phase of research, a systematic review, is described in the next chapter, providing

a more precise synthesis of what is known about the comorbidity of chronic pain, cardiometabolic disease and depression.

Chapter 3 Methodology

3.1 Introduction

3.1.1 Overview of this chapter

This chapter provides a theoretical background and overview of the rationale for the three methods used in the study: 1) systematic review of existing literature (Chapter 4); 2) quantitative analysis of UK Biobank data (Chapters 5 & 6); and 3) qualitative analysis, through secondary data analysis of semi-structured interview transcripts (Chapter 7). It also outlines the reasons for using multiple methods (a multimethod approach) to address the study objectives.

3.1.2 Rationale

Based on the current knowledge and evidence gaps outlined in Chapter 2, research methods have been used to allow the four research questions to be answered.

This thesis used multiple methods to enable a broad exploration of the comorbidity of the three health conditions of interest (chronic pain, cardiometabolic disease, and depression) from different perspectives. The three methods, systematic review, quantitative and qualitative data analysis, did not investigate the same or parallel research question but addressed closely connected yet distinct research questions. The systematic review aimed to provide an overall picture of what is known on the subject thus far and to identify key gaps in knowledge. The quantitative and qualitative studies complement each other, both addressing evidence gaps highlighted by the systematic review.

3.2 Multimethod

3.2.1 The paradigm of quantitative & qualitative approaches

Much has been written about the different paradigms underlying quantitative and qualitative approaches (Brannen and Coram, 1992, Creswell, 1994) and the key differences between them. At the core, the divergence is rooted in the ontology (the nature of reality) and epistemology (how reality is known) of each approach (Arghode, 2012). Here, an overview of the different approaches is provided, with the key differences compared.

3.2.1.1 Deductive vs inductive approach

Quantitative studies originated in natural science to measure observations in experimental conditions, while qualitative studies originated in social science and foreground interpretation (Tuli, 2010).

Quantitative approaches could be inductive but are typically deductive, with rigorously observed subjects and statistical tests to assess the reliability of a hypothesis based on existing theory or knowledge (Queirós et al., 2017). Data is collected from observations and experiments to arrive at speculative answers to accept or reject a falsifiable hypothesis. It could be problematic when the premise and assumptions of the hypothesis are invalid (Khaldi, 2017).

Qualitative approaches are inductively focused on the process and meaning instead of merely outcomes (Ochieng, 2009). Qualitative research may simplify data without dismissing the complexity and context. However, there exists the subjection bias from researchers and the control of the situations and conditions of the observations. In addition, the findings are unique and not as applicable to general populations to the same extent as quantitative studies (Khaldi, 2017).

3.2.1.2 Positivism vs interpretivism

Positivism is aligned with deductive approaches to testing a priori hypothesis (Park et al., 2020). Positivist science argues that reality exists as an objective entity

and is accessible to be understood, identified and measured (Alharahsheh and Pius, 2020). The reality should be obtained objectively to examine the explanatory or casual relationships, and the researchers should be independent of the research participants (Goduka, 2012) and create knowledge through the value-free procedure (Sobh and Perry, 2006).

On the contrary, interpretivism believes that reality is subjective and based on people's experiences and insights (Ryan, 2018). Researchers are not independent of their subjective values influenced by culture and history, and knowledge is linked with socially constructed minds (Ritchie et al., 2013).

3.2.1.3 Choice of research instruments

The decision to choose quantitative or qualitative approaches should be made after considering which approach is most able to answer any given research question effectively. Different research designs can better answer different research questions (Casebeer and Verhoef, 1997).

For example, the quantitative analysis could examine the pattern of the diseases, the characteristic of the patients, and the association between exposures and outcomes. In comparison, the qualitative analysis could show the insights and experiences of the patients, health professionals and policymakers. Practically speaking, available resources, time consumption and funding should also be considered when choosing methods to explore any given research topic (McCusker and Gunaydin, 2015).

3.2.2 Multimethod and mixed methods

3.2.2.1 Combination of approaches

As the assumptions in paradigms of quantitative and qualitative approaches are conflicting, the validity of combining methods is often questioned. However, the boundaries between quantitative and qualitative approaches are less fixed, and the use of methodologies combining the two paradigms has now expanded rapidly over several decades (Khaldi, 2017).

Multimethod and mixed methods aim to understand a phenomenon, disease, or other issues from multiple perspectives (Shorten and Smith, 2017). More than one approach is used to address a range of research questions that neither quantitative nor qualitative methods can answer alone and provides a deeper understanding of the research topic (Ivankova et al., 2006). It compensates for the limitations of the single research method (Bryman, 2016) and can be viewed as more powerful than single studies (Estabrooks et al., 1994). The combination of different approaches may identify overlapping findings and contradictions from different approaches (Dixon-Woods et al., 2004). With overlapping findings, they corroborate and complement each other; with contradicted findings, they address the limitations of each other. For complex research questions, multiple approaches together could provide better answers to see the complex question from different viewpoints (Khaldi, 2017).

3.2.2.2 Multimethod vs mixed methods

Mixed methods are research designs combining qualitative and quantitative approaches in the same study to answer the same question from different angles, in either parallel or sequential phases (Tashakkori and Teddlie, 2010). Multimethod research involves two or more sources of data or research methods to examine different but related research questions (Lewis-Beck et al., 2003).

Multimethod and mixed methods are similar in that they use a combination of different approaches; they are different in terms of data sources and research questions for each approach. Mixed methods usually refer to the combination of quantitative and qualitative methods; instead, multimethod is open to various combinations of methods (Anguera et al., 2018).

3.2.2.3 Multimethod approach in this thesis

In this thesis, instead of choosing between one of the approaches, a combination of multiple methods (multimethod) was used. Multimethod rather than mixed methods is more appropriate, as this thesis was not limited to parallel research questions but a series of progressive and linked research questions that were used to fulfil the overall aim of the research to explore the comorbidity of chronic pain,

cardiometabolic disease and depression in terms of prevalence, health outcomes and patients' perspectives.

As mentioned above and detailed in Chapters 4-7, this thesis applied a narrative systematic review to present how much is known about the comorbidity of the three LTCs of interest, data analyses of a large cohort to quantify the comorbidity, and secondary analysis of interviews with people with the comorbidity to describe their lived experienced and insight into the comorbidity.

3.3 Systematic review

A narrative systematic review was undertaken to identify the current literature involving the comorbidity of the three conditions of interest and to determine how much is known about the prevalence, health outcomes and patients' perspectives of the comorbidity.

3.3.1 Systematic review types

The purpose of a systematic review is to collect and combine evidence for specific research questions (Ahn and Kang, 2018). It is an essential and commonly used approach in medical research (Jahan et al., 2016). There are two main ways of analysis: a meta-analysis using a statistical calculation to combine several quantitative studies into one estimated effect (Field and Gillett, 2010) or a narrative analysis to summarise the descriptive information from the studies (Popay et al., 2006).

3.3.1.1 Meta-analysis

Meta-analysis usually applies to medical findings with numeric measures performed in a few or many studies to provide enough evidence for the statistical procedure (Rosenthal and DiMatteo, 2001). It is suitable when multiple studies exist so that meta-analysis can reach an evidence-based conclusion for clinical decisions (Haidich, 2010). Studies need to homogeneous results to be used for arriving a summary measure in a meta-analysis (L'abbé et al., 1987).

3.3.1.2 Narrative analysis

Narrative analyses of a systematic review aim to synthesise the findings from multiple studies. Quantitative studies with numeric measures are synthesised using text rather than a statistical procedure (Popay et al., 2006). Narrative systematic reviews differ from narrative literature reviews in that a narrative systematic review aims to conduct narrative synthesis and combine the findings from heterogeneous studies using a systematic review approach (Green et al., 2006), such as following The Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) (Page et al., 2021). Whereas a narrative literature review tends to be an overview of available literature on a topic without a fully systematic approach.

Narrative systematic reviews are widely used when heterogeneous data are included, and meta-analyses are not possible (Rychetnik et al., 2004). In medical research, this method has been commonly used for the exploration of mental health conditions (Rice et al., 2016, Boath et al., 2005), perspectives and experiences of patients (Ingram et al., 2020, Gadkari and McHorney, 2010, Lu et al., 2020, Harden et al., 2004) and research questions about reasoning and decision-making (Day et al., 2016, Contandriopoulos et al., 2010, Gough and Elbourne, 2002).

A narrative systematic review involves a systematic search of the current literature in all the main scientific publication databases with a detailed search strategy, eligibility criteria, double reviewing to minimise selection bias, quality appraisal, and synthesising to collate the data of interest and interpret the findings (Uman, 2011).

3.3.2 Systematic review in this thesis

This thesis focuses on the combination of both physical and mental health conditions. To fulfil the objectives of examining the prevalence, health outcomes and patients' perspectives of the comorbidity, both quantitative and qualitative studies were included. Moreover, there was sparse literature examining the

comorbidity of chronic pain, cardiometabolic disease and depression; therefore, a meta-analysis to estimate the prevalence across multiple studies was not possible (Barendregt et al., 2013). Thus, with the heterogenous data and limited data, a narrative systematic review provided the most suitable mechanism to produce a summary and critique of the existing evidence in this field.

Detailed step-by-step methods for the systematic review are outlined in Chapter 4.

3.4 Quantitative study

In order to quantify the prevalence, associated factors and health outcomes in those with the comorbidity of chronic pain, cardiometabolic disease and depression, a quantitative analysis of a large UK-based cohort, UK Biobank, was undertaken.

3.4.1 Datasets for the analysis

3.4.1.1 UK Biobank

UK Biobank (Biobank, 2022) is a large prospective biomedical dataset with a wide range of exposures of over 500,000 adults aged 38-73 years from England, Scotland and Wales recruited between 2006-2010 (Allen et al., 2012). The Medical Research Council (MRC) and Wellcome Trust established UK Biobank to investigate biomedical research of middle and old aged people. Around 9.2 million people registered with the National Health Service (NHS), aged around 40-70 and living up to about 25 miles from one of the 22 study assessment centres in England, Scotland and Wales, were invited to participate, and 503,325 participants were recruited in UK Biobank cohort, with the response rate around 5.47%.

The datasets included information about genetic and environmental determinants of disease collected through questionnaires, physical measurements, and biological samples. Additional questionnaires and investigations are also being undertaken in subsets of the population. In addition to the baseline data, the cohort is being followed up through linkages to routine data of subsequent health outcomes, with

over 8,500 deaths from national mortality registry (NMR) and over 600,000 cases of hospital admission from hospital episodes statistics (HES) (Sudlow et al., 2015).

To be more detailed, at baseline, verbal interviews were conducted by trained nurses at the 22 UK Biobank Assessment Centres after completing a touchscreen questionnaire. The data of exposures like early life factors (e.g. birth weight and location), employment, medical conditions, medications and operations were collected. The questions asked in the verbal interview were linked to the responses in the touchscreen questionnaire. The participants were asked if a doctor had told them that they have cancer or other chronic conditions (e.g. heart attack, angina, stroke, hypertension, diabetes) in the touchscreen questionnaire. If they reported having been told by a doctor that they had any chronic condition, they would be asked for more details in the verbal interview. From the verbal interview, the diseases were coded in the system using the 10th version of the International Statistical Classification of Diseases (ICD-10) (Hirsch et al., 2016). Similarly, for medication, the participants were asked for details about current medications if they answered “yes” to the question asking whether they took regular prescription medications in the touchscreen questionnaire. If the answer were "no" or "not sure", they would be asked the question again in the interview to confirm the response was accurate. The details of the interview procedure were obtained from the manual published in March 2012 (Biobank, 2012).

In this thesis, the eligible study sample was identified through the responses to the self-reported chronic conditions and the prescribed medications (anti-depressants) to aid the diagnosis of depression. Epidemiological studies (cross-sectional and longitudinal) examined the prevalence, sociodemographic, lifestyle and health factors, and health-related outcomes of the three LTCs of interest. Variables of medications, health conditions, and sociodemographic and lifestyle factors used in this study are described fully in Chapter 5. The linkage data of NMR and HES are described in Chapter 6.

3.4.1.2 Ethics & data management

Ethical approval has been received for UK Biobank projects (16/NW/0274) (Appendix 1). This work has been conducted under UK Biobank approved project 14151. I am an approved and registered UK Biobank user on this project. The data is stored in a secure, password-protected University server.

3.4.1.3 Strengths and limitations of UK Biobank

The most significant strength of UK Biobank is that it is a large dataset with extremely rich information, on over half a million participants. When collecting the data on self-reported cardiometabolic diseases, depression and additional LTCs, a questionnaire followed by a verbal interview was conducted. Furthermore, the participants were blind to the objective of the research question for future studies during the baseline data collection, which can reduce the recall bias and reverse causation bias (Allen et al., 2012).

Despite the significant strengths of using UK Biobank data, there were also limitations of using UK Biobank.

The response rate of recruitment is around 5.47% from 9.2 million people. In addition, all the participants volunteered to come to the assessment centre for the recruitment, so they are considered to care about their health more than nonparticipants (Fry et al., 2017). This is called healthy volunteer bias (Struijk et al., 2015). The study sample is not entirely representative of the general population in health-related issues. UK Biobank population are healthier, more affluent and includes more white participants than the general population (Hanlon et al., 2022). The study sample was not randomly selected as the participants were voluntary, which may cause collider bias and make the results less generalisable. Collider bias means a third variable influenced by exposure and outcome is improperly controlled for during sampling (Griffith et al., 2020).

UK Biobank data was collected prior to this study's design and some variables, which may have been important to this study were not available. Taking alcohol intake as an example, no variable was available to indicate the alcohol by volume

precisely. Nevertheless, more than 300 variables are available in UK Biobank for this study. Regarding the alcohol intake, there are variables including whether having alcohol with meals, whether having alcohol for more than ten years, reason for reducing the alcohol intake, the status of alcohol drinker and alcohol intake frequency, which are good alternatives for summarising alcohol intake.

In the touchscreen and interview, chronic pain was classified using the the binary response question "have you had pain for the past three months?". The measurement of chronic pain is not very accurate to indicate whether the pain is episodic or constant. Participants may have different understandings when answering this question. Being episodic doesn't mean the pain is not chronic. Low back pain has episodic and recurrent nature (McGorry et al., 2000). It was found that patients with both constant and episodic pain are distinguished from acute pain with significantly higher scores on the McGill Pain Questionnaire (Strittmatter et al., 2005). Therefore, although the measurement of chronic pain in UK Biobank does not allow us to elucidate episodic pain, it is still consistent with the definition by IASP that pain lasts for more than three months /12 weeks (Treede et al., 2019).

Nevertheless, UK Biobank is a valuable resource as a sufficiently large dataset. It has been argued that UK Biobank is generalisable by comparing the estimates of the effect of risk factors on mortality in UK Biobank and representative studies and it is a reliable source of data to provide critical information on prevalence and association data (Batty et al., 2020).

3.4.2 Research design

Both cross-sectional and longitudinal analyses were undertaken using UK Biobank.

3.4.2.1 Cross-sectional study

A cross-sectional analysis was undertaken to examine the prevalence and the factors associated with the comorbidity of chronic pain, cardiometabolic disease, and depression.

A cross-sectional study is a type of observational study in which the outcome and exposures are measured at the same time (Mann, 2003). It is considered a relatively straightforward and convenient method to estimate the prevalence and the pattern of outcomes or exposures of interest (Pandis, 2014). It is widely used to examine the prevalence and association between exposures and outcomes.

However, since a cross-sectional study is measurement at one particular time point, it cannot examine the effect of the exposures on health outcomes over time. The main limitation of cross-sectional studies is that they simultaneously examine the association between exposure and outcome and thus cannot provide evidence of causation (Solem, 2015). It evaluates prevalence instead of incidence of diseases, treatments, causal relationships, or outcomes. Participants with the outcome or disease of interest who die before a particular time point of the study would be excluded, and this would cause survivorship bias, a sample selection bias caused by only including surviving participants (Rothman et al., 2008).

Despite these limitations, the cross-sectional study is a practical study designed for generating hypotheses (Carlson and Morrison, 2009). It requires fewer resources to conduct a cross-sectional study than other observational studies (Rothman et al., 1998). Therefore, to examine the comorbidity of interest in this thesis as a novel research topic, the cross-sectional study is an excellent first step.

The cross-sectional study was used for the analysis of baseline data of UK Biobank in this study. The process of performing the cross-sectional study is detailed in Chapter 5.

3.4.2.2 Cohort study

A longitudinal or cohort study design was used to address the effect of the comorbidity on the health outcomes of this thesis. A cohort study is a type of longitudinal study to follow participants over time (Euser et al., 2009). During the follow-up period, participants are exposed or not exposed to factors of interest, and the developing health outcomes are measured after the follow-up period. Thus, it is possible to examine the associations and identify the relationship

between factors of interest (exposures) and health outcomes (Barrett and Noble, 2019).

More powerful than a cross-sectional study, longitudinal data can be used to measure the incidence of disease or outcome and allows multiple exposures and outcomes to be measured. It could indicate explanatory associations and may make it possible to establish a cause-effect relationship (Noordzij et al., 2009). To be noted, longitudinal cohorts do not necessarily prove causation, as the exposures are not randomly assigned, which is the major limitation of cohort studies. It is unknown if the exposure is the cause or a proxy of the outcome. Other factors may play a role in the association of the exposures and outcomes, which is the effect of confounding factors (Euser et al., 2009). In regression models examining the association of the exposure and the outcome, adjusting or controlling the confounding factors is to control the bias from the factors caused partially by the exposure and correlated with the outcome as well (Weinberg, 1993).

In some cohort studies, participants with particular exposures are followed to see if they develop the disease of interest (Mutambudzi et al., 2021, Rubinstein et al., 2016, Chang et al., 2016a). In this study, participants with particular diseases (i.e. the comorbidity of chronic pain, cardiometabolic disease and depression was the "exposure") were followed to examine the health outcomes of interest (death & health outcomes detailed in Chapter 6).

Prospective or retrospective approaches of cohort studies depend on the study's starting point (Euser et al., 2009). If the outcomes are completed when the study starts and the researcher looks back in time at exposures, then it is considered a retrospective study; if the cohort starts to follow from the start of the study, and the outcomes are assessed in the future, then it is prospective. The retrospective study has its strength in that it is less costly and easier to access in terms of time and resources. With the available data, a retrospective study is an efficient and valuable approach (Vandenbroucke, 2008), but it is limited to the existing data so that no more new measurements could be added. The main strength of prospective cohort is the accurate data collected specifically for the exposures, confounders and endpoints (Euser et al., 2009).

In our study, the data from UK Biobank is prospective in nature in that participants have been followed for over ten years since the initial recruitment at baseline between 2006-2010. The baseline data was then linked to the data of health outcomes of mortality registrations and HES in 2020, and the full details were provided in Chapter 6.

3.4.3 Statistical methods

Descriptive analysis, together with inferential analysis, was conducted in the quantitative studies of this thesis. Descriptive analysis simply describes a sample (Delaney, 2010). For example, the mean and median age reflected the average age level of the study sample, and the SD measured the variation of the age distribution.

Inferential analysis is a powerful method to make conclusions from examination of a sample to a population (Delaney, 2009). The theoretical knowledge of statistics of inferential analysis involved in the thesis are introduced here, and the specific details of descriptive and inferential analysis of UK Biobank is detailed in Chapter 5 and 6.

3.4.3.1 T-Test and Chi-squared Test

Student's T-test (Fay and Proschan, 2010) and Pearson's Chi-squared test (Shih and Fay, 2017) are used to compare variables across different groups of interest and were performed in a cross-sectional study in Chapter 5. The *t-test* is a statistical hypothesis test used to compare the means of continuous variables of interest (e.g. age) of two groups and can be used to test the hypothesis that two groups are different from one another. A chi-squared test is a statistical hypothesis test used to explore whether categorical variables (e.g. gender) in a given population are related (Plackett, 1983, Zibran, 2007).

Null-hypothesis (H_0) significance testing is a widely used method in inferential analysis (Nickerson, 2011). The significance level is the probability of rejecting the null hypothesis when there is actually no difference between the variables, typically set at 0.05 or 0.01 (Lehmann, 1958). P-value is the probability that the

difference in the association between the outcome and the exposure was just a result of a random chance (Feise, 2002). An association was considered statistically significant if the p-value was less than the significance level.

P-values of a large sample are generally closer to zero as the power of the test increases with the sample size. Thus, a lower significance level would be set for large samples (Khalilzadeh and Tasci, 2017). UK Biobank is a very large study sample, so the significance level was set at 0.001, which means there is less than 1 in a thousand chance of rejecting the null hypothesis and concluding that there was a difference when there was no difference. In this study, it is considered statistically significant if the p-value was less than the significance level of 0.001.

3.4.3.2 Logistic regression

Logistic regression (Tolles and Meurer, 2016) is used to quantify the association between a dependent binary variable and one or more independent variables. The logistic regression results are interpreted as Odds Ratios (ORs) (Schmidt and Kohlmann, 2008) with 95% CI. The odds are the measure of the likelihood of the outcome variable with the exposure variables. The 95% CI is a range of values with 95% confident that the true value is contained (Smithson, 2003). Here, 95% CI is used to indicate the precision of the estimate i.e. that you can say with 95% confidence that the true value of the OR lies within that range.

In this study, logistic regression was applied in the cross-sectional study in Chapter 5. The dependent variable was whether the participant had the comorbidity of chronic pain, cardiometabolic disease and depression. This was a binary variable, i.e. having the comorbidity (1) or not (0). Thus, logistic regression models were appropriate and fitted to examine the association between sociodemographic and lifestyle factors and the comorbidity.

To fit a continuous variable into the model, the distribution of the variable need not be a normal distribution, but it is assumed that the relationship between the log odds of the variable and the outcome should be linear (LaValley, 2008).

Continuous variables that do not fulfil this assumption will be manipulated into categorical variables.

The OR shows the odds of the outcome of the comorbidity occurring given the exposure to certain sociodemographic and lifestyle factors compared to the odds of the comorbidity occurring under the same exposure in the reference group. The null hypothesis was that the likelihood of the outcome of comorbidity was the same for different categories of the independent factors. As above, the significance level was set at 0.001.

3.4.3.3 Survival analysis

Survival analysis is a technique to investigate the time between entry to baseline and a subsequent event or health outcome (Lee and Go, 1997). To examine how long the participants could live and the chances of surviving with the exposure or not, survival analysis is used to explore the impact of the exposure on outcomes of interest. In this study, survival analysis was detailed in Chapter 6.

3.4.3.4 Censored data

Censorship happens when participants drop out of the study for some reason, and their survival time to event is unknown (Gijbels, 2010). Censored data are participants 1) whose event of interest has not occurred by the end of the follow-up; 2) withdrawing their participation and leaving the study; 3) loss to follow-up (Leung et al., 1997). In these cases, censoring time rather than survival time is obtained. Right censorship is that real survival time exceeds censoring time, and left censorship is the opposite, that the event happened before the starting point of follow-up (Prinja et al., 2010). Left censorship is usually rare and not applicable in this study with the outcome of death.

The problem of censored data is about missing values and potential bias. Given the nature of the data linkage and ethics of UK Biobank, withdrawals and loss to follow-up is not applicable to this study, as the outcomes data was from linked NMR and HES (Littlejohns et al., 2019), and the withdrawals would be removed from baseline study population (Biobank, 2007a).

3.4.3.5 Kaplan-Meier plot and log-ranked test

Kaplan-Meier (KM) plot (Goel et al., 2010) estimates the probability of surviving (survival function), at least to any given time point, for single predictor variables. The log-rank test (Koletsi and Pandis, 2017) is a non-parametric test used to compare the survival curves. The log-rank test compares the observed number of events in the exposure and reference groups with the expected number if the null hypothesis were true. The log-rank test statistic is calculated by

$$Z = \frac{(O - E)^2}{V}$$

where *O* stands for the observed number of events, *E* stands for the expected number of events if the null hypothesis were true, and *V* stands for the variance of the observed number of events.

In our study, the KM plot and log-ranked test were used to compare the survival times for participants with and without the comorbidity of chronic pain, cardiometabolic disease and depression, but they were unable to take confounding variables into account.

3.4.3.6 Cox-proportional hazard models

As the KM plot was used for single predictors, to control for putative confounding variables, Cox-proportional hazard models (Bender et al., 2005) were fitted with multiple predictors.

To run the Cox regression, it was assumed that the hazards were proportional, and the hazard was the risk of the health outcome at a given moment in time (Kuitunen et al., 2021). This assumption was tested by creating the interactions of all the factors fitted in the Cox regression model with time. To examine the differences in survival curves between the exposure and reference groups, the hazard is compared between the exposure group and the reference group by dividing one hazard by another (HR) (Kong et al., 1998). The HR less than one means the hazard is less in participants with the exposure compared with the

reference group; the HR more than one means the exposure is associated with a higher hazard of the outcome (De Neve and Gerds, 2020). The 95% CI was calculated with the HR that it was 95% confident that the true value of HR was contained in the range.

3.5 Qualitative study

The final study of this thesis aimed to get personal insights into living with the comorbidity of chronic pain, cardiometabolic disease and depression. Secondary data analyses of a sub-set of interviews that had been conducted for a large qualitative study (described in the section of primary research) with ten participants with the comorbidity of chronic pain, cardiometabolic disease and depression were analysed to examine the experience of living with the comorbidity.

3.5.1 Qualitative analysis

3.5.1.1 Data collection

Qualitative study is to answer a research question as a humanistic or idealistic approach (Anderson et al., 2016). Qualitative data include interviews (Adhabi and Anozie, 2017), focus groups (Moretti et al., 2011), observations and field notes (Pope et al., 2000), and journals/diaries (Gonzalez and Lengacher, 2007). Qualitative interviews are categorised into structured, semi-structured, and unstructured interviews, each holding a different level of power with the interviewer. Unstructured interviews are free conversations between the interviewers and participants with no prior guidelines (Low, 2007). On the other end of the spectrum, structured interviews stick to predefined questions and are mainly used for psychiatric diagnoses (Mueller and Segal, 2014). In a semi-structured interview, the interviewer has an outline of the interview questions and topics, but with the flexibility of the participants' to talk and to follow their lead (Adhabi and Anozie, 2017). Semi-structured interviews are the most widely used type of qualitative data collection (Magaldi and Berler, 2020).

3.5.1.2 Data analysis

Thematic analysis, content analysis, grounded theory and framework analysis are common approaches to analysing qualitative data. Thematic analysis is widely used to identify, analyse and report the patterns and themes within data (Braun and Clarke, 2014). Content analysis is to describe and quantify written texts and verbal or visual communication messages (Elo and Kyngäs, 2008), and is commonly used for analysing large amounts of textual data to identify the trends and patterns of frequency and relationships of the words (Vaismoradi et al., 2013). Framework analysis is flexible that data analysis could be conducted during the collection process, so that the data is refined with key issues and themes (Srivastava and Thomson, 2009). Grounded theory is a method of systematically generating a substantive theory grounded in empirical data (Walker and Myrick, 2006).

Thematic analysis was selected as the appropriate means of analysis, considering the nature of the available data and the objective of this qualitative study to describe the lived experience of the participants and identify their insights (Braun and Clarke, 2014). There are two steps of thematic analysis: the data management of coding and categorising the scripts aided by computer-assisted qualitative data analysis software (CAQDAS), and the interpretation using the one sheet of paper (OSOP) (Ziebland and McPherson, 2006) to illustrate with extracts or verbatim quotes from the interview data, to find the story and answer the research questions. The details of the methods used in this study are described in Chapter 7.

3.5.2 Secondary analysis

3.5.2.1 Primary research

This study used existing data from the MAP study, funded by Versus Arthritis (grant number 21970).

The MAP study was designed to investigate the disease management and treatment burden (Mair and May, 2014) of participants with and without the presence of more

than two LTCs (multimorbidity). The MAP study is a combination of quantitative study (McQueenie et al., 2021) and qualitative study, particularly focused on treatment burden and capacity. The qualitative study recruited adult patients with persistent MSK pain or Rheumatoid arthritis (RA) from outpatient clinics (RA and pain) and General Practices during 2020-2021. To be more detailed, the participants included 20 with MSK pain only, 20 with RA only, 20 with MSK pain along with other LTCs, and 20 with RA along with other LTCs. A total of 80 participants were invited to a semi-structured interview about their personal experiences and feelings about living with their health conditions.

3.5.2.2 Secondary analysis types

Secondary analysis is the re-use of existing data obtained from previous studies or archived resources to examine different research questions or demonstrate and verify the findings of existing research (Johnston, 2017).

There are several types of secondary analyses: 1) supplementary analysis is the analysis of an issue not thoroughly investigated in the primary study; 2) supra analysis is to extend the scope of the primary study; 3) re-analysis is to re-examine and verify the findings from existing research; 4) amplified analysis is to compare two or more existing pieces of research; 5) assorted analysis is to re-use the data during the collection and analysis of the primary data for the same study (Heaton, 2008).

In this study, a secondary analysis was conducted to revisit the existing data of semi-structured interviews in the MAP study. This study is a supplementary analysis that explores issues not covered in the primary analysis.

A comparison of the aims and recruited participants is detailed in Table 3-1. The primary research was interested in the treatment burden and capacity of participants with multimorbidity, while the focus on this particular subset of the participants with the comorbidity of the three conditions of interest is to understand their lived experience and insights on the relationship between the diseases. The primary research sample comprised 40 participants with MSK pain

only or RA only, who would not meet the inclusion criteria of this secondary analysis and another 40 participants with multimorbidity that possibly has the three conditions of interest in this thesis. Of the 40 participants with multimorbidity, ten self-reported chronic pain, cardiometabolic disease, and depression. The inclusion of the participants for the secondary analysis is detailed in Chapter 7.

Table 3-1. The comparison of the primary research and the secondary analysis in this thesis

	Primary research in the MAP study	Secondary analysis in this thesis
Aims	To investigate the disease management, treatment burden and capacity of participants with multimorbidity	To investigate the lived experience and insights of participants with the comorbidity of chronic pain, cardiometabolic disease and depression
Participants	20 adults with persistent MSK pain only; 20 adults with RA only; 40 adults with MSK pain or RA alongside multimorbidity	10 adults with the comorbidity of chronic pain, cardiometabolic disease and depression

Abbreviations: MAP, Multimorbidity in Arthritis and persistent musculoskeletal Pain; MSK, musculoskeletal; RA, rheumatoid arthritis

3.5.2.3 Benefits & challenges of secondary analysis

The benefits of conducting secondary analysis are that it adds value by making use of existing data to bring additional or different insights, to answer research questions distinct to the primary research, to apply a new perspective in addition to the primary research question, and to study on the population that difficult to access (Long-Sutehall et al., 2011). The use of secondary analysis is a growing methodology (Johnston, 2017) and potentially contributes to policy decision-making (Ziebland and Hunt, 2014).

In addition, it has been noted that secondary analysis could provide training for researchers when empirical work is unavailable (Corti and Thompson, 1998) and benefit the economies of money and time (Clarke and Cossette, 2000). In this thesis, the project was changed from conducting an original study of interviews with health professionals to a secondary analysis of existing semi-structured interviews with patients with the comorbidity due to the impact of the pandemic of COVID-19. The detail of this adjustment is explained in Chapter 8.

Several challenges arise from the secondary analysis of qualitative data (Ruggiano and Perry, 2019). A key criticism is that data collected for other purposes may not be suitable for answering additional research questions (Tripathy, 2013). However, in this study, the data was transcripts of semi-structured interviews with rich information, where the participants not only discussed issues of treatment burden and capacity but more broadly discussed the impact of living with the comorbidity of the conditions of interest. Thus, there were spaces for investigating other research questions besides the primary research aims of the original study (Table 3-1).

One of the main practical challenges of conducting secondary analysis is being unable to talk face-to-face with the participants. Interviews are about more than just words; expressions on people's faces, eye contact, appearance, manners, voice pitch and tone are all important to enhance understanding. Researchers undertaking secondary analysis are required to "imagine" interviewees and to reproduce the interview in their minds. The physical observations from talking with the participants are lost, and the interpretation may be less accurate (Kleinman, 2020). The ethical constraints of this study permitted access to the cleaned text scripts only. The voice pitch and tone were lost in transforming the speech into the text. Nevertheless, this is an extremely rich data set that, although the original recordings were not accessible, the pauses, interruption of saying "well", and crying were captured in the scripts. The emotions (laughing and crying), actions (interruptions by pets, answering the phone) and pauses were marked in the scripts, which could address some of the gaps between the texts and the actual interview. In addition, I had access to the researchers who conducted

the interviews that could help me understand the details of the interview if needed.

There is also a general ethical concern of secondary analysis about whether participants have consented to re-use their data and this is often considered a limitation (Irwin, 2013). Participants in the MAP study consented to future use of their anonymised data for research purposes during the informed consent stage.

In this study, ethical approval (Appendix 2) was granted by the College of Medical, Veterinary & Life Sciences Ethics Committee for Non-Clinical Research Involving Human Participants (200180073) and NHS ethics via the Integrated Research Application System (IRAS) (19/SW/0101). In addition, only the scripts of the interviews were shared by the primary researchers, and the data was anonymised to avoid any participant identification.

3.5.3 Sample size

Unlike quantitative research, the sampling for a qualitative study does not aim to represent a population; thus, a relatively lower number of participants also has the power of information (Ritchie et al., 2013). Nevertheless, there is no standardised guidance for justifying sample size decisions, and there are debates on the adequate sample size for qualitative studies (Boddy, 2016). Summarised from 81 qualitative studies, the *sample size* ranges from 20 to 30 is recommended as sufficient for grounded theory studies, and for single case studies that focus on one group, the recommendation is 15 to 30 (Marshall et al., 2013). It is reported to be acceptable to examine 5 to 50 participants in qualitative studies (Dworkin, 2012). It has also been argued that a sample size of 10 could be adequate for certain situations of single case studies (Sandelowski, 1995). There is a lack of evidence on the appropriate sample size for mixed methods or multimethod studies.

The factors for estimating the sample size of a semi-structured study include the scope of the study, the nature of the research question, and the quality of data (Morse, 2000); it also depends on the investigator and practical issues, including funding and time (Morse, 2015). Besides, there are views on using the power of

information from the data to assess the sample size rather than just the number. If the study sample could provide adequate, relevant information, the number of participants needed could be lower (Malterud et al., 2016).

For secondary analyses, a subsample is selected from the overall sample of the primary analyses. A larger sample size is preferable as it could show a richer picture of the issue of interest but similar to the primary analyses, it depends on the factors listed above – a smaller sample is sufficient if the data is richer (Chatfield, 2020).

The primary study was sampled from a homogeneous population, and the secondary study had ten interviews. Given that the research objective is to explore a novel issue with little knowledge and the available data is rich, a larger sample is desirable, but smaller sample size is acceptable in this study (Malterud et al., 2016).

3.6 Conclusion

This chapter has presented the theoretical background and considerations of the methods involved in this thesis, as well as related concepts and potential strengths and weaknesses. A multimethod approach of a narrative systematic review, quantitative analysis of a large dataset, and qualitative analysis of interviews has been used. This approach has allowed different viewpoints to explore the comorbidity of chronic pain, cardiometabolic disease, and depression. Full details of the methods used and the results from each study are given in the following three chapters.

Chapter 4 The comorbidity of chronic pain, cardiometabolic disease and depression: a systematic review

4.1 Introduction

4.1.1 Overview of the chapter

This chapter describes a narrative systematic review of the existing literature that explores the prevalence, health outcomes and patient experience of the comorbidity of chronic pain, cardiometabolic disease and depression, in order to answer research question 1 of the thesis: what do we know about the comorbidity of chronic pain, cardiometabolic disease and depression?

4.1.2 Rationale

There is a lack of evidence regarding the comorbidity of chronic pain, cardiometabolic disease and depression as discussed in Chapter 2. Guidelines for the treatment of these three conditions are often addressed individually as single diseases despite evidence showing that LTCs often co-occur together and must be treated as such (Barnett et al., 2012). Patients with comorbidity tend to receive multiple prescriptions, which raises concerns over drug safety because of adverse drug effects and drug interactions (Calderón-Larrañaga et al., 2012). The prevalence of comorbidity of these three conditions, and the experiences of individuals affected by it is largely unknown. This is essential to inform the development of interventions designed to optimise management of this combination of common conditions and improve the care of people living with this specific comorbidity.

The first step is to examine what is currently known in the literature about the comorbidity of chronic pain, cardiometabolic disease and depression. A scoping search of these three comorbid conditions was conducted by entering key search terms into the Cochrane Database of Systematic Reviews (CDSR) (Starr et al., 2009) and International Prospective Register of Systematic Reviews (PROSPERO). The search retrieved no existing or ongoing review studies conducted on the

comorbidity of chronic pain, cardiometabolic disease, and depression. Therefore, in answering research question 1 of this thesis, this chapter presents a systematic review that sought to identify and summarise published studies that focuses on the prevalence, patient experience, and health outcomes of people with comorbidity of chronic pain, cardiometabolic disease, and depression.

4.1.3 Aims for the systematic review

This systematic review aimed to summarise evidence in relation to the following three key questions:

1. What is the prevalence of the comorbidity of chronic pain, cardiometabolic disease and depression?

2. What effects do this combination of comorbidities have on health outcomes (mortality, hospitalisation, health care utilisation, and quality of life)?

3. What are patients' perspectives on living with this combination of comorbidities?

4.2 Methods

PRISMA (Moher et al., 2009) guided the search and study selection process. The protocol has been registered on PROSPERO (CRD42018106525).

4.2.1 Search strategy

Literature searching together with citation and reference checking were used to identify studies involving the comorbidity of chronic pain, cardiometabolic disease and depression. As the terms comorbidity and multimorbidity are relatively new concepts, any identified studies providing data on this combination of three conditions were included. This meant that included studies did not need to examine the comorbidity of the three conditions specifically but needed to involve data on the combination.

4.2.1.1 Databases

Previous systematic reviews of studies conducted on either chronic pain, cardiometabolic disease or depression were examined in order to identify the relevant electronic databases for this review. Five commonly used medical and psychological databases were found including: MEDLINE, Ovid Embase, Cumulative Index to Nursing and Allied Health Literature (CINAHL), PsycINFO, and Web of Science. For Web of Science, the "overall databases" rather than the "core databases" were used in order to identify as many citations as possible.

4.2.1.2 Search terms

MEDLINE, a bibliographic database containing more than 26 million records, was the database used to create the search strategy initially. Medical Subject Headings (MeSH) in the MEDLINE were used for information retrieval, and the medical terms were systematically indexed. When searching for one MeSH term, all the related phrases were also searched. The search used a combination of MeSH terms (when applicable) and keywords (Appendix 3). MeSH terms were also used to find synonyms. The search strategies of other databases were created based on the MEDLINE search strategy and modified to fit the characteristics of the individual database search system. The search results of each of the three conditions (chronic pain, cardiometabolic disease and depression) were combined to find studies that included all three conditions. The search date was 31 May 2018. Full searches applied in each database are available in Appendix 3.

4.2.1.3 PECOS

Population, Exposure, Comparators, Outcomes and Study Designs (PECOS) (Morgan et al., 2018) was used to formulate the search criteria to address the research questions. Details of the search strategy are available in Table 4-1.

Table 4-1. PECOS of the systematic review

PECOS items	Details
Population	Adults in the general population
Exposure	Presence of the combination of chronic pain, cardiometabolic disease and depression/depressive symptoms.
Comparators	A comparison group was not essential. When applicable, the comparator was participants without the three combined chronic conditions, instead, the participants in the comparator group could have none, one or two of the conditions of interest.
Outcomes	1. Prevalence and incidence of the combination of chronic pain, cardiometabolic disease and depression/depressive symptoms. 2. Health outcomes: mortality, morbidity, hospitalization, health care utilization, quality of life in people with the combination of these three conditions. 3. Patient perspectives and patient experience of living with these three conditions.
Study designs	Observational studies of datasets, survey, cohort studies, and also qualitative study design to capture experience.

4.2.1.4 Inclusion & exclusion criteria

Chronic pain was defined as pain lasting at least three months or 12 weeks (Treede et al., 2015a), excluding migraine, headache, cancer pain and chest pain. Migraine and headaches were excluded as these are usually not persistent, and particularly with headaches, most people have them from time to time. Cancer pain and chest pain have specific causes. The cardiometabolic diseases included were all types of cardiovascular diseases and metabolic diseases (heart diseases, hypertension, cardiomyopathies, heart failure, cerebrovascular disorders, heart attack, coronary artery disease, hypotension, angina, arrhythmias, atrial fibrillation, metabolic syndrome, diabetes, dyslipidaemia), excluding obesity, overweight and congenital

heart disease. Depression was considered if it was assessed through history or measurement of depression, depressive symptoms or low mood.

Obesity and overweight are considered as lifestyle factors in this study.

Journal articles on epidemiology study design and qualitative studies were included. Case studies, intervention studies, randomised controlled trials (RCTs) and other experimental studies, animal studies and reviews were excluded as this investigation focused on the prevalence, health outcomes and patients' experiences of living with the comorbidity. Editorial opinion pieces without original data were excluded.

Only articles published in English language that reported on all three conditions of chronic pain, cardiometabolic disease and depression/depressive symptoms, and included content regarding prevalence, health effect, patients' experiences, or the relationship between the three conditions were included. Any studies with pain defined without a clear duration of at least three months / 12 weeks were excluded. Years of publishes date was not limited in the search.

The inclusion and exclusion criteria are detailed in Table 4-2.

Table 4-2. Inclusion and exclusion criteria of the study selection

Items	Details
Inclusion criteria	1. Adults 2. Study types: epidemiology studies: observational studies, survey, cohort studies, cross-sectional studies, case-control studies and qualitative studies 3. Studies that presented data on the combination of the three conditions?
Exclusion criteria	1. Child and Adolescent 2. Study types: case studies, intervention studies, randomized controlled trials and other experimental/intervention-based studies; animal studies; reviews, including systematic reviews; editorials, conference proceedings, commentaries and letters 3. Chronic pain not clearly defined or does not meet our definition of "pain lasting at least three months or 12 weeks" 4. Studies that did not report on the three conditions of interest

4.2.2 Literature search

4.2.3 Paper selection

4.2.3.1 Double screening

After removing the duplicates, titles/abstracts and full texts were double screened by me, my supervisors (Dr Barbara Nicholl, Professor Frances Mair, Professor Sara Macdonald), and a research fellow (Dr Peter Hanlon) who assisted with screening to identify papers that met the pre-specified inclusion and exclusion criteria. Any disagreements were adjudicated by a third reviewer and resolved by consensus. Reference lists of included studies and their citations identified from Web of Science were also checked to identify other relevant studies.

4.2.3.2 Process and the platform

All titles and abstracts retrieved from electronic searches of each database were exported into reference management Endnote software and then to DistillerSR, a systematic review platform (Van der Mierden et al., 2019), before the removal of duplicate articles. Before the screening process, the review team agreed by consensus on their understanding of the eligibility criteria. The process of study selection on Distiller:

Level 1: title and abstract double screening

Many studies did not mention all three conditions of interest (chronic pain, cardiometabolic disease and depression) in the title. Therefore, the first tier of screening was to screen the title and abstract together. The title and abstract of each citation were screened by two reviewers independently, and the decisions were included, excluded or not sure. The system then determined whether articles were “excluded” or “remained for further screening”. For an article to be excluded, both reviewers had to choose to exclude it.

Level 2: title and abstract conflicts screening

If both reviewers included the paper, this citation would proceed directly to level 3 of full-text screening; other situations (included + excluded, included + not sure, excluded + not sure, not sure + not sure) were marked as conflicts. A third reviewer decided whether to include, exclude or mark as not sure (also going through to the next level).

Level 3: full-text double screening

All the included citations from level 1 and 2, and citations marked "not sure" from level 2 were included for full-text screening. At this stage, the citations without new data (editorial, commentary letters) or with no full text applicable (conference abstract, supplement abstract) or non-English language full text (only the abstract was in English) were excluded. Then all the full texts were screened by two reviewers independently.

Level 4: full-text conflicts screening

The same way of proceeding with "included/excluded/conflicts" citations was applied for the full-text screening as for the title and abstract screening explained above, and a third reviewer screened the conflicts.

Level 5: included studies

The full text considered as eligible by both reviewers in level 3 or identified as relevant by the third reviewer in level 4 were included in the study. The eligibility of full texts marked as "not sure" in level 4 were discussed by the research team and a decision agreed upon on whether to include the article in the final selection of studies.

PRISMA flow chart was made to illustrate the selection process (Figure 4-1).

4.2.4 Reference checking

The reference list and citation list of the included studies from the literature search were identified in Web of Science in September 2019. The reference lists

were the reference papers cited in the included studies, and the citation lists were studies that cited the included studies. This complements the systematic literature search to capture potentially missed studies. The lists of papers were screened the same way as the citations from the literature search. This also allowed us to check that the literature search covered most studies.

4.2.5 Data extraction

Standardised data extraction tools designed for single index condition studies had limited applicability in comorbidity studies. A bespoke data collection form (Appendix 4) was designed specifically for this study. The form was used to collect the data on the study characteristics, objectives, methods (including the measurement of chronic pain, cardiometabolic disease and depression), and findings (especially the findings related to the comorbidity of the three conditions). This data extraction form was modified to be especially suitable for studies with multiple conditions or collecting the data focused on multiple conditions. I conducted the data extraction, and this was double-checked by a second reviewer (my supervisors) to confirm that no critical information was missing from the data extraction.

4.2.6 Quality appraisal

Quality appraisal tools were used to enable us to appraise the quality of the included studies consistently. Several tools were considered: the form of Quality Assessment Tool for Observational Cohort and Cross-sectional Studies by National Heart, Lung and Blood Institute, checklist from Critical Appraisal Skills Programme, and critical appraisal tools from Joanna Briggs Institute (Sanderson et al., 2007).

However, none of them were entirely suitable, as the existing widely used quality appraisal tools were principally designed for studies with single diseases, not studies considering multiple LTCs. Decisions on the quality appraisal tools were made post-screening to reflect the range of study designs included in the final sample of studies. The Newcastle-Ottawa Quality Assessment Form was one of the most commonly used tool (Seehra et al., 2016). A modified version of The

Newcastle-Ottawa Quality Assessment Form was used for observational studies. It was changed to allow the examination of studies exploring the comorbidity of both physical and mental health LTCs (Appendix 5) (Modesti et al., 2016, Wells et al., 2000). No qualitative studies were identified to be included in the review, and thus tools for qualitative studies were not considered.

As with article screening, the quality appraisal was conducted by two reviewers independently, and disagreements were resolved by discussion or through consulting a third reviewer.

Given that the existing evidence was limited, the quality appraisal was not used to filter poor-quality studies. The quality appraisal was conducted to assess the quality and power of the included studies, and no studies were excluded based on quality.

4.2.7 Narrative analysis

The included studies were synthesised narratively and summarised in data extraction tables. The tables describe the information of the study (author, publishes year and study region), study population and their characteristics/recruitment, study period, findings of the comorbidity and the measurement of the three conditions.

The available data did not permit meta-analysis because of the heterogeneity of studies in terms of the types of data used and in the study designs.

4.3 Results

4.3.1 Search results

From the initial search, 9,785 citations were identified from the five key medical databases searched: Ovid MEDLINE (n = 605), Ovid EMBASE (n = 3,231), Web of Science (n = 5,364), PsycINFO (n = 328), and CINAHL (n = 257). After screening, 14 publications involving 12 separate studies met our inclusion criteria (van Hecke et al., 2017, D'Amato et al., 2016, Harno et al., 2014, Ziegler et al., 2014, Selvarajah

et al., 2014, Choiniere et al., 2014, Bouhassira et al., 2013, Klit et al., 2011, Hoffman et al., 2009, Gore et al., 2006, Zelman et al., 2006, Gore et al., 2005, Krein et al., 2005, Widar et al., 2004).

Title screening of the reference lists of these 14 publications and their citing lists (n = 1,711) identified 16 citations for full-text screening. Finally, one citation (Sadosky et al., 2013) was added to the included studies, and thus 15 publications involving 13 studies were included in this systematic review.

Figure 4-1 illustrates the PRISMA flow chart of the study selection. Three of the 15 publications used the same data from the same study (Gore et al., 2006, Zelman et al., 2006, Gore et al., 2005).

It should be noted that the study by van Hecke et al (van Hecke et al., 2017) analysed two independent cohorts; only one of the cohorts (General Scotland, GS:SFHS) is relevant to our study. The other one is a population-based study of female twins from TwinsUK Registry involving the examination of genetic information from blood samples. Thus, the information extracted and presented from this study only came from the GS:SFHS cohort.

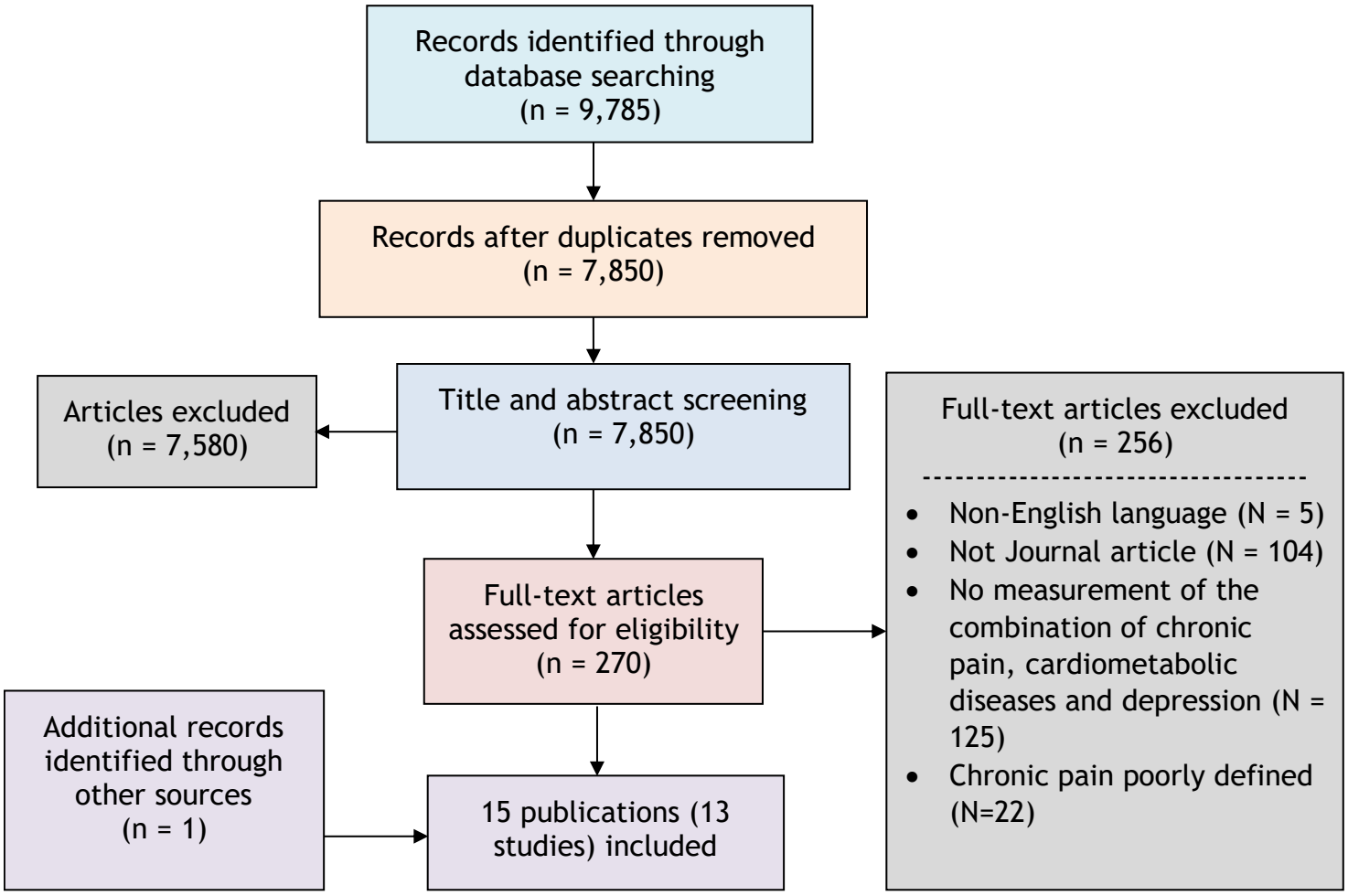

Figure 4-1. Flow diagram of the study selection

4.3.2 Study settings

4.3.2.1 Study design & data source

The sample size of the included studies ranged from 43 to 24,042, with a median of 608 participants; the sample size of the sub-group of interest (people with the combination of chronic pain, cardiometabolic disease and depression) ranged from 6 (Widar et al., 2004) to 377 (Ziegler et al., 2014), with a median of 58.5 subjects (Table 4-3).

Among the 13 included studies, 12 were conducted in the Global West - three in the US (Gore et al., 2006, Sadosky et al., 2013, Krein et al., 2005), one in Canada (Choiniere et al., 2014), and eight in UK (van Hecke et al., 2017, Selvarajah et al.,

2014) and European countries (D'Amato et al., 2016, Harno et al., 2014, Ziegler et al., 2014, Bouhassira et al., 2013, Klit et al., 2011, Widar et al., 2004). The remaining study was conducted in 19 countries and regions across Asia, Latin America and the Middle East, but it only examined 401 participants (Hoffman et al., 2009).

Five of the 13 included studies were cross-sectional. Four studies (Hoffman et al., 2009, Ziegler et al., 2014, Krein et al., 2005, van Hecke et al., 2017) were reported to be cohort study designs. However, the publication only examined the baseline data, and thus their study designs were considered cross-sectional. There were three cohort (Harno et al., 2014, Choiniere et al., 2014, Klit et al., 2011) and one mixed-methods study (Widar et al., 2004). The mixed-methods study, although had a qualitative component, focused on the quality of life of those experiencing pain, rather than on the experience of living with the comorbidity of interest. There were no qualitative studies examining the experience of living with all three conditions.

4.3.2.2 Characteristics of the participants

The characteristics of the participants of the included studies are presented in Table 4-3. There was a lack of standardisation in reporting the age of participants. The mean age was provided in 11 of the 13 studies, ranging from 49.2 (Harno et al., 2014) to 66 years (Widar et al., 2004). The other two studies reported median ages of 49 years (van Hecke et al., 2017) and 72.6 years (Klit et al., 2011) to summarise the age distribution of the participants. Only two studies reported the age range of the participants: 21-86 years (Choiniere et al., 2014) and 33-82 years (Widar et al., 2004).

Females made up 4% (Krein et al., 2005) to 61% (Hoffman et al., 2009) of the study sample. Only five studies reported the ethnic background of their participants (Selvarajah et al., 2014, Hoffman et al., 2009, Gore et al., 2006, Krein et al., 2005, Sadosky et al., 2013), and Caucasian was the most common ethnic group in three studies.

BMI was reported in six of the 13 included studies. The lowest mean BMI (SD) with the unit of kilograms divided by the square of the height in metres (Kg/m^2) was 25.5 (3.9) in a study population of Asian background (Hoffman et al., 2009) and 28.6 (6.0) (Bouhassira et al., 2013) of the people in France. The highest mean BMI (SD) was 32.6 (6.4) (Selvarajah et al., 2014) with the population in the UK. Recommended weight is defined by the WHO as 18.5-24.9 (WHO, 2000). This data suggests that the populations of these six studies were generally overweight or obese.

Other demographic variables examined in some of the studies included smoking status (Ziegler et al., 2014), alcohol intake (Ziegler et al., 2014), physical activity (D'Amato et al., 2016), marital status (Selvarajah et al., 2014) and whether living with a partner (Widar et al., 2004), presented as “other” characteristics in Table 4-3.

Table 4-3. Characteristics of the included studies examining the comorbidity of chronic pain, cardiometabolic disease and depression

First author, year	Country of study	Study type	Data source	Sample size	Sub-group size*	Participants of the study population							
						Gender (female)	Age (years)	Ethnicity	Deprivation	Occupation	Education	BMI (kg/m^2)	Other(s)
van Hecke, 2017	UK	Cross-sectional	Population based cohort (GS:SFHS)	24,042	169	58.70%	Mean: N/R Median age: 49 IQR: 36-59	N/R	SIMD • 1 (most deprived): 12.9% • 2: 14.1% • 3: 16.3% • 4: 25.7% • 5 (least deprived): 31.1%	N/R	• Degree, diploma or technical qualification: 61.7% • School leaving: 27.1% • No qualification: 11.2%	N/R	N/R
D'Amato, 2016	Italy	Cross-sectional	Interviews with patients recruited from diabetic clinic	181	11	41.40%	Mean: 60.7±11.5	N/R	N/R	PDPN unemployment: 30.4%	PDPN high school graduation rate: 20.0%	29.6±5.0 PDPN: 31.1±4.4	Marital status: PDPN single 9.1% Smoking: PDPN current smoker 16.0% Physical activity 16.0%
Harno, 2014	Finland	Cohort	Telephone questionnaire of patients recruited from stroke registry	824	49	39.40%	Mean (age at follow-up): 49.2 SD: 9.1	N/R	N/R	N/R	N/R	N/R	N/R

First author, year	Country of study	Study type	Data source	Sample size	Sub-group * size	Participants of the study population							
						Gender (Female)	Age (years)	Ethnicity	Deprivation	Occupation	Education	BMI (kg/m^2)	Other(s)
Ziegler, 2014	Germany	Cross-sectional	Clinical records of patients attending for clinical care (secondary analysis)	2575	377	51.90%	Mean: 65.2 SD: 11.6	N/R	N/R	Work for pay: 19.9%	N/R	N/R	Alcohol (drinks per week) • Mean: 5.1 (SD:9.1) Smoking: current 14.6%, Past 23.3%
Selvarajah, 2014	UK	Cross-sectional	Clinical assessment of patients attending outpatient service	142	N/R	42.90%	Mean: 61.2 SD: 11.2	• White British: 137 (95.7%) • Afro-Caribbean: 4 (2.9%) • Other: 1 (0.7%)	• Social Deprivation Score Mean: 27.3 SD: 17.5	Currently employed or retired at pensionable age: 27.1% Unemployed or retired before pensionable age: 70.7% • Missing: 2.1%	• Left school: 14–16 years 7.9% • A-levels: 2.9% • Diploma/ undergraduate degree: 16.9% Postgraduate: 1.4% • Missing: 0.7%	Mean: 32.6 SD: 6.4	Marital status (%, single): 12.1%
Choinière, 2014	Canada	Cohort	Interview of patients recruited from clinic before cardiac surgery	1247	N/R	21.00%	Mean: 61.9 SD: 10.2 Range: 21-86	N/R	N/R	N/R	Education level: • Elementary school 150 (15.4) • High school 348 (35.7) • College or technical school 245 (25.1) • University 232 (23.8)	Mean: 28.7 SD: 4.8	N/R

First author, year	Country of study	Study type	Data source	Sample size	Sub-group * size	Participants of the study population							
						Gender (Female)	Age (years)	Ethnicity	Deprivation	Occupation	Education	BMI (Kg/m^2)	Other (s)
Bouhassira, 2013	France	Cross-sectional	Interview of patients recruited by diabetes specialists	766	N/R	44.80%	Mean: 57.2 SD: 1.49	N/R	N/R	N/R	N/R	Mean: 28.6 SD: 6.0	N/R
Klit, 2011	Denmark	Cohort	Telephone questionnaire of hospitalized acute stroke patients from NIP database	608	N/R	44.10%	Mean and SD N/R Median 72.6	N/R	N/R	N/R	N/R	N/R	N/R
Hoffman, 2009	19 countries across Asia, Latin America and the Middle East	Cross-sectional	Post hoc analysis of patients in a randomized controlled trial	401	N/R	61.00%	Mean: 57 SD: 10	• Asia: white (0) black (0) Asian (100%) other (0) • Latin America: white (33.6%) black (10.9%) Asian (0) other (55.5%) • Middle East: white (64.1%) black (0) Asian (34.3%) other (1.6%)	N/R	N/R	N/R	Mean ± SD Asia: 25.5 ± 3.9 Latin America: 29.0 ± 5.6 Middle East: 30.6 ± 5.6	N/R

First author, year	Country of study	Study type	Data source	Sample size	Sub-group* size	Participants of the study population							
						Gender (Female)	Age (years)	Ethnicity	Deprivation	Occupation	Education	BMI (Kg/m^2)	Other(s)
Gore, 2006	the US	Cross-sectional	Mail survey of patients recruited by primary care physicians, endocrinologists, anaesthesiologist, and neurologists	255	Not clear in the study Estimated value 71 or 72 according to depression rate	51.40%	Mean: 61.3 SD: 12.8 Range =N/R	• Caucasian (53.3%) • African American /Black (18.8%) • Latino (9.8%) • multiracial (3.1%) • Asian (2.4%) • Native American (0.4%)	N/R	• Employed, full-time (>=30 hours) (20.0%) • Employed, part-time (<29 hours) (8.6%) • Homemaker (7.8%) • Unemployed (14.9%) • Retired (46.7%)	N/R	N/R	N/R
Zelman, 2006	the US	Cross-sectional	Same as above	255	Same as above	51.40%	Same as above	Same as above	N/R	Same as above	N/R	N/R	N/R
Gore, 2005	the US	Cross-sectional	Same as above	255	Same as above	51.40%	Same as above	Same as above	N/R	Same as above	N/R	N/R	N/R

First author, year	Country of study	Study type	Data source	Sample size	Sub-group * size	Participants of the study population							
						Gender (Female)	Age (years)	Ethnicity	Deprivation	Occupation	Education	BMI (kg/m^2)	Other(s)
Krein, 2005	the US	Cross-sectional	Telephone interview of outpatient visits (sub-group study of a larger study)	993	267	4.00%	Mean: 64 SD: 10	White 67% (358/538)	N/R	N/R	Education, high school or greater 83 (444/538)	31.5 ± 6.4	Annual household income, > $20,000: 53%
Widar, 2004	Sweden	Mix methods	Clinical records of inpatient data from a neurological clinic	43	6	30.23%	Mean: 66 Range: 33-82	N/R	N/R	Working status (N) • Full-time (3) • Sick-leave part-time (5) • Sick-leave full-time (1) • Early retirement /disability pension (10) • Old-age pension (24)	N/R	N/R	Household status (N): • Living with partner (30) • Living alone (13)
Sadosky, 2013	the US	Cross-sectional	Retrospective chart review of subjects recruited from physician practices	112	46	52.7%	Mean: 61.1 SD: 12.1	Missing 2 (1.8%) American Indian or Alaska Native 2 (1.8%) Asian 2 (1.8%) Black or African American 15 (13.4%) Native Hawaiian or other Pacific Islander white 0 Multiracial 77 (68.8%) Other 12 (10.7%)	N/R	Employment status Missing 5 (4.5%) Employed for pay 20 (17.9%) Disabled 38 (33.9%) Retired 41 (36.6%) Unemployed 6 (5.4%) Other 2 (1.8%)	Missing 3 (2.7%) Less than high school 22 (19.6%) High school and beyond 87 (77.7%)	N/R	N/R

Abbreviations: BMI, Body Mass Index; kg/m^2, kilogram/(metre^2); N/R, Not Reported; GS:SFHS, General Scotland: Scottish Family Health Study; IQR, Interquartile Range; SD, standard deviation; PDPN, Painful Diabetic Peripheral Neuropathy; UK, United Kingdom; US, United States

*Sub-group: the participants with the combination of chronic pain, cardiometabolic disease and depression

4.3.3 Findings relating to the comorbidity of interest

None of the included studies primarily sought to investigate our comorbidity of interest. All studies considered one of the three conditions as an index condition - their primary condition of interest (Table 4-4) and then provided information on comorbidities. Three studies were secondary analyses and used data initially collected for other purposes (Hoffman et al., 2009, Ziegler et al., 2014, Krein et al., 2005). The cardiometabolic disease examined in eight of the 14 studies was diabetes; three studies investigated patients with stroke (Harno et al., 2014, Klit et al., 2011, Widar et al., 2004), and two studies examined angina (van Hecke et al., 2017, Choiniere et al., 2014).

Only one study examined the prevalence of the comorbidity of chronic pain, cardiometabolic disease and depression among the general population (van Hecke et al., 2017). This study looked specifically at patients with a combination of angina, chronic pain and depression. The study examined data from a large general population-based cohort (n = 24,042) (GS: SFHS) from 2006 to 2011 in Scotland. Angina was the only cardiometabolic condition examined for comorbidity with chronic pain and depression. In this study, the prevalence of the single diseases of chronic pain, angina and major depressive disorder were 18.1% (3,664 / 20,199), 10.0% (2,009 / 20,115) and 12.9% (2,755 / 21,380), respectively. And the prevalence of co-occurrence of chronic pain + depression, chronic pain + angina, and depression + angina was 5.3% (714 / 13,422), 4.6% (678 / 14,616) and 2.3% (371 / 16,284), respectively. It reported a prevalence of the comorbidity of all three conditions among their general population sample of 1.8% (169 / 9,492 valid responses).

4.3.3.1 Prevalence of depression in cardiometabolic disease and chronic pain

Five studies reported the prevalence of depression in people with diabetes and chronic pain, which ranged from 24.8% (Ziegler et al., 2014) to 49% (Krein et al., 2005). The number of participants with the combination of chronic pain, cardiometabolic disease and depression was 11 (D'Amato et al., 2016), 377 (Ziegler et al., 2014), 71 (Gore et al., 2006), 267 (Krein et al., 2005) and 46 (Sadosky et al., 2013). One study showed that the prevalence of depression in people with stroke and pain was 34.14% (HADS-D > 8) (Widar et al., 2004) (Table

4-4). Depression was defined by self-report or measured by diagnostic or screening instruments in all the included studies, summarised in Table 4-5.

4.3.3.2 Relationship between chronic pain, cardiometabolic disease and depression

In 11 studies, chronic pain or depression was reported as the health outcome in patients with diabetes or stroke. Patients with diabetes or stroke were reported to have a higher incidence (D'Amato et al., 2016) or severity (Gore et al., 2005) of depression if they have pain or vice versa, a higher risk of chronic pain if they have depression (Klit et al., 2011). This implied a potential concern with this combination of conditions. Yet, no information was provided about sociodemographic or lifestyle factors associated with the comorbidity of chronic pain, cardiometabolic disease and depression. The measurements of the three conditions are detailed in Table 4-5.

4.3.3.3 Health outcomes

The second research question of this systematic review aimed to identify the effect of comorbidity of chronic pain, cardiometabolic disease and depression on health outcomes. However, none of the included studies examined the health outcomes experienced by people with the three conditions of interest. Eight studies examined Quality of Life as an outcome in their study (Widar et al., 2004, Selvarajah et al., 2014), but the sample being examined were patients with only one or two conditions, not the combination of all three conditions.

4.3.3.4 Patient experience

The third research question of this systematic review is about the effect of comorbidity on patient experience. One mixed-methods study was included, which involved a cross-sectional study and a qualitative interview (Widar et al., 2004). The interview was conducted with 41 patients with unequivocal stroke and long-term post-stroke pain at a neurological clinic in Sweden. However, the participants with depression were not specified in the findings. Thus, it did not provide any useful data on patient experience of living with all three conditions of interest.

Table 4-4. Findings of the comorbidity from the included studies

Study	Cardiometabolic disease	Findings				
		Prevalence of comorbidity	Relationship between chronic pain, cardiometabolic disease and depression	Prevalence of depression*	Health outcome	Patient experience
van Hecke, 2017	Angina	1.8% (169 / 9,492)	Individuals with both angina and depression had greater odds (adjusted OR 9.43[6.85–12.98]) of also having chronic pain	N/R	N/R	N/R
D'Amato, 2016	Diabetes	N/R	The diabetic patients with neuropathic pain showed a higher BDI score and higher percentage than those with non-painful DPN; The only independent predictors of depression were found to be female and PDPN	44% PDPN patients having depression	N/R	N/R
Harno, 2014	Stroke	N/R	The mean (SD) Beck Depression Score in patients with CPSP was 11.5 (9.2), suggesting mild depression. 6% of the 49 patients with CPSP named depression or anxiety as their worst health problem.	N/R	N/R	N/R
Ziegler, 2014	Diabetes	N/R	N/R	24.8% of the PDPN patients having depression	N/R	N/R
Selvarajah, 2014	Diabetes	N/R	HADS-D were significantly correlated with age, marital status, employment history, pain intensity, duration of diabetes and the presence of diabetic and non-diabetic complications and QoL	N/R	N/R	N/R
Choinière, 2014	Angina	N/R	The Crude OR (95% CI) of HADS-D to predict persistent postoperative nonanginal pain of moderate to severe intensity is 1.12 (1.07-1.16) The Crude OR (95% CI) of HADS-D to predict presence of any persistent postoperative nonanginal pain is 1.06 (1.03-1.10)	N/R	N/R	N/R

Study	Cardiometabolic disease	Findings				
		Prevalence of comorbidity	Relationship between chronic pain, cardiometabolic disease and depression	Prevalence of depression*	Health outcome	Patient experience
Bouhassira, 2013	Diabetes	N/R	Patients with chronic pain had significantly higher anxiety and depression scores	N/R	N/R	N/R
Klit, 2011	Stroke	N/R	Depression was identified as significant risk factors for development of post-stroke pain	N/R	N/R	N/R
Hoffman, 2009	Diabetes	N/R	The mean (SD) of HADS-D is 7.1 (3.8), 8.2 (3.9), 8.7 (4.0) in Asia, Latin America and Middle East, respectively	N/R	N/R	N/R
Gore, 2006	Diabetes	N/R	N/R	27.8% of the PDPN patients have moderate to severe depression	N/R	N/R
Zelman, 2006	Diabetes	N/R	Greater levels of depression and pain predicted higher Sleep Problem Index among patients with PDPN	Same as above	N/R	N/R
Gore, 2005	Diabetes	N/R	Patients with more severe pain have higher depression scores	Same as above	N/R	N/R
Krein, 2005	Diabetes	N/R	N/R	49% of the diabetic patients with chronic pain also had depression	N/R	N/R
Widar, 2004	Stroke	N/R	N/R	14.63% and 19.51% post stroke pain patients are depression cases (HADS-D: >10) and “doubtful” cases (HADS-D: 8-10)	N/R	N/R
Sadosky, 2013	Diabetes	N/R	Higher proportion of subjects with depressive symptoms in patients with higher pain severity	41.1% with depressive symptoms among patient with PDPN	N/R	N/R

Abbreviations: N/R, Not Reported; SD, standard deviation; PDPN, Painful Diabetic Peripheral Neuropathy; CI, Confidence Interval; OR, Odds Ratio; BDI, Beck Depression Inventory; CPSP, Central Post-Stroke Pain; HADS-D, Hospital Anxiety and Depression Scale for Depression; QoL, Quality of Life
*Some studies looked at the combination of pain and cardiometabolic disease and then the incidence/prevalence of depression in that group
Note: Methods used to ascertain the three conditions of interest are reported in section 4.3.4

4.3.4 Measurement of the three conditions

The included studies measured the three conditions in a variety of ways. Table 4-5 summarises how the three conditions were defined in each study.

4.3.4.1 Chronic pain

This systematic review's design defined chronic pain as having pain for at least three months or 12 weeks. Many of the publications screened stated that participants had chronic pain but did not provide a clear definition for the term "chronic pain" or did not meet our criteria and were therefore excluded from our systematic review. Four of the included studies defined chronic pain as having pain for more than six months (Selvarajah et al., 2014, Krein et al., 2005, Widar et al., 2004, D'Amato et al., 2016) and one study used 12 months as the duration timeline (Hoffman et al., 2009). The other eight studies defined chronic pain as having pain for at least three months as per the widely accepted IASP classification (Treede et al., 2015a).

4.3.4.2 Cardiometabolic disease

Table 4-5 shows that cardiometabolic diseases were defined by clinical diagnosis (n = 9), self-reported in questionnaire (n = 3) and treatment (n = 1).

4.3.4.3 Depression

Depression or depressive symptoms were examined by the HADS and the modified version in eight of the 13 studies (Selvarajah et al., 2014, Sadosky et al., 2013, Choiniere et al., 2014, Bouhassira et al., 2013, Hoffman et al., 2009, Widar et al., 2004, Gore et al., 2005, Gore et al., 2006, Zelman et al., 2006, Ziegler et al., 2014). Beck Depression Inventory (BDI) score was used in two studies (D'Amato et al., 2016, Harno et al., 2014) and the 10-item Centre for Epidemiologic Studies Depression Scale (CES-D 10) was used in one of the studies (Krein et al., 2005). Structured Clinical Interview for the fourth

version of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) (van Hecke et al., 2017) was the only clinical diagnosis of depression used in the included studies.

Table 4-5. Measurement of the three conditions of the included studies

Study	Chronic pain		Cardiometabolic disease		Depression measurement
	Definition	Measurement	Condition	Measurement	
van Hecke, 2017	Pain or discomfort persisting longer than 3 months	The Chronic Pain Grade	Angina	Shortened WHO Rose Angina Questionnaire	Structured Clinical Interview for DSM-IV Disorders
D'Amato, 2016	Clinician-diagnosed chronic (>6 months) neuropathic pain, with symmetrical and distal distribution in the lower limbs, and of at least moderate severity	Clinical diagnosis	Diabetes	Patients attending the Diabetic clinic	BDI-II
Harno, 2014	Pain duration for at least 3 months	PainDETECT (Freynhagen et al., 2006); BPI	Stroke	Received treatment of stroke	BDI-IA
Ziegler, 2014	Pain for at least 3 months due to their DPN	Treatment and diagnose	Diabetes	Treatment and diagnose	HADS ≥ 8: possible cases; HADS ≥ 11: probable cases
Selvarajah, 2014	Symptoms of painful DPN for at least 6-month duration and patients on medications for pain	Neuropathic Pain Scale	Diabetes	Neuropathy Disability Score	HADS
Choinière, 2014	Pain presenting for at least 3 months	Structured interview	Angina	Canadian Cardiovascular Society Grading Scale	HADS
Bouhassira, 2013	Chronic daily pain for more than 3 months in the distal lower limbs	DN4-interview questionnaire(Bouhassira et al., 2005)	Diabetes	Clinical diagnosis	HADS
Klit, 2011	Constant or remitting pain lasting more than 3 months	Self-reported	Stroke	Clinical diagnosis	Self-reported
Hoffman, 2009	Diagnosis of painful symmetrical sensorimotor DPN for least 12 months	Clinical diagnosis	Diabetes	Clinical diagnosis	HADS

Study	Chronic pain		Cardiometabolic disease		Depression measurement
	Definition	Measurement	Condition	Measurement	
Gore, 2006 Zelman, 2006 Gore, 2005	Pain due to diabetes with healthcare professionals over the preceding 3 months	Self-reported modified scale: BPI-DPN	Diabetes	Clinical diagnosis	HADS-D
Krein, 2005	Pain for at least 6 months during the past year	Self-reported	Diabetes	Clinical diagnosis	CES-D 10 score ≥10
Widar, 2004	Pain after the stroke for at least 6 months	Self-reported	Stroke	Clinical diagnosis	HADS-D Scale > 10; "doubtful" cases HADS-D 8-10
Sadosky, 2013	Neuropathic pain symptoms for at least 3 months	Clinical diagnosis	Diabetes	Clinical diagnosis	HADS-D

Abbreviations: DPN, Diabetic Peripheral Neuropathy; BDI, Beck Depression Inventory; HADS, Hospital Anxiety and Depression Scale; WHO, World Health Organization; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, fourth edition; BPI, Brief Pain Inventory; CES-D, Centre for Epidemiologic Studies Depression Scale

4.3.5 Quality appraisal

The overall quality of the seven included studies was good (van Hecke et al., 2017, Harno et al., 2014, Ziegler et al., 2014, Selvarajah et al., 2014, Choiniere et al., 2014, Bouhassira et al., 2013, Hoffman et al., 2009), three studies fair (D'Amato et al., 2016, Klit et al., 2011, Sadosky et al., 2013), and five publications (three studies) were considered to be of poor quality (Gore et al., 2006, Zelman et al., 2006, Gore et al., 2005, Krein et al., 2005, Widar et al., 2004). The main problems with this literature were samples not being representative, lack of information about the non-respondents' details, no measurement of potential confounders, and the existence of competing interests.

4.4 Discussion

4.4.1 Summary of results

This systematic review identified 15 publications (13 studies) that included participants with the comorbidity of chronic pain, cardiometabolic disease and depression. Only one study was conducted outside the US, Canada or Europe, and it only had 401 participants. Eight studies reported diabetes as the index condition, three studies examined patients with stroke, and two examined angina.

Only one of the studies examined the prevalence of having the three conditions together and showed that angina, depression and chronic pain co-occurred in 1.8% of the general population study sample (van Hecke et al., 2017). For the participants with cardiometabolic disease, they have a higher prevalence or severity of depression with pain, or vice versa, higher risk or severity of chronic pain with depression. None of the included studies analysed health outcomes for people with the comorbidity of chronic pain, cardiometabolic disease and depression. There was no information about the sociodemographic and lifestyle factors associated with the comorbidity. No studies reported the patient experience of living with all three conditions. Finally, none of the included studies specifically aimed to investigate our comorbidities of interest.

4.4.2 Comparison with existing literature

To our knowledge, this is one of the first studies to systematically synthesise the existing literature on the comorbidity of chronic pain, cardiometabolic disease and depression. A systematic review was conducted focused on the combination of painful diabetic neuropathy and depression (Naranjo et al., 2019). Findings from eight relevant studies that met eligibility criteria (four of them did not meet the inclusion criteria of this review due to unclear duration of pain) from 206 articles returned in their search and found that the prevalence of depression ranged between 13.6% and 50.6% in patients with Painful Diabetic Peripheral Neuropathy (PDPN). Our review findings which are based on a more comprehensive search strategy and a stringent definition of chronic pain identified five relevant studies that revealed that the prevalence of depression

in patients with PDPN ranged from 24.8% to 49%. A study examining association between pain and depression found the prevalence of pain in patients with diabetes (57.8%) was higher than other studies (19% to 50%) because it included both acute and chronic pain (Bair et al., 2010).

There is more evidence published on two out of three of the conditions of interest (Xie et al., 2018). A review of 321 articles found that the prevalence of DPNP reported in patients with diabetes was 26 - 47% (Barrett et al., 2007). 1,493 participants with spinal cord injury across Canada was examined, and neuropathic pain and depression were found to be significantly associated with cardiovascular disease (Cragg et al., 2015). However, not all three conditions (chronic pain, cardiometabolic disease and depression) were examined in these studies.

In addition, some studies have examined multimorbidity in general, but not precisely these three conditions (chronic pain, cardiometabolic disease and depression). A cross-sectional study in Australia found a higher incidence of depression and pain in patients with multimorbidity than in people with single diseases or no disease (Sharpe et al., 2017). An observational multicentre cohort study found chronic pain relating to depression, heart disease, cardiac insufficiency, neuropathies from the cardiovascular/metabolic cluster and other multimorbidity (Scherer et al., 2016).

4.4.3 Evidence gap identified from the systematic review

4.4.4 Main evidence gap

This systematic review highlights the absence of data on the prevalence of chronic pain, cardiometabolic disease and depression in the general population and a lack of evidence about the effects of this pattern of comorbidity on health outcomes and patient experience. Given the impact that these conditions are known to have when experienced alone (Vos et al., 2017, James et al., 2018), further studies are needed to examine the prevalence, health outcomes and patient experience of people with this pattern of comorbidity.

In 11 of the 13 included studies, the index conditions were diabetes or stroke. These studies were included as the study sample involved patients with all three conditions. They provided data on their relationship, but none examined the prevalence of the comorbidity of the three conditions or the health outcomes and patient experience. Diabetic neuropathic pain and post-stroke pain are the most common complications of diabetes and stroke (Schreiber et al., 2015, Harrison and Field, 2015). Therefore, there is a need to focus on the combinations with stroke or diabetes.

Also, our review shows that the prevalence and impacts of the comorbidity of chronic pain, cardiometabolic disease and depression across different groups of ethnicity and socioeconomic status remain unknown. In addition, there is an absence of data from LMIC.

4.4.5 Definitions of chronic pain

The review also highlights the lack of consistent terminology and definitions for chronic pain.

Cardiometabolic disease was commonly defined by clinical diagnosis, while chronic pain was poorly defined and lacked standardisation across the included studies. The internationally accepted definition of chronic pain is having pain for at least three months (Treede et al., 2015a). However, some potentially eligible studies examined the comorbidity of the three conditions but did not clarify the timeline of pain (Kamradt et al., 2017) or considered pain that had been present for less than three months; for example, one survey conducted on older adults asked if they had had pain in the past week, which is insufficient to evaluate the presence of chronic pain (Hornsten et al., 2016), and therefore it was excluded from this systematic review. It is important to clarify if the pain experienced is chronic. Absence of reporting of the timeline of the duration of pain makes it hard to compare study findings. Our systematic review, only included studies that provided a clear definition of chronic pain (i.e. reporting pain for at least three months or 12 weeks) and so relevant studies may have been excluded based on their imprecise descriptions of chronic pain.

Further, there are also different types of chronic pain such as persistent musculoskeletal pain (low back pain, neck pain, joint pain, widespread pain) (Main and de C Williams, 2002), PDPN (Davies et al., 2006), and central neuropathic pain (Watson and Sandroni, 2016). Different types of pain will be experienced differently and present specific challenges for clinical management (Bouhassira et al., 2013, Udall et al., 2019).

Neuropathic pain is a common complication of diabetes. The prevalence of PDPN was reported to be 26.4% among patients with type 2 diabetes, with a significant adverse impact on the quality of life (Davies et al., 2006). Among the included studies in this systematic review, some studies involved and specified multiple types of pain. In addition to the neuropathic pain, 41.5% reported other chronic pain in a study of 2575 participants with painful DPN (Ziegler et al., 2014). A higher proportion of 62.7% of painful DPN patients reported other chronic musculoskeletal pain (Gore et al., 2006). Lower acceptance of chronic pain among patients with diabetic neuropathic pain was strongly associated with more depressive symptoms in 142 participants using the painful DPN multidisciplinary outpatients service in Sheffield (Selvarajah et al., 2014). On the other hand, a cross-sectional study mixed the neuropathic pain and other pain (Krein et al., 2005). Differences in the types of pain examined make it hard to compare studies. But due to the limited evidence, all these different types were included in this study to ensure that all literature involving the combination of the three conditions were obtained.

4.4.6 Strengths and limitations

There are some limitations of this study. First, the limitation of the English language in the search strategy could potentially bias the information we obtained on the global pattern of the epidemic of the comorbidity of chronic pain, cardiometabolic disease and depression. Grey literature and conference abstracts were excluded, which could result in language or publication bias, although there is increasing evidence that show that this is not a problem for systematic reviews (Morrison et al., 2012).

Second, the various definitions of chronic pain made it harder to compare the studies. Some studies may be missed from the study selection because they did

not clarify whether the pain was chronic or acute. Due to the heterogeneity of the data, a formal meta-analysis was not possible. Also, because the included studies were observational, no information is available about disease trajectories.

Despite these limitations, there are also some strengths. This systematic review involved a comprehensive search of the existing evidence. Studies related to but not aimed at the specific investigation of the comorbidity of chronic pain, cardiometabolic disease and depression were included. Article screening, data extraction, and quality appraisal were conducted independently by two researchers, with a third party available for adjudication in case of disagreements.

In addition, the quality appraisal instrument for multimorbidity was modified to assess the included citations in this study. The commonly used quality appraisal forms are mainly designed to evaluate studies that examine single conditions. Thus, it is not suitable to directly apply the tools to multimorbidity or comorbidity studies involving two or more conditions. The Newcastle-Ottawa tool was modified to adapt to these studies in this study, which is an acceptable tool to use.

4.4.7 Conclusion

This review has identified key evidence gaps regarding the prevalence, effects and patient experience of the comorbidity of chronic pain, cardiometabolic disease and depression. Further research to examine this pattern of comorbidity, the effects on health outcomes and patient experience are needed to understand the challenges posed by this combination of conditions. A cross-sectional study will be described in the next chapter, designed to examine the prevalence and sociodemographic and lifestyle factors associated with the comorbidity of the three conditions of interest.

Chapter 5 The pattern of the comorbidity of chronic pain, cardiometabolic disease, and depression: a cross-sectional study of UK Biobank

5.1 Introduction

5.1.1 Overview of this chapter

This chapter shows the findings from a cross-sectional study that examined the prevalence and the factors associated with the comorbidity of UK Biobank participants with chronic pain, cardiometabolic disease, and depression to answer research question 2 of this thesis: how common is it to have this comorbidity and what sociodemographic and lifestyle factors are associated with the comorbidity?

5.1.2 Rationale

The systematic review in Chapter 4 identified an evidence gap related to this pattern of comorbidity and factors associated with this combination of LTCs. Very little research has specifically focused on this combination of conditions, and the studies that mentioned the three conditions were limited. Those participants with diabetes or stroke who also experienced symptoms of depression were more likely to have chronic pain (D'Amato et al., 2016, Gore et al., 2005). As depression severity increased, in those with stroke, the severity of chronic pain also increased (Klit et al., 2011). Only one study (van Hecke et al., 2017) analysed a large population dataset that examined the prevalence of the comorbidity of chronic pain, depression and angina. Unfortunately, the prevalence of the combination of pain and depression with other cardiometabolic diseases was not explored. There was also a lack of evidence on the association between this combination of conditions and sociodemographic or lifestyle factors.

5.1.3 Aims and hypothesis

5.1.3.1 Aims and objectives

The overall aim of this cross-sectional study was to examine the prevalence of chronic pain alongside cardiometabolic disease and depression in the UK Biobank baseline population and explore sociodemographic and lifestyle factors in relation to the comorbidity of the three conditions of interest. The specific objectives were:

1. To examine the comorbidity of chronic pain, cardiometabolic disease and depression, specifically:

   a) determine the prevalence of the comorbidity; and

   b) identify the most common combinations of chronic pain, different types of cardiometabolic diseases, and depression.

2. To identify sociodemographic and lifestyle factors associated with the comorbidity of chronic pain, cardiometabolic disease and depression.

3. To examine the relationship between the three conditions of interest, taking sociodemographic and lifestyle factors into account.

5.1.3.2 Hypotheses

In this cross-sectional study, the central hypothesis is that the comorbidity of chronic pain, cardiometabolic diseases, and depression will be more likely to occur in those from more socioeconomically deprived backgrounds and with less healthy lifestyles. In detail, we hypothesise that:

1. the comorbidity of the three conditions will be more likely in people with specific characteristics: female, older age, more deprivation, more alcohol intake, smoking, less physical activity, and higher BMI (being overweight or classified as having obesity);

2. the three conditions are related to each other, and each condition is more likely to occur in people with the other two.

5.2 Data management

5.2.1 Data source: UK Biobank

This study examined UK Biobank Data (Biobank, 2022), a large dataset of over 500,000 adults aged 38-73 years from England, Scotland and Wales. The results presented in this chapter were from the baseline data. The background of the dataset, including the recruitment process, has been detailed in Chapter 3. In summary, the baseline data were collected during an initial assessment visit using touchscreen questionnaires and verbal interviews from 2006 to 2010. The verbal interview data contained the health conditions and medication data utilised in this study (Biobank, 2012).

The sample included in this study is those who self-reported complete data on chronic pain, cardiometabolic diseases and depression at the baseline assessment visit. This work has ethical approval of UK Biobank projects (16/NW/0274) and was conducted under UK Biobank approved project 14151.

5.2.2 Measurement of health conditions of interest

5.2.2.1 Chronic pain

Upon the baseline visit to the assessment centre, chronic pain in the past three months was self-reported by a touchscreen questionnaire.

The question *"In the last month, have you experienced any of the following that interfered with your usual activities?"* (Field ID 6159) had eight possible answers of seven sites of pain and "pain all over the body": head pain, facial pain, neck/shoulder pain, back pain, stomach/abdominal pain, hip pain, knee pain and pain all over the body. In this study, CWP refers to pain all over the body, as has been done in other studies using UK Biobank (Macfarlane et al., 2017), distinguished from multiple sites of pain.

If any site of pain was chosen, the participant was then directed to the next question, *"Have you had xx pain for more than three months?"* and the options were *"Yes"*, *"No"*, *"Do not know"*, and *"Prefer not to answer"*. The latter three answers (*"No"*, *"Do not know"*, and *"Prefer not to answer"*) were grouped as

not self-reported chronic pain. If they chose "*pain all over the body*", they could not select the specific body sites of pain. The answers were then categorised into binary variables of *"Yes"* (self-reported chronic pain) or *"No"* (not self-reported chronic pain). Incomplete answers were marked as "NA" (not applicable) as missing values.

A yes/no binary variable "chronic pain" was created to identify the presence of chronic pain in any of the seven body sites or CWP. Chronic pain was also categorised based on the number of sites (extent of chronic pain: 0-7, or CWP). However, there was no measure of the severity of pain in the baseline data.

5.2.2.2 Cardiometabolic diseases

The touchscreen questionnaire and verbal interview captured several types of chronic cardiometabolic diseases in the baseline data. These were grouped into seven conditions based on previous work from this research group (Jani et al., 2019): PVD, CHD, Stroke/TIA, diabetes, hypertension, HF, AF. A complete list of cardiometabolic diseases in the baseline data included in this study is attached in Appendix 6.

Participants with any of the cardiometabolic diseases (PVD, CHD, Stroke/TIA, diabetes, hypertension, HF, AF) were categorised as "yes" to cardiometabolic disease; participants with none of the cardiometabolic diseases were categorised as "no". They were then divided into four sub-groups: participants with no cardiometabolic diseases, one cardiometabolic disease, two cardiometabolic diseases, and three or more cardiometabolic diseases.

5.2.2.3 Depression

Depression in this study was defined using self-reported depression and the use of antidepressant medications, as these were thought to represent clinically diagnosed depression rather than merely depressive symptoms. There are several options of depression data sources in UK Biobank data: self-reported LTCs, medication history, current depressive symptoms score, and algorithm for MDD.

In this study, we used self-reported depression as a chronic condition (Field ID 20002) and the medication use of antidepressant SSRIs and related drugs as indicators of depression (Field ID 20003).

Self-reported depression

Depression was identified in the touchscreen questionnaire on self-reported LTCs as psychological/psychiatric problems. The participants' self-reported depression was then checked during the verbal nurse-led interview.

Medication - Selective Serotonin Reuptake Inhibitors (SSRIs)

Participants were identified as taking antidepressant medication in the verbal interview. The medications listed in Appendix 7 show the SSRIs and other antidepressants used to classify a participant as taking antidepressants. This group of medications has been used in a previously published study using the same approach (Hanlon et al., 2018b).

A binary variable of "yes" or "no" was created to identify those who reported self-reported depression or medication of SSRIs as having depression; those who did not report either of these were considered to have no depression.

5.2.2.4 Comorbidity

The comorbidity of chronic pain, depression, and cardiometabolic diseases was grouped as a binary variable: "yes" or "no" to having the three conditions of interest, and those with zero, one or two of the three conditions of interest were categorised as "no" to the comorbidity.

5.2.3 Sociodemographic and lifestyle variables

The following sociodemographic and lifestyle variables, the factors that were examined an association with the three conditions, were chosen to fulfil objective 2 of this study.

5.2.3.1 Sociodemographic variables

Age groups

The age data was the age of the participant at the baseline assessment centre. A histogram was constructed to show age distribution was skewed. As a result, age was categorised into six groups, with intervals of five years based on the distribution: 38-44 years, 45-49 years, 50-54 years, 55-59 years, 60-64 years, and 65-73 years.

Gender

The gender data was the binary variable of female and male obtained from the NHS records and the participants' self-reports.

Ethnicity

Participant's ethnicity was classified as white (British, Irish, other white backgrounds), Mixed (white & Black Caribbean, white & Black African, white & Asian, other mixed backgrounds), Asian or Asian British (Indian, Pakistani, Bangladeshi, other Asian backgrounds), Black or Black British (Caribbean, African, other Black backgrounds), Chinese and others. Although the ethnicity was reported by the participants in detail, only the higher level of the categories was used in the study. All ethnic groups except for white had a very small (<6%) proportion of participants among the study population. These categories were combined as "other ethnic groups", leaving ethnic groups in this study as white and other.

Townsend score

The Townsend Deprivation Index (Morris and Carstairs, 1991) is an area-based measure of socioeconomic status calculated according to the postcode of the geographical area. It was calculated when the participants joined UK Biobank based on the preceding national census output areas. In the study, quintiles of the Townsend score from one to five were calculated to categorise the deprivation of the participants from least to most deprived, respectively.

5.2.3.2 Lifestyle variables

Alcohol intake frequency

In this study, the alcohol intake frequency was used. Based on previous work (Jani et al., 2021), the variable of alcohol intake frequency captured in the touchscreen questionnaire was grouped into the following categories: never or special occasions only, 1-3 times a month, 1-4 times a week, and daily or almost daily.

Smoking status

In the touchscreen questionnaire, a series of questions about smoking were asked. This study categorised smoking status as current/previous, or never (Prats-Uribe et al., 2021).

Physical activity

Self-reported physical activity levels were measured by an adapted version of the International physical activity questionnaire (IPAQ) (Craig et al., 2003) in the touchscreen questionnaire. The activities examined included walking and moderate and vigorous physical activity (Cassidy et al., 2016). The participants were asked how many days they engaged in each exercise per week and how many minutes they were engaged each day. Physical activity was categorised as low, moderate and high.

Body Mass Index

BMI was a continuous variable recorded by an anthropometric measurement during the baseline assessment centre visit and calculated by the weight divided by the square of the height (kg/m^2). BMI was then categorised into "underweight < 18.50", "recommended weight 18.50 - 24.99", "overweight 25.00 -29.99", "obese >= 30.00", according to the WHO internationally recognised categories (WHO, 2000).

5.2.3.3 Additional LTCs

In addition to chronic pain, depression, and the seven cardiometabolic conditions listed, 37 other self-reported LTCs, including Parkinson's disease, chronic liver disease, chronic obstructive pulmonary disease (COPD), chronic kidney disease, epilepsy, cancer, along with the rest of the LTCs listed in

Appendix 8, were counted. These additional LTCs were chosen based on previous work (Jani et al., 2019).

The variable "additional LTCs" was categorised as "yes" or "no" to having any of the additional 37 LTCs, and it was included in the study as covariate to the association between the comorbidity of the three conditions of interest and the sociodemographic and lifestyle factors

5.2.4 Missing values

The participants included in this study were participants with complete data on the three conditions of interest: chronic pain, cardiometabolic disease and depression.

As described above, cardiometabolic disease and depression were ascertained through data from the touchscreen questionnaire and nurse-led interview; therefore, a response was recorded for all participants, and no participants are considered to have missing data for these two conditions of interest.

The data on chronic pain was collected from multiple questions. Given that the definition of chronic pain in our study is pain for at least three months, those who did not report any pain or pain for one month only were categorised as not reporting chronic pain. A total of 2,190 (0.44%) participants did not provide complete pain data and thus were considered missing and removed from the analysis for this study.

A flow chart illustrating the numbers included is shown in Figure 5-1.

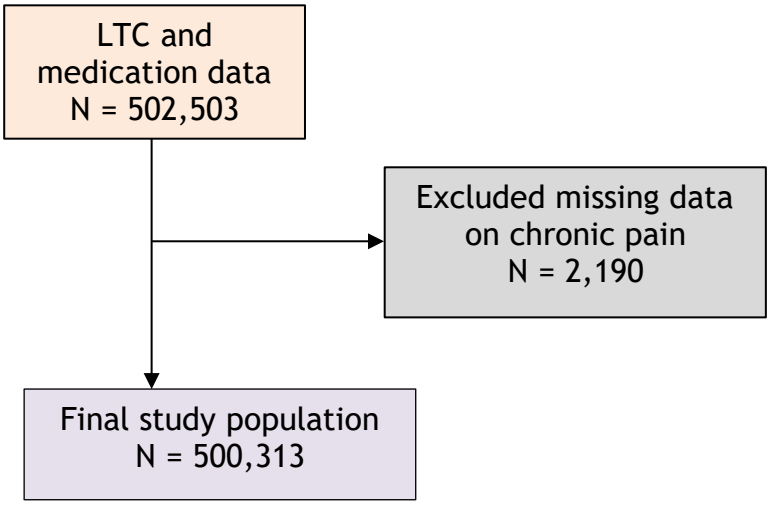

Figure 5-1 Diagram of the data cleaning of the study sample

5.3 Statistical Analysis

This section outlines how the characteristics of the study population were described, how the prevalence of the three conditions and comorbidity were calculated (objective 1a), how the participants with different health conditions were compared (objective 1b), and the logistic analysis performed to identify sociodemographic, health and lifestyle factors associated with the comorbidity (objective 2), alongside the relationship between the three conditions (objective 3).

5.3.1 Descriptive analysis

5.3.1.1 The characteristics of the study sample

Descriptive analysis was conducted to summarise the variables of interest in the study population. To show the distribution within the study population, summary statistics were used: for continuous variables, the mean, SD (Lee et al., 2015a), and range were summarised; for categorical variables, the number and percentages were calculated for each group.

5.3.1.2 Prevalence of single diseases

A descriptive analysis of the single diseases was performed. The prevalence of each site of chronic pain (head pain, face pain, neck/shoulder pain, back pain,

stomach/abdominal pain, hip pain, knee pain, and CWP), each type of cardiometabolic disease (PVD, CHD, Stroke/TIA, diabetes, hypertension, HF, AF) and depression was calculated, as the following equation:

$$Prevalence = \frac{Number\ of\ cases}{Total\ study\ sample\ size} \times 100\%$$

5.3.1.3 Prevalence of the combination of two of the conditions

The combination of two conditions (chronic pain + cardiometabolic disease, chronic pain + depression, depression + cardiometabolic disease) was described. The most common combinations of different extent of chronic pain, different cardiometabolic disease types and depression were identified. CWP was examined separately from different sites of chronic pain.

5.3.1.4 Prevalence of the comorbidity of the three conditions

The prevalence of the comorbidity of the three conditions (chronic pain + cardiometabolic disease + depression) (objective 1a) and the prevalence of combinations of chronic pain, depression and certain cardiometabolic diseases were calculated.

Any cardiometabolic disease and different types of cardiometabolic disease were examined to find out which were the most commonly reported alongside chronic pain and depression (objective 1b).

5.3.1.5 Sociodemographic and lifestyle factors

The characteristics, in terms of sociodemographic and lifestyle factors (age, gender, ethnicity, Townsend, smoking, alcohol intake, physical activity, and BMI) of participants with single diseases (chronic pain, cardiometabolic disease or depression) and with the combination of three conditions were compared by describing the frequency, and the corresponding percentages, as all were considered as categorical variables (objective 2).

The frequency and percentages of the factors associated with participants with different chronic pain sites, different types of cardiometabolic disease and depression were also calculated.

5.3.2 Test of association

Pearson's Chi-squared test (Shih and Fay, 2017) were used to compare whether there were differences in sociodemographic and lifestyle factors between those with the comorbidity and those free of the comorbidity (objective 2).

The rationale for chi-square and the explanation of hypothesis testing has been detailed in Chapter 3. The null hypothesis for the chi-square tests was that there were no differences in gender, age group, ethnicity group, Townsend score quintile, smoking status, alcohol intake frequency, physical activity and BMI between participants in the different comorbidity groups. The significance level was set at 0.001.

5.3.3 Inferential statistics

Logistic regression was used to investigate the association between having the comorbidity (binary, yes or no) and the sociodemographic and lifestyle variables discussed above (objective 2); and the relationship between the three conditions (objective 3).

5.3.3.1 Dependent variables

The dependent variables to fit in the logistic regression models are binary variables of chronic pain, cardiometabolic disease, depression and comorbidity:

Comorbidity (objective 2): yes/no to the combination of the three conditions (having zero or one or two of the three conditions was a "no" to this variable)

Chronic pain (objective 3): yes/no to any chronic pain

Cardiometabolic disease (objective 3): yes/no to any cardiometabolic disease

Depression (objective 3): yes/no to depression

5.3.3.2 Independent variables

Age, Townsend score and BMI were originally continuous variables in the raw data. To fit continuous in the a logistic regression model, it is assumed that the

relationship between the log odds of the independent variable and the outcome is linear (Nick and Campbell, 2007). Given that the assumption could not be fulfilled, these three variables were classified into categorical variables as described above.

Additional categorical variables included gender, ethnicity, smoking status, alcohol frequency and physical activity levels. An appropriate reference category was chosen from each categorical variable. For ethnicity and gender, white participants and males were considered the normative groups and set as the reference category to compare other categories in the group. The reference groups were defined for other variables: the youngest age group, recommended weight (classified by BMI), least deprived Townsend score, never smoking, and least alcohol intake frequency.

The binary variable of additional LTCs was categorical, with the reference group of "no" to any additional LTCs.

5.3.3.3 Univariable models

Univariable models of the dependent variable with single independent variables were fitted to examine the relationship between the comorbidity (combination of chronic pain, cardiometabolic disease and depression) and single determinants of sociodemographic and lifestyle factors and additional LTCs. The significance level was set at 0.001, the same as in multivariable models.

5.3.3.4 Multivariable models

Four multivariable models were fitted to examine the independent variables of interest and all were adjusted for putative confounding variables (Table 5-1).

In model 1, the regression model between the comorbidity (combination of chronic pain, cardiometabolic disease and depression) and the sociodemographic and lifestyle factors were fitted and adjusted for the presence (yes/no) of any additional LTCs (objective 2). In the hypotheses testing (hypothesis 1), the null hypothesis was that the likelihood of the dependent variable of the comorbidity was the same for all categories of the independent variables.

In models 2-4, the relationship between chronic pain, cardiometabolic disease and depression was examined (objective 3), adjusted for the sociodemographic and lifestyle factors and additional LTCs. In the hypotheses testing (hypothesis 2), the null hypothesis was that the likelihood of having chronic pain in participants with cardiometabolic disease or depression was the same for those without cardiometabolic disease or depression; the likelihood of having cardiometabolic disease in participants with chronic pain or depression was the same for participants without chronic pain or depression; and the likelihood of having depression in participants with cardiometabolic disease or depression was the same for participants without cardiometabolic disease or depression.

Table 5-1. Multivariable logistic regression models

Logistic model	Objective	Dependent variable	Independent variable	
			Covariates of interest	Other covariates
Model 1	2	Comorbidity	Age, gender, ethnicity, Townsend score, smoking, alcohol intake, physical activity, BMI	Additional LTCs
Model 2	3	Chronic pain	Cardiometabolic disease, depression	Age, gender, ethnicity, Townsend score, smoking, alcohol intake, physical activity, BMI, additional LTCs
Model 3	3	Cardiometabolic disease	Chronic pain, depression	Age, gender, ethnicity, Townsend score, smoking, alcohol intake, physical activity, BMI, additional LTCs
Model 4	3	Depression	Chronic pain, cardiometabolic disease	Age, gender, ethnicity, Townsend score, smoking, alcohol intake, physical activity, BMI, additional LTCs

Abbreviations: LTC, long-term condition; BMI, Body Mass Index

5.3.4 Analysis of missing values

In the logistic regression model, there were 12,667 (2.53%) missing values on individual variables of interest, and 487,646 were actually included in the multivariable logistic regression models.

As the amount of missing data was small compared to the whole sample, it was not thought to be particularly informative to compare the characteristics of those with the missing data and the study sample to assess potential bias.

5.3.5 Statistical software

The statistical analysis was conducted using RStudio, the statistical software version 3.1.2. The descriptive cross-tabulation analysis was performed using "sjPlot" packages to customise the plot appearance; the chi-square tests were conducted using "MASS" packages; the "glm" function was used for fitting the logistic regression models.

5.4 Results

5.4.1 Description of the study population

5.4.1.1 Characteristics of the study sample

The age of the study sample ranged from 38-73 years, with an average age of 56.53 ± 8.09 years (mean ± SD), and the median was 58 years (Figure 5-2).

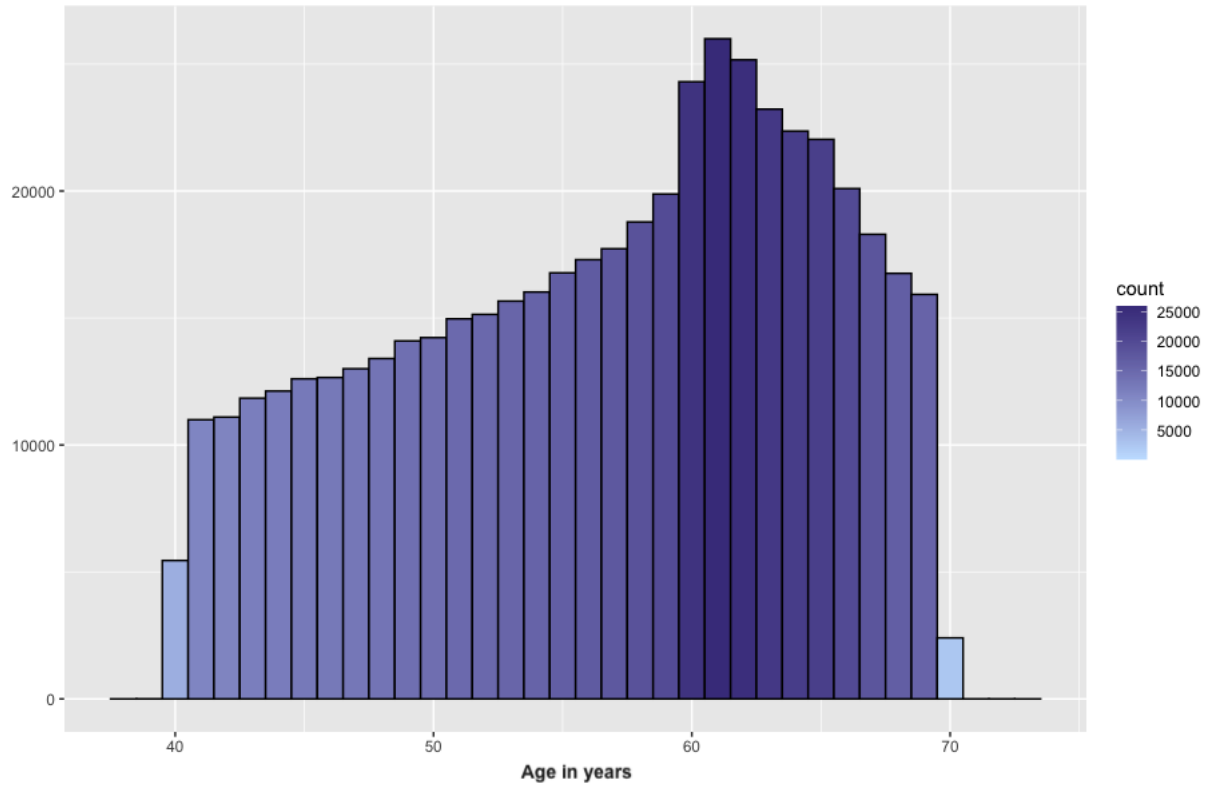

Figure 5-2 Histogram of the age distribution of the study sample

A total of 272,235 participants were female, which made up 54.41% of the study sample. The average age of the females was 56.35 ± 8.00 years, and the average age of males was 56.75 ± 8.19 years.

There were 471,851 (94.31%) white participants and 26,749 (5.35%) participants of other ethnic group: 9,744 (1.95%) Asian or Asian British, 1,558 (0.31%) Chinese, 7,995 (1.60%) Black or Black British, 1,558 (0.31%) Chinese, 2,948 (0.59%) Mixed, 4,504 (0.90%) others, and 1,713 (0.34%) missing values.

5.4.1.2 Prevalence of single diseases

Chronic pain

43.70% (218,657 / 500,313) of the study population reported the presence of chronic pain in any of the seven sites or CWP. The three most common sites of chronic pain were: back pain (17.65%), knee pain (16.78%) and neck/shoulder pain (15.92%). 7,128 (1.42%) participants reported CWP (Table 5-2).

Table 5-2. Prevalence of different sites of self-reported chronic pain among the total study sample (n = 500,313)

Site of chronic pain	N	Prevalence
Head pain	45,416	9.08%
Facial pain	4,406	0.88%
Neck or shoulder pain	79,634	15.92%
Back pain	88,298	17.65%
Stomach or abdominal pain	24,004	4.80%
Hip pain	43,166	8.63%
Knee pain	83,941	16.78%
CWP	7,128	1.42%

Abbreviations: CWP, chronic widespread pain

Cardiometabolic disease

The prevalence of any self-reported cardiometabolic disease in the study population was 31.22% (156,209 / 500,313) (Table 5-3). Of the participants with any cardiometabolic disease, 21.32% (33,309 / 156,209) reported two or more. 24 participants had the most cardiometabolic diseases – they reported five of the seven types of cardiometabolic disease studied. The prevalence of different types and numbers of cardiometabolic diseases showed hypertension (26.55%) had the highest prevalence, followed by diabetes (5.06%), CHD (4.53%) and stroke/TIA (1.76%).

Table 5-3. Prevalence of cardiometabolic diseases

	Prevalence in the whole study sample (n = 500,313)		Prevalence in participants with chronic pain (n = 218,657)		Prevalence in participants with depression (n = 35,940)	
Types of cardiometabolic diseases						
Diabetes	25,324	5.06%	13,191	6.03%	2,470	6.87%
Hypertension	132,818	26.55%	65,624	30.01%	11,043	30.73%
CHD	22,650	4.53%	12,801	5.85%	2,206	6.14%
Stroke/TIA	8,805	1.76%	4,947	2.26%	1,058	2.94%
AF	3,640	0.73%	1,732	0.79%	238	0.66%
PVD	1,275	0.25%	748	0.34%	132	0.37%
HF	797	0.16%	388	0.18%	82	0.23%
Number of cardiometabolic diseases (0-7)						
0	344,104	68.78%	141,522	64.72%	22,824	63.51%
1	122,900	24.56%	58,565	26.78%	9,751	27.13%
2	28,054	5.61%	15,236	6.97%	2,705	7.53%
≥3	5,255	1.05%	3,334	1.52%	660	1.84%

Abbreviations: PVD, peripheral vascular disease; TIA, Transient Ischaemic Attack; MI, myocardial infarction; CHD, coronary heart disease; HF, heart failure; AF, Atrial fibrillation

Depression

The prevalence of depression was 7.18% (35,940 / 500,313). Among the participants who self-reported depression in the study (n = 35,940), 24,480 (68.11%) of them reported taking SSRIs and related drugs in their medication history, 28,363 (78.92%) of them reported diagnosed depression as a chronic condition, and 16,903 (47.03%) reported both.

Additional LTCs

There were 216,806 (43.43%) participants having at least one additional LTC (other than a cardiometabolic disease, chronic pain or depression). Of the individual 37 LTCs considered, those with the highest prevalence were: asthma (11.61%), treated dyspepsia (7.78%) and cancer (7.70%) (details provided in Appendix 8.

5.4.1.3 Prevalence of the combination of two conditions

The prevalence of the combination of two conditions among the whole study sample was 15.42% (chronic pain + cardiometabolic disease), 4.31% (chronic pain + depression), 2.62% (cardiometabolic disease + depression), respectively.

Table 5-4 and Table 5-5 summarise the prevalence of cardiometabolic diseases and depression across chronic pain sites and extent, respectively. To be more detailed, the highest proportion of depression in participants with other sites of pain was the combination of depression and face pain at 18.13% (799 / 4,406) (Table 5-4). 36.49% of the participants with depression also had at least one cardiometabolic disease. Prevalence of depression was 5.10% (14,373 / 281,656) in participants with no pain, 9.86% (21,567 / 218,657) in chronic pain and 20.97% (1,495 / 7,128) in CWP (Table 5-5). The prevalence of diabetes was 5.06% (25,324 / 500,313) in the study population and 6.03% (13,191 / 218,657) in participants with chronic pain (Table 5-3), and 12.46% (888 / 7,128) in participants with CWP (Table 5-5).

Table 5-4 The prevalence of cardiometabolic disease and depression in participants with different sites of chronic pain

	Head pain		Face pain		Neck/shoulder pain		Back pain		Abdominal/ stomach pain		Hip pain		Knee pain	
	n = 45,416		n = 4,406		n = 79,634		N = 88,298		n = 24,004		n = 43,166		n = 83,941	
Different types of cardiometabolic diseases														
Diabetes	1,701	3.75%	238	5.40%	5,177	6.50%	5,688	6.44%	1,516	6.32%	3,395	7.86%	6,126	7.30%
Hypertension	10,813	23.81%	1,215	27.58%	24,335	30.56%	28,180	31.91%	7,290	30.37%	15,440	35.77%	29,081	34.64%
CHD	1,837	4.04%	290	6.58%	5,303	6.66%	6,052	6.85%	1,725	7.19%	3,609	8.36%	5,720	6.81%
Stroke/TIA	1,086	2.39%	186	4.22%	1,971	2.48%	2,177	2.47%	655	2.73%	1,346	3.12%	2,100	2.50%
AF	252	0.55%	23	0.52%	654	0.82%	738	0.84%	206	0.86%	436	1.01%	766	0.91%
PVD	133	0.29%	25	0.57%	325	0.41%	355	0.40%	123	0.51%	200	0.46%	275	0.33%
HF	69	0.15%	8	0.18%	165	0.21%	169	0.19%	49	0.20%	103	0.24%	153	0.18%
Any cardiometabolic disease	12,687	27.94%	1,484	33.68%	28,982	36.39%	33,039	37.42%	8,642	36.00%	18,104	41.94%	33,826	40.30%
Number of cardiometabolic diseases														
0	32,729	72.06%	2,922	66.32%	50,652	63.61%	55,259	62.58%	15,362	64.00%	25,062	58.06%	50,115	59.70%
1	10,045	22.12%	1,092	24.78%	21,609	27.14%	24,559	27.81%	6,283	26.17%	12,917	29.92%	25,171	29.99%
2	2,157	4.75%	302	6.85%	5,978	7.51%	6,831	7.74%	1,862	7.76%	4,089	9.47%	7,084	8.44%
≥3	485	1.07%	90	2.04%	1,395	1.75%	1,649	1.87%	497	2.07%	1,098	2.54%	1,571	1.87%
Depression	6,152	13.55%	799	18.13%	9,007	11.31%	9,795	11.09%	3,509	14.62%	4,965	11.50%	8,083	9.63%

Abbreviations: PVD, peripheral vascular disease; TIA, Transient Ischaemic Attack; MI, myocardial infarction; CHD, coronary heart disease; HF, heart failure; AF, Atrial fibrillation

Table 5-5 The prevalence of cardiometabolic disease and depression by extent of chronic pain, CWP and depression

	No chronic pain n = 281,656		One pain site n = 115,197		Two pain sites n = 55,783		Three or more pain sites n = 40,549		CWP n = 7,128		Depression n = 35,940	
Different types of cardiometabolic diseases												
Diabetes	12,133	4.31%	5,812	5.05%	3,276	5.87%	3,215	7.93%	888	12.46%	2,470	6.87%
Hypertension	67,194	23.86%	31,243	27.12%	16,992	30.46%	14,427	35.58%	2,962	41.55%	11,043	30.73%
CHD	9,849	3.50%	5,144	4.47%	3,267	5.86%	3,527	8.70%	863	12.11%	2,206	6.14%
Stroke/TIA	3,858	1.37%	1,939	1.68%	1,242	2.23%	1,394	3.44%	372	5.22%	1,058	2.94%
AF	1,908	0.68%	827	0.72%	458	0.82%	378	0.93%	69	0.97%	238	0.66%
PVD	527	0.19%	291	0.25%	189	0.34%	207	0.51%	61	0.86%	132	0.37%
HF	409	0.15%	158	0.14%	100	0.18%	96	0.24%	34	0.48%	82	0.23%
Any cardiometabolic disease	79,074	28.07%	36,646	31.81%	19,837	35.56%	17,049	42.05%	3,603	50.55%	13,116	36.49%
Number of cardiometabolic diseases												
0	202,582	71.93%	78,551	68.19%	35,946	64.44%	23,500	57.95%	3,525	49.45%	22,824	63.51%
1	64,335	22.84%	29,074	25.24%	15,066	27.01%	12,084	29.80%	2,341	32.84%	9,751	27.13%
2	12,818	4.55%	6,477	5.62%	3,935	7.05%	3,884	9.58%	940	13.19%	2,705	7.53%
>3	1,921	0.68%	1,095	0.95%	836	1.50%	1,081	2.67%	322	4.52%	660	1.84%
Depression	14,373	5.10%	8,347	7.25%	5,426	9.73%	6,299	15.53%	1,495	20.97%	/	/

Abbreviations: CWP, chronic widespread pain; LTC, long-term conditions; PVD, peripheral vascular disease; TIA, Transient Ischaemic Attack; MI, myocardial infarction; CHD, coronary heart disease; HF, heart failure; AF, Atrial fibrillation

5.4.1.4 Prevalence of the comorbidity of the three conditions

The prevalence of the comorbidity of all three conditions of interest, chronic pain, cardiometabolic disease and depression, was 1.73% (8,640 / 500,313).

1.22% (6,126 / 500,313) of participants had one cardiometabolic disease, along with chronic pain and depression. The prevalence of the comorbidity of involving the most commonly reported cardiometabolic diseases was: hypertension, diabetes, CHD, or stroke, together with chronic pain and depression was 1.06% (4,932 / 467,004), 0.09% (433 / 467,004), 0.09% (425 / 467,004), and 0.05% (231 / 467,004), respectively.

5.4.2 Sociodemographic and lifestyle factors

5.4.2.1 Chronic pain and CWP

The cross-tabulation of the proportion of sociodemographic and lifestyle factors in participants with different chronic pain sites showed that participants with CWP differed from the rest of the study population in ethnic group,, Townsend score and lifestyle factors (Table 5-6).

The proportions of participants from other ethnic groups across different sites of chronic pain ranged from 4.42% to 7.04%, while 12.12% of participants with CWP reported being from other ethnic groups. Similarly, the most deprived group made up 22.75% to 28.31% of participants across the different sites of chronic pain and 37.65% of participants with CWP.

The highest percentages of current smoking (18.46%), never drinking or on special occasions only (44.53%), none (23.08%) and low (8.70%) degree of physical activity, obesity (42.30%) and overweight (36.07%), were reported in CWP in comparison to different sites of chronic pain.

Table 5-6. Descriptive analysis of different sites of chronic pain with sociodemographic and lifestyle factors at the baseline of UK Biobank (n = 500,313)

	Head pain n = 45,416		Face pain n = 4,406		Neck/Shoulder Pain n = 79,634		Back pain N = 88,298		Abdominal /stomach pain n = 24,004		Hip pain n = 43,166		Knee pain n = 83,941		CWP n = 7,128	
Gender																
Male	13,405	29.52%	1,203	27.30%	32,160	40.38%	39,601	44.85%	9,036	37.64%	15,641	36.23%	38,639	46.03%	2,586	36.28%
Female	32,011	70.48%	3,203	72.70%	47,474	59.62%	48,697	55.15%	14,968	62.36%	27,525	63.77%	45,302	53.97%	4,542	63.72%
Missing	0	0.00%	0	0.00%	0	0.00%	0	0.00%	0	0.00%	0	0.00%	0	0.00%	0	0.00%
Age, years																
38-44	6,177	13.60%	500	11.35%	6,787	8.52%	8,575	9.71%	3,289	13.70%	2,486	5.76%	5,846	6.96%	516	7.24%
45-49	8,219	18.10%	659	14.96%	9,886	12.41%	11,230	12.72%	3,910	16.29%	3,983	9.23%	8,739	10.41%	826	11.59%
50-54	8,727	19.22%	795	18.04%	12,355	15.51%	13,037	14.76%	3,987	16.61%	5,855	13.56%	11,931	14.21%	1,199	16.82%
55-59	8,680	19.11%	878	19.93%	15,051	18.90%	15,971	18.09%	4,167	17.36%	7,888	18.27%	15,769	18.79%	1,507	21.14%
60-64	8,553	18.83%	953	21.63%	19,660	24.69%	21,610	24.47%	4,884	20.35%	12,077	27.98%	22,418	26.71%	1,716	24.07%
65-73	5,060	11.14%	621	14.09%	15,895	19.96%	17,875	20.24%	3,767	15.69%	10,877	25.20%	19,238	22.92%	1,364	19.14%
Missing	0	0.00%	0	0.00%	0	0.00%	0	0.00%	0	0.00%	0	0.00%	0	0.00%	0	0.00%
Ethnicity																
White	42,603	93.81%	4,155	94.30%	74,399	93.43%	82,305	93.21%	22,223	92.58%	41,110	95.24%	78,580	93.61%	6,226	87.35%
Other	2,638	5.81%	232	5.27%	4,959	6.23%	5,660	6.41%	1,691	7.04%	1,910	4.42%	5,038	6.00%	864	12.12%
Missing	175	0.39%	19	0.43%	276	0.35%	333	0.38%	90	0.37%	146	0.34%	323	0.38%	38	0.53%
Townsend score quintile																
1 (least deprived)	8,561	18.85%	713	16.18%	14,288	17.94%	15,591	17.66%	3,848	16.03%	7,540	17.47%	14,794	17.62%	866	12.15%
2	8,577	18.89%	787	17.86%	14,765	18.54%	16,162	18.30%	4,111	17.13%	8,058	18.67%	15,593	18.58%	924	12.96%
3	8,811	19.40%	827	18.77%	15,470	19.43%	16,971	19.22%	4,346	18.11%	8,300	19.23%	16,355	19.48%	1,155	16.20%
4	9,070	19.97%	945	21.45%	16,141	20.27%	17,765	20.12%	4,866	20.27%	8,836	20.47%	17,195	20.48%	1,491	20.92%
5 (most deprived)	10,332	22.75%	1,127	25.58%	18,854	23.68%	21,686	24.56%	6,796	28.31%	10,376	24.04%	19,875	23.68%	2,684	37.65%
Missing	65	0.14%	7	0.16%	116	0.15%	123	0.14%	37	0.15%	56	0.13%	129	0.15%	8	0.11%
Smoking																

Never	26,019	57.29%	2,355	53.45%	39,596	49.72%	43,112	48.83%	11,955	49.80%	20,194	46.78%	41,733	49.72%	3,358	47.11%
Previous	14,186	31.24%	1,448	32.86%	29,245	36.72%	32,602	36.92%	8,255	34.39%	17,024	39.44%	32,080	38.22%	2,405	33.74%
Current	5,052	11.12%	586	13.30%	10,429	13.10%	12,156	13.77%	3,685	15.35%	5,745	13.31%	9,762	11.63%	1,316	18.46%
Missing	159	0.35%	17	0.39%	364	0.46%	428	0.48%	109	0.45%	203	0.47%	366	0.44%	49	0.69%
Alcohol frequency																
Never or special occasions only	13,436	29.58%	1,390	31.55%	19,728	24.77%	21,930	24.84%	6,942	28.92%	11,183	25.91%	19,979	23.80%	3,174	44.53%
1-3 times/month	6,709	14.77%	619	14.05%	9,339	11.73%	10,270	11.63%	3,035	12.64%	5,190	12.02%	9,748	11.61%	847	11.88%
1-4 times/week	19,116	42.09%	1,764	40.04%	35,921	45.11%	39,437	44.66%	10,093	42.05%	18,864	43.70%	38,371	45.71%	2,327	32.65%
Daily or almost daily	6,115	13.46%	629	14.28%	14,558	18.28%	16,556	18.75%	3,897	16.23%	7,891	18.28%	15,770	18.79%	767	10.76%
Missing	40	0.09%	4	0.09%	88	0.11%	105	0.12%	37	0.15%	38	0.09%	73	0.09%	13	0.18%
Physical activity																
High	3,223	7.10%	254	5.76%	5,397	6.78%	6,164	6.98%	1,497	6.24%	2,308	5.35%	6,553	7.81%	148	2.08%
Medium	35,438	78.03%	3,320	75.35%	61,618	77.38%	67,107	76.00%	18,017	75.06%	32,766	75.91%	63,996	76.24%	4,326	60.69%
Low	2,115	4.66%	238	5.40%	4,012	5.04%	4,711	5.34%	1,313	5.47%	2,572	5.96%	4,366	5.20%	620	8.70%
None	3,977	8.76%	508	11.53%	7,325	9.20%	8,785	9.95%	2,708	11.28%	4,714	10.92%	7,706	9.18%	1,645	23.08%
Missing	663	1.46%	86	1.95%	1,282	1.61%	1,531	1.73%	469	1.95%	806	1.87%	1,320	1.57%	389	5.46%
BMI																
Recommended weight	15,793	34.77%	1,389	31.53%	23,155	29.08%	23,019	26.07%	7,194	29.97%	9,868	22.86%	17,064	20.33%	1,355	19.01%
Underweight	305	0.67%	37	0.84%	379	0.48%	367	0.42%	240	1.00%	163	0.38%	210	0.25%	44	0.62%
Overweight	17,498	38.53%	1,726	39.17%	32,953	41.38%	36,731	41.60%	9,291	38.71%	17,239	39.94%	34,376	40.95%	2,571	36.07%
Obese	11,560	25.45%	1,223	27.76%	22,587	28.36%	27,560	31.21%	7,108	29.61%	15,567	36.06%	31,760	37.84%	3,015	42.30%
Missing	260	0.57%	31	0.70%	560	0.70%	621	0.70%	171	0.71%	329	0.76%	531	0.63%	143	2.01%

Abbreviation: BMI, Body Mass Index

5.4.2.2 Different types of cardiometabolic disease

In the cross-tabulation of the proportion of sociodemographic and lifestyle factors in participants with different types of cardiometabolic diseases (Table 5-7), particular interest was focused on diabetes, hypertension, CHD and stroke, as the most prevalent types of cardiometabolic disease of the study population.

Obesity (as classified by BMI) was reported in 53.87% participants with diabetes, in comparison with that reported in 38.03% of participants with any cardiometabolic disease. 12.52% of participants with diabetes and 6.25% of participants with any cardiometabolic disease were from other ethnic groups. 28.94% of CHD participants were female, while 54.4% and 46.31% of participants with cardiometabolic disease and total study sample were females. Current smokers made up 15.21% of participants who have has a stroke, which was higher than the percentage of participants with any cardiometabolic disease (10.08%).

Table 5-7. Descriptive analysis of the types of cardiometabolic disease with sociodemographic and lifestyle factors at the baseline of UK Biobank (n = 500,313)

	Diabetes (n = 25,324)		Hypertension (n = 132,818)		CHD (n = 22,650)		Stroke/TIA (n = 8,805)		AF (n = 3,640)		PVD (n = 1,275)		HF (n = 797)	
Gender														
Male	15,797	62.38%	69,179	52.09%	16,095	71.06%	5,058	57.44%	2,483	68.21%	596	46.75%	534	67.00%
Female	9,527	37.62%	63,639	47.91%	6,555	28.94%	3,747	42.56%	1,157	31.79%	679	53.25%	263	33.00%
Missing value	0	0.00%	0	0.00%	0	0.00%	0	0.00%	0	0.00%	0	0.00%	0	0.00%
Age, years														
38-44	925	3.65%	5,132	3.86%	327	1.44%	248	2.82%	61	1.68%	80	6.27%	36	4.52%
45-49	1,730	6.83%	9,262	6.97%	763	3.37%	446	5.07%	137	3.76%	132	10.35%	69	8.66%
50-54	2,970	11.73%	15,689	11.81%	1,691	7.47%	841	9.55%	252	6.92%	156	12.24%	97	12.17%
55-59	4,472	17.66%	24,144	18.18%	3,297	14.56%	1,411	16.02%	484	13.30%	225	17.65%	146	18.32%
60-64	7,398	29.21%	40,037	30.14%	7,194	31.76%	2,597	29.49%	1,211	33.27%	345	27.06%	211	26.47%
65-73	7,829	30.92%	38,554	29.03%	9,378	41.40%	3,262	37.05%	1,495	41.07%	337	26.43%	238	29.86%
Missing value	0	0.00%	0	0.00%	0	0.00%	0	0.00%	0	0.00%	0	0.00%	0	0.00%
Ethnicity														
White	22,020	86.95%	124,297	93.58%	21,279	93.95%	8,380	95.17%	3,580	98.35%	1,239	97.18%	755	94.73%
Other ethnic groups	3,171	12.52%	8,033	6.05%	1,273	5.62%	394	4.47%	48	1.32%	35	2.75%	36	4.52%
Missing value	133	0.53%	488	0.37%	98	0.43%	31	0.35%	12	0.33%	1	0.08%	6	0.75%
Townsend score quintile														
1 (least deprived)	3,699	14.61%	24,579	18.51%	3,536	15.61%	1,371	15.57%	767	21.07%	242	18.98%	127	15.93%
2	4,093	16.16%	25,440	19.15%	3,957	17.47%	1,516	17.22%	780	21.43%	203	15.92%	132	16.56%
3	4,538	17.92%	25,992	19.57%	4,164	18.38%	1,631	18.52%	743	20.41%	210	16.47%	140	17.57%
4	5,348	21.12%	26,660	20.07%	4,546	20.07%	1,758	19.97%	730	20.05%	266	20.86%	177	22.21%
5 (most deprived)	7,609	30.05%	29,979	22.57%	6,419	28.34%	2,519	28.61%	617	16.95%	354	27.76%	220	27.60%
Missing value	37	0.15%	168	0.13%	28	0.12%	10	0.11%	3	0.08%	0	0.00%	1	0.13%
Smoking														

Never	11,456	45.24%	66,485	50.06%	8,236	36.36%	3,685	41.85%	1,789	49.15%	471	36.94%	374	46.93%
Previous	10,916	43.11%	52,978	39.89%	11,291	49.85%	3,717	42.21%	1,605	44.09%	554	43.45%	332	41.66%
Current	2,776	10.96%	12,749	9.60%	2,959	13.06%	1,339	15.21%	223	6.13%	246	19.29%	86	10.79%
Missing value	176	0.69%	606	0.46%	164	0.72%	64	0.73%	23	0.63%	4	0.31%	5	0.63%
Alcohol frequency														
Never or special occasions only	8,882	35.07%	30,131	22.69%	6,069	26.79%	2,572	29.21%	731	20.08%	334	26.20%	217	27.23%
1-3 times a month	3,076	12.15%	13,984	10.53%	2,314	10.22%	947	10.76%	338	9.29%	137	10.75%	111	13.93%
1-4 times a week	9,686	38.25%	60,274	45.38%	9,871	43.58%	3,568	40.52%	1,628	44.73%	513	40.24%	330	41.41%
Daily or almost daily	3,644	14.39%	28,285	21.30%	4,359	19.25%	1,703	19.34%	941	25.85%	290	22.75%	137	17.19%
Missing value	36	0.14%	144	0.11%	37	0.16%	15	0.17%	2	0.05%	1	0.08%	2	0.25%
Physical activity														
High	926	3.66%	7,438	5.60%	862	3.81%	375	4.26%	259	7.12%	82	6.43%	31	3.89%
Medium	18,701	73.85%	105,029	79.08%	17,156	75.74%	6,384	72.50%	2,904	79.78%	925	72.55%	552	69.26%
Low	1,509	5.96%	6,525	4.91%	1,376	6.08%	530	6.02%	178	4.89%	76	5.96%	75	9.41%
None	3,603	14.23%	11,784	8.87%	2,729	12.05%	1,248	14.17%	265	7.28%	166	13.02%	114	14.30%
Missing value	585	2.31%	2,042	1.54%	527	2.33%	268	3.04%	34	0.93%	26	2.04%	25	3.14%
BMI														
Recommended weight	2,800	11.06%	23,939	18.02%	3,682	16.26%	1,895	21.52%	808	22.20%	478	37.49%	161	20.20%
Underweight	32	0.13%	297	0.22%	55	0.24%	37	0.42%	13	0.36%	18	1.41%	3	0.38%
Overweight	8,588	33.91%	55,890	42.08%	9,749	43.04%	3,648	41.43%	1,583	43.49%	459	36.00%	317	39.77%
Obese	13,643	53.87%	51,893	39.07%	8,976	39.63%	3,096	35.16%	1,215	33.38%	310	24.31%	309	38.77%
Missing value	261	1.03%	799	0.60%	188	0.83%	129	1.47%	21	0.58%	10	0.78%	7	0.88%

Abbreviations: PVD, Peripheral vascular disease; TIA, Transient Ischaemic Attack; MI, myocardial infarction; CHD, coronary heart disease; HF, heart failure; AF, Atrial fibrillation; BMI, Body Mass Index

5.4.2.3 Comorbidity of the three conditions

This section of the results addresses objective 2. Table 5-8 shows the cross-tabulation of the proportions of sociodemographic and lifestyle factors in participants with chronic pain (any site), cardiometabolic disease (any condition), depression, and the comorbidity of the three conditions and healthy participants with no LTCs.

The distribution of gender was different in participants with cardiometabolic disease and the other two health conditions of interest. Participants with cardiometabolic disease reported that 46.31% were female, which is less than that reported in the total sample (54.41%). In comparison, 57.50% and 66.49% of those with chronic pain and depression, respectively, reported being female. 59.71% of the participants with the comorbidity (and 52.94% of healthy participants with no LTCs were females.

In the total study sample (n = 500,313), 43.28% of participants were aged over 60 years. In comparison with the total study sample, higher percentages of participants aged ≥60 years (age groups of 60-64 and 65-73) had chronic pain (44.28%) and cardiometabolic disease (59.59%), and a lower percentage had depression (36.87%). To combine the three conditions together, those aged over 60 years (age groups of 60-64 and 65-73) made up 47.15% of participants with the comorbidity. The participants aged over 60 (age groups of 60-64 and 65-73) made up 32.15% of the healthy participant group.

Other ethnic groups (than white) made up 5.85%, 6.25%, 3.62% and 4.71% of the participants with chronic pain, cardiometabolic disease, depression, and the comorbidity group, respectively; and 5.36% and 5.35% in healthy participants (0 LTCs) and total study sample.

Regarding the Townsend score quintile, the most deprived group made up 22.66%, 22.93% and 26.48% of participants with chronic pain, cardiometabolic disease, depression. The proportion of that in healthy participants and total study sample was 16.99% and 19.87%. However, when combining the three conditions together, 34.13% of participants with the comorbidity lived in the most deprived areas.

The percentage of smoking currently was 17.70% in the comorbidity of chronic pain, cardiometabolic disease, depression. 12.14%, 10.08% and 16.76% of participants with chronic pain, cardiometabolic disease, and depression, were reported as current smokers, respectively. Smoking was reported in 9.64% of healthy participants and 10.55% of total study sample.

The alcohol intake frequency of 1-4 times a week was reported the most among all the frequencies in all groups except the group with the comorbidity of the three conditions (33.59%). Never drinking or on occasions only was reported most by those with the comorbidity of interest (36.99%).

The proportion of participants who reported no physical activity was 8.57% in those with chronic pain, 9.01% in those with cardiometabolic disease, 11.71% in participants with depression, and 18.58% in participants with the comorbidity of all three conditions. Only 2.02% of participants with the comorbidity reported a high level of physical activity, while 15.07% of healthy participants with no LTCs reported a high level of physical activity.

Less than 1% of participants reported being underweight in all groups. Obesity was reported in 52.00%, 14.71% and 24.33% participants with the comorbidity of the three conditions, healthy participants (0 LTC) and total participants.

Chi-squared tests were used to compare the proportions of the factors in participants having all the comorbidity of the three conditions with the proportion of the factors with healthy participants (n = 125,562). All associations between sociodemographic and lifestyle factors significantly differed between the comorbidity group and the group with no LTCs ($p<0.001$) (Table 5-8).

Table 5-8. Descriptive analysis of the comorbidity of chronic pain, cardiometabolic disease and depression with sociodemographic and lifestyle factors at baseline in UK Biobank (n = 500,313)

	Chronic pain		Cardiometabolic Disease		Depression		Comorbidity		Healthy group*		Total participants	
Total	218,657	43.70%	156,209	31.22%	35,940	7.18%	8,640	1.73%	125,562	25.10%	500,313	100.00%
Gender												
Male	92,924	42.50%	83,872	53.69%	12,043	33.51%	3,481	40.29%	59,093	47.06%	228,078	45.59%
Female	125,733	57.50%	72,337	46.31%	23,897	66.49%	5,159	59.71%	66,469	52.94%	272,235	54.41%
Missing	0	0.00%	0	0.00%	0	0.00%	0	0.00%	0	0.00%	0	0.00%
Age, years												
38-44	20,471	9.36%	6,133	3.93%	3,901	10.85%	482	5.58%	19,076	15.19%	51,510	10.30%
45-49	28,021	12.82%	10,951	7.01%	5,322	14.81%	828	9.58%	21,699	17.28%	65,760	13.14%
50-54	33,468	15.31%	18,189	11.64%	6,208	17.27%	1,378	15.95%	21,824	17.38%	76,022	15.19%
55-59	39,876	18.24%	27,842	17.82%	7,258	20.19%	1,878	21.74%	22,593	17.99%	90,460	18.08%
60-64	53,137	24.30%	46,929	30.04%	8,070	22.45%	2,330	26.97%	25,275	20.13%	121,043	24.19%
65-73	43,684	19.98%	46,165	29.55%	5,181	14.42%	1,744	20.19%	15,095	12.02%	95,518	19.09%
Missing	0	0.00%	0	0.00%	0	0.00%	0	0.00%	0	0.00%	0	0.00%
Ethnicity												
White	205,073	93.79%	145,865	93.38%	34,509	96.02%	8,197	94.87%	118,417	94.31%	471,851	94.31%
Other ethnic groups	12,786	5.85%	9,759	6.25%	1,301	3.62%	407	4.71%	6,735	5.36%	26,749	5.35%
Missing	798	0.36%	585	0.37%	130	0.36%	36	0.42%	410	0.33%	1,713	0.34%
Townsend score quintile												
1 (least deprived)	40,380	18.47%	28,710	18.38%	5,894	16.40%	1,133	13.11%	27,363	21.79%	100,430	20.07%
2	41,524	18.99%	29,650	18.98%	6,283	17.48%	1,275	14.76%	26,257	20.91%	99,860	19.96%
3	42,937	19.64%	30,433	19.48%	6,734	18.74%	1,457	16.86%	25,605	20.39%	100,086	20.00%
4	43,986	20.12%	31,396	20.10%	7,452	20.73%	1,809	20.94%	24,867	19.80%	99,921	19.97%
5 (most deprived)	49,537	22.66%	35,824	22.93%	9,518	26.48%	2,949	34.13%	21,327	16.99%	99,397	19.87%
Missing	293	0.13%	196	0.13%	59	0.16%	17	0.20%	143	0.11%	619	0.12%

Smoking												
Never	112,097	51.27%	76,826	49.18%	17,216	47.90%	3,656	42.31%	76,301	60.77%	272,899	54.55%
Previous	79,081	36.17%	62,858	40.24%	12,568	34.97%	3,414	39.51%	36,816	29.32%	172,763	34.53%
Current	26,551	12.14%	15,753	10.08%	6,025	16.76%	1,529	17.70%	12,100	9.64%	52,788	10.55%
Missing	928	0.42%	772	0.49%	131	0.36%	41	0.47%	345	0.27%	1,863	0.37%
Alcohol frequency												
Never or special occasions only	51,234	23.43%	36,552	23.40%	10,392	28.91%	3,196	36.99%	18,347	14.61%	98,160	19.62%
1-3 times a month	25,772	11.79%	16,588	10.62%	4,454	12.39%	1,088	12.59%	13,386	10.66%	55,748	11.14%
1-4 times a week	100,585	46.00%	70,380	45.06%	14,351	39.93%	2,902	33.59%	67,429	53.70%	244,326	48.83%
Daily or almost daily	40,843	18.68%	32,508	20.81%	6,671	18.56%	1,426	16.50%	26,329	20.97%	101,658	20.32%
Missing	223	0.10%	181	0.12%	72	0.20%	28	0.32%	71	0.06%	421	0.08%
Physical activity												
High	16,890	7.72%	8,830	5.65%	2033	5.66%	190	2.20%	18,916	15.07%	50,027	10.00%
Medium	169,117	77.34%	123,130	78.82%	27079	75.35%	5,889	68.16%	97,120	77.35%	392,688	78.49%
Low	10,518	4.81%	7,696	4.93%	1,993	5.55%	664	7.69%	3,132	2.49%	18,891	3.78%
None	18,743	8.57%	14,073	9.01%	4,210	11.71%	1,605	18.58%	5,099	4.06%	32,661	6.53%
Missing	3,389	1.55%	2,480	1.59%	625	1.74%	292	3.38%	1,295	1.03%	6,046	1.21%
BMI												
Recommended weight	60,935	27.87%	29,348	18.79%	9,674	26.92%	1,135	13.14%	52,862	42.10%	161,921	32.36%
Underweight	1,003	0.46%	393	0.25%	205	0.57%	24	0.28%	794	0.63%	2,614	0.52%
Overweight	90,299	41.30%	66,082	42.30%	13,987	38.92%	2,899	33.55%	52,893	42.13%	211,416	42.26%
Obese	64,990	29.72%	59,402	38.03%	11,848	32.97%	4,493	52.00%	18,469	14.71%	121,719	24.33%
Missing	1,430	0.65%	984	0.63%	226	0.63%	89	1.03%	544	0.43%	2,643	0.53%

Abbreviation: BMI, Body Mass Index; LTC, long-term condition

*Participants with no LTCs

5.4.3 Logistic regression

5.4.3.1 Sociodemographic and lifestyle factors

The association between the sociodemographic and lifestyle factors and the comorbidity of the three conditions were quantified using logistic regression models (objective 2).

Univariable model

All the sociodemographic and lifestyle factors as well as the binary variable of additional LTCs were found to be significantly associated with the comorbidity in univariable models (Table 5-9). The number of participants in each univariable models varied depending on the number of missing values for each variable, as presented in Table 5-8.

Female participants were 1.25 times (OR 95% CI: 1.19-1.30) more likely to have the comorbidity of the three conditions than males. Being in the older age groups was associated with increased odds of the comorbidity compared to the youngest group. In particular, the group aged 55-59 years had the highest odds (OR 2.24, 95% CI: 2.03-2.48) of the comorbidity compared to the reference group. Participants from other ethnic groups were less likely to have the comorbidity (OR 0.87, 95% CI: 0.79-0.96) than the white ethnic group. Participants in the most deprived quintile were 2.68 (OR 95% CI: 2.50-2.87) times more likely to have the comorbidity compared to participants from the least deprived quintile.

With regards to lifestyle factors investigated, previous smokers (OR 1.48, 95% CI: 1.42-1.56) and current smokers (OR 2.20, 95% CI: 2.07-2.33) had a higher likelihood of the comorbidity than participants who self-reported never having smoked. Any alcohol drinking group was associated with a lower risk of the comorbidity. Drinking 1-4 times a week had the lowest risk (OR 0.36, 95% CI: 0.34-0.38) of the comorbidity in comparison with never drinking or drinking on special occasions only. Participants who reported no physical activity (OR 13.56, 95% CI: 11.69, 15.81) and who were classified by their BMI as obese (OR 5.43, 95% CI: 5.09-5.80) had the highest odds of having the comorbidity compared to

participants with high level of physical activity and recommended BMI, respectively.

Multivariable model

All the sociodemographic and lifestyle factors were fitted into the multivariable model as independent variables of interest, and the binary variable of additional LTCs was adjusted for. Fitting these variables into the model produced 12,667 (2.52%) missing values, and thus the total number of participants included in this analysis was 487,646.

After adjusting for the covariates, the relationship between the comorbidity and the sociodemographic and lifestyle factors remained statistically significant, albeit attenuated. In the multivariable model assessing the relationship with the comorbidity of interest (model 1), female participants had a 1.11 (OR 95% CI: 1.06-1.16) higher odds of having the comorbidity of the three conditions than males. Participants aged 55-59 years (OR 1.88, 95% CI: 1.70-2.10) were at the most risk of the comorbidity compared to reference group. Participants from other ethnic groups were less likely to have the comorbidity (OR 0.65, 95% CI: 0.79-0.96) than the white ethnic group. The most deprived participants had a 1.73 (OR 95% CI: 1.61-1.86) times higher odds of having the comorbidity compared to the participants from the least deprived quintile.

For lifestyle factors, previous smokers (OR 1.29, 95% CI: 1.23-1.36) and current smokers (OR 1.79, 95% CI: 1.68-1.91) were more likely to have comorbidity than participants who never smoked. Drinking 1-4 times a week had the lowest risk of the comorbidity than the risk of other frequencies of alcohol intake in comparison with never drinking or drinking on special occasions only. No physical activity (OR 5.03, 95% CI: 4.32-5.90) and a high BMI (classified as having obesity) (OR 4.01, 95% CI: 3.74-4.29) had the highest OR for the comorbidity.

Table 5-9 Logistic regression of the association between sociodemographic and lifestyle factors and the comorbidity (chronic pain, cardiometabolic disease and depression) at baseline (n = 487,646)

Independent variable	Univariable model* OR (95% CI)	p-value	Multivariable model (model 1) OR (95% CI)	p-value
Gender				
Male	*(Reference group)*			
Female	1.25 (1.19, 1.30)	<0.001	1.11 (1.06, 1.16)	<0.001
Age, years				
38-44	*(Reference group)*			
45-49	1.35 (1.21, 1.51)	<0.001	1.29 (1.15, 1.45)	<0.001
50-54	1.95 (1.76, 2.17)	<0.001	1.74 (1.57, 1.95)	<0.001
55-59	2.24 (2.03, 2.48)	<0.001	1.88 (1.70, 2.10)	<0.001
60-64	2.08 (1.88, 2.30)	<0.001	1.70 (1.53, 1.89)	<0.001
65-73	1.97 (1.78, 2.18)	<0.001	1.51 (1.36, 1.68)	<0.001
Ethnicity				
White	*(Reference group)*			
Other ethnic groups	0.87 (0.79, 0.96)	0.008	0.65 (0.58, 0.72)	<0.001
Townsend score quintile				
1 (least deprived)	*(Reference group)*			
2	1.13 (1.05, 1.23)	0.002	1.06 (0.98, 1.15)	0.147
3	1.29 (1.20, 1.40)	<0.001	1.13 (1.04, 1.22)	0.003
4	1.62 (1.50, 1.74)	<0.001	1.28 (1.19, 1.39)	<0.001
5 (most deprived)	2.68 (2.50, 2.87)	<0.001	1.73 (1.61, 1.86)	<0.001
Smoking				
Never	*(Reference group)*			
Previous	1.48 (1.42, 1.56)	<0.001	1.29 (1.23, 1.36)	<0.001
Current	2.20 (2.07, 2.33)	<0.001	1.79 (1.68, 1.91)	<0.001
Alcohol frequency				
Never or special occasions only	*(Reference group)*			
1-3 times a month	0.59 (0.55, 0.63)	<0.001	0.71 (0.66, 0.77)	<0.001
1-4 times a week	0.36 (0.34, 0.38)	<0.001	0.52 (0.49, 0.55)	<0.001
Daily or almost daily	0.42 (0.40, 0.45)	<0.001	0.63 (0.59, 0.67)	<0.001
Physical activity				
High	*(Reference group)*			
Medium	3.99 (3.47, 4.63)	<0.001	2.51 (2.17, 2.91)	<0.001
Low	9.56 (8.14, 11.27)	<0.001	4.19 (3.56, 4.96)	<0.001
None	13.56 (11.69, 15.81)	<0.001	5.03 (4.32, 5.90)	<0.001
BMI				
Recommended weight	*(Reference group)*			
Underweight	1.31 (0.85, 1.92)	0.189	0.71 (0.43, 1.09)	0.139
Overweight	1.97 (1.84, 2.11)	<0.001	1.89 (1.76, 2.03)	<0.001
Obese	5.43 (5.09, 5.80)	<0.001	4.01 (3.74, 4.29)	<0.001
Additional LTCs				
No	*(Reference group)*			
Yes	3.27 (3.12, 3.43)	<0.001	2.64 (2.51, 2.77)	<0.001

Abbreviations: OR, Odds Ratio; CI, Confidence Interval; BMI, Body Mass Index; LTC, long-term condition

* Note that the number in each of the univariable models varied depending on the number of missing responses to each question

5.4.3.2 Relationship between the three conditions

To address objective 3, the relationship between the three conditions of chronic pain, cardiometabolic disease and depression, was examined by logistic regression. After controlling for the covariates (age, gender, ethnicity, Townsend, smoking status, alcohol intake frequency, physical activity, BMI, and additional LTCs), the participants were more likely to self-report cardiometabolic disease if they self-reported chronic pain or depression; similarly, chronic pain was more common in those who reported cardiometabolic disease or depression, and depression was more common in those who reported chronic pain or cardiometabolic disease (Table 5-10).

Depression and chronic pain had the strongest relationship, statistically. To be more detailed, the likelihood of chronic pain in participants with depression was 1.61 (OR 95% CI: 1.57-1.64) times higher compared to those without depression. Chronic pain as the outcome variable was also associated with an increase in the odds of cardiometabolic disease (OR 1.18, 95% CI: 1.16-1.19). Cardiometabolic disease as the outcome variable was 1.17 (OR 95% CI: 1.15-1.19) and 1.23 (OR 95% CI: 1.20-1.26) times more likely to be reported in participants with chronic pain and depression, respectively. Depression as the outcome variable was associated with an increased odds of chronic pain (OR 1.59, 95% CI: 1.55-1.63) and cardiometabolic disease (OR 1.22, 95% CI: 1.19-1.25).

Table 5-10. Logistic regression of association between the three conditions (chronic pain, cardiometabolic disease and depression) at baseline (n = 487,646)*

Independent variable	Dependent variable (outcome of interest)								
	Chronic pain (model 2)			Cardiometabolic disease (model 3)			Depression (model 4)		
	OR (95% CI)		p-value	OR (95% CI)		p-value	OR (95% CI)		p-value
Chronic pain	/			1.17	(1.15, 1.19)	<0.001	1.59	(1.55, 1.63)	<0.001
Cardiometabolic disease	1.18	(1.16, 1.19)	<0.001	/			1.22	(1.19, 1.25)	<0.001
Depression	1.61	(1.57, 1.64)	<0.001	1.23	(1.20, 1.26)	<0.001	/		

Abbreviations: OR, Odds Ratio; CI, Confidence Interval

*All models were adjusted for: age, gender, ethnicity, Townsend score, smoking status, alcohol intake frequency, physical activity, BMI, any additional LTCs

5.5 Discussion

5.5.1 Summary of the findings

To address the evidence gap identified in the systematic review, a cross-sectional study was conducted using UK Biobank, a population-based cohort study that included half a million participants aged between 38-73 years across England, Scotland and Wales between 2006-2010. This chapter presented the results showing the prevalence, sociodemographic and lifestyle factors associated with this combination of conditions using the baseline data. Participants with complete data on self-reported comorbidity were included in the analysis. This study, to our knowledge, is the first to examine the prevalence and associated sociodemographic and lifestyle factors of the comorbidity of chronic pain, cardiometabolic disease and depression in a large population-based dataset.

The baseline analysis shows the prevalence of chronic pain was 43.70%, cardiometabolic disease was 31.22%, and depression was 7.18%. 8,640 participants had this combination of conditions, representing 1.73% of the total population. The prevalence of the comorbidity amongst the most common cardiometabolic conditions was hypertension (1.06%), diabetes (0.09%), CHD (0.09%), or stroke (0.05%), together with chronic pain and depression.

Aged 45 years and above (particularly aged 55-59 years), being female, from a more deprived area, current or past history of smoking, overweight and obese were all associated with an increased odds of having this combination of conditions. From an ethnic group other than white, drinking alcohol and doing any physical activity had lower risk of comorbidity compared with the reference groups. The three conditions were found to relate to each other after controlling for the covariates (age, gender, ethnicity, Townsend, smoking status, alcohol intake frequency, physical activity, BMI, and additional LTCs) in logistic regression models.

5.5.2 Justification of choosing the variables

5.5.2.1 Depression

This study used self-reported depression and medication of antidepressants to indicate depression. There were other sources to measure depression in UK Biobank but not used: the current depressive symptom score or algorithm for MDD.

The current depressive symptom score assessed depressive symptoms over the past two weeks (Nicholl et al., 2014). The touchscreen questionnaire for the baseline data had a series of questions measuring the current depressive symptoms score, which was assessed through four questions about the depressive symptoms over the past two weeks. The symptoms over the past two weeks reflected the short-term situation of the participants and were not appropriate for this study interested in chronic conditions.

Self-reported MDD was an algorithm based on multiple questions, including self-reported single probable MDD, probable recurrent MDD (moderate) or probable recurrent MDD (severe) (Smith et al., 2013). A total of 172,745 participants assessed the mental health survey of the touchscreen questionnaire from 2008 to 2010, comprised only 34.53% of the total study sample. Thus, both sources of depression data were not used.

5.5.2.2 Sociodemographic and lifestyle factors

Key factors likely to be associated with chronic pain, cardiometabolic disease and depression, were chosen to include in this study (Hanlon et al., 2018b).

Townsend score was used in this study to indicate socioeconomic status (Fry et al., 2017). Other variables available in the baseline data could have been used to assess socioeconomic status: income, type of accommodation, employment status and paid employment, household income, whether retired, age left education and education qualification status. Townsend score was chosen as it is a good summary variable to indicate the deprivation. Furthermore, when deprivation is not the focus of the study but is included as a covariate, this is acceptable, as has been used in other studies (Nicholl et al., 2014, McQueenie et

al., 2021, Jani et al., 2018, McPeake et al., 2021, Cassidy et al., 2016). Townsend score, as an area-based measurement, may not precisely reflect and underestimate the actual conditions of the householders, especially in rural areas (Jordan et al., 2004). Despite this, it is a widely used summary measure of deprivation. Including other variables as a supplementary indicator of socioeconomic status would be helpful. Nevertheless, fitting these variables into the model would produce more missing values.

5.5.3 In context of previous literature

5.5.3.1 Prevalence of the comorbidity

Chronic pain is thought to be prevalent in 20% of the population in Europe (Breivik et al., 2006) and in over 40% in the UK general population (Fayaz et al., 2016). The pooled prevalence of diabetes, hypertension, and cardiovascular disease examined from 17 studies in a systematic review were 11.2%, 25.0% and 15.6%, respectively (Ma et al., 2021). The aggregate point prevalence of depression was calculated at 12.9% in a meta-analysis of 68 studies (Lim et al., 2018). In this study, chronic pain was reported by 43.70% of the study sample; the prevalence of diabetes, hypertension, and cardiovascular disease (Stroke, CHD, AF, PVD, HF) was 5.06%, 26.55% and 7.43%, respectively; and the prevalence of depression was 7.18%.

The only study identified from the systematic review that examined the prevalence of the comorbidity of chronic pain, cardiovascular disease and depression investigated Generation Scotland (a population-based cohort) (van Hecke et al., 2017). An increased co-occurrence of chronic pain, depression and cardiovascular disease was found in both cohorts.

The analysis of Generation Scotland examined 24,024 participants with the co-occurrence of chronic pain, angina, and depression. The prevalence of the comorbidity of chronic pain, angina and depression was 1.8% (169/9,492). In our study, the prevalence of the comorbidity of chronic pain, cardiometabolic disease and depression was very similar, at 1.73% (8,640 / 500,313). The characteristics of the two study samples were different. For example, the median age of the Generation Scotland cohort was 49 years (IQR 36–59), and the

median age of the UK Biobank baseline in our study was 58 years (IQR 50–63). With a larger sample size, our study provided a more robust analysis of the prevalence of the co-occurrence of the three conditions, and more types of cardiometabolic disease, in addition to angina, were examined.

5.5.3.2 Sociodemographic and lifestyle factors

A population-based study with a study sample of 1,408 participants examined the clusters of musculoskeletal pain, cardiometabolic disease and psychological distress, but only calculated the prevalence of two of the conditions (Slagboom et al., 2021). The clusters of the three conditions (musculoskeletal pain, cardiometabolic disease and psychological distress) were found to be associated with age, female gender, financial stress and increased body weight, and low physical activity from logistic regression, which were similar findings of our study.

In our study, aged 55-59 years had higher odds than older age groups of having the comorbidity in comparison to the reference group. This finding is consistent with existing evidence that chronic pain was found to be more strongly associated with depression at a younger age (18-39 years) (Schaakxs et al., 2017), while cardiometabolic disease was related to an advancing age (Sniderman and Furberg, 2008).

The finding of the association between the comorbidity and other ethnic groups could result from distribution of ethnicity in the UK Biobank data. The white ethnic group comprised more than 94% of the total study sample and the small number in other ethnic group means there was less power to be confident of a relationship. However, chronic pain is found to be more prevalent in ethnic minority groups (Riley III et al., 2002) and this could be linked to mental health (Nicholl et al., 2014).

It was found that taking part in no physical activity was associated with a 5.03 (OR 95% CI: 4.32-5.90) increased odds of the comorbidity. This could be that lacking physical activity is a risk factor for poor health, or the result of reduced physical activity due to the mobility restrictions from these conditions. It is likely that participants with less physical activity have more severe restrictions

in mobility and poor health conditions. Unfortunately, in this cross-sectional study, we are unable to determine the cause-and-effect relationship between low physical activity and having the comorbidity. Exploring this relationship between the physical activity and health could be potential further work.

There is an unexpected finding that drinking alcohol was associated with lower risk of the comorbidity than never drinking or on special occasions only, as more drinking is expected to be a less healthy lifestyle that associated with higher risk of the comorbidity. There are several potential reasons. First, people with poorer health may be advised to give up drinking. Second, some studies have a U-shaped relationship between alcohol intake and cardiovascular disease (Klatsky, 2015, Marmot and Brunner, 1991, Marmot et al., 1981, O'Keefe et al., 2007). Third, the variable indicating alcohol intake only showed the frequency, not the alcohol by volume. People may drink frequently but with a small amount of alcohol by volume each time. The results from this study does not mean that it is encouraged to drink more regularly, as the amount, type and volume of alcohol, and the way of drinking (binge drinking vs normal drinking) should be considered too (Murray et al., 2002).

5.5.3.3 Relationship of the three conditions

Some published literature has examined the combination of two of the conditions of interest. In a literature review, pain was reported in 15% to 100% of participants with depression in 14 studies; chronic pain with a clear timeline of more than three months was reported in 59% of patients from private practice with depression; the average prevalence of depression in participants with chronic pain from 15 studies of pain clinics or inpatient pain programme was 52% (Bair et al., 2003). The population-based study mentioned above (Slagboom et al., 2021) examined 17 LTCs in total and found the combinations of musculoskeletal pain & cardiometabolic disease (15.1%), musculoskeletal pain & psychological distress (8.8%), and cardiometabolic disease & psychological distress (7.1%) were the most prevalent.

In the Generation Scotland cohort (van Hecke et al., 2017), after adjusting for confounding factors, individuals with depression (OR 2.64, 95% CI: 2.34-2.97) and angina (OR 4.19, 95% CI: 3.64-4.82) were more likely to have chronic pain, and

those with depression were also more likely to have angina (OR 2.20, 95% CI: 1.90-2.54). In our study, the analysis findings were consistent with this result. After adjusting for confounders, individuals with depression (OR 1.61, 95% CI: 1.57-1.64) and cardiometabolic disease (OR 1.18, 95% CI: 1.16-1.19) were more likely to have chronic pain, and those with depression were also more likely to have a cardiometabolic disease (OR 1.22, 95% CI: 1.19-1.25).

5.5.4 Strengths and limitations

5.5.4.1 The data source

The strengths and limitations of using UK Biobank have been described in detail in Chapter 3. In summary, the most significant strength of this study is examining a large sample size, around half a million participants. The main limitation is that UK Biobank data does not represent the general UK population. However, it is reliable and powerful for examining prevalence and associations (Batty et al., 2020).

UK Biobank is a useful resource to answer the research questions outlined in this study which focuses on people with a combination of conditions: chronic pain, cardiometabolic disease and depression. Chronic pain and cardiometabolic diseases are chronic conditions that commonly occur in people of middle and old age, which is the age range of the UK Biobank data. For the participants with these three conditions, first, we wanted to examine the prevalence among the general population. UK Biobank data is a large and rich that can fulfil the calculation of the prevalence of the comorbidity with solid power. Secondly, we were interested in the sociodemographic and lifestyle factors associated with the comorbidity. UK Biobank includes extensive and reliable measurement of sociodemographic and lifestyle determinants of the diseases to provide adequate and comprehensive data for the research question.

5.5.4.2 Limitations of the variables

The main limitation is the self-report nature of the morbidities in UK Biobank. The three conditions of interest and additional LTCs were self-reported data (Raisi-Estabragh and Petersen, 2020).

The chronic pain was only measured in terms of the duration and sites, and no indicator could show the severity of chronic pain from the baseline data. Self-reported depression and medication of antidepressants to indicate depression could potentially underestimate the prevalence of depression.

Social desirability bias comes from the tendency to give responses to satisfy the social desires rather than the truth (Grimm, 2010). This is likely to happen when responding to socially sensitive and personal issues like drug use and smoking (Chung and Monroe, 2003). For example, in this study, some participants who were current smokers may actually have reported themselves as previous smokers.

Moreover, there was potentially the bias from the health condition of the participants. For example. some participants may have stopped smoking due to health issues, reflected in the data as previous smokers and seemed to have a healthier lifestyle. In this study, 40.24% of participants with cardiometabolic disease were previous smokers and only 10.08% were current smokers. The reason for quitting smoking could be advised by a doctor to do so, as smoking harms the participants' health.

5.5.4.3 The study design

A cross-sectional study can only show prevalence and associations at baseline, and further studies are needed to identify the effect of the comorbidity on health outcomes.

5.5.5 Conclusion

This chapter shows the findings from a cross-sectional study that the prevalence of the comorbidity with chronic pain, cardiometabolic disease, and depression was 1.73% in the UK Biobank population. Aged 45 years and above (particularly aged 55-59 years), being female, from a more deprived area, current or past history of smoking, being overweight or classified as having obesity were associated higher risk of the comorbidity; being from an ethnic group other than white, drinking alcohol and doing any physical activity were associated lower risk of the comorbidity. The next chapter of this thesis goes on to examine the impact of this comorbidity on health-related outcomes.

Chapter 6 The effect of the comorbidity of chronic pain, cardiometabolic disease, and depression on health outcomes: a cohort study of UK Biobank

6.1 Introduction

6.1.1 Overview of this chapter

The cohort study presented herein utilises sample data from UK Biobank to examine whether the comorbidity of chronic pain, cardiometabolic disease, and depression is associated with adverse health-related outcomes to answer research question 3 of this thesis: what are the effects on health outcomes of this comorbidity?

6.1.2 Rationale

Our systematic review (Chapter 4) on the prevalence and experiences of people with the comorbidity of chronic pain, cardiometabolic disease and depression identified no studies that examined the health outcomes associated with this type of comorbidity. Findings from our cross-sectional analysis of data provided by UK Biobank (Chapter 5) showed that this combination of comorbidities was common, with a prevalence of 1.73%. Specifically, the combinations of diabetes, stroke, hypertension and CHD, along with chronic pain and depression were found to be the most prevalent for this combination of comorbidity. Key sociodemographic and lifestyle factors (age, gender, ethnicity, Townsend score, smoking status, alcohol intake frequency, physical activity, and BMI) were associated with the comorbidity.

Health outcomes are used to reflect the sequence and the impact of health conditions. In addition to all-cause mortality, MACE (Major adverse cardiovascular events) is commonly used to assess cardiovascular outcomes (Hanlon et al., 2020). MACE is defined as a combination of adverse endpoints of cardiovascular events: hospital admission with MI, stroke, or CVD death. Cardiovascular disease is a leading cause of death, which is why MACE has become a common target in randomised controlled clinical trials and why it is increasingly uses as a key health outcome of interest (Bosco et al., 2021). There

has also been considerable work undertaken examining multimorbidity using UK Biobank that has used MACE as an outcome (McQueenie et al., 2020b, Hanlon et al., 2021).

The incidence of the health outcomes with the comorbidity in the overall study sample (N = 500,313) was examined first. Then the work presented in this chapter addresses the evidence gap by analysing whether the comorbidity and specific combinations of the comorbidity of chronic pain (e.g. CWP), cardiometabolic disease (one cardiometabolic disease, diabetes, stroke, hypertension or CHD) and depression have an effect on certain health outcomes using a subsample (N = 128,066) of UK Biobank (Research question 3 outlined in Chapter 2).

6.1.3 Aims and hypothesis

6.1.3.1 Aims and objectives

The overall aim of this cohort study was to examine the effects of specific combinations of the comorbidity of chronic pain, cardiometabolic disease and depression on associated health outcomes using a subsample of UK Biobank. The specific objectives were:

1) To examine the incidence of health outcomes (mortality, MACE) in participants with the comorbidity of chronic pain, cardiometabolic disease and depression in the overall study population (N = 500,313);

2) To investigate the effects that comorbidity of chronic pain, cardiometabolic disease and depression has on health outcomes, adjusting for confounding factors including age, gender, ethnicity, Townsend score, smoking status, alcohol intake frequency, physical activity and BMI, specifically:

    a) in a subsample of the participant population with the three comorbid conditions as compared to healthy participants with no LTCs (N = 128,066);

    b) in subgroups with specific combinations of different cardiometabolic diseases (e.g. one cardiometabolic disease, diabetes, stroke, hypertension

and CHD), chronic pain (e.g. CWP) and depression as compared with healthy participants with no LTCs.

6.1.3.2 Hypotheses

In this cohort study, the central hypothesis is that the comorbidity of chronic pain, cardiometabolic diseases, and depression and the specific combinations (e.g. CWP, one cardiometabolic disease, diabetes, stroke, hypertension or CHD) will be associated with a greater risk of death and MACE as compared to their healthy counterparts with no reported LTCs.

6.2 Data management

6.2.1 Study sample

6.2.1.1 Total sample: UK Biobank cohort

This study analysed the UK Biobank cohort described in detail in Chapters 3&5. Participants were linked to health outcome data provided by the NMR and HES (containing data up to 12/06/20) (N = 500,313). Death was assessed by use of all-cause mortality data provided by NMR. MACE data used included nonfatal MI (Saleh and Ambrose, 2018), nonfatal stroke (Langhorne et al., 2011), and death due to CVD (Shah et al., 2019, Bhatnagar et al., 2016). Data linkage of death and MACE was carried out by UK Biobank; the merged datasets and data used for this study are presented in Figure 6-1.

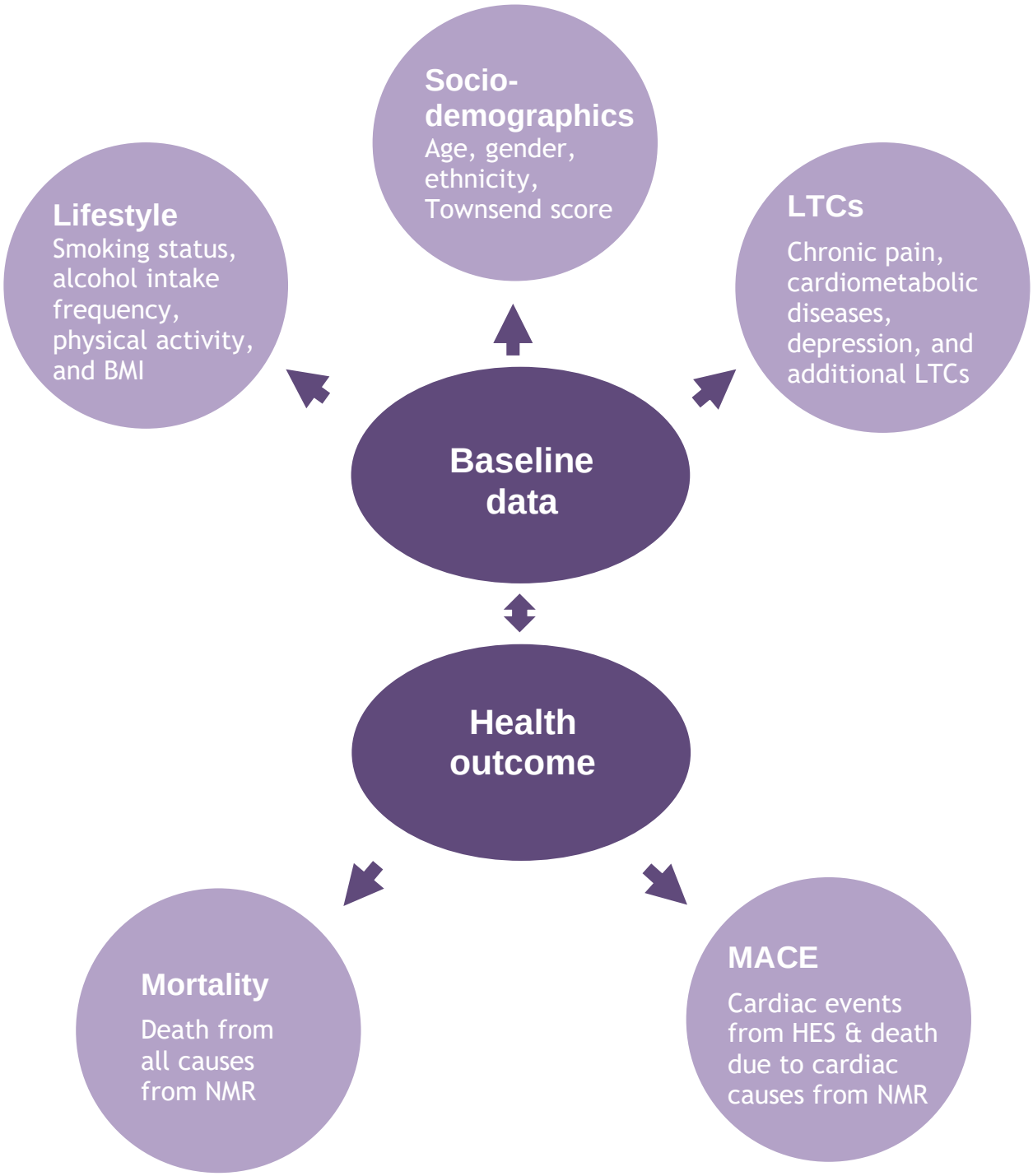

Figure 6-1. Overview of UK Biobank cohort as the total sample (N = 500,313) linked in this study.

LTC, long-term condition; NMR, National Mortality Registry; HES, Hospital Episodes Statistics; MACE, major adverse cardiovascular events

The diseases and cause of death were calculated using ICD-10. The detailed definitions of MACE are listed in Table 6-1.

Table 6-1. Explanations for MACE in this study

Outcome	ICD-10 Code	Data source	Definition
Nonfatal MI	I21	HES	MI, also known as heart attack, is a severe medical emergency caused by a sudden lack of blood flow (usually by a blood clot) supplying to the heart, resulting in severe damage to the heart muscle.
Nonfatal stroke	I63 and I64	HES	Stroke is a medical emergency caused by the sudden cutting off blood supply to part of the brain. It is a common disease and one of the most severe global health challenges.
CVD death as the primary cause	I	NMR	CVD is related to the heart or blood vessels, and it is one of the leading causes of mortality worldwide.

Abbreviations: MACE, major adverse cardiovascular events; ICD-10, 10th version of the International Statistical Classification of Diseases and Related Health Problems; MI, myocardial infarction; CVD, cardiovascular disease; HES, hospital episode statistics; NMR, national mortality registry

The overall cohort was used for the examination of the incidence of death and MACE to address objective 1.

As with the cross-sectional study in Chapter 5, ethical approval for this cohort study has been obtained by UK Biobank projects (16/NW/0274) under UK Biobank approved project 14151.

6.2.1.2 Subsample

To address objective 2, a survival analysis of a subsample of the UK Biobank dataset was performed. This involved the assessment of health outcomes between participants with the comorbidity of chronic pain, cardiometabolic disease and depression, and healthy participants with no LTCs.

As shown in Figure 6-2, participants with any additional LTCs were removed. Participants with only one or two of the three conditions (chronic pain,

cardiometabolic disease, depression, chronic pain + cardiometabolic disease, chronic pain + depression, cardiometabolic disease + depression) were also removed. After removal of these participants from the total study sample, the remaining subsample of participants (N = 128,066) were arranged into the following two groups: participants with all three conditions of the comorbidity (chronic pain + cardiometabolic disease + depression) (N = 2,504), and healthy participants without any LTCs (N = 125,562) acting as the reference group. So, in summary, a subsample of 128,066 participants were used in our survival analysis after removal of 372,247 (74.08%) participants deemed ineligible. Please see Figure 6-2 for a descriptive analysis of the characteristics of the total study sample and the subsample.

Analysing this specific subsample of participants (as opposed to using the total study sample which include those with additional LTCs) allows for accurate examination of the effect of the combination of the three specific conditions on death and MACE. Excluding these participants clarified the comparison and dismissed the effect of additional LTCs. Further justification for choosing this subsample is detailed in the Discussion section of this chapter.

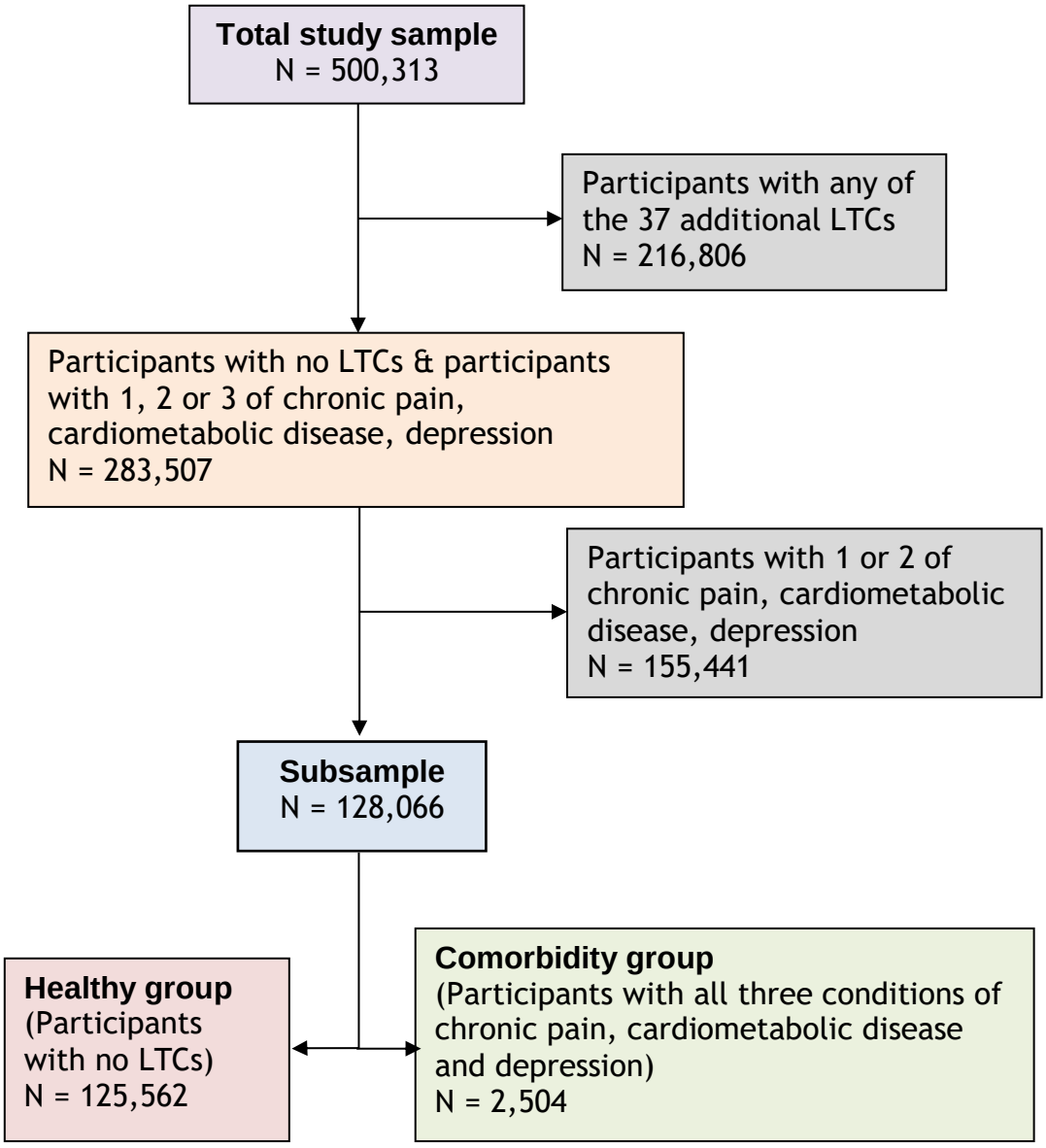

Figure 6-2. Flow chart of getting the subsample from UK Biobank cohort

6.2.1.3 Exposure and reference groups

Seven exposure groups of different combinations of the comorbidity were created to examine specific cardiometabolic and pain conditions in the comorbidity using Cox regression models: comorbidity group, CWP group, one cardiometabolic disease group (one CMD group), diabetes group, stroke groups, CHD group and hypertension group. CWP was selected as evidence shows that CWP can have significant adverse impact on health outcomes (Macfarlane et al., 2017). The individual cardiometabolic conditions were chosen to examine in detail as they were the most common cardiometabolic conditions in the cohort.

The reference group is the healthy group (N = 125,562) of participants with no LTCs. Participants in the healthy group as the reference group had none of the three conditions of interest and no additional LTCs. The process of obtaining these subgroups is presented in Figure 6-3 and the eligibility of each subgroup is detailed in Table 6-2.

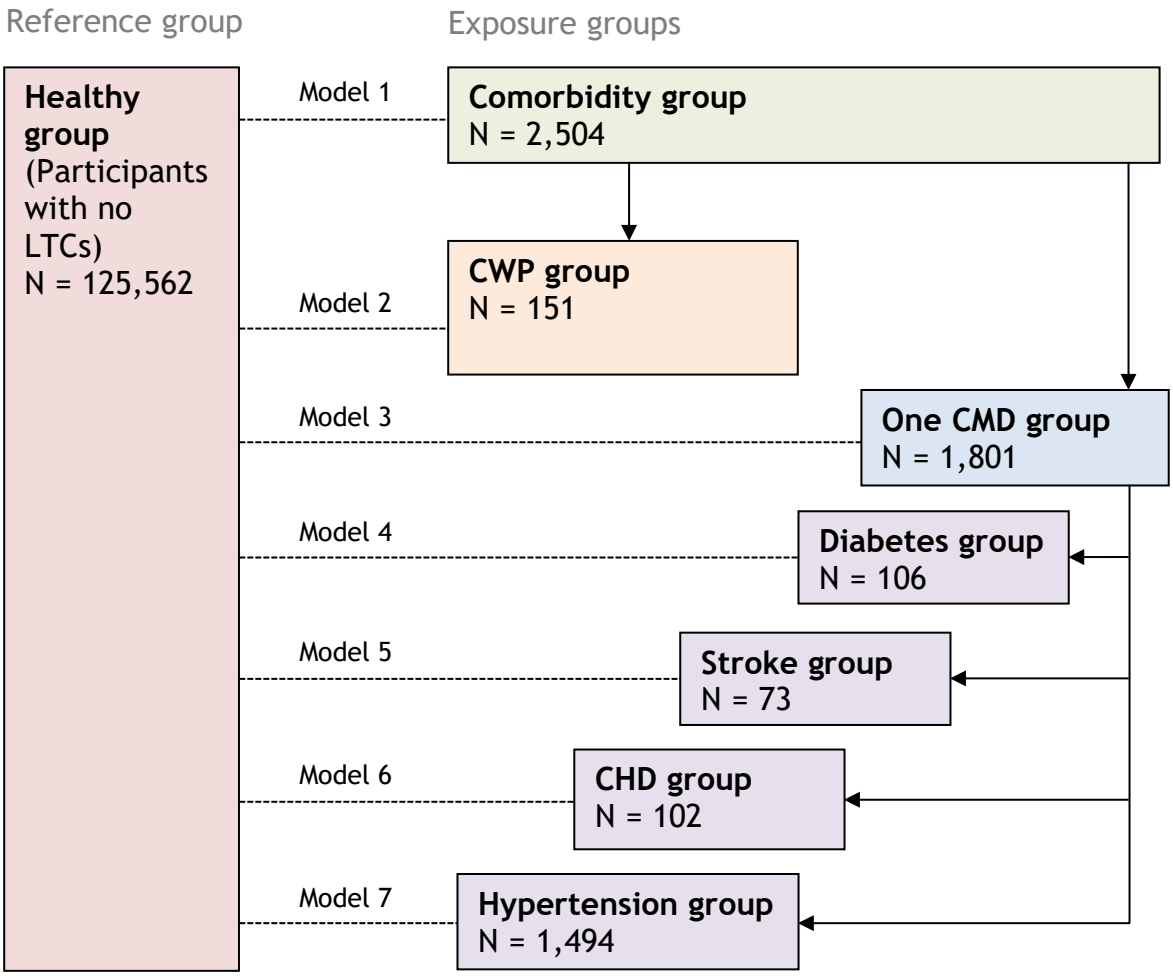

Figure 6-3. Flow chart of data cleaning of the subgroups of the study.

CMD, cardiometabolic disease; CWP, chronic widespread pain; LTC, long-term condition

Table 6-2. The description of participants included in the survival analysis models

Subgroups	Examined in the model	Objective	Cardiometabolic disease	Chronic pain	Depression
Exposure group					
Comorbidity group	Model 1	2a	Yes, any	Yes, any	Yes
CWP group	Model 2	2b	Yes, any	Yes, CWP only	Yes
One CMD group	Model 3	2b	Yes, one	Yes, any	Yes
Diabetes group	Model 4	2b	Yes, diabetes only	Yes, any	Yes
Stroke group	Model 5	2b	Yes, stroke only	Yes, any	Yes
CHD group	Model 6	2b	Yes, CHD only	Yes, any	Yes
Hypertension group	Model 7	2b	Yes, hypertension only	Yes, any	Yes
Reference group					
Healthy group*	Reference group for all models	2	No	No	No

Abbreviations: CMD, cardiometabolic disease; LTC, long-term condition; CHD, coronary heart disease

*Participants with no LTCs

6.2.1.4 Missing values

In the subsample for survival analysis (N = 128,066), adjusting the sociodemographic and lifestyle variables produced 2,828 missing values, which comprised of 2.21% of the subsample. 125,238 participants were actually fitted in the multivariable Cox regression models.

6.2.2 Data preparation

6.2.2.1 Creating time to event variables

When following up participants from baseline, we are interested in whether the outcome of death or MACE had occurred and the length of time to such an event. Survival analysis was used to examine the relationship between the comorbidity of chronic pain, cardiometabolic disease and depression and the time to death, MACE, or end of follow-up (censoring).

The mortality dataset of these participants included the unique identity of each participant (for linkage of different datasets), the date of visiting the assessment centre, the assessment centre the participant visited, the date of death, the primary cause of death, and the event of MI and stroke.

The health outcomes were dichotomised as binary. The death status variable was created based on the date of death. Participants with a date of death were marked as dead (N = 30,005; 6.00%), and participants without a date of death were marked as alive (N = 470,308; 94.00%). Participants were censored at the end of the follow-up period if they had not experienced the event of interest (death or MACE).

Follow-up data were available for each participant and updated on 12/06/2020.

To create the time to event variable, a continuous variable of the length of follow-up was created for each participant by subtracting the date of the baseline assessment centre visit from the censor date (date of death or end of follow-up).

For participants alive by the end of follow-up:

$$Length\ of\ time\ (months) = End\ date - Start\ date$$

For participants dead before the end of follow-up:

$$Length\ of\ time\ (months) = Date\ of\ death - Start\ date$$

6.2.2.2 Creating the MACE variable

Clinical outcomes of MACE were identified from linkage to mortality data from NMR and hospital admission data from HES over around ten years of follow-up. Any new episode of MI or stroke, or CVD death was recorded in the data, and the three events were combined as MACE. In the same way, the length of time variable was created.

For participants who did not experience MACE by the end of follow-up:

$$Length\ of\ time\ (months) = End\ date - Start\ date$$

For participants who experienced MACE during the follow-up:

$$Length\ of\ time\ (months) = Date\ of\ MACE - Start\ date$$

6.2.2.3 Censored data

In the survival analysis of this study (objective 2), censored data included any data where time of death or MACE was unknown (Gijbels, 2010). If the participants were still alive by the end of the follow-up, then the time until their deaths were unknown.

It could also come from loss to follow-up, and whether and when the event happened is unknown. However, the outcomes of death and MACE in this study were obtained from data linkage. Due to the nature of the data source, there were no missing values from the data linkage process. During the follow-up years, some participants withdrew their consent and had to be removed from the whole dataset. Their mortality status was unknown to us at the time of drop out, but because we removed these cases from baseline, these participants were not included in any analysis.

Censoring of data of all participants took place on the 12/06/2020. The data of those who died during the ten-year follow up period were censored at the time of their recorded death. This approach to censoring data was also applied to MACE.

6.3 Statistical analysis

6.3.1 Descriptive analysis

6.3.1.1 In the total study sample

Descriptive analysis to show the incidence of health outcomes in those with the comorbidity of chronic pain, cardiometabolic disease and depression was conducted using the total study sample (objective 1). The mean (SD), and range of the length of time to death and time to MACE with the comorbidity of the three conditions were calculated. Health outcomes of death and MACE were also examined in participants with different types of cardiometabolic disease (diabetes, stroke, CHD, hypertension, AF, PVD, HF) and numbers of cardiometabolic disease (0, 1, 2, ≥3), as well as different pain sites (head, face, neck/shoulder, back, stomach/abdominal, hip, knee) and numbers of chronic pain sites (0, 1, 2, ≥3, CWP).

Cross-tabulation of the sociodemographic (age, gender, ethnicity, Townsend score quintile) and lifestyle (smoking, alcohol intake, physical activity, BMI) factors with the health outcomes was calculated to show the distribution of health outcomes in different groups of participants.

6.3.1.2 In the subsample

Descriptive analysis of the health outcomes of death rate and the incidence of MACE during the follow-up period among the exposure groups (comorbidity group, CWP group, one CMD group, diabetes group, stroke group, CHD group, hypertension group) and reference group (healthy group) were calculated.

6.3.1.3 Comparison between the subsample and total study sample

The sociodemographic (age, gender, ethnicity, Townsend score) and lifestyle factors (smoking, alcohol intake, physical activity, BMI) of the subsample (N =

128,066) conducting the survival analysis were compared with that of the total study sample (N = 500,313).

6.3.2 Survival analysis

To address objective 2, survival analysis was used to explore the impact of the comorbidity on health outcomes (death, MACE). The survival analysis was undertaken using the subsample dataset which involved only participants with either the comorbidity of chronic pain, cardiometabolic disease and depression, or healthy participants with no LTCs.

Continuous variables of the length of time to death and time to MACE and binary categorical variables of death and MACE were dependent variables. Death and MACE were examined separately as the dependent variables for each model. The binary variable "comorbidity" was the independent variable of interest, where “yes” meant having all three conditions, and “no” meant the healthy group as described above. The covariates included the sociodemographic and lifestyle factors of age, gender, ethnicity, Townsend score, smoking status, alcohol intake frequency, physical activity and BMI.

6.3.2.1 Kaplan-Meier plot and log-ranked test

KM plots were used to compare survival times of participants with single predictors of the comorbidity of chronic pain, cardiometabolic disease and depression.

The null hypothesis was that there was no difference in survival between the exposure group with the comorbidity and the reference group of healthy participants. If the p-value is less than 0.001, the difference between the participants with and without the comorbidity is considered statistically significant.

6.3.2.2 Cox-proportional hazard models

As the KM plot was used for single predictors to adjust the covariates (multi-adjusted) (Kyriacou and Lewis, 2016) of sociodemographic and lifestyle factors, Cox-proportional hazard models were fitted with multiple predictors. The

outcome variables were fitted in Cox models from time to event, adjusting for sociodemographic and lifestyle factors, including age, gender, ethnicity, Townsend score, smoking, alcohol intake frequency, physical activity and BMI. The reasons for choosing these variables were explained in Chapter 5 but in brief: these variables were chosen based on their importance and common use by other studies.

In this study, the hazard ratio was the risk of death or MACE at a given moment. The hazards were assumed to be proportional, and the effect of the comorbidity and covariates were constant over time. This assumption was tested before fitting the models. HR with 95% CI was to indicate the differences in survival curves between the exposure and reference groups.

First, the single predictor of the binary variable of comorbidity was fitted in the univariable Cox model. The outcome variables were the time to event and the binary variable of death or MACE. Then, the multivariable Cox model was fitted with the covariates (sociodemographic and lifestyle factors). The reference group for all survival analysis models was the healthy group (i.e. No LTCs).

6.3.3 Statistical software

All the statistical analysis was conducted using RStudio (version 3.1.2). The “survival” and "survminer” packages were used for the survival analysis. The “survfit” function within the “survival” package was used for the KM plot, the “survdiff” function was used to compute the log-rank test comparing the survival curves, and the “coxph” function in “survminer” was used for running the Cox models. The “cox.zph” function in the “survival” package was used for testing the proportionality assumption. The “ggplot2” package was used for plotting and interpreting the results.

6.4 Results

6.4.1 Descriptive analysis of total study sample

6.4.1.1 Incidence of outcomes in the total study sample

The calculation of the incidence of outcomes in the total study sample fulfilled objective 1. The death rate of the total study sample was 6.00% (30,005 / 500,313) during the follow-up period. The median of follow-up time of death was 4,079 days. The incidence of MACE was 3.57% (17,840 / 500,313) in the total study sample. The median length of follow-up until a MACE event was 3,238 days.

The incidence of all-cause mortality and MACE of participants with different health conditions are shown in Table 6-3. The incidence of death and MACE with the comorbidity of interest was 12.96% (1,120 / 8,640) and 8.01% (692 / 8,640), respectively.

The death rate and incidence of MACE with any cardiometabolic disease was 9.79% (15,294 / 156,209) and 6.44% (10,065 / 156,209). Moreover, the death rate and incidence of MACE with three or more cardiometabolic diseases were as high as 27.29% (1,434 / 5,255) and 19.35% (1,017 / 5,255). Diabetes, stroke/TIA, CHD and hypertension had the highest prevalence in the overall study population; HF, PVD, AF, and CHD had the highest incidence of all-cause mortality and MACE.

For participants with different sites of chronic pain, the death rate ranges from 4.60% (2,091 / 45,416) for head pain to 8.45% (3,648 / 43,166) for hip pain. The death rates of participants with no pain and single site of chronic pain were close, with the incidence of 5.43% (15,304 / 281,656) and 5.96% (6,868 / 115,197), respectively. However, the death rate of participants with CWP was 12.23% (872 / 7,128), much higher than the death rate of participants with three and more sites of chronic pain, with an incidence of 7.80% (3,162 / 40,549). Compared with participants with single or multiple sites of chronic pain, participants with CWP had an extraordinarily higher incidence of death and MACE.

Table 6-3. Incidence of the health outcomes in the total study sample (n = 500,313)

	All-cause mortality		MACE		N
	N	%	N	%	
Chronic pain	14,701	6.72%	9,077	4.15%	218,657
Cardiometabolic disease	15,294	9.79%	10,065	6.44%	156,209
Depression	2,810	7.82%	1,572	4.37%	35,940
Comorbidity	1,120	12.96%	692	8.01%	8,640
Different types of cardiometabolic diseases					
Diabetes	3,883	15.33%	2,509	9.91%	25,324
Stroke/TIA	1,514	17.19%	832	9.45%	8,805
CHD	3,894	17.19%	2,861	12.63%	22,650
Hypertension	12,378	9.32%	8,189	6.17%	132,818
AF	507	13.93%	393	10.80%	3,640
PVD	226	17.73%	150	11.76%	1,275
HF	184	23.09%	136	17.06%	797
Number of cardiometabolic diseases					
0	14,711	4.28%	7,775	2.26%	344,104
1	9,654	7.86%	6,207	5.05%	122,900
2	4,206	14.99%	2,841	10.13%	28,054
≥3	1,434	27.29%	1,017	19.35%	5,255
Different sites of chronic pain					
Headache	2,091	4.60%	1,383	3.05%	45,416
Facial pain	267	6.06%	167	3.79%	4,406
Neck or shoulder pain	5,404	6.79%	3,426	4.30%	79,634
Back pain	6,377	7.22%	3,961	4.49%	88,298
Stomach or abdominal pain	1,771	7.38%	1,063	4.43%	24,004
Hip pain	3,648	8.45%	2,302	5.33%	43,166
Knee pain	5,999	7.15%	3,904	4.65%	83,941
Number of chronic pain sites					
0	15,304	5.43%	9,274	3.29%	281,656
1	6,868	5.96%	4,153	3.61%	115,197
2	3,799	6.81%	2,326	4.17%	55,783
≥3	3,162	7.80%	2,087	5.15%	40,549
CWP	872	12.23%	511	7.17%	7,128

Abbreviations: MACE, Major Adverse Cardiovascular Event; LTC, long-erm conditions; PVD, peripheral vascular disease; TIA, Transient Ischaemic Attack; CHD, coronary heart disease; HF, heart failure; AF, Atrial fibrillation; CWP, chronic widespread pain

6.4.1.2 Sociodemographic and lifestyle factors with the health outcomes

In the total study sample, the incidence of both death and MACE outcomes was higher in males than in females (Table 6-4). The all-cause mortality of males in the total study sample was 7.85% (17,893 / 228,078), and the mortality of females was 4.45% (12,112 / 272,235). The incidence of MACE in males was

5.27% (12,012 / 228,078), and the incidence in females was 2.14% (5,828 / 272,235).

The incidence of MACE in white participants (3.58%, 16,894 / 471,851) and participants in other ethnic groups (3.20%, 855 / 26,749) were similar, while the death rate of white participants (6.11%, 28,820 / 471,851) was much higher than the death rate of other ethnic groups (3.92%, 1,048 / 26,749).

The death rate of participants living in the most deprived areas was 8.12% (8,070 / 99,397), while for the participants in other areas, the death rates were similar, between five to six per cent.

Current smokers had the highest incidence of all-cause mortality (11.15%, 5,887 / 52,788) and MACE (6.51%, 3,437 / 52,788) among all the smoking status. Participants who reported never drinking or drinking on special occasions only had a higher incidence of all-cause mortality (7.80%, 7,661 / 98,160) and MACE (4.50%, 4,420 / 98,160) than participants who reported drinking more frequently.

Participants who reported no physical activities had the highest death rate (11.21%, 3,661/ 32,661) and MACE (6.17%, 2,014 / 32,661). Classified by BMI, participants with obesity had the highest incidence of MACE (4.89%, 5,953 / 121,719), while underweight participants had the highest death rate (11.17%, 292 / 2,614).

Regarding the missing values, the death rates of those who failed to provide complete data on ethnicity (8.00%, 137 / 1,713), smoking (10.74%, 200 / 1,863), alcohol frequency (11.64%, 49 / 421), physical activity (14.09%, 852 / 6,046) and BMI (15.85%, 419 / 2,643) were high, which indicate a potential underestimation of the incidence of death and MACE in the total study sample.

Table 6-4. Descriptive analysis of the health outcomes with sociodemographic and lifestyle factors in total study sample (n = 500,313)

	All-cause mortality N %		MACE N %		N
Gender					
Male	17,893	7.85%	12,012	5.27%	228,078

Female	12,112	4.45%	5,828	2.14%	272,235
Missing	0	0.00%	0	0.00%	0
Age, years					
38-44	672	1.30%	468	0.91%	51,510
45-49	1,326	2.02%	962	1.46%	65,760
50-54	2,448	3.22%	1,703	2.24%	76,022
55-59	4,369	4.83%	2,743	3.03%	90,460
60-64	9,025	7.46%	5,289	4.37%	121,043
65-73	12,165	12.74%	6,675	6.99%	95,518
Missing	0	0.00%	0	0.00%	0
Ethnicity					
White	28,820	6.11%	16,894	3.58%	471,851
Other ethnic group	1,048	3.92%	855	3.20%	26,749
Missing	137	8.00%	91	5.31%	1,713
Townsend score quintile					
1 (least deprived)	5,101	5.08%	3,052	3.04%	100,430
2	5,268	5.28%	3,128	3.13%	99,860
3	5,572	5.57%	3,470	3.47%	100,086
4	5,967	5.97%	3,559	3.56%	99,921
5 (most deprived)	8,070	8.12%	4,610	4.64%	99,397
Missing	27	4.36%	21	3.39%	619
Smoking					
Never	11,344	4.16%	7,177	2.63%	272,899
Previous	12,574	7.28%	7,104	4.11%	172,763
Current	5,887	11.15%	3,437	6.51%	52,788
Missing	200	10.74%	122	6.55%	1,863
Alcohol frequency					
Never or special occasions only	7,661	7.80%	4,420	4.50%	98,160
1-3 times a month	2,871	5.15%	1,805	3.24%	55,748
1-4 times a week	12,530	5.13%	7,777	3.18%	244,326
Daily or almost daily	6,894	6.78%	3,812	3.75%	101,658
Missing	49	11.64%	26	6.18%	421
Physical activity					
High	1,408	2.81%	1,025	2.05%	50,027
Medium	22,297	5.68%	13,329	3.39%	392,688
Low	1,787	9.46%	1,001	5.30%	18,891
None	3,661	11.21%	2,014	6.17%	32,661
Missing	852	14.09%	471	7.79%	6,046
BMI					
Recommended weight	7,987	4.93%	3,981	2.46%	161,921
Underweight	292	11.17%	93	3.56%	2,614
Overweight	12,162	5.75%	7,623	3.61%	211,416
Obese	9,145	7.51%	5,953	4.89%	121,719
Missing	419	15.85%	190	7.19%	2,643

Abbreviation: MACE, Major Adverse Cardiovascular Event; BMI, Body Mass Index

6.4.2 Descriptive analysis of the subsample

6.4.2.1 Incidence of outcomes in subgroups

The incidence of all-cause mortality and MACE in the subsample of different subgroups are shown in Table 6-5. The death rate and incidence of MACE in comorbidity group was 10.46% (262 / 2,504) and 6.63% (166 / 2,504). Other exposure groups had relatively small sample sizes. CHD group had the highest incidence of death (16.67%, 17 / 102) and MACE (8.82%, 9 / 102). The death rate in the healthy group was 3.12% (3,923 / 125,562), and the incidence of MACE was 1.88% (2,360 / 125,562).

Table 6-5. Incidence of all-cause mortality and MACE in subgroups

Subgroups	All-cause mortality		MACE		N
Comorbidity group	262	10.46%	166	6.63%	2,504
CWP group	19	12.58%	12	7.95%	151
One CMD group	148	8.22%	84	4.66%	1,801
Diabetes group	6	5.66%	2	1.89%	106
Stroke group	8	10.96%	6	8.22%	73
CHD group	17	16.67%	9	8.82%	102
Hypertension group	116	7.76%	66	4.42%	1,494
Healthy group*	3,923	3.12%	2,360	1.88%	125,562

Abbreviations: CMD, cardiometabolic disease; LTC, long-term condition; CHD, coronary heart disease

*Participants with no LTCs

6.4.2.2 Comparison with total study sample

74.40% of the total study population were excluded from the subsample examined for survival analyses. The characteristics of the subsample and the whole study sample were compared. Cutting down the sample size did not make substantial changes in the distribution of the sociodemographic factors of the total study population. The main changes were in physical activity and BMI: a higher percentage of obesity and of no physical activity was found in the subsample (Table 6-6).

Table 6-6. Comparison of sociodemographic factors of the subsample and the total study population

	Total participants N = 500,313		Subsample N = 128,066	
Comorbidity	8,640	1.73%	2,504	1.96%
Gender				
Male	228,078	45.59%	60,240	47.04%
Female	272,235	54.41%	67,826	52.96%
Missing	0	0.00%	0	0.00%
Age, years				
38-44	51,510	10.30%	19,239	15.02%
45-49	65,760	13.14%	21,963	17.15%
50-54	76,022	15.19%	22,256	17.38%
55-59	90,460	18.08%	23,145	18.07%
60-64	121,043	24.19%	25,905	20.23%
65-73	95,518	19.09%	15,558	12.15%
Missing	0	0.00%	0	0.00%
Ethnicity				
White	471,851	94.31%	120,767	94.30%
Other ethnic group	26,749	5.35%	6,876	5.37%
Missing	1,713	0.34%	423	0.33%
Townsend score quintile				
1 (least deprived)	100,430	20.07%	27,713	21.64%
2	99,860	19.96%	26,647	20.81%
3	100,086	20.00%	26,033	20.33%
4	99,921	19.97%	25,382	19.82%
5 (most deprived)	99,397	19.87%	22,141	17.29%
Missing	619	0.12%	150	0.12%
Smoking				
Never	77,358	60.40%	272,899	54.55%
Previous	37,823	29.53%	172,763	34.53%
Current	12,531	9.78%	52,788	10.55%
Missing	354	0.28%	1,863	0.37%
Alcohol frequency				
Never or special occasions only	19,141	14.95%	98,160	19.62%
1-3 times a month	13,728	10.72%	55,748	11.14%
1-4 times a week	68,332	53.36%	244,326	48.83%
Daily or almost daily	26,788	20.92%	101,658	20.32%
Missing	77	0.06%	421	0.08%
Physical activity				
High	18,990	14.83%	50,027	10.00%
Medium	98,914	77.24%	392,688	78.49%
Low	3,321	2.59%	18,891	3.78%
None	5,471	4.27%	32,661	6.53%
Missing	1,370	1.07%	6,046	1.21%
BMI				

Recommended weight	53,198	41.54%	161,921	32.36%
Underweight	796	0.62%	2,614	0.52%
Overweight	53,771	41.99%	211,416	42.26%
Obese	19,738	15.41%	121,719	24.33%
Missing	563	0.44%	2,643	0.53%

Abbreviations: LTC, long-term condition

6.4.3 Survival analysis

The survival analysis was performed using the subsample (N = 128,066) to address objective 2.

6.4.3.1 KM plot and log-rank test

The KM plots of Figure 6-4 and Figure 6-5 show the survival probability of death and MACE over time since visiting the assessment centre, respectively. At the left of the plot, zero days after visiting the assessment centre, the cumulative survival probability is 1.0 (100%) and falls as the participants die or have MACE. The blue line represents the comorbidity group, and the red line represents the healthy group.

The plots show that the survival of the participants in death and MACE with the comorbidity was worse than those without the comorbidity. The risk table below each plot presents the specific numbers of participants at risk at each time point.

The p-values of all the log-rank tests here were less than 0.0001, and the differences in the survival curves were statistically significant.

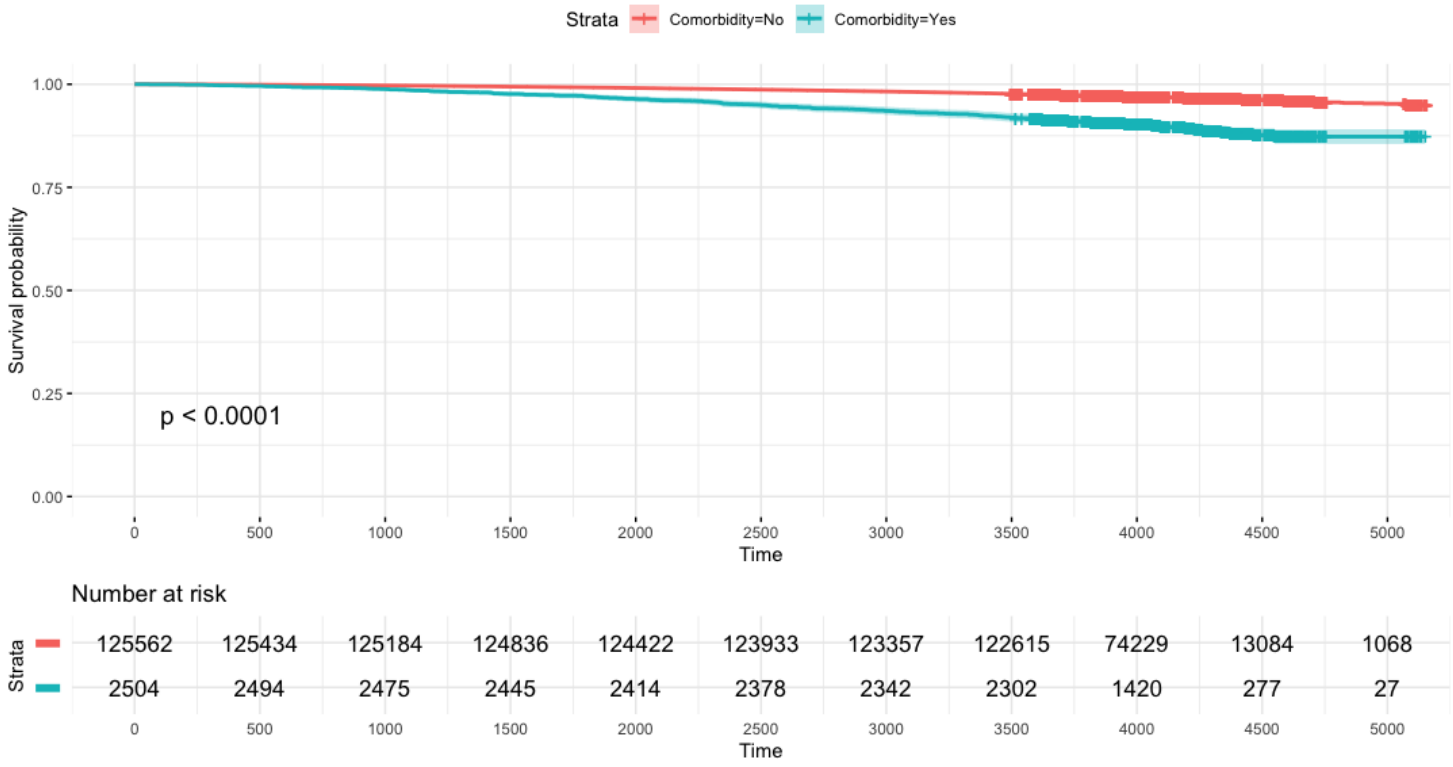

Figure 6-4. Kaplan-Meier Plot of survival probabilities of death in participants with and without the comorbidity over time

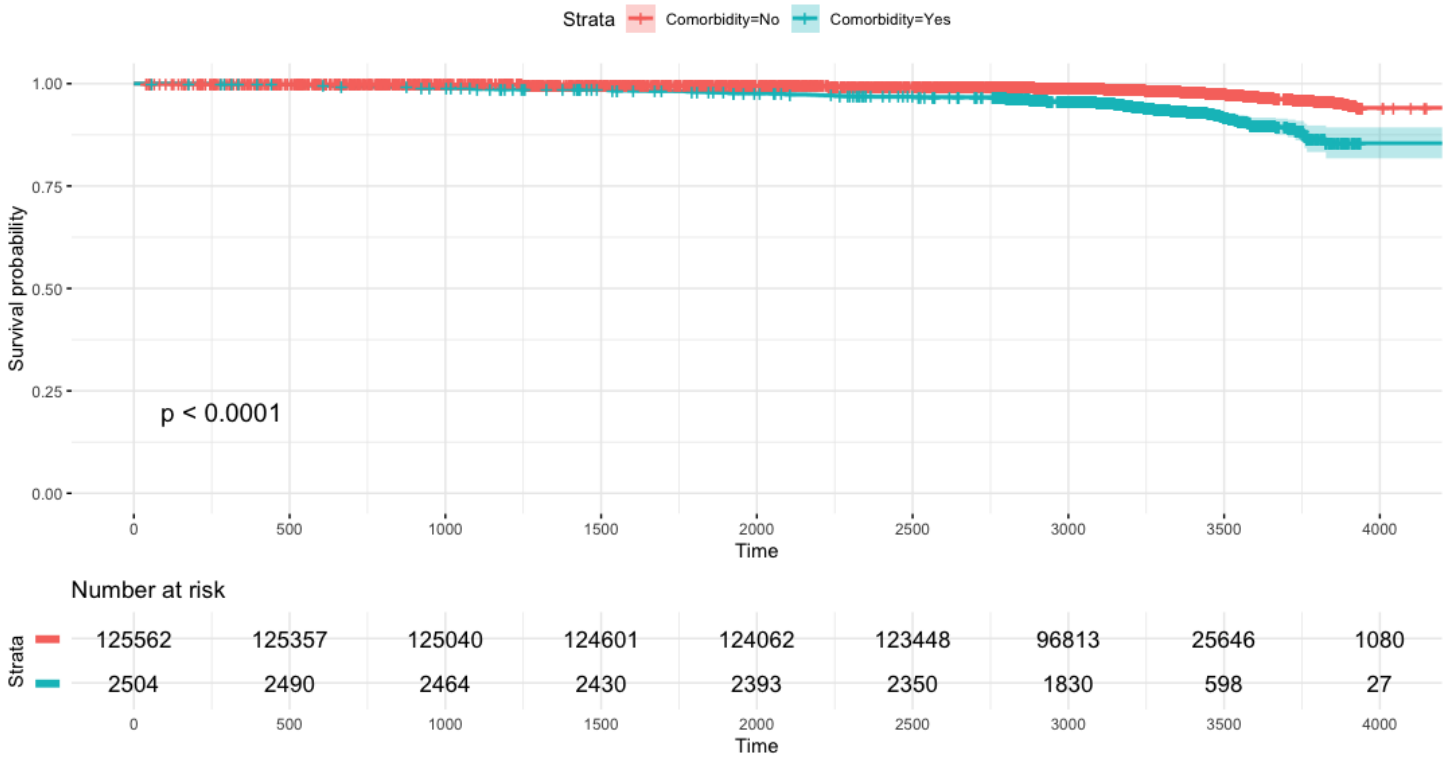

Figure 6-5. Kaplan-Meier Plot of survival probabilities of MACE in participants with and without the comorbidity over time

6.4.3.2 Cox models

Cox models were used to examine the effect of comorbidity on death and MACE adjusting for the confounders (age, gender, ethnicity, Townsend score, smoking status, alcohol intake frequency, physical activity, BMI). The proportionality assumption was tested, and the p-values were not significant, showing assumption of proportionality was not violated.

Univariable model

Before adjusting for any confounding variables, the univariable model showed the comorbidity group had a 3.46 (HR 95% CI: 3.05-3.92) and 3.49 (HR 95% CI: 2.98-4.08) increased likelihood of experiencing death and MACE compared with the healthy group, respectively. At any particular time, participants with the comorbidity in CWP group, one CMD group, stroke group, CHD group and hypertension group had a statistically significantly increased risk of death and MACE compared to healthy participants with no LTCs. No significant association between the comorbidity and death or MACE was found in the group with diabetes.

Multivariable model

After adjusting for the confounding factors in the model, 2,828 (2.21% of the subsample) observations were excluded because of missing data on the sociodemographic and lifestyle factors.

After adjusting for the covariates, the association between the comorbidity and death in CWP group and stroke group was no longer statistically significant; the association between the comorbidity and MACE in CHD group and stroke group lost the significance.

At any particular time, after adjusting for confounders, participants with the comorbidity had a 2.10 (HR 95% CI: 1.84-2.41) increase in the risk of dying compared to healthy participants with no LTCs. It was 1.83 (HR 95% CI: 1.54-2.18) times the likelihood of death for one CMD group, 2.34 (HR 95% CI: 1.43-3.84) for the CHD group, and 1.83 (HR 95% CI: 1.51-2.22) for the hypertension

group, compared to the healthy group. The p-values of the Cox regression of the association of comorbidity and hazard of death in the diabetes group, stroke group and CWP group were more than 0.001, and thus the associations were not statistically significant.

The hazard ratios of MACE in the comorbidity group, one CMD group, hypertension group and CWP group were 2.13 (HR 95% CI: 1.79-2.52), 1.61 (HR 95% CI: 1.28-2.03), 1.67 (HR 95% CI: 1.29-2.16) and 2.62 (HR 95% CI: 1.48-4.64), respectively.

Table 6-7. Survival analysis of the relationship between all-cause mortality and the comorbidity (chronic pain, cardiometabolic disease and depression) in different exposure groups

	Univariable model				Multivariable model*			
	N	Number of deaths	HR (95% CI)	p-value	N	Number of deaths	HR (95% CI)	p-value
Comorbidity group + healthy group	128,066	4,185	3.46 (3.05, 3.92)	<0.001	125,238	4,024	2.10 (1.84, 2.41)	<0.001
CWP group + healthy group	125,713	3,942	4.25 (2.70, 6.66)	<0.001	122,988	3,798	2.17 (1.31, 3.62)	0.003
One CMD group + healthy group	127,363	4,071	2.67 (2.27, 3.15)	<0.001	124,581	3,922	1.83 (1.54, 2.18)	<0.001
Diabetes group + healthy group	125,668	3,929	1.87 (0.84, 4.16)	0.127	122,956	3,788	1.01 (0.42, 2.44)	0.978
Stroke group + healthy group	125,635	3,931	3.67 (1.84, 7.35)	<0.001	122,922	3,790	2.18 (1.04, 4.57)	0.040
CHD group + healthy group	125,664	3,940	5.56 (3.45, 8.95)	<0.001	122,954	3,799	2.34 (1.43, 3.84)	<0.001
Hypertension group + healthy group	127,056	4,039	2.52 (2.09, 3.03)	<0.001	124,285	3,893	1.83 (1.51, 2.22)	<0.001
Healthy group**	*(reference)*							

Abbreviations: CMD, cardiometabolic disease; HR, Hazzard Ratio; CI, Confidence Interval; PVD, peripheral vascular disease; CHD, coronary heart disease

*Note that the number in each of the univariable models varied depending on the number of missing responses to each question

**Participants with no LTCs

Table 6-8. Survival analysis of the relationship between MACE and the comorbidity (chronic pain, cardiometabolic disease and depression) in subgroups with different combinations of the comorbidity

	Univariable model				Multivariable model*			
	N	Number of MACE	HR (95% CI)	p-value	N	Number of MACE	HR (95% CI)	p-value
Comorbidity group + healthy group	128,066	2,526	3.49 (2.98, 4.08)	<0.001	125,238	2,429	2.13 (1.79, 2.52)	<0.001
CWP group + healthy group	125,713	2,372	4.26 (2.41, 7.51)	<0.001	122,988	2,284	2.62 (1.48, 4.64)	<0.001
One CMD group + healthy group	127,363	2,444	2.42 (1.94, 3.00)	<0.001	124,581	2,350	1.61 (1.28, 2.03)	<0.001
Diabetes group + healthy group	125,668	2,362	1.00 (0.25, 4.01)	0.997	122,956	2,274	0.55 (0.14, 2.21)	0.399
Stroke group + healthy group	125,635	2,366	4.73 (2.12, 10.54)	<0.001	122,922	2,277	2.57 (1.07, 6.19)	0.035
CHD group + healthy group	125,664	2,369	4.54 (2.36, 8.73)	<0.001	125,664	2,369	1.54 (0.77, 3.10)	0.223
Hypertension group + healthy group	127,056	2,426	2.28 (1.78, 2.91)	<0.001	124,285	2,334	1.67 (1.29, 2.16)	<0.001
Healthy group**	*(reference)*							

Abbreviations: MACE, major adverse cardiovascular events; CMD, cardiometabolic disease; HR, Hazzard Ratio; CI, Confidence Interval; PVD, peripheral vascular disease; CHD, coronary heart disease

*Note that the number in each of the univariable models varied depending on the number of missing responses to each question

***Participants with no LTCs

6.5 Discussion

6.5.1 Summary of findings

In the previous chapters, the systematic review identified the evidence gaps in the epidemiology of the comorbidity of chronic pain, cardiometabolic disease and depression. The cross-sectional study, described in the previous chapter, examined the prevalence of the comorbidity at the baseline (1.73%) and the association of the comorbidity with sociodemographic and lifestyle factors. However, the effect of the comorbidity on health outcomes was unknown. This study, to our knowledge, is the first to examine the effect of the comorbidity of chronic pain, cardiometabolic disease and depression on death and MACE in a large cohort.

This chapter presents the results of the incidence of the health outcomes in the total study sample (N = 500,313) and survival analyses of the comorbidity on health outcomes in the subsample (N = 128,066) of those with the comorbidity but without additional LTCs, and healthy participants with no LTCs.

Clinical outcomes were identified from linkage to NMR and HES for approximately 10 years of follow-up. In the total study sample, the incidence of death and MACE was 6.00% (30,005 / 500,313) and 3.57% (17,840 / 500,313).

In the subsample, the death rate and incidence of MACE in the comorbidity group were 10.46% (262 / 2,504) and 6.63% (166 / 2,504). Participants in the comorbidity group had an increased risk of death (HR 2.10, 95% CI: 1.84-2.41) and MACE (HR 2.13, 95% CI: 1.79-2.52) compared with the healthy group after adjusting for covariates of sociodemographic and lifestyle factors.

6.5.2 Justification of the subsample

A subsample instead of the total study sample was used for survival analyses. The eligibility of the subsample was participants with the comorbidity of chronic pain, cardiometabolic disease and depression (N = 125,562) and healthy participants with no LTCs (N = 2,504). Figure 6-2 shows the process of creating the subsample from the total study sample. Survival analysis could have been done in either way– in the total study sample or in the subsample. In this

section, this approach is justified to fulfil the objective 2 under the limitation of the complex nature of the co-occurrence of multiple LTCs.

6.5.2.1 Exclusion of participants with other LTCs

In the subsample, participants with any of the additional LTCs considered (N = 216,806) were removed to dismiss the impact of having other LTCs.

Chronic conditions with the leading cause of death in the US in 2020 were heart disease, cancer, stroke, chronic lower respiratory disease (COPD, chronic bronchitis, emphysema, and asthma) (Lee et al., 2021), Alzheimer's disease, diabetes, chronic kidney disease (Murphy et al., 2021a), as well as chronic liver disease, hypertension, and Parkinson's disease reported in 2018 (Murphy et al., 2021b). In UK Biobank data, in addition to the health conditions of interest (prevalence) - heart diseases (5.41%), stroke (1.76%), diabetes (5.06%), hypertension (26.55%), chronic pain and depression, there were additional LTCs classified, the most prevalent ones being: asthma (11.61%) and cancer (7.70%), as well as COPD (1.66%), chronic liver disease (0.19%), Parkinson's disease (0.17%) and dementia (0.02%). These LTCs were prevalent in the total study sample and strongly associated with death based on existing evidence as listed above (Murphy et al., 2021a).

Having one or more additional LTCs was captured with a binary variable, *yes* to having one or more of the 37 additional LTCs and *no* to having none of the 37 additional LTCs. Logistic regression in Chapter 5 and survival analysis in this chapter treated the additional LTCs variable in different ways. In Chapter 5, the variable was fitted in the logistic regression models as a binary variable to examine the association between the comorbidity and sociodemographic and lifestyle factors. This allowed the examination of additional LTCs as a covariate, as it is potentially related to the comorbidity of the three conditions (outcome of interest) and related to the sociodemographic and lifestyle factors examined in the models (independent variables). In the survival analysis in this chapter, the outcome of interest changed from the comorbidity to all-cause mortality and MACE. Multiple LTCs has been shown to have a substantial impact on death (Jani et al., 2019) that is potentially stronger than the exposure of interest (the comorbidity of chronic pain, cardiometabolic disease and depression). The

purpose of this study was not to examine the effect of the additional LTCs on health outcomes; rather it was to focus on the three conditions of interest as an exemplar of multimorbidity, and hence participants with any additional LTCs were removed.

6.5.2.2 Clarification of the comparison

After removing participants with any additional LTCs, those with only one or two of the conditions of chronic pain, cardiometabolic disease, and depression (N = 155,441) were also removed from the subsample, leaving the exposure group with the comorbidity of the three conditions of interest only and a reference group with no LTCs.

In Chapter 5, the investigation of the combinations of the three conditions shows the complexity of the comorbidity. Various distributions of age, gender and ethnicity of single diseases and the combination of two conditions were examined. In the survival analysis, without additional LTCs, the exposure group was the participants with all three conditions, and two options for reference group: 1) participants with none of the three conditions; 2) participants with none, one or two of the three conditions. Both ways are reasonable, while the former was chosen to make a clearer comparison.

6.5.2.3 Removed participants

The subsample comprised 25.60% (128,066 / 500,313) of the total study sample and 74.08% (372,247 / 500,313) were removed. To check if any bias was produced from cutting down the sample, characteristics of sociodemographic and lifestyle factors of the total study sample and the subsample were compared (Table 6-6). No substantial changes were found in the distribution of sociodemographic factors (age, gender, ethnicity and Townsend score) between the subsample and the total study sample. The proportions of lifestyle factors differed slightly, but the trend of the categories was unchanged.

6.5.3 In context with previous literature

6.5.3.1 Chronic pain

A systematic review identified ten citations that examined the relationship between chronic pain and mortality from an initial search of 15,057 citations (Smith et al., 2014). After adjusting for confounding factors, only four of the ten studies found a significant association between chronic pain alone and mortality (Sjøgren et al., 2010, Macfarlane et al., 2001, Nitter and Forseth, 2013, McBeth et al., 2009). In a cohort of 2,261 females in Norway followed for 17 years, the mortality rate was found to be significantly higher for participants with chronic musculoskeletal pain compared to participants without the pain, adjusting for age (HR 2.1, 95% CI: 1.1-4.2) (Nitter and Forseth, 2013).

A survival analysis of a cohort of 6,940 participants followed up for 10 years in Scotland found a significant association between self-reported severe chronic pain and linked all-cause mortality after adjusting for sociodemographic factors and LTCs (HR 1.49, 99% CI 1.21-1.84); nevertheless, no significant association was found between any chronic pain and all-cause mortality after adjusting for confounding factors (Torrance et al., 2010). In our study, the impact of other LTCs was adjusted for by excluding the participants with any additional LTCs. Moreover, the effects of sociodemographic factors were examined by adjusting the Cox regression models. Our study found a significant association between the comorbidity of chronic pain along with cardiometabolic disease and depression and all-cause mortality (HR 2.10, 95% CI: 1.84-2.41) after adjusting for confounding factors.

6.5.3.2 CWP

In the quantitative studies in this thesis, high comorbidity rates were observed in participants with CWP, and significant increased risk of death and MACE was associated with participants with CWP, cardiometabolic disese and pain. These findings are consistent with previous literatures.

A UK Biobank study examined the effect of CWP on premature mortality, and found 7,130 participants with CWP experienced excess mortality with the mortality risk ratio of 2.43 (95% CI: 2.17-2.72) (Macfarlane et al., 2017). The

hazard ratio of mortality was observed to be higher in participants with CWP than in participants with no pain (HR 1.31, 95% CI: 1.05-1.65) after adjusting for sociodemographic factors in a cohort study of 6,569 participants followed for 12 months in the North West of England (Macfarlane et al., 2001). In our study, a higher hazard of mortality was found in participants with the comorbidity of pain all over the body, cardiometabolic disease and depression after adjusting for sociodemographic and lifestyle factors (HR 2.17, 95% CI: 1.31-3.62). In another cohort study of UK Biobank, excess death due to cardiovascular disease was significantly associated with CWP after adjusting for age and sex (HR 3.24, 95% CI: 2.55-4.11) (Macfarlane et al., 2017). In our study, MACE was associated with the comorbidity of CWP, cardiometabolic disease and depression (HR 2.26, 95% CI: 1.48-4.64) after adjusting for age, sex and other sociodemographic and lifestyle variables.

Participants with CWP reported “pain all over the body” for three months or longer, which may lead to a significant decreased quality of life and increased functional impairment. Moreover, the impact of CWP on individuals' physical, mental and social wellbeing may further increase the risk of death and MACE through several pathways such as decreased or no physical activity, sleep disturbance, and reduced social engagement. Further research is needed to fully understand the underlying causes of this increased risk and develop effective interventions for individuals with CWP.

6.5.3.3 Cardiometabolic disease

CHD was reported to contribute the most to the increasing mortality of cardiovascular deaths globally (Roth et al., 2015). Moreover, in a cohort study, the incidence of MACE was 0.8% (619 / 74,329) within 30 days of discharge from the emergency department, and MACE was associated with hypertension (OR 4.74, 95% CI: 4.02-5.59) and diabetes mellitus (OR 3.76, 95% CI: 3.10-4.57) and cardiovascular diseases (AF, Stroke, MI, angina, HF, PVD) (Omstedt et al., 2016).

In this study, MACE was associated the comorbidity of hypertension, chronic pain and depression (HR 1.67, 95% CI: 1.29-2.16). No significant relationships were found between MACE and the comorbidity of diabetes or stroke or CHD, along with chronic pain and depression.

6.5.3.4 Depression

In a cohort study of 3,410 participants in Canada, depression was found to be associated with a higher risk of death during the follow-up period between 1990 to 2011 (Gilman et al., 2017). In another cohort followed for three years, after adjustment for confounding factors, among the participants treated with percutaneous coronary intervention, depression was found to be statistically significantly associated with MACE (HR 2.51, 95% CI: 1.57-4.02) (Wang et al., 2013). In this study, MACE was associated the comorbidity of one cardiometabolic disease, chronic pain and depression (HR 1.61, 95% CI: 1.28-2.03).

In the context of the previous studies that examined the impact of chronic pain, cardiometabolic disease and depression on the health outcomes individually, our study provides new insight into the impact on health outcomes of having all three conditions.

6.5.4 Strengths and limitations

6.5.4.1 The data linkage

The strengths and limitations of using UK Biobank as a large study sample have been noted in Chapters 3&5. In addition, the main strength of this study was the availability of registry data for health outcomes.

The UK Biobank dataset is linked to mortality data and hospital admission data. The data linkage allows the investigation of the association of a range of health outcomes and the health conditions in a large cohort followed for around 10 years. As each participant had a unique identification number, there was no loss of follow-up from the data linkage.

Participants withdrew and were removed from the baseline and not censored in the study (Biobank, 2007b). This might cause some bias in the further analysis, but the number of withdrawals was tiny compared with the large cohort sample size.

6.5.4.2 Subsample

Within the subsample (N = 128,066), the number of the events of death and MACE were small in each subgroup: six in diabetes, eight in stroke, 17 in CHD and 19 in the CWP group. This could lead to bias and less power in the calculation when fitting with the Cox regression models (Johnson et al., 1982). The validity of the proportionality assumption of the Cox regression models in this study was assessed, and it was satisfied (Austin, 2018). Further studies of UK Biobank could consider more complicated methods like Sparse-Group regularised Cox regression (Li et al., 2021) to deal with this situation or use study samples with higher incidence to examine the combination of specific diseases in smaller groups.

6.5.4.3 Sociodemographic and lifestyle factors

The data of sociodemographic and lifestyle factors provided in UK Biobank data were collected from baseline. Therefore, there was a potential bias that the information was not updated for around 10 years and cannot take potential changes of these factors into account (Mutambudzi et al., 2021). The outcome data has been updated recently in 2020, while the baseline data has not been updated since the recruitment between 2006 to 2010. For factors like gender and ethnicity, the data was unlikely to change over the follow-up period. Surely age will change over time, but the age after the follow-up can be calculated. However, for the factors like the Townsend score, smoking status, alcohol intake frequency, physical activities and BMI, there is the possibility to change.

This is a limitation of using the UK Biobank data, but the association of the health outcomes and the baseline data still provided critical information on the effect of the comorbidity on health outcomes (Mutambudzi et al., 2021).

6.5.4.4 The Cox regression models

Instead of fitting in different variables and running stepwise models to compare and choose the best model, all the sociodemographic and lifestyle factors were fitted in the multivariable Cox regression model. These variables were chosen not just for statistical meaning but also because of theoretical plausibility. As stated in Chapter 5, the factors of age, gender, ethnicity and deprivation were

fitted in the model regardless of the power of the models, and the lifestyle factors were of great importance as well. These variables have been commonly used in other health outcome analysis of the UK Biobank data (McQueenie et al., 2020b, Jani et al., 2018, Hanlon et al., 2022, McPeake et al., 2021).

6.5.5 Conclusion

Increased risk of mortality and MACE has been found for those with the comorbidity of chronic pain, cardiometabolic disease and depression. Further studies on cohorts with specific combinations of chronic pain, cardiometabolic disease and depression, especially with CVD, are needed; as is research into the impact of this comorbidity on QoL. The next chapter presents a qualitative study examining the experience of individuals living with the comorbidity of the three conditions.

Chapter 7 Living with the comorbidity of chronic pain, cardiometabolic disease, and depression: patients' perspectives

7.1 Introduction

7.1.1 Overview of this chapter

This chapter presents a qualitative study that aims to explore the experience of those living with the chronic illnesses of interest (chronic pain, cardiometabolic disease and depression) and to describe the everyday lived experience of those managing the comorbidity of the three conditions. Specifically answering research question 4: what is the lived experience and insight of people living with this comorbidity?

7.1.2 Rationale

The previous results chapters reported: 1) a systematic review that highlighted a large evidence gap regarding the comorbidity of chronic pain, cardiometabolic disease and depression (Chapter 4); 2) an analysis of the baseline data from UK Biobank that demonstrated that the prevalence of the comorbidity was 1.73% (Chapter 5); 3) an analysis of UK Biobank that found the comorbidity was associated with an increased risk of adverse health outcomes. In the systematic review there was a complete absence of any qualitative work exploring the lived experience of people with this combination of conditions. Both the systematic review and the data analysis examined the evidence and impact of comorbidity at a population level.

At the individual level, the challenges for single conditions are likely to be amplified when they are combined (Hughes et al., 2013). The comorbidity of chronic pain, cardiometabolic disease and depression may create significant cumulative difficulties in patients' lives. Despite all the potential challenges and the commonality of these three conditions occurring together (van Hecke et al., 2017), there is no existing research focused on the patients' perspective of the three conditions. In this chapter, a qualitative secondary analysis of semi-structured interviews with those who live with the comorbidity was undertaken to enable learning about the experience of living with the comorbidity. It drew

on data from an existing dataset and examined research questions that were distinct from the primary research.

7.1.3 Aims and objectives

The overall aim of this secondary qualitative study was to examine the patients' perspectives of living with the comorbidity of chronic pain, cardiometabolic disease and depression using existing data from the MAP study.

The research aims to provide preliminary insights into the experiences of people with this combination of conditions. The specific research questions to be addressed are:

1. How does living with the comorbidity of chronic pain, cardiometabolic disease and depression impact the everyday life of participants?

2. What are the insights of the participants about the three conditions and how they are managed by healthcare professionals?

7.2 Study sample

7.2.1 Primary research: MAP study

7.2.1.1 Details of the MAP study

The MAP study generated data from in-depth interviews that considered multimorbidity in people with RA and MSK pain. The qualitative aspects of the MAP study aimed to explore the treatment burden (Mair and May, 2014) and the participants' capacity (Shippee et al., 2012) to manage either RA or MSK pain, with and without the presence of more than two LTCs (multimorbidity). As outlined in Chapter 2, in addition to the burden of symptoms, patients and their caregivers are challenged by burdens of treatment, which are the workload of demands such as the modification to recommended lifestyle, monitoring and managing symptoms at home, adherence to complex treatment regimens, coordination of multiple drugs, and barriers from complex administrative systems, uncoordinated health and social care systems (Mair and May, 2014). Correspondingly, capacity refers to the abilities, resources or preparation of

patients and their caregivers to address the demands (Shippee et al., 2012) placed upon them by healthcare systems.

Data from the MAP study spoke directly to the particular interest of this thesis as it included information on the combination of conditions of interest and was therefore deemed suitable for secondary analysis. In this secondary research, the focus was on the experience of living with the comorbidity of chronic pain, cardiometabolic disease and depression, and the insights into the relationship between the three conditions from the participants. Treatment burden and capacity were not the focus of this study, as they had been covered by the primary analysis of the MAP study. The MAP study and the current study addressed different evidence gaps, and the comparison of the aims in the primary and secondary research has been detailed in Chapter 3.

7.2.1.2 Recruitment of participants

In the primary research of the MAP study, participants were recruited via general practices and rheumatology and pain clinics. Eighty adults with persistent MSK pain or RA were interviewed about their personal experiences and feelings about living with the diseases.

All original 80 participants were separated into two eligible groups: those living with either persistent MSK pain and/or RA (N = 40) only or persistent MSK pain and/or RA alongside a range of co-occurring conditions (N = 40). In detail, the eligible participants were listed:

- Group 1: adults with persistent MSK pain only (N = 20)
- Group 2: adults with RA only (N = 20)
- Group 3: adults with MSK pain alongside multimorbidity (N = 20)
- Group 4: adults with RA alongside multimorbidity (N = 20)

Participants in Groups 1 & 2 only had single diseases of either MSK pain or RA and thus were not eligible for the secondary analysis. The 40 participants in Groups 3 & 4 potentially meet the eligibility of this secondary study, and their

self-reported LTCs were examined to determine eligibility for the current secondary analyses.

7.2.2 Subsample for the secondary research

7.2.2.1 Eligibility for the secondary analysis

The study presented here was interested in patients with the comorbidity of chronic pain, cardiometabolic disease and depression, and aligned with the inclusion criteria for the systematic review study in Chapter 4, so the eligibility criteria set for this secondary analysis are as outlined below:

- Chronic pain was defined as pain lasting at least three months or 12 weeks, excluding migraine, headache, chest pain and pain from cancer.

- Cardiometabolic disease includes all types of cardiovascular diseases and metabolic diseases (heart diseases, hypertension, cardiomyopathies, heart failure, cerebrovascular disorders, heart attack, coronary artery disease, hypotension, angina, arrhythmias, atrial fibrillation, metabolic syndrome, diabetes, dyslipidaemia), excluding obesity, overweight and congenital heart disease.

- Depression was assessed through history or measurement of depression, depressive symptoms, or low mood.

The listed conditions of the 40 participants with multimorbidity in the MAP study were screened to identify those living with the three conditions of interest. After applying the filter conditions, ten participants met the eligibility criteria and were included in the present study. The transcripts of their interviews were revisited by me for secondary analysis as part of the work presented in this thesis.

7.2.2.2 Characteristics of the participants

The sociodemographic variables of age, sex, ethnicity and deprivation, and the list of LTCs were described for the ten included participants. The postcodes of the participants were used to calculate the Scottish Index of Multiple

Deprivation (SIMD), an area based measurement of deprivation reflecting the socioeconomic level in Scotland (Payne and Abel, 2012). In our study, it was presented in deciles of ten categories, from the most deprived (SIMD = 1) to the least deprived (SIMD = 10).

All the participants in this subsample were diagnosed with chronic pain, one or more cardiometabolic diseases, and depression. Regarding cardiometabolic disease, although all types of cardiometabolic diseases were included in the eligibility criteria as outlined above, the included participants had been diagnosed with type 2 diabetes, hypertension or high blood pressure, and heart diseases. This participant profile is consistent with the data analysis in Chapter 5 that the most prevalent cardiometabolic diseases of participants with the comorbidity of these three conditions were hypertension, diabetes and heart disease.

The ten participants were middle- and old- aged people at 50-74 years, with an average age of 63.2 years. The SIMD decile of the participants ranged from 5 to 9, which referred to less deprived areas among the general in Scotland. Eight of the ten (80%) participants were female. In the MAP study, females comprised 70% (56 / 80) of the study sample. Females were found to associate with higher likelihood of the comorbidity in Chapter 5. Moreover, the sampling of these ten participants was not random, and it cannot reflect the average distribution of the characteristics of the population with the comorbidity of chronic pain, cardiometabolic disease and depression.

Table 7-1. Characteristics of the participants

	Age	Gender	SIMD decile	LTC
MAP01	65	Female	7	Pain, CHD, diabetes, depression; RA, asthma
MAP10	67	Female	5	Pain, depression, diabetes; weak bladder, shrink of brain
MAP11	58	Male	9	Pain, diabetes, high blood pressure, depression; osteo arthritis, blood clot on left side near kidneys, kidney stones,
MAP26	65	Female	6	Pelvic pain, back pain, PoTS, depression; EDS, osteoarthritis, coeliac, ME, anaemia, anxiety

MAP29	60	Female	8	Pain, heart disease, angina, depression; RA, bad chest,
MAP34	50	Female	5	Pain, heart disease, depression; osteoarthritis, thyroid, incontinence, hemochromatosis
MAP35	69	Female	8	Pain, collapsed veins in legs, type 2 diabetes, depression; spondylitis,
MAP38	64	Female	7	Pain, sciatica, mytrovalve regurgitation, depression; RA, colitis/diverticular disease, fibromyalgia, diabetes, HS, pernicious anaemia
MAP75	60	Female	5	Pain, diabetes, high blood pressure, depression; RA, stomach problems
MAP76	74	Male	5	Pain, high blood pressure, depression; RA, ulcerative colitis, IBS, sleep apnoea, renal protein in kidneys, enlarged prostate, water retention

Abbreviations: SIMD, Scottish Index of Multiple Deprivation; LTC, long-term condition; HS, Hidradenitis suppurativa; ME, Myalgic encephalomyelitis; PoTS, Postural tachycardia syndrome; EDS, Ehlers-Danlos syndromes; IBS, Irritable bowel syndrome; RA, Rheumatoid arthritis

7.2.3 Ethical approval

The MAP study received approval from IRAS (19/SW/0101), and the ethical approval for research involving already available data of this study was approved by the College of Medical, Veterinary & Life Sciences Ethics Committee for Non-Clinical Research Involving Human Participants (200180073). The original ethical approval allowed the future use of data by other researchers.

7.3 Secondary analysis

The overall research in this chapter is a secondary study with a thematic analysis (Braun and Clarke, 2014) of the interview data. Thematic analysis refers to the coding process and the way the data is interpretated to identify, analyse and report the themes of the lived experience and insights of the participants. The six phases of thematic analysis are familiarization with the transcripts with notes, coding, “searching” for themes, reviewing themes, defining and naming the themes, and finally, writing the report (Braun and Clarke, 2006).

7.3.1 Process of forming the analysis

The proposal of this secondary analysis and the inclusion and exclusion criteria were created independently based on the existing evidence and the findings from the systematic review. The proposal was then discussed with the primary researchers who were familiar with the interview data to see if the available data could feasibly help to answer the research questions.

The transcripts were obtained from the primary researchers who conducted the interview and were available to offer any support regarding any questions about the transcripts.

7.3.2 Coding

7.3.2.1 Line-by-line coding

This study used line-by-line coding (Chenail, 2012) which involved reading the transcript word-by-word and then undertaking line-by-line coding. Each line of the ten transcripts was scrutinised to capture maximum information, and to enable me to immerse myself in the text, and deeply engage with it (Williams and Moser, 2019).

The previous notes of the preliminary codes on the transcripts were essential references, but the official coding process was a new process throughout the scripts based on the coding frame. My supervisor, Professor Sara Macdonald, with rich experience in qualitative studies, who oversaw the analysis of the MAP Study, monitored the coding process but did not participate in the coding directly. The final coding process was conducted by a secondary analysis researcher (myself) independently.

7.3.2.2 Preliminary codes

The first step was familiarisation with the data. Two researchers (my supervisor Professor Sara Macdonald and I) read through one transcript independently to develop a preliminary coding frame. The early reading allowed identification of a series of initial codes to assist in cataloguing and organising the data. Each additional transcript was then repeatedly re-read to enable me to become

familiar with the depth of the data. Critical information was highlighted and summarised in the form of margin notes and memos, which provided the foundation for the creation of a more detailed coding frame. While early codes were informed by the research questions, this did not restrict the identification of new themes and sub-themes. Emergent themes that were judged to be interesting and important but unrelated to the initial research questions were also highlighted (Thomas, 2006, Elliott, 2018).

7.3.2.3 Coding frame development

In this study, a coding frame (Saldaña, 2021) was developed from preliminary codes as a set of themes and structured and generated into categories, sub-categories and codes (Appendix 9).

In detail, any interesting and significant phrases and keywords were extracted comprehensively from the transcripts. When addressing the same topic, different words and phrases summarised from the original texts were debriefed to the same code. For example, “dosette box for the weekly amount”, “delivery of the drugs to nearby pharmacy”, and “tablets after meals” were combined as “management of prescriptions”. In addition to the codes reduced from the phrases in the original text, some codes were a priori and based on the research questions, like the relationship of the diseases.

The development of the coding frame was not linear (Williams and Moser, 2019). Instead, it was cyclical, and the raw notes marked in the margin were iteratively added to the coding frame. This iterative process moved between the initial codes identified from the interview scripts and existing literature to build the coding frame (Linneberg and Korsgaard, 2019). The coding frame was finalised following minor adjustments throughout the coding process. It was then applied to a further sample of the transcripts to ensure that all the relevant data were captured sufficiently.

A long list of codes was then categorised into four broad themes: comorbidity of the three conditions, positive and negative feelings, support, and treatment burden. The complete codebook with the coding dictionary of details explaining the meaning and definition of the codes is attached as Appendix 9. The final

codes covered all the significant information in the data, while only the relevant ones to answer the research questions of this study were interpreted in this chapter (Table 7-2).

Table 7-2. Codebook of the codes illustrated in this study

Theme	Category	Sub-category	Code	Explanation
Comorbidity	Health conditions	Pain	Chronic widespread pain	Self-reported chronic pain all over the body
			Chronic pain	Self-reported pains of more than 3 months/12 weeks
		Cardiometabolic disease	Heart diseases	Self-reported angina, or other cardiovascular diseases
			Diabetes	Self-reported diabetes
			Hypertension	Self-reported hypertension or taking medication to high blood pressure
		Depression	Depression	Self-reported depression or taking antidepressants
	Comorbidity	Relationship of the diseases	Relationship of the diseases	Diseases that led to development of other diseases, or made other diseases more severe
		Polypharmacy	Balancing the drugs	Co-prescribing multiple medications and finding the balance; different diseases restricted each other's treatment
			Side effects of drugs	Dependence and bad reactions of the medication
	Awareness	Health professionals	Holism	Health professionals being holistic and dealing with all conditions together
			Communication with other health professionals	Communication between health professionals about different conditions
		Patients	Communication with patients	Communication and understanding between health professionals and patients

Feelings	Negative feelings	Biographical disruption	Enslaved by the diseases	Reluctant to try new things, giving up struggling after the seesaw battle, feeling uncontrolled and just tolerating
			Dependence	Cannot accept the fact of becoming dependent when previously an independent person, cannot see one's value and meaning of life

7.3.2.4 Software for qualitative analysis

Qualitative data analysis application NVivo 12 was used to assist with the cataloguing and organisation of the data (Basit, 2003). The transcripts obtained were already cleaned. The files were formatted to fit the software and imported to NVivo 12. The nodes were set in NVivo according to the coding frame. The transcript texts were coded with the nodes and automatically aggregated to the corresponding categories and themes.

7.3.3 Interpretation of the data

In the interpretation phase, OSOP technique (Ziebland and McPherson, 2006) was used to illustrate with extracts and report the themes of this study. Each sub-category from the coding frame (Table 7-2) was read through, and the issues were identified from data extraction and illustrated by exemplar quotes. The thematic materials were weaved together to give a narrative of the participants' daily experiences living with the comorbidity of the three chronic conditions of interest.

After the coding, discussions with the primary researchers about the themes at this stage ensured the findings from this secondary analysis were unique and did not overlap with the primary research. Living with the comorbidity of the three conditions would touch on treatment burden and capacity, which is the focus of the primary research. To avoid overlapping with the MAP study and ensure the current study was distinct from the MAP study, treatment burden and capacity were deliberately not covered in this secondary analysis. Developing the research proposal, generating the coding frame, conducting the line-by-line coding, and building the themes were independent of the primary research. The following analysis and report were also independent of the primary research.

All the components were combined to provide a complete story of the daily life and experience of living with the comorbidity and how participants felt, to identify their insights on the relationship between the three conditions and provide some clues for implications for policymakers.

7.4 Results

The main overall narrative is about the experience of living with the three conditions of interest, and insights into how the participants consider these conditions together as "holism" were provided – both from their own understanding and how they perceive the care they receive from healthcare professionals. Results are presented according to the themes, categories and codes presented in Table 7-2.

7.4.1 Living with the three conditions

In this theme, the participants' perceptions of each of the three conditions individually are introduced before going on to discuss the experience of all three together and their perception of how collectively they impact everyday life.

7.4.1.1 Pain

Pain was reported as having a major impact and clouded all aspects of participants' everyday lives. The pain described by the participants came from several causes: physical damage and harm, complications of diabetes or rheumatoid arthritis, or pain without a specific cause. Participants' pain sites included low back pain, pelvic pain, hand pain, shoulder pain, knee pain, abdominal pain, hip pain, joint pain, foot pain, head pain and CWP.

The participants provided vivid descriptions and used language that illustrated the relentless nature of pain. The participants described chronic pain as "*horrific pain*", "*all the time*", "*horrendous all the time*", "*no better at all*" through the years, "*the biggest problem*" among the lots of health issues, and "*every day*", "*no escape from it*", "*sorest and hottest*", "*on fire*", "*stiffness*", "*never stopped*", "*constant*", "*wakes me up in the night*", as the following extracts illustrate, pain could be perceived as all-encompassing:

> I've been wakened all night, I can hardly get a sleep……it's the pain, and it's just everything is going through my head……I've even dreamt that what you call it, that I've been on fire and all that……It's horrible. (MAP34)

Here the participant describes the impact of pain on sleep patterns. Severe pain was not uncommon, and many participants had been experiencing pain for a long time. In the following extract, a participant, who has been living with pain for 22 years, describes how pain affects sleep:

> The pain, yeah, I can't lie. If I lie on my left-hand side, I feel sick right, and if I lie flat, my back is too sore, and then I go to……go to the right-hand side, and I can't, I just can't' get comfy on my right-hand side so I'm tossing and turning all night and I'm awake you know what I mean. (MAP11)

This participant used comparisons to contextualise the extent of pain in her daily life during pregnancy, even more severe than labour pain, as in the following extract, where the participant discusses childbirth:

> But I decided right, I'm not having any relief this time and because I don't care, the pain that I have been through for this pregnancy is nothing compared to this……to have a baby; I'd rather have about ten babies in a row than go through 9 months of that whole misery of being pregnant honestly, I mean that's the way I honestly felt. (MAP26)

Two participants reported CWP, which was notably different from other specific chronic pains. According to their descriptions, CWP differs from multiple sites of pain.

> All over……widespread, yeah, widespread……between the pain in my fingers and the swellings and the pins and needles, it was horrendous. So, my neck gets quite sore as well. I think your whole body sees when you are getting a flare-up. I feel it all over. (MAP01)

> It's everywhere. My back……everywhere, but I don't know if it's something to do with the thyroid or arthritis itself. Because even when the thyroid has still got pain and you know you feel absolutely drained with it all. That's the way I'm actually feeling just now, tired, out of breath and all that. (MAP34)

The participants provided rich details about their feelings and the major adverse impact of pain on their daily lives. The constant and strong unpleasant feelings caused sleep disturbance, restriction of daily functioning and mobility.

7.4.1.2 Cardiometabolic disease

In contrast to the descriptions of chronic pain, participants provided fairly routine discussion of management of cardiometabolic disease, often talking about prescriptions and treatment, appointments, and the importance of a healthy lifestyle and diet in the interviews.

> Last week I got a phone call last week to say that my blood sugar, the pharmacy up in my surgery……when I was up there. Right, she phoned me last week to say that they got a letter back in from the diabetic clinic and wanted to up my medicine for my diabetes to……to two in the morning and two at night to see how that helped. So that started this Monday too. (MAP11)

There is an exception for more unusual conditions, like Postural tachycardia syndrome (PoTS), a relatively rare heart disease (Low and Sandroni, 2012) and the symptoms of which are difficult to disentangle. In such conditions, which are less commonplace, it took the participant a long journey to get the correct diagnosis and treatment. Diagnostic overshadowing happened when the rushing heartbeats as the symptom of cardiovascular disease were misleading with the similar symptom of a mental health condition, and the abnormal blood pressure was misleading for hypertension.

> I think that was why I was diagnosed initially with, well I was diagnosed with anxiety early on, because my heart was racing so much so obviously I had PoTS from way back but I didn't actually feel anxious that was, that was the thing that really puzzled me you know I used to get dizzy and I would feel my heart going like rapid you know just crossing a road or you know going my shopping.

> You know when I was kind of in my early 20s when they were saying oh your heart rate is awful high have you been rushing, my blood pressure would be high, so I was put on blood pressure pills but that actually just made things worse you know. So then I was given another pill to, to, do you know what I mean? So I ended up with all these pills which I didn't really realise why you know what I mean. (MAP26)

The participants talked little about living with cardiometabolic disease, where the discussion tended to be a restricted discussion of the clinical management of the disease, which for most participants, was well-managed.

7.4.1.3 Depression

Depression was discussed briefly in the interviews, and the participants reported their use of antidepressants and reluctance to take the prescriptions. Depression was described as something invisible, as the following extracts illustrate:

> It just happens. I don't even, I wouldn't say I don't notice it anymore but it's just there. It happens and you deal with it. (MAP01)

A participant described her feeling of being depressed and crying for nothing sometimes.

> That's why I just want to, and I don't want to go anywhere, just stay home. I don't feel to go outside, everybody says to go for a walk and this and that, but I don't like to go, you know, I don't' know why just to like to stay home. I'm doing nothing, you know, but because it all helped me, but I don't know why like before I was taking the tablet, I was crying a lot. Just start crying for nothing. Sometimes I do as well at home when I'm at home, you know. Just start crying for nothing; everything is okay, but……I feel sad, so sad, really……tablets help me, you know tablets help me [tearfully]. (MAP10)

The participants mainly talked about medication, of prescription and tablets, but not counselling or other treatments for depression. There seemed a general reluctance to take antidepressants among the participants, as the following extracts illustrate:

> Those antidepressants I got put on, yeah, I feel as if they were trying to force me to take them, and they weren't doing any good. And it's funny when I spoke to the pain clinic doctor, and he knew exactly what one it was, and he's given me a leaflet about a different one to give to my doctor, and he's going to write to my doctor and let her know. (MAP35)

> I don't really know. I've never really made enquiries about it, you know, if there's any support, I know, I know when I lost my wife, I knew myself I was suffering from quite a bad depression. Dr XX came out to see me, and she wanted to give me some medication, but I refused. I say no, no I say I'll struggle by, so that's what I do, you know I just sit in the house now, I very seldom would go out, you know. (MAP76)

> In fact, I'm on duloxetine; I've just remembered about that duloxetine that's a wee antidepressant, it's not a high, high dose, but I just take

> it; I was very, very loathed to go onto any sort of antidepressants, you know you hear that many bad things, and my twin sister she had, she used to work in the hospice but she had a complete mental breakdown just before, in fact, she was 41, 42, she died at 45 you know. (MAP38)

one participant thought the COVID-19 pandemic had the most impact on his depression.

> Probably the only thing I could say is like my depression did get worse. I don't think it was particularly because of COVID because I don't do anything that I haven't done prior to that if I was honest, but I think it was the isolation more than that. I couldn't go and see friends or anything like that, so I did phone my GP for that, and she was very good actually and increased my medication, and so far, it seems okay. (MAP75)

This section shows that cardiometabolic disease was discussed and described mainly in relation to managing treatment, appointments, and medication. However, when the participants talked about chronic pain, they mainly described their subjective feelings about pain and the overwhelming impact of pain on their daily lives. Although depression was discussed in less detail, participants did hint at the role of depression in their daily lives and described their feelings about antidepressant medication. The accounts thus showed the variable effects of different types of conditions on participants daily lives.

7.4.2 The comorbidity of the three conditions

As well as discussing the experience of the three conditions individually, participants often discussed the conditions interchangeably and described their understanding of the relationship between the three conditions and which ones have a particular impact on their lives.

7.4.2.1 The relationships between the diseases

The participants talked about the pain from cardiometabolic disease and provided detailed explanations of the mechanisms behind it, as the following extracts illustrate, alluding to how one condition could lead to another:

> I just, I couldn't walk to the front door without being in total agony. I had been told it was my diabetes. And I had just had enough. (MAP35)

> And I think that's part of the whole PoTS EDS (Ehlers-Danlos syndromes) thing because apparently the reason they think that I've got PoTS is because of the EDS, because they say that EDS gives you flexible muscles and joints, so you're getting extra pull and play if you see what I mean which gives you the pain. But they're also associating that now with if you've got that then stretchy arteries so, so it means that in PoTS like the, the blood is pulling down with the veins being too elastic, the veins aren't you know, like they're supposed to kind of pulsate I think, right that's what the doctor explained to me, and that helps circulation go up to your head and your heart, back to your heart. So because that's not working my veins are too stretchy, the blood pulls down so the heart starts stressing out so it starts to beat faster and to try and get the blood back and up to your head to stop you blacking out or getting too dizzy. So as I say the, so that gives me I think migraine because of blood vessels in your head or, you know what I mean or a different, or constantly changing like getting old, so I think that's what makes me prone to migraine but things like codeine just, unfortunately, makes it worse because they make me more constipated which is you know what I mean, it's a vicious circle. (MAP26)

Some participants believed that their current medication and treatment could be identified as a potential cause for other conditions. As the following extracts show:

> That was about two years ago, just about two years ago but Dr XX told me there he's wanting me to phase out the Nabumetone because that and high blood pressure, blood pressure medication causes heart disease, he said long term, and I thought: "I've been on that for about 27 years," and I had high blood pressure tablets, medication for years, this is the first I've heard that it can cause, so that's maybe what's caused that and this is why he's trying to take that away you know, but he says: "Just phase it out," phase it out and we'll see how you go but I think that's, that's everything……But I was having really bad problems with one leg, the left side in particular but that was the, down to the Amlodipine see the blood pressure tablet I was on because of swelling and as soon as I came off that that's all, I got put onto the wee water tablet it's all went away they went: "Well, oh for goodness sake, this is doing the job of like the Amlodipine that's been, and it's better for your heart as well," they said: "all that swelling was not good you know it wasn't good," so I still as I say, I have, always have swelling, you know, puffy in my hands and that, but the pain is not as bad. (MAP38)

> ……I was put on a different high blood pressure tablet because of the side effect was it helped with the pain of rheumatoid. (MAP75)

Biographical disruption is a theoretical concept in medical sociology that describes chronic illness fundamentally breaking people's social and cultural

experience, leading to disruption of their self-identities and the trajectory of their lives (Bury, 1982), and it could, in turn, play a role in the onset of other illness like depression (Williams, 2000). In the interview, participants talked about their subjective understanding of the causal effect of pain and depression. Depression was often inextricably linked with pain, the relationship of which was described as related to increased dependency. Based on the participants' narratives, chronic pain is one of the major causes of loss of independence. The independence blow leads to the biographical disruption which then leads to or exacerbates depression.

Regarding the timeline of the diseases, some were diagnosed with chronic pain before being diagnosed with depression. They believed the depression was a result of living with pain; either because of the feelings of frustration caused by living with pain or because they perceived that living with pain made them dependent on others, as the following extracts illustrate:

> It's coping with the pain. It becomes very frustrating because you never tell anybody, and you never voice it, and it can be pretty frustrating, but apart from that, if I didn't have the pain, I probably wouldn't be depressed. (MAP01)

The son of one participant believed that chronic pain significantly restricted his mother's ability to participate fully in routine daily activities, therefore, increasing her reliance on others. Her reduced independence negatively impacted her mental wellbeing. It also indicates that the biggest problem was not necessarily what people saw as the most important condition but rather the comorbidity of chronic pain and depression in this case. This reminds us not to see the co-occurrence of two or more LTCs simply as the sum of the chronic conditions. Instead, the comorbidity interacts to have an integral impact on the participants.

> See mum is a very independent person she's never been like this before coming from my young age I've always seen her working and to have her lying on a sofa all day is a bit difficult……Hence the reason that's the next solution that pain reliever thing. So everything that's happening with her is all going towards pain relief. There is no actual medication which is fixing the problem, they are all coping mechanisms and that's all it is. And the restriction and the mental effect on her, which is probably the worst problem that she's got, doesn't help because if you are someone that does everything

> themselves and doesn't rely on anybody that does take a toll. You know, so that's her biggest issue. (MAP01 Son)

A similar experience was shared by others of feeling down about the restrictions on their abilities because of pain which clearly led to biographical disruption. One participant described himself as "a big man", and it was tough for him to accept the fact that he could no longer engage in activity that he once enjoyed and was no longer that handy, which was a dreadful harm to his independence. Such enforced changes also contributed to his depression which he attributed to the experience of pain:

> I would say that (my depression a result of pain) aye because I was quite handy, I'm handy with my hands you know what I mean I could turn myself to plumbing work, electrical work, tiling, wallpapering, you know what I mean, and I'm having to pay people to come in and do it you know what I mean……that gets me down having to pay somebody to do it for me. It gets me down badly; you know what I mean. (MAP11)

Similarly, another participant described the relationship between pain, depression and dependence. She once had several jobs to do and "*really liked the feeling of independence*". Then she started to have the symptoms and "*had to give that up*" at the age of as early as 25. She linked the presence of pain and her issues with her mental wellbeing.

> See if I never had pain and all that and I could do things I want to do, then I would be all right. But it's because when I want to when I do things, I get a lot of pain, and that brings me down more……(I can't) do the things that I used to do. I can't do it anymore. (MAP34)

Some participants did not talk about the relationship between chronic pain and depression directly, but they showed low mood and negative feelings towards the disability from pain.

> I did not have time to do it during the day and I thought: "I'm not letting standards slip because I'm on my own," that was a pride thing, so I was on the go constantly and then when that happened I couldn't even change my bed, I couldn't lift a, even the kids' beds, you know the wee single duvet, I was exhausted after doing it, and I was in pain and I'm saying: "Oh this is awful, how am I going to, how can I manage with this?" you know what I mean? I was up three flights of stairs you know, and: "Oh my God this is awful even trying to put a washing out" or I, I didn't, I didn't think I was depressed I really didn't think, I

> thought I was fine, but it really did, it got me down, but I am being honest, I mean I cried but I cried at night, I didn't let anybody see me crying and I was like: "I can't cope with this, if this is the way I'm going to be forever how can I cope with all the things that I need to do?"……Oh that's years, years because I worked with kids in the school, primary school and you just couldn't, you know there was no way that you could work with them because they were young and different ages right up through primary school, but after-school care and stuff and just gave them you know, and the summer holidays and you were taking them, taking them on trips and stuff and it's like: "Oh my God it takes me all my time to manage my own kids," you know, but I was sad that I had to give it up you know, I really was but, and I wasn't qualified for anything else and I just did not like, I don't like computers and stuff so that's. (MAP38)

The participant described herself as a "*perfectionist*" and found it "*annoying*" to depend on others.

> You understand that I was a, I loved my DIY. I could do everything, plastering, the whole lot. I can't do anything now. It's so annoying, I laid this floor and it took me 3 days when normally it would have took me a day……And I don't like it (the way it's laid). (MAP35)

For others, the diagnostic sequence was the opposite, first with a diagnosis of depression, followed by pain. Even if depression developed before the chronic pain, participants believed that pain impacted their depression and may exacerbate their symptoms. As the following extracts illustrate:

> It (diabetes) is just all over the place; it could be down to the pain……do I have mental health problems through this, through the pain? And I went yeah because I've worked all my days and now all of a sudden, I can't work, and it's terrible……that (depression) was before (my sore arm) yeah……yes the pain makes it (depression) worse. (MAP35)

> It's not the pain that caused the depression; I think it's just like circumstances when I was a child and then there was a lot of things going on then that I think that's actually……if it's if my pain is really bad, my mood does get very low because I get angry with myself that I can't do simple tasks like putting washing on……you know or make a bed……So I suppose from that point of view, it does……impact on my mood as well, I suppose. I've never thought about it, to be honest. (MAP75)

Some participants recognised the relationship between pain and their broader mental health, and the antidepressants were prescribed not only for depression but also for bodily pain of this participant. This is somatisation, that

psychological distress experienced in the form of somatic symptoms (Al Busaidi, 2010).

> The mental health nurse has said to me that until I get my pain sorted, it's a waste of time going to see them. The pain clinic doctor basically says the same thing. He'll try and get the pain sorted. I need to get the GP to put me on antidepressants. They might help my mood, which might help the pain as well, and the pain will help my mood……I must admit, see, after seeing him, it gave me a wee bit of hope. Somebody has actually explained some stuff to me, and he says that he was going to suggest sending me to a psychologist. And I must admit nobody has put the pain down to the mental health problems. It's - you are told you are like this because you are not working or anything like that, you are inactive, but the reason I'm inactive and all that is because of the pain. So, get that sorted and see what happens.

To summarise what was mentioned in the transcripts about the relationship between the three conditions, pain could be developed from cardiometabolic disease as a complication; depression could cause bodily pain through somatisation; pain could lead to or exacerbate depression or low mood as the limitation of capacity and mobility harmed the independence of the participants. Among the three conditions, chronic pain appeared to be the most important condition compared to the other two conditions from the participants' descriptions mainly because of the direct negative impacts on quality of life.

7.4.2.2 Index condition

Comorbidity usually refers to the combination of an index disease which has the major impact and one or more secondary diseases by some researchers (Boyd and Fortin, 2010). Different opinions of the condition with the most impact from the health professionals and patients were discussed in this section.

The participant "complained" that the health professional attributed all the problems to diabetes. However, it was not the central health management issue for the participant.

> Yeah, because he's a diabetic doctor and yes, I've seen a specialist in diabetes at the hospital and even he says they will, everything goes to diabetes when you have got diabetes……The diabetes, I actually don't care about it anymore……I just, I've got that much going on. I just……It's not a priority at the moment aye. (MAP35)

When the participants were asked about the condition that bothered them the most, some discussed how chronic pain had the biggest impact on their daily life. They described pain as a direct struggle, as the following extracts illustrate:

> The pain is the worst……It's the biggest problem, yes. (MAP10)

> Well, the pain and what do you call it the thyroid trouble, and just having the toilet and all that. (MAP34)

Besides cardiometabolic disease and chronic pain, depression was relatively invisible to both the participants and health professionals and there was not much data about the management of depression except for comments about taking medication.

The participants talked much less about living with cardiometabolic disease and depression. In comparison, pain was discussed in a more detailed way. The ways in which the participants described the three conditions individually show that pain results in the greatest burden on their daily lives. Nevertheless, from the overall discussion of the diseases, it is difficult for participants to really disentangle their illnesses. Instead of distinguishing the one most influential "index condition", it is more important to see the combined conditions as a whole.

7.4.3 Awareness of the comorbidity

This section identified the conflict between treating the comorbidity in isolation as single diseases by health services and the need for holistic treatment.

7.4.3.1 Holism

Participants discussed a need to adopt a more holistic approach to their care and regard all conditions simultaneously. Holism here refers to the understanding that both participants and healthcare professionals have of the need to consider all three conditions (chronic pain, cardiometabolic disease and depression) collectively.

Participants talked about how some health professionals saw their conditions as a whole rather than as single diseases. Often this related to their satisfaction with the health professionals, and one participant praised the "holistic package" she received from primary care, as the following extracts illustrate:

> They do annual reviews on everything, heart, you name it, they do it……they don't treat the one, they come, and they say how is everything else, you know if you are going in for treatment for six weeks, and you are going once a week for six weeks for your hands they will ask you if there is anything else that is bothering you, it's holistic……it's a really super clinic. It's good……the clinic itself is extremely good. As I said, they run the holistic approach……They are pretty good. (MAP01)

Participants expected a more comprehensive understanding of holism. Several participants discussed the holism issue with regards to polypharmacy, in terms of drug interactions and balancing the side-effects of drugs.

> So first of all for my, my prostate I'm taking Altasa 400mg I take 6 a day then high blood pressure I'm on candesartan I've got 2 tablets one is a 16mg and one is an 8mg, aspirin, finasteride for my prostate, I take, take 2 tablets for, what's the other one, a tamsulosin, I take for my stomach I'm taking omeprazole and for, that's not high blood, simvastatin I'm taking that at night and I think oh I'm taking methotrexate and I take that once a week 8 tablets on a Monday and to combat any sickness or anything like that I take folic acid except a Monday, I think that, I think that's everything. (MAP76)

> Yeah, yeah, because they have to check because there are some tablets that conflict with the ones I'm on at the moment. (MAP11)

Participants often emphasised the need for professionals to adopt a more holistic approach, considering all conditions together rather than as single diseases. While some participants praised health professionals, others felt that they had to be more proactive and encourage health professionals to consider all conditions together. The following extracts illustrate the variability in participants' experiences:

> Like I went to the doctor, I was at the doctor's today. I'm a diabetic, and I had to proactively ask loads of questions in order to get an answer which I understood right and for them to understand what actually my individual problem is, my lifestyle, how my day goes, how I eat my food, what physical exercise I do because all these things matter when you are diabetic. But they don't ask those questions,

> you know, so if they were asking. If they were to ask my mum how much physical exercise you do, she does nothing. You know, because she finds it really, really difficult. You know, what conditions are you living in, is the house cold, is it hot? This is the kind of stuff that she has to tell them, or they don't ask any questions, and sometimes she forgets. (MAP10 Son)

> No, I can't fault them. Actually, I feel they're really good, and I mean, there was Professor XX, but it took him to see that you know about that tablet that has been causing, so I wasn't too happy about that, I thought you know that should have been picked up a long time ago because he did say it was over long term, he says: "and you have been on this a long time" so I felt maybe that should have been picked up even with my GP, but more so like the hospital, that that can cause heart disease. (MAP38)

Where a holistic approach was lacking from the treatment, participants noted that this could be frustrating and an extra burden for patients when there was a failure to appreciate the "whole problem" entirely by health professionals:

> But I think there is an added pressure given to participants, which doesn't help. Because they (health professionals) are struggling with the whole problem as it is, and then you are telling them to do stuff that they can't really do. I mean, in mum's case, that really affects her by far……but again, it's such an individual, subjective thing, you know, it's quite difficult to sort of give an overall answer for everything, so I understand where the doctors are coming from, but in her specific case, you can see that that doesn't help. (MAP10 Son)

One of the difficulties of being holistic was that the participants engaged with several health professionals, and their commitment to a holistic approach was inconsistent. Indeed, even when there was an acknowledgement of the value of a holistic approach, not all professionals acted on this.

> Yeah, they probably do because it depends what nurse you get. They will maybe say to you like how's your joints and that been and that kind of thing, but they don't go into anything. That's not what they deal with. (MAP29)

These participants had the awareness of being holistic from their own experience living with the comorbidity, not from health professionals or education. Furthermore, they would be dissatisfied if they were not treated holistically by the health services.

7.4.3.2 Communication with health professionals

Lack of continuity, fragmentation of care and inadequate communication between different health professionals often resulted in participants' treatment plans changing with little explanation. Participants, therefore, questioned the changes and were unconvinced by the need for change. Questioning strategies or feeling undermined in treatment decisions may risk adherence, as the following excerpt illustrates:

> Well, it's like, although I'm under a consultant……and like when it was four monthly, six months or whatever I never saw the same person, I've never seen the same person in all the years, every time I've went it's been a different registrar I think what they are or whatever and I always, sometimes I think if I say to them, this last doctor suggested this, this and this and they have got a different idea so that can be quite irritating thinking well this person has set out a plan for me and then they have just decided that they are not going to follow that plan they will just do something else……so sometimes I feel as if there is no communication with them all. (MAP75)

The fragmentation of care resulting from a lack of communication between healthcare professionals led some to question recommendations and plans. Still, ultimately participants were guided by how they felt:

> Yet one doctor says no, and one doctor says aye, so who do you believe? I believe the other one because I've still got my breathlessness, you know what I mean, so that's it……I still get wee pains there, too, so I know it's still there. I know it is still there, and I've got a wee pain there and right at the back sore too, so I know it's still there. (MAP11)

Some participants felt there were gaps between their knowledge and that of health professionals. Such communication gaps between health professionals providing care to the patients could be confusing and dispiriting for participants. Participant accounts reveal the need for them to engage with healthcare professionals throughout the system, as the following excerpt illustrates:

> They phoned me up with results, and I got a letter through, come down and see about your blood results and then when I go down they don't know what I'm talking about, but they've sent a letter out you know what I mean? Then you've got to explain to them; right, I had a blood test here. How did that come back? Oh, aye, you need to and then like, I get high blood pressure, so I've got to go down and say will you take my blood pressure and see if it's still high and all that kind of

> stuff. But some of them, I don't think, understand what you are going through, to be quite honest. (MAP34)

It was not uncommon for participants to repeat their symptoms and medical history to many different healthcare professionals who used a siloed approach, focusing on single disease treatments. Lack of continuity was clearly a major problem for the participants.

> ……if you're seeing different people, if you're not consistent with the same and you're not, even the nursing staff, if you're seeing different nurses, you're kind of having to go through everything with them that you're on, say, and then they'll say: "Oh right, I didn't realise you had this", and I thought: "Right okay, well you can't know everything," but I think it would be better if you had the, you know, that can't be the case, so you know, you understand people move on and all the rest of it but sometimes I do feel that you're kind of having to say everything to them. (MAP35)

> I find that strange sometimes when it's different doctors that phone you because sometimes I, I tell them I've got to remind them about things, see it's the same as when you go to the clinics it's, it's different doctors……(MAP76)

> Well, I don't think they always sort of confab with each other sometimes I feel as if there is a kind of breakdown in communication between all the different, you know like I was put on a different high blood pressure tablet because of the side effect was it helped with the pain of rheumatoid. But during the COVID, I couldn't get it. So, I had to go to another one, and I don't even think my GP was aware that that's why I was on that, you know, it wasn't just because it was a blood pressure tablet. It was like there was a reason for it, and they just couldn't get it. (MAP75)

The participants need extra workload to repeat their situation for multiple health professionals, yet the they usually had insufficient time to communicate fully.

> Well, it all depends on what hospital they go to and what GP they have to go to. Know what I mean, some GPs, you are in and out in five minutes. You don't get enough time to talk to GPs about pain and all that so. (MAP11)

Participants had little control over their care or treatment, even when they felt the treatment was insufficient. As one participant account demonstrates – there is a need to be proactive:

> Right without question, because obviously, they are professionals. And it was only recently; I think maybe last year or earlier this year, we found that she was taking antidepressants for about two years. So we questioned that. Why is she on this and basically whatever diagnosis they done, which we disagreed with because we feel that instead of tablets, there are other methods that could be used to help her, you know to stay, you know, sort of active mentally, and we took her off of them which made a big difference……if you question them, but you have to proactively do it, this is basically what I'm saying. So it's not really; you've got to be very proactive. (MAP10 Son)

Without adequate awareness of the comorbidity, healthcare provided by health professionals was deemed inadequate by the participants.

7.5 Discussion

7.5.1 Overview of findings

This study, to our knowledge, is the first to examine the everyday lived experience of those managing the comorbidity of the three conditions.

To address the evidence gap identified in the systematic review, a sub-set of data in the MAP study was drawn on in this chapter to explore and characterise the everyday lived experience with the three conditions of interest: chronic pain, cardiometabolic disease and depression, and potentially provide information for policymakers (Ziebland and Hunt, 2014). The results described in this chapter have added to the knowledge obtained from the systematic review and data analysis from the previous chapters and supplemented the primary research as it has provided novel information that the experience of living with the three conditions which was described individually, along with the participants' insights on the relationship and awareness of holistic approach of the comorbidity.

7.5.2 In context with previous literature

No previous literature describes the everyday lived experience of managing the comorbidity of chronic pain, cardiometabolic disease and depression, so this research is novel.

In this study, the constant and severe pain had a major impact on participants' everyday lives. Participants described restrictions on mobility and daily activities (e.g. combing hair and sitting on a chair) and sleep disturbance caused by chronic pain. Chronic pain has been reported to negatively impact daily activities, personal relationships, and economic status (Hassett et al., 2014, Leadley et al., 2014). Patients with severe physical pain may lose the capability of Activities of Daily Living (ADLs) (Edemekong et al., 2021) and essential skills required to care for themselves independently. Sleep disturbance is a common complaint of chronic pain, and it is possibly associated with pain in a reciprocal way: the pain causes poor quality of sleep and disturbs the continuity, and the poor sleep exacerbates symptoms of pain in turn (Smith and Haythornthwaite, 2004).

Participants complained of repeating their symptoms and medical histories to different healthcare professionals, resulting from the siloed approach of single disease treatments and lack of continuity of care. These challenges have been discussed in the literature previously, namely that individuals with cardiometabolic disease which usually comorbids with other LTCs receiving siloed care could experience suboptimal treatment and find it more burdensome to access multiple health services (Reiter-Brennan et al., 2021).

Participants and their health professionals had different views of the condition with the most impact, and it is important to consider the patients' values and needs when providing care and advice. Health professionals traditionally dominated healthcare provision, and patient-centred care (PCC) has emerged as a new approach (Delaney, 2018). PCC does not have a standardised definition, but it is agreed that healthcare should consider patients' preferences and values embedded with holism (Ekman et al., 2012). A qualitative analysis of patients who self-reported chronic heart failure suggested the need to improve treatment and quality of PCC (Gallacher et al., 2011). Management following PCC requires consideration of co-occurrence of LTCs, especially a combination of physical and mental conditions (Izadi and Schmajuk, 2022).

This study adds new insights into living with the comorbidity of all three conditions of chronic pain, cardiometabolic disease and depression. Participants' insights on the relationship between chronic pain, cardiometabolic

disease and depression were important to understand to inform future healthcare strategies. Within the combination of these three conditions, chronic pain was described as the most important condition directly impacting participants' daily lives and related to cardiometabolic disease and depression. Chronic pain was associated with cardiometabolic disease as an important and common complication and associated with depression often as a result of the biographical disruption experienced secondary to becoming more dependent. Nevertheless, seeing the combined conditions as a whole is more important than focusing on the condition with the most impact. The participants with the comorbidity emphasised the importance of holism and desired the health service to be holistic.

7.5.3 Strengths and limitations

The strengths and limitations of conducting secondary analysis in general have been detailed in Chapter 3. During the pandemic of COVID-19 when collecting original data was unavailable, with limited resources, money and time (Clarke and Cossette, 2000, Corti and Thompson, 1998), the availability of data from the MAP study presented an opportunity to conduct a secondary analysis to address the evidence gaps identified in the previous chapters of this thesis. This secondary analysis is supplementary to the MAP study and has made good use of existing data and re-analysed the data to understand the lived experience with the comorbidity and gain participant insights on the comorbidity. This has provided new knowledge and insights which are distinct from those uncovered in the MAP study.

Limited data on depression could be because of the limitation of the nature of the secondary analysis, that the questions in the primary research were not explicitly designed to ask about depression (Tripathy, 2013). It could also be the participants' lack of awareness and attention to this condition, so they did not have much to discuss.

The sample size in this qualitative study is relatively small. Ten semi-structured interviews from the MAP study were available to describe the everyday experience of living with the comorbidity of the three conditions. The acceptable and sufficient sample size for qualitative studies has been discussed

in Chapter 3. In summary, there is no standardised guidance for justifying sample size decisions, and a larger sample size is generally preferable. Inadequate data could make it challenging to identify the patterns and potentially miss important features or introduce bias (Guest et al., 2006). However, it is the information power of the data, not merely the quantity of sample size, that matters (Malterud et al., 2016). The scope of the study, the nature of the research question, and the quality of data determine the adequate sample size altogether (Morse, 2000). Practical issues of funding and time should be taken into consideration as well (Morse, 2015). Therefore, although we would like to investigate more participants, we used the interviews that were available for eligible participants, and the sample size of this study is acceptable. It is a single case study recruited from a homogeneous population to understand the personal lived experience of individuals. The data from primary research was extremely rich and allowed the secondary analysis to examine new research questions. Moreover, given the scarcity of evidence in this area, it is worth examining the available interviews, even though the data is limited.

7.5.4 Initial proposal

Prior to the COVID-19 pandemic, the initial proposal of the qualitative study was to conduct an original study collecting original data from health professionals and patients. However, due to the pandemic of COVID-19 and the suspension of data collection in all research studies, the original plan for a qualitative component study required complete re-evaluation. Finally, the research was changed to a secondary analysis of the MAP study as this chapter presents.

The initial proposal was developed from a poster presentation at NAPCRG (North American Primary Care Research Group) annual meeting, North America's largest primary care research conference, in 2019. Considering that hundreds of clinicians and primary care researchers would come to the conference, I used the opportunity to present my research to conduct an engagement activity with the help of my supervisor. It was a brilliant opportunity to get insights from the clinicians and primary care researchers to form the proposal for the qualitative study of this thesis.

The health professionals who passed this poster were asked to dot their views about the comorbidity of chronic pain, cardiometabolic disease and depression. The backgrounds of the research topic and findings of existing knowledge from the systematic review study (Chapter 4) were presented together. The common concerns raised by the comorbidity included drug interactions, adherence and treatment burden. A question about what issues were considered important and whether they were discussed when treating someone with the comorbidity was asked. Stickers of coloured dots and sticky notes were provided to make a choice and leave a note as a supplement (Figure 7-1).

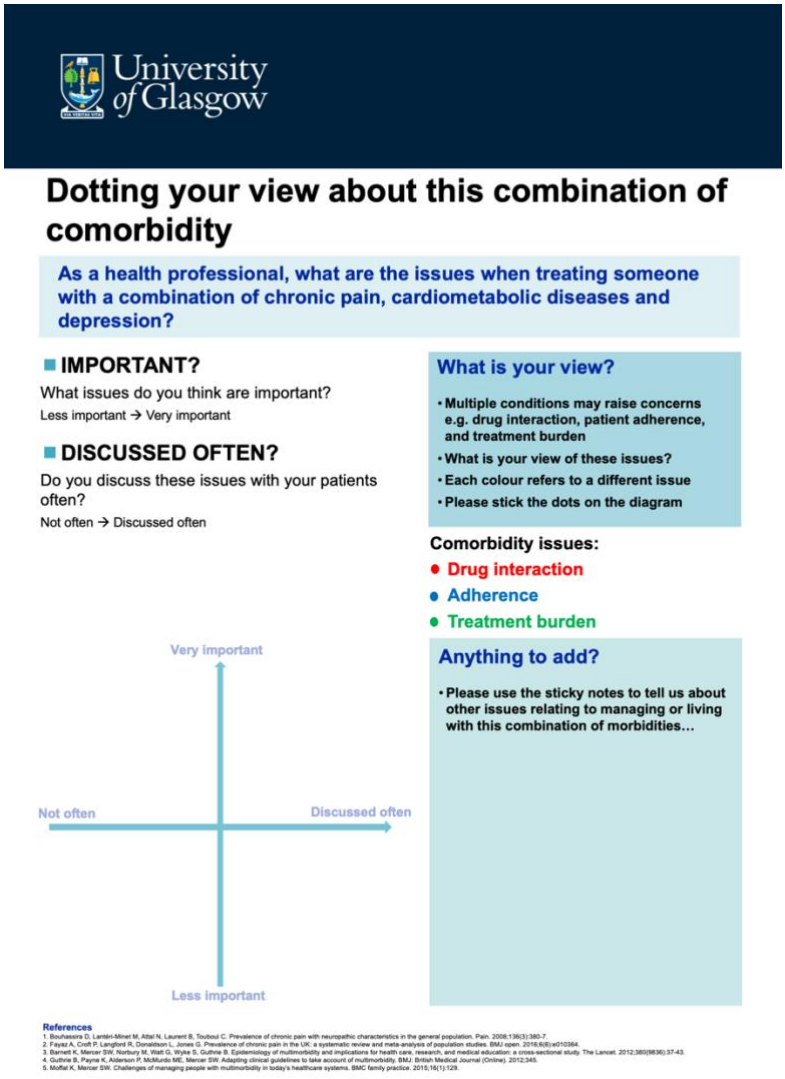

Figure 7-1. Interactive poster on NAPCRG annual meeting in 2019

More than fifteen people participated, and the results from the poster on-site transferred to the digital version diagram are presented in Figure 7-2. Almost all the dots were in the first and second quadrants, that the participants thought these issues were of importance, and thus implied that they were aware of the comorbidity issues. More dots were in the second quadrant that the participants thought were important, and they discussed them with their patients often. We are especially interested in the dots in the first quadrants that the issues were believed to be important, but they did not discuss them with the patient often. This reflected how the issues were neglected in the clinical practice. Treatment burden was the most neglected issue but believed to be very important (Dobler et al., 2018).

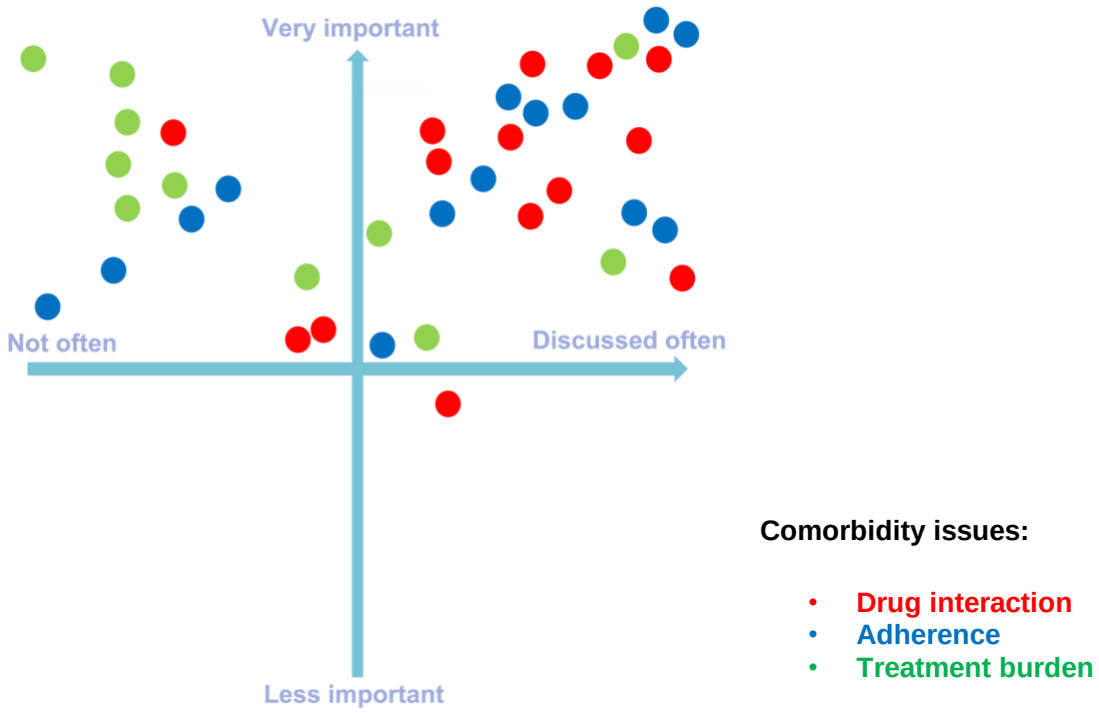

Figure 7-2. Diagram with dots on health professionals' insights of comorbidity issues

Three participants of the poster activity shared their insights to supplement the comorbidity concerns: patients' personal value-based health goals; patients' fears, available resources, and own experience; soliciting patient priorities or concerns.

The participants suggested that the goals of health outcomes should be based on the patient's personal values. Personal values were found to play an important

role in the decision-making (Ariail et al., 2015). It was suggested to consider patients' fears and their own experiences and provide available resources. To solicit patient priorities or concerns is also about patient-centred care, that the health service should be based on the patients and their needs (Oates et al., 2000, Epstein and Street, 2011).

Although it was not a rigorous study design, this activity collected valuable and inspiring insights from health professionals and gave a clue about healthcare provision for potential comorbidity concerns. When there is a chance, future research involving focus groups of health professionals investigating the insights of their knowledge on the comorbidity concerns in the clinical practice and potential interventions for improvements would be helpful.

7.5.5 Conclusion

To our knowledge, this is the first qualitative study that examined the everyday lived experience of living with the comorbidity of chronic pain, cardiometabolic disease and depression. It has highlighted the severe negative impact of chronic pain on quality of life and ability to function independently. Further studies with more original data from patients and health professionals investigating the impact of the comorbidity are needed with a particular emphasis on how best to manage invisible disabilities such as chronic pain.

Chapter 8 Discussion

8.1 Introduction

8.1.1 Overview of this chapter

This chapter brings together the findings from the four studies of this thesis: the systematic review (Chapter 4), cross-sectional study (Chapter 5), cohort study (Chapter 6) and the qualitative study (Chapter 7) to understand the comorbidity of chronic pain, cardiometabolic disease and depression from different viewpoints. The implications of comorbidity from the findings are discussed in the context of the existing literature. The strengths and limitations of the whole thesis are then discussed. The findings are then related to clinical practice and policy to suggest how to reduce the adverse impact of the comorbidity and raise awareness of the challenges faced by those living with the combination of the three conditions. Finally, further research is suggested, and conclusions drawn.

8.1.2 Fulfilling the objectives of the thesis

The exploration of the comorbidity of chronic pain, cardiometabolic disease and depression was examined using a multimethod approach that consisted of a systematic literature review, two quantitative data analyses using UK Biobank, and a secondary qualitative data analysis. Together, findings from the four phases have answered the research questions and fulfilled the objectives of the thesis.

This thesis was interested in the co-occurrence of chronic pain, cardiometabolic disease and depression. It was already known that the three chronic conditions are common among the population individually (Treede et al., 2015b, Breivik et al., 2006, Balakumar et al., 2016, Reiter-Brennan et al., 2021), and the impacts of the combination of two out of the three conditions were well recognised (Reid et al., 2011, Sattar et al., 2020, Holden, 2000). The first research question of the thesis was answered by a systematic review of peer-reviewed journal articles involving the combination of all three conditions that was carried out to provide an overall picture of the existing literature on the comorbidity (Chapter 4). The narrative analysis identified 15 publications (13 studies) that involved

all three conditions. However, only one study examined the prevalence of the comorbidity of interest, explicitly involving chronic pain, angina and depression and there were no studies examining the patient experience of living with this combination of conditions. Thus, it is clear that this comorbidity has not been well researched despite several studies having the data available to do so (D'Amato et al., 2016, Gore et al., 2005, Klit et al., 2011). The health impacts and patient experience of this pattern of comorbidity remain unknown. The systematic review provided a comprehensive investigation of the existing evidence on the comorbidity. The findings highlighted the evidence gaps in the investigation of the comorbidity and underlined the need and direction for further analysis using quantitative and qualitative methods.

As the existing literature about the comorbidity was extremely limited, the second research question was how common the comorbidity was among the general population and what are the sociodemographic and lifestyle factors associated with having this combination of conditions. In this phase, a quantitative study used UK Biobank, a large biomedical resource that includes over 500,000 participants from the general population in the UK (Chapter 5). The cross-sectional study examined 8,640 participants with the comorbidity, representing 1.73% of the total study sample (N = 500,313). Sociodemographic and lifestyle factors associated with the comorbidity were examined using logistic regression models. Factors associated with a higher risk of comorbidity included: age 45 years and above (particularly aged 55-59 years); being female; living in more deprived areas; being from an ethnic group other than white; current or past history of smoking; and being overweight or classified as having obesity. Participants who reported drinking alcohol and undertaking any physical activity had a lower risk of the comorbidity compared with non-drinkers (or drinking on special occasions only) and not doing physical activity.

The third research question of the thesis was answered by quantifying the effects of the comorbidity on health outcomes at the population level. UK Biobank baseline data was linked to national mortality registers, and HES, and followed for around ten years. The descriptive analysis showed the incidence of death and MACE was 6.00% and 3.57% in the total study sample (N = 500,313), respectively. The survival analysis examined a subsample (N = 128,066) of

participants with all three conditions of the comorbidity and no additional LTCs, compared to healthy participants with no LTCs. In the Cox regression model, compared with healthy participants, the participants with the comorbidity showed an increased risk of death (HR 2.10, 95% CI: 1.84-2.41) and MACE (HR 2.13, 95% CI: 1.79-2.52) after adjusting for potential confounding sociodemographic and lifestyle variables.

Finally, to answer the fourth research question, a secondary qualitative analysis was conducted to explore the everyday lived experience and insights of ten participants with the comorbidity, from a larger study examining treatment burden and capacity in people with chronic pain and additional LTCs. Using these transcripts allowed the examination of the impact of the comorbidity at the individual patient level. Participants described their lived experience with these three conditions in combination and their difficulty in disentangling them. Their insights indicated that chronic pain was the condition with the greatest negative impacts on participants' daily lives. Chronic pain was described as a common complication of cardiometabolic disease and potentially led to or exacerbated depression. The combination of conditions should be seen as a whole and treated holistically.

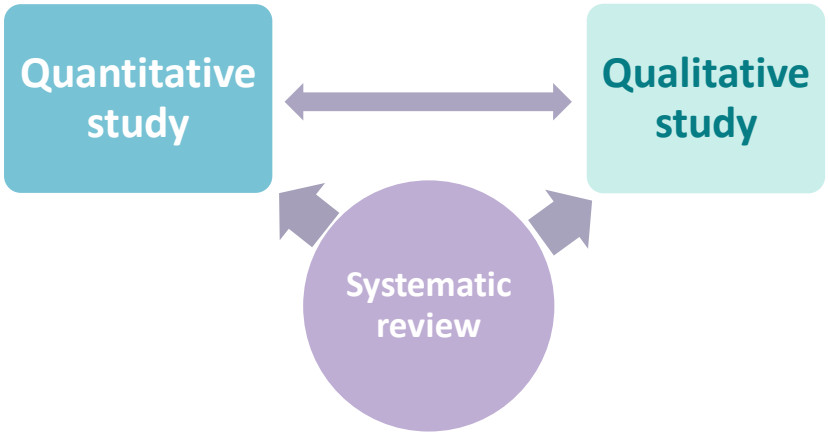

Figure 8-1. Relationship of the multimethod studies in this thesis

The multimethod approach used in this thesis provides a comprehensive picture of people with the comorbidity. Together, all the four phases complement each other and highlight a crucial evidence gap. The relationship of the multimethod studies is presented in Figure 8-1.

8.2 Implications of the comorbidity

In this section, the implications of the comorbidity of chronic pain, cardiometabolic disease and depression from the four studies are discussed in context with previous studies.

8.2.1 Concept of comorbidity

8.2.1.1 Definitions

The concept and related theoretical knowledge of comorbidity were detailed in the Background (Chapter 2). In summary, Feinstein introduced comorbidity in 1970, which refers to the presence of one or more long-term conditions (LTCs) co-occurring with a specified index condition (Feinstein, 1970). This definition is still commonly used (Harrison et al., 2021, Boyd and Fortin, 2010). In public health, the index condition is believed to play the most crucial role among the comorbid LTCs. In clinical practice, the index condition is the condition that medical specialists focus on (Starfield et al., 2003). However, interestingly work in this thesis suggests that participants were most focused on the condition that had the greatest negative impact on their lives. In this instance for the comorbidity of chronic pain, depression and cardiometabolic disease, it was very clearly the chronic pain that seemed to dominate patient accounts.

The definition of comorbidity has developed alongside the growing prevalence and research on the co-occurrence of LTCs. Another way to define comorbidity, as the co-occurrence of several specific diseases, has been used by many researchers (Verbrugge et al., 1989, Seeman et al., 1989, Cornoni-Huntley et al., 1991, Jakovljević and Ostojić, 2013), and it was the definition used in this thesis. It is to be noted that this definition of comorbidity is distinguished from multimorbidity, which refers to the presence of two or more LTCs *without* reference to particular conditions (Boyd and Fortin, 2010).

8.2.1.2 Justification of the definition

This thesis contributes to the development of the concept of comorbidity by examining the co-occurrence of chronic pain, cardiometabolic disease, and depression which was the combination of interest explored in this thesis. There are two ways to see this combination: one as the index condition in conjunction with the other two as secondary conditions; or three conditions together without an index condition defined. This thesis used the latter one, and the findings support that this definition is more reasonable, as detailed below.

In quantitative studies

A large population-based study in Scotland (N = 24,024) identified in the systematic review was the only study that examined the prevalence of the co-occurrence of all three conditions (van Hecke et al., 2017). Chronic pain, cardiovascular disease and depression were examined as being equally important, and no index condition was defined. However, in some other studies, it was clear that the authors saw cardiometabolic disease as the index condition, chronic pain as the complication condition (i.e. diabetic neuropathic pain and post-stroke pain) or outcome condition (Harno et al., 2014, Ziegler et al., 2014, Hoffman et al., 2009), and depression as an outcome condition (D'Amato et al., 2016, Selvarajah et al., 2014, Hoffman et al., 2009) or predictor (Bouhassira et al., 2013, Choiniere et al., 2014, Klit et al., 2011). The participants were recruited as, e.g. “diabetic patients” and “stroke patients”.

People with cardiometabolic disease were the population of interest for the researchers; chronic pain and depression were two factors or outcomes examined in this population. Cardiometabolic disease has received the most attention in research that involved these three conditions, most likely as it is one of the leading causes of death globally (Harikrishnan et al., 2018), while chronic pain and depression are rarely directly fatal (Holden, 2000).

In qualitative studies

The quantitative studies in Chapters 5&6 did not identify any of the three conditions to be more important in terms of health outcomes and found these

three conditions were associated with each other from the logistic regression. The qualitative study further emphasised the need for researchers and health professionals to consider the meaning of comorbidity and index conditions from a patient perspective. In the interviews, some participants complained that the diabetic specialist attributed everything to diabetes. When describing lived experience of their conditions, the participants were not able to disentangle the conditions.

The findings of patients' perspectives break the common perception for a need for an index condition in comorbidity. There could be more than one index condition in different circumstances; different conditions could dynamically play this role, and the index condition may be fluid. There could be more potential ways to define comorbidity based on the need of the patients rather than the priorities of researchers or clinical practice. It would seem important therefore to put greater emphasis on patient perspectives and the issues that are important to the individual being treated when determining management or treatment plans.

8.2.2 Neglect of the comorbidity

This thesis identified a lack of research into this relatively common comorbidity.

8.2.2.1 By researchers

There was a lack of attention to the comorbidity of chronic pain, cardiometabolic disease and depression amongst the published research literature, despite research into the combination of a single disease and two diseases being well recognised and researched (Bahramali, 2016, Saravanan and Krishnaraju, 2013, Holden, 2000).

The systematic review identified 15 articles (13 studies) that involved all three conditions but failed to provide much knowledge of the comorbidity. Except for one study (van Hecke et al., 2017), all other studies were not initially designed to examine the combination of these three conditions altogether. Some studies only examined the prevalence of depression in people with cardiometabolic disease and chronic pain - the three conditions were not examined together

(D'Amato et al., 2016, Ziegler et al., 2014, Gore et al., 2006, Krein et al., 2005, Sadosky et al., 2013, Widar et al., 2004).

These samples were available for further investigation of the comorbidity, but the researchers neglected this issue and only focused on the examination of people with the index condition. The reason for neglecting the combination of the conditions could be because comorbidity is a relatively new concept, and not enough attention has been paid to this issue, or it could be because research disease specific charities and other funders have, until recently, prioritised supporting single disease research funding.

8.2.2.2 By health services

Lack of awareness of the comorbidity of chronic pain, cardiometabolic disease and depression in health services produced what was reported as an additional burden on participants in the secondary qualitative analysis.

In the interviews, participants discussed the responses of health professionals to the combination of chronic pain, cardiometabolic disease and depression, and treating them holistically. The participants did not explicitly use the term comorbidity, but they acknowledged the collective impact of the chronic conditions simultaneously from their experience of living with them. Where applicable, participants were satisfied when health professionals used a holistic rather than a siloed approach to treat their conditions. However, other participants were dismayed when health professionals failed to provide comprehensive healthcare. Instead of receiving the knowledge of managing the combination of multiple LTCs collectively from health professionals, some participants had to proactively encourage their health professionals to consider all conditions together. There was an extra burden on the participants due to the lack of continuity and fragmentation of care which meant they had to interact with different health professionals who provided an inconsistent commitment to a holistic approach to managing the combination of conditions. This resulted in participants having to repeat their stories, resulting in limited time to communicate thoroughly with their health professionals, during time constrained consultations.

Insufficient treatment from siloed healthcare adds burdens for patients to access multiple health services (Reiter-Brennan et al., 2021). The comorbidity was reported to be neglected by health services, providing healthcare in fragmentation, which cannot sufficiently fulfil the needs of the patients with the comorbidity.

8.2.2.3 Common phenomenon

The comorbidity of chronic pain, cardiometabolic disease and depression were shown to be common, yet had received inadequate attention from researchers and health services.

Existing literature

Researchers have examined the prevalence of multimorbidity using UK Biobank data (McQueenie et al., 2021) and the association between different LTCs (Zemedikun et al., 2018), sociodemographic and lifestyle factors (Gallacher et al., 2018), but not the particular combination of chronic pain, cardiometabolic disease and depression. Equally researchers have examined the effect of multimorbidity on health outcomes but again have not focused on the effects of this specific combination of conditions (Jani et al., 2019, Hanlon et al., 2022). Only one study of another large population-based data identified from the systematic review showed that the prevalence of the comorbidity of chronic pain, angina and depression was 1.8% in the examination of Generation Scotland (van Hecke et al., 2017).

Findings from the thesis

The examination of prevalence of the co-occurrence of chronic pain, cardiometabolic disease and depression that has been undertaken within this thesis adds to the currently sparse literature on this topic. From the cross-sectional analysis (Chapter 5), the prevalence of the comorbidity was 1.73% among the UK Biobank population. Given that the prevalence of depression was 7.18% and the prevalence of depression in those with cardiometabolic disease was 2.62%, 1.73% is an important proportion. Depression in this data analysis was defined as a self-reported chronic condition diagnosed by a doctor or self-

reported medication of anti-depressants, and participants with only depressive symptoms and low mood were omitted. In addition, the self-reported nature of depression in this study could result in a potential underestimation of the prevalence of depression (Hunt et al., 2003, Vigo et al., 2016), and the same could be true for chronic pain as being only self-reported (Johannes et al., 2010). Thus, the actual prevalence of comorbidity presented here could be an underestimation of the true prevalence. In addition, as outlined earlier UK Biobank is a volunteer cohort that has been shown to be healthier than the general population suggesting that the data source used could be leading to conservative estimates of prevalence for the combination of the conditions (Hanlon et al., 2022).

8.2.3 Impact of the comorbidity

The health effects of the combination of conditions were explored through the population-based study and the examination of qualitative data regarding the everyday lived experience of the impact of the comorbidity.

8.2.3.1 At the population level

Existing literature

UK Biobank has been used to examine the relationship between multimorbidity and health outcomes like mortality (Jani et al., 2019, Jani et al., 2018, Gallacher et al., 2018, Hanlon et al., 2021), COVID-19 (McQueenie et al., 2020a), MACE (Hanlon et al., 2022, Hanlon et al., 2021), hospitalisations (Hanlon et al., 2021). While modification effects have been examined , such as the association between lifestyle factors and life expectancy (Chudasama et al., 2020), physical activity and mortality/life expectancy (Chudasama et al., 2019), frailty and mortality (Hanlon et al., 2018a) in people with and without multimorbidity. These studies have investigated adverse health outcomes of the co-occurrence of multiple LTCs in general, but not specific to any certain combinations. UK Biobank has also been used to examine the comorbidity of different cardiometabolic diseases, along with mental health conditions, in some studies (Brailean et al., 2020, Atkins et al., 2020, Mak et al., 2021, Siebert et al., 2016,

Whitelock et al., 2021), but none of these UK Biobank studies has examined the health effects of the comorbidity of interest of this thesis.

Findings from the thesis

This thesis added new knowledge from the survival analysis of the UK Biobank cohort. The comorbidity was found to be statistically associated with increased risk of adverse health outcomes, with a two-fold higher hazard ratio of death and MACE compared with healthy participants, after adjusting for confounding factors (age, gender, ethnicity, Townsend score, smoking status, alcohol intake frequency, physical activity and BMI).

8.2.3.2 At individual level

The qualitative study, which provided details of an individual's daily life, brought numbers to life and added new knowledge on the impact of the comorbidity on patients' daily lives. Kleinman highlights four areas that are helpful for understanding the impact of chronic illness on individuals: 1) the patients themselves; 2) the circle of their family members living together (partner, children and parents) and the wider family circle (siblings, grandchildren); 3) social circle at the community level (friends, colleagues); 4) the society level (financial support and social welfare) (Kleinman, 2020). These areas are useful when applied to our understanding of comorbidity at the individual level.

Living with the comorbidity

It was recognised in the qualitative study (Chapter 7) that living with chronic pain, cardiometabolic disease and depression had a significant impact on daily life.

Pain was described as a horrible feeling by many participants and described as being even more severe than labour pain by one participant. CWP was described as notably different from multiple sites of pain. A major characteristic was the constancy and persistency of the pain. Some participants illustrated that it was neither cured, nor subsided, and had no remission even with medication. It was

something horrendous all the time with no escape. The actual duration could be much longer than the three months typically regarded as the minimum duration in defining chronic pain. Some participants described experiencing pain for decades, and several started to develop symptoms from an early age (as early as in their twenties).

Living with chronic pain was not described as only living with the horrible and constant feeling itself but also by the resultant challenges and changes brought about by the presence of pain. The comorbidity of chronic pain, cardiometabolic disease and depression collectively had an impact on mobility and capability and the ADLs (Edemekong et al., 2021).

With the limitations of mobility and capacity, some participants had to give up their careers and social activities. Their marriage and relationships were affected, and their partners had to assume a caring workload and emotional burden. Their body shapes were altered due to disease, changing diets, and fewer physical activities. There was also some stigma that the participants' reduced abilities were embarrassing for others, making the participants more reluctant to socialise with people. Some symptoms of pain and depression are invisible, so it may be difficult to get others' understanding of what they are suffering (Kleinman, 2020). Most importantly, their independence was severely curtailed, damaging their self-esteem. They felt frustrated, panicked, hopeless and even desperate. Supporting the theory of chronic illness causing biographical disruption (Williams, 2000), as discussed in chapter 7.

Treatment burden

Treatment burden, not a deliberate focus of the qualitative study (Chapter 7), was inevitably touched on by the participants when discussing the three conditions, especially cardiometabolic disease. The treatment burden of these three conditions collectively is based on the individual burdens of single diseases but not simply the sum of the cumulative burdens.

As noted, the most common cardiometabolic disease experienced by participants in the qualitative study was type 2 diabetes. The management of diabetes (Shrivastava et al., 2013) involves medication such as insulin or other tablets

using a dosset box (Bunker et al., 2011), monitoring blood sugar, special diets, physical activities, appointments with doctors, and the care of complications, like diabetic retinopathy (Lee et al., 2015b) and diabetic foot problems (Jeffcoate and Harding, 2003), which were all described by the participants in Chapter 7. The management of high blood pressure is mainly to improve lifestyle, monitor the BP and take the medicines to control blood pressure. When the participants talked about the treatment of angina, they mentioned using inhalers or sprays.

Patients with type II diabetes are required to change their eating habits and follow a strict diet to control their blood sugar levels (Hu, 2011), which was described in Chapter 7. Patients with depression may have dizziness, a common side effect of anti-depressants (Kim et al., 2016), making self-management harder. Participants with the comorbidity had to visit different clinics and communicate with various health professionals. In addition to primary care, they also attended secondary care services like diabetes clinics and other specialists. Regarding the communication between primary and secondary care, the participants made appointments to see their GP, were put on the waiting list for surgery and waited to be phoned or receive an appointment letter for specialists and complained of poor communication between health professionals making their experiences of care less satisfying.

Economic burdens

Comorbidity has also been shown to place economic burdens on those living with illnesses (Mensah and Brown, 2007). In the Global Burden of Disease study, in terms of years lived with disability (YLDs), since 2007, the leading causes have been low back pain, headache, and depressive disorder (James et al., 2018). Except for cancer, cardiovascular disease and diabetes, which are the most costly chronic illnesses in the United States (Kahn et al., 2008). Living with illnesses often requires care and support from family and social networks. It may worsen family members' professional work performance, affect their career development, and lead to wage loss for the family (Hsieh et al., 2020).

In the UK, the NHS provides medical services for free. In addition, financial supports like Universal Credit, Personal Independence Payment (PIP), Disability

Living Allowance (DLA), and Employment and Support Allowance (ESA) are available to cover the daily expenses of some patients. Thus, there may not be much direct cost for the patients and their families. However, there may be indirect costs like family members' informal care and transportation to access different clinics (Hsieh et al., 2020). However, there are issues with eligibility and stigma to living on financial support (Jun, 2022). There are burdens of applying for financial support, which usually involves a lot of paperwork and forms to fill, and some also require interviews. Moreover, there may be problems of inequity in assessing the eligibility for financial support (Pybus et al., 2019). An analysis of 5.3 million carers in the UK examined the impact of informal care on families and found that 2.1 million informal carers are living in poverty (Aldridge and Hughes, 2016).

8.2.4 Understanding the comorbidity

This section discusses further thoughts on the understanding of this combination of conditions. Understanding of the comorbidity was shallow, and further exploration is needed.

8.2.4.1 Relationship between the three conditions

The relationship between the three conditions was implied from different viewpoints.

From the systematic review

Diabetic neuropathic and post-stroke pain were commonly identified in the combination of chronic pain, cardiometabolic disease and depression from the systematic review study (Chapter 4). In the studies identified from the systematic review, patients with diabetes or stroke reported a higher prevalence of depression (D'Amato et al., 2016) or more severe symptoms of depression (Gore et al., 2005) with pain or a higher risk of chronic pain with depression (Klit et al., 2011).

From the quantitative study

In the cross-sectional data analysis of the baseline of UK Biobank (Chapter 5), the prevalence of the combination of chronic pain and cardiometabolic disease was 15.42%. Among participants with depression, 36.49% of them also self-reported cardiometabolic disease. Furthermore, logistic regression models were fitted to examine the relationship between the three conditions. After adjusting for confounding factors (age, gender, ethnicity, Townsend score, smoking status, alcohol intake frequency, physical activity, BMI, and any additional LTCs), participants were found more likely to self-report depression if they had self-reported chronic pain or cardiometabolic disease; a higher risk of chronic pain was also found in participants with depression or cardiometabolic disease. The findings were consistent with previous studies identified from the systematic review.

From the qualitative study

In the qualitative study (Chapter 7), pain was described as a common complication of cardiometabolic disease, like diabetes. Nevertheless, the discussion of the relationship between these three conditions mainly focused on chronic pain and depression. This thesis adds new qualitative empirical insights into the physiological links between chronic pain and depression.

Although depression and chronic pain commonly occur together, their relationship is controversial (Bair et al., 2003). Somatisation is the somatic expression of psychological distress like anxiety and depression, connecting mental health issues with physical symptoms (Al Busaidi, 2010, So, 2008). The symptoms of depression can also be physical, and pain is one of the common presenting symptoms of depression (Trivedi, 2004). Vice versa, the frustration and low mood caused by continuous pain may lead to depression. Chronic pain was described by the participants in Chapter 7 to directly impact sleep patterns, as examined in previous literature (Katzman et al., 2014). While sleep disturbance is also associated with depression (Franzen and Buysse, 2022). Both depression as a precursor to pain and pain as a precursor to depression have been observed. The relationship between the conditions is not clearly in one direction. Furthermore, this suggests we should see the combination of the chronic conditions holistically rather than simply as single conditions.

In the qualitative component of this thesis, according to the discussion of participants, chronic pain had such a great impact that their independence and other self-identities were disrupted, losing the capability of work and even ADL, and their life track was changed, which was biographical disruption (Bury, 1982). The biographical disruption then caused or exacerbated depression, as discussed in previous literature (Williams, 2000).

8.2.4.2 Role of the three conditions

Cardiometabolic diseases usually have clinical investigations to show the existence of the illness. Unlike cardiometabolic diseases, chronic pain is a subjectively unpleasant feeling only the participants could "see" or feel, especially if the chronic pain does not have a specific cause. The prevalence of chronic pain was the highest (43.70%) among the three conditions in the UK Biobank baseline data. The participants from the qualitative study (Chapter 7) described the pain they suffered as a variety of extremely unpleasant feelings, with the sense that this was unrelenting. The treatments provided did not seem to take away the pain entirely, so they could not get rid of it and had to live with this pain, as outlined above in the section on the impact. Chronic pain was described as having the most significant impact on their daily lives.

Among the three conditions, depression was relatively invisible in the interviews. In the qualitative interviews, participants discussed much about chronic pain and cardiometabolic diseases. However, there was limited data about the experience of managing and living with depression in the interview, and the detailed diagnosis process, symptoms, feelings, management, and insights were not clear. In the quantitative data analysis, the age distribution of participants with depression differed from that of participants with chronic pain or cardiometabolic disease. A higher prevalence of chronic pain and cardiometabolic disease was observed in older participants but fewer elder participants aged over 60 years had depression.

8.2.4.3 Comorbidity as a whole

The work outlined in this thesis shows that the comorbidity of different chronic conditions should be considered collectively rather than in isolation. Taking a

holistic approach requires health professionals to consider all conditions, treatment and management, as well as the unique context of patients' lives. A lack of holism in treating and managing patients may result in a waste of health services, unnecessary return visits to clinics, and an increased treatment burden. Exploring the relationship between the diseases reminds us not to see the co-occurrence of two or more LTCs simply as the sum of the chronic conditions. Instead, the comorbidity is experienced as a whole.

8.3 Strengths and limitations

The detailed strengths and limitations of the four studies have been discussed in each chapter. In this section, the multimethod approach will be appraised.

The biggest strength of using a multimethod approach is that this thesis comprehensively explores the comorbidity of chronic pain, cardiometabolic disease and depression from different perspectives. The systematic review initially identified almost ten thousand citations before screening. The quantitative study analysed a large dataset of half a million participants with linked health outcomes data for approximately ten years. The qualitative study supplemented the systematic review and the quantitative study to provide insights into the individual level experience of the comorbidity. The exploration was conducted progressively, and the studies also supplemented each other. The findings of combining multiple approaches would be more robust than either method individually, and the added knowledge was more than the sum of the individual methods (Malina et al., 2011).

Mixed-methods or multimethod approaches have been used in the existing literature to examine multimorbidity or comorbidity and to care for patient's needs: a mixed-methods study protocol combined a qualitative descriptive study and RCTs to explore innovations in patient-centred care for those with multimorbidity (Stewart and Fortin, 2017); a mixed-method case study quantified the health outcomes and described the cases as a qualitative approach to understanding patients' health needs, in addition to the disease-oriented care model (Lai et al., 2021). The multimethod approach of this thesis was a suitable methodology to explore comorbidity as a novel and complex research topic, which could be analysed quantitatively and qualitatively.

This thesis made the best use of available resources to examine different but closely related research questions. The systematic review collected existing evidence, the quantitative studies examined UK Biobank, an open access resource (Sudlow et al., 2015), and the qualitative study examined transcripts from the MAP study and re-used the data, which is a good way for making use of existing resources (Long-Sutehall et al., 2011, Cheng and Phillips, 2014). The approaches chosen also to enable the work to be completed during a pandemic which was a major challenge during this PhD.

The main limitation of the multimethod approach is the controversial integration and validity of combining various methods. The differing paradigms underpinning quantitative and qualitative research were outlined in Chapter 3. The epistemological and ontological assumptions in these two approaches are conflicting and may not be compatible. The reality of knowledge can be seen in both perspectives, as both paradigms exist (Sommer Harrits, 2011). It matters more how to combine the methods. The findings from each approach were independent on their own and combined to supplement each other. It was a good practice to apply the multimethod approach and embrace its benefits without breaking the assumptions of each approach.

8.4 Challenges under the pandemic of COVID-19

The main challenges faced during the pandemic of COVID-19 were outlined in Chapter 7. The original plan was to collect primary data with health professionals about the management of the comorbidity through qualitative methods such as interviews or focus groups. However, the pandemic restrictions required a complete re-evaluation of the fourth study. The availability of data from an ongoing study within my research group allowed me to engage in a secondary analysis, and therefore achieve the original research objectives at least in part. A secondary analysis of data relating to the individual experience of living with the comorbidity including their perspectives of healthcare management was undertaken. A secondary analysis is judged to offer an appropriate and beneficial alternatives to primary data collection (Cheng and Phillips, 2014). It is of value to "re-use" the data (Long-Sutehall et al., 2011), considering the feasible sources to create new knowledge under the influence of COVID-19.

There were also challenges from working from home to deal with the data. UK Biobank contained personal data that should be accessed under the ethics guidance. During the pandemic, the datasets were temporarily accessed through my personal computer and had to be deleted every day to ensure the safety of the personal data. This added difficulties to the continuity of conducting a complex and large amount of data analyses.

The negative impact of COVID-19 on mental health, through lockdowns and lack of peer support, also resulted in inefficiency and generally slowed progress.

8.5 Significance for clinical practice and policy

The findings of this study have significant implications for both policy and practice. Comorbidity should not only be for researchers as a concept in theory but also a practical issue for the patients, their caregivers, family members and social network, health professionals, and health service policymakers (Valderas et al., 2009). The issue of comorbidity is clinically relevant as highlighted by the conference engagement activity outlined in Chapter 7.

The interviews in this study highlight the need for a shift in healthcare policy towards a more holistic approach to care. The health outcomes of increased death and MACE associated with comorbidity, underscore the importance of addressing comorbidity to improve the management and treatment. Often there is little continuity within health care systems, with participants seeing different professionals at each visit. Some participants reported from the qualitative study that they felt required to repeat their stories afresh with each visit. Effective communication between different health professionals is crucial as it impacts on the quality of care that can be provided by the health professionals and impacts on the work patients have to do to overcome communication deficits and the effects of discontinuity. In the interviews, participants anticipated that health care professionals would understand and appreciate their circumstances and have a holistic view of their needs and were disappointed to find their treatment often fell short of expectations in this regard. The medication and investigation history are linked electronically in the NHS in the UK. Yet not all the information is accessible to all the health professionals with whom the patients are in contact. It is important to make patients feel

understood, a lack of a holistic approach regarding all conditions simultaneously from health services was raised by participants in the qualitative study (Chapter 7) as a key difficulty. These findings suggest that a comprehensive, integrated approach to care, which addresses all comorbid conditions, is necessary to effectively manage the health of individuals with comorbidity.

The neglect of comorbidity in both clinical practice and research highlights the need for increased awareness and education among healthcare providers and patients. For the patients and their caregivers, communication and being acknowledged by health professionals were the most important resource of disease and treatment information, and potential resource to obtain the comorbidity knowledge (Chapter 7). Moreover, there are other potential resources like leaflets in the clinic, health courses, books, the internet and social networks but most of these remain single disease focused. An important initiative in supporting patients with comorbidity is the intervention of treating and managing the comorbidity and providing information resources on the comorbidity (something which is often available at present). For example, the comorbidity could be acknowledged in clinical guidelines (Boyd et al., 2005). Actions could be taken to raise awareness of the comorbidity for practice and policy.

8.6 Future research

This thesis has laid a foundation for exploring and understanding the comorbidity of chronic pain, depression and cardiometabolic disease, examining the impact on health outcomes and patients' daily lives. The comorbidity has been neglected and further dissemination of findings should raise the awareness of patients, clinical practice and policymakers. The findings from the thesis and the limitations discussed above suggest directions for future research.

Although UK Biobank data is already a very comprehensive dataset with rich information, variables are limited as it is an existing dataset. For future research, quantitative work examining additional variables from different datasets could be considered. In the current study, we have examined the relationship between the comorbidity and sociodemographic and lifestyle factors and used these sociodemographic and lifestyle factors as covariates in the

examination of the relationship between the comorbidity and death and MACE. These variables were chosen based on the availability within UK Biobank. However, it is important to note that there may be other variables and datasets that could provide additional insight into these relationships and from an international / differing ethnic group perspective. For example, future research should consider incorporating additional variables from other big datasets like China Kadoorie Biobank (Chen et al., 2011) and HUNT study in Norway (Drøyvold et al., 2006) to further understand the complexity of this relationship and provide more comprehensive insights. In addition, the use of interaction variables would potentially identify new or moderating factors of the health effects of the comorbidity and could give a clue for the development of intervention and prevention points. It would also be interesting to explore further the longitudinal relationship between factors associated with the comorbidity like physical activity/BMI that where we have not been able to explore the cause-effect relationship with cross-sectional data in UK Biobank.

In this study, the subgroup analysis of participants with diabetes and other types of cardiometabolic diseases did not show statistically significant associations between the comorbidity and health outcomes. The subsamples were too small to have adequate power for calculation. Future research should utilize subgroup analysis to identify potential heterogeneity in different combinations of the comorbidity and to allow detailed examination and understanding of subgroups within the CMD and chronic pain groupings, which again could improve clinical application of the findings.

Participants described the responses of their health professionals in Chapter 7. Future research involving focus groups with health professionals investigating their perspectives on the comorbidity in clinical practice and potential interventions for improvements would be helpful. Further exploratory qualitative studies should be conducted to deepen our understanding of the comorbidity. Research should extend beyond patients and health professionals to include families, caregivers and policymakers. Such research is needed to help to determine how to improve management and support for this participant population.

Further exploration of biographical disruptions that stem from the comorbidity is recommended along with further investigation of the beliefs and attitudes of patients dealing with life-changing illnesses. The original study collecting primary data did not focus on the management of depression so further research examining the comorbidity that placed greater emphasis of the experience of living with depression as part of the comorbidity or other combinations of chronic conditions would help us better understand whether the management of depression was neglected. Additional insights from such further research could inform development of a unique system of managing the comorbidity holistically as a guidance for the health services and patients.

Unclear terminology (i.e. the duration of pain not clarified) and a variety of measurements of the health conditions (i.e. self-report data, medication record, hospitalisation) lead to different estimates and barriers to comparison (Katona et al., 2005). Further research to compare the estimates of different measurements of chronic pain, cardiometabolic disease and depression could examine whether the prevalence was underestimated.

Regarding the study method, observational studies (Benson and Hartz, 2000) of cross-sectional and cohort studies were conducted. This work did not seek to identify the potential evidence-based interventions for supporting patients with the comorbidity, and this warrants further exploration. RCTs could be designed to ascertain the efficacy of an intervention for minimising the burden and adverse impact of the comorbidity. The interventions may be more physical activity and losing weight to have a lower BMI, and training and education about the knowledge of comorbidity. Corresponding mixed-methods or multimethod studies to examine the impacts and interventions from different viewpoints would be worth conducting as well.

The findings were concluded from the examination of this specific combination of comorbidity. Whether other exemplars of the co-occurrence of multiple prevalent single diseases would have similar findings requires further exploration, to ensure a deeper and broader understanding of different patterns of comorbidity.

8.7 Conclusion

This thesis used a multimethod approach comprising systematic review, quantitative and qualitative studies to explore the comorbidity of chronic pain, cardiometabolic disease and depression. The co-occurrence of these three conditions was prevalent and associated with adverse health outcomes. The everyday lives of individuals with the comorbidity were described, and insights into the holism of treating the comorbidity were discussed. Together, these studies complement each other and highlight a crucial evidence gap. The awareness of the comorbidity by health professionals is inadequate for some patients. There are potential actions for health service provision to take to improve clinical practice and policy to raise awareness and better support patients with the comorbidity.

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Appendix 3 - Search strategy in Ovid MEDLINE

1. exp Chronic Pain/ or ((chronic adj3 pain*) or (persistent adj3 pain*)).tw.
2. (neuralgia or "neuropathic pain*").tw.
3. "musculoskeletal pain*".tw.
4. 1 or 2 or 3
5. exp Cardiovascular Diseases/ or "cardiovascular disease*".tw.
6. exp Heart Diseases/ or (heart adj3 (disease* or disorder*)).tw.
7. exp Rheumatic Heart Disease/
8. exp HYPERTENSION/ or ("high blood pressure*" or hypertensi*).tw.
9. "ischaemic heart disease*".tw.
10. exp Pulmonary Heart Disease/
11. exp Cardiomyopathies/ or exp Cardiomyopathy, Hypertrophic/ or exp Diabetic Cardiomyopathies/ or cardiomyopath*.tw.
12. exp Heart Failure/ or exp Heart Failure, Systolic/ or ("cardiac failure" or (heart adj3 failure) or "biventricular failure" or "left ventricular systolic dysfunction" or HFrEF or HFpEF).tw.
13. exp Cerebrovascular Disorders/ or ((vascular or cerebrovascular) adj3 (disorder* or disease*)).tw.
14. exp Cerebral Infarction/ or exp STROKE/ or (stroke* or apoplexy or ((subarachnoid or brain or intracranial or cerebral or cerebrovascular or intracerebral) adj3 (embol* or thrombo* or infarct* or h?emorrhag* or isch?emi*))).tw.

15. exp Myocardial Infarction/ or ("heart attack*" or "myocardial infarction*" or "heart infarction*").tw.

16. exp ATHEROSCLEROSIS/ or exp Coronary Artery Disease/ or (atherosclerosis* or atherogenes* or "coronary artery disease*").tw.

17. exp HYPOTENSION/ or ("low blood pressure*" or "hypotensi*").tw.

18. exp Coronary Disease/ or (coronary adj3 disease*).tw.

19. exp ANGINA, STABLE/ or exp Microvascular Angina/ or exp ANGINA PECTORIS/ or angina*.tw.

20. exp Arrhythmias, Cardiac/ or arrhythmia*.tw.

21. exp Atrial Fibrillation/ or "atrial fibrillation".tw.

22. exp METABOLIC SYNDROME/ or "metabolic syndrome*".tw.

23. exp Metabolic Diseases/ or (thesaurismos* or "metabolic disease*" or “metabolic disorder*”).tw.

24. exp Diabetes Mellitus, Type 2/ or exp DIABETES MELLITUS/ or exp Diabetes Mellitus, Type 1/ or diabetes.tw.

25. exp Dyslipidemias/ or exp Hyperlipidemias/ or (dyslipemia* or dyslipidemia* or hyperlipidemia* or hyperlipemia*).tw.

26. (5-25 with or)

27. exp DEPRESSION/ or exp DEPRESSIVE DISORDER/ or (depression* or depressive or "low mood*").tw.

28. 4 and 26 and 27

Appendix 4 - Modified data collection form

RefID in Distiller & Endnote	Date of data extraction	Reviewer	Second reviewer

Notes:

General Information

1. **Title of the study**	
2. **Author(s)**	
3. **Journal article info** *(Journal, Vol, Issue, Page No)*	
4. **Region of the study** *(Country, city or area of the study population)*	
5. **Study funding source** *(Including role of funders)*	
6. **Possible conflicts of interest** *(For study authors)*	
7. **Notes:**	

Study Characteristics

8. **Type of study**	Cross-sectional study	
	Observational cohort study *(cross-sectional observation of a cohort at baseline or over a specific period)*	
	Cohort study	
	Case-control study	
	Qualitative study	
	Other design (specify):	
9. **Study aims/objectives/research question**		
10. **Study period** *(mm/yyyy - mm/yyyy)*		
11. **Notes:**		

Population and setting

12. **Participant characteristics** *(from which study participants are drawn)*	**Sex/ gender** *(ratio of women, %)*	
	Age *(mean yeas, SD, range)*	Mean: SD: Range:
	Ethnicity / Race	
	Deprivation	
	Occupation	
	Education	
	BMI *(mean Kg/m^2, SD)*	Mean: SD:
13. **Sample size** *(the sample size of the study)*		
14. **Sub-group size** *(the size of the sub-group of interest)*		
15. **Eligibility criteria**		
16. **Exclusion criteria**		
17. **Matching criteria**		
18. **Baseline and follow-up** *(the description of the baseline and follow-up population)*		
19. **Data source**		
20. **Recruitment procedures** *(details of how to recruit the participants)*		
21. **Quality control**		
22. **Response rate/ follow-up rate**		
23. **Bias, missing data, withdraws** *(description and analysis of the sampling bias, missing data and withdraws)*		
24. **Notes:**		

Methods

25. **Index condition** *(the index condition of the research question)*		
26. **Chronic pain** *(to list all types of the chronic pain examined in the study)*	Definition/type	
	Measurement *(self-reported, interviewed, clinical diagnosed, etc.)*	
27. **Cardiometabolic diseases** *(to list all types of the cardiometabolic diseases examined in the study)*	Definition/type	
	Measurement	
28. **Definition of depression**	Definition/type	
	Measurement	
29. **Other health conditions** *(to list all types of the other diseases examined in the study)*	Definition/type	
	Measurement	
30. **Health effect measurement** *(to list all types of the health outcomes and patient perspectives examined in the study)*	Definition/type	
	Measurement	
31. **Statistical analysis**		

32. **Notes:**	

Outcomes

33. **Outcome of interest**	**Comorbidity prevalence** *(ratio of comorbidity in the population)*	
	Health effects of the comorbidity	
	Patient experience of the comorbidity	
34. **Relevant outcome**	**Depression prevalence** *(ratio of depression among patients with two conditions)*	
	Relationship between the three conditions	
35. **Main results of the study**		
36. **Notes:**		

Discussion

37. **Strengths**	
38. **Limitations**	
39. **Comorbidity**	
40. **Conclusion**	
41. **Further study**	
42. **Notes:**	

Appendix 5 - Modified quality appraisal tool

Selection (single choice)

1. Representativeness of the sample

a) Truly representative *
b) Somewhat representative *
c) Selected group
d) No description of the derivation of the study population

2. Selection of the participants

a) Justified and satisfactory *
b) Not justified or satisfactory
c) No description of the derivation of the recruitment

3. Ascertainment of the three conditions

a) Secure record or self-reported of chronic pain and depression with valid instruments of the three conditions*
b) Self-reported without a valid instrument of any of the three conditions
d) No description of any of the three conditions
e) Other

4. Non-respondents

a) Comparability between respondents and non-respondents characteristics is established, and the response rate is satisfactory*
b) The response rate is unsatisfactory, or the comparability between respondents and non-respondents is unsatisfactory.
c) No description of the response rate or the characteristics of the responders and the non-responders.

Rate the section (3-4 stars: Strong; 2 stars: Moderate; 0-1 stars: Weak)

Comparability (maximum two choices)

5. Key potential confounders measured and controlled

a) The study controls for age, sex and race*
b) Study controls for other factors: deprivation, education level, alcohol, smoking, BMI*
c) Sub-groups are not comparable on the basis of the design or analysis controlled for confounders or no description of sub-groups

Rate the section (1-2 stars: Strong; 0 star: Weak)

Outcome and discussion (single choice)

8. Assessment of health effects

a) Independent blind assessment*
b) Record linkage*
c) Self report with valid instrument*
d) Self report without valid instrument
e) No description
f) Other

9. Were the limitation of the study discussed?

a) Yes*
b) No

10. Were there any conflicts of interest declared?

a) No conflicts of interested*
b) Funding sources explained and no effect of the study results*
c) Competing interests exist
d) No statement

Rate the section (2-3 stars: Strong; 0-1 star: Weak)

Overall rating (all Strong: Good; at least one Weak: Poor; rest: Fair)

Appendix 6 - List of self-reported LTC of cardiometabolic diseases

Cardiometabolic disease	Conditions included from the UK Biobank baseline
PVD	PVD Leg claudication/intermittent claudication
CHD	Heart attack/MI Angina
Stroke/TIA	Stroke TIA Subarachnoid haemorrhage Brain haemorrhage Ischaemic stroke
Diabetes	Diabetic nephropathy Diabetic neuropathy/ulcers Diabetes Type 1 diabetes Type 2 diabetes Diabetic eye disease
Hypertension	Hypertension Essential hypertension
HF	Cardiomyopathy Hypertrophic cardiomyopathy Heart failure/pulmonary oedema
AF	AF

Abbreviations: LTC, long-term condition; PVD, peripheral vascular disease; TIA, Transient Ischaemic Attack; MI, myocardial infarction; CHD, coronary heart disease; HF, heart failure; AF, Atrial fibrillation

Appendix 7 - List of SSRI and related drugs in the UK Biobank

Class	Codes	Drug
SSRI	1140921600	Citalopram
SSRI	1141180212	Escitalopram
SSRI	1141151946	Cipramil 10mg tablet
SSRI	1141190158	Cipralex 5mg tablet
SSRI	1140879540	Fluoxetine
SSRI	1140867876	Prozac 20mg capsule
SSRI	1140879544	Fluvoxamine
SSRI	1140867860	Faverin 50mg tablet
SSRI	1140867888	Paroxetine
SSRI	1140882236	Seroxat 20mg tablet
SSRI	1140867878	Sertraline
SSRI	1140867884	Lustral 50mg tablet
Related	1141200564	Duloxetine
Related	1141201834	Cymbalta 30mg gastro-resistant capsule
Related	1141152732	Mirtazapine
Related	1141152736	Zispin 30mg tablet
Related	1141151978	Reboxetine
Related	1141151982	Edronax 4mg tablet
Related	1140916282	Venlafaxine
Related	1140916288	Efexor 37.5mg tablet

Abbreviation: SSRI, Selective Serotonin Reuptake Inhibitor

Appendix 8 - Prevalence of other LTCs in the whole study sample (n = 500,313)

LTC	N	Prevalence
Asthma	58,108	11.61%
Treated dyspepsia	38,906	7.78%
Cancer	38,531	7.70%
Thyroid disorders	29,027	5.80%
Psoriasis or eczema	17,785	3.55%
Migraine	14,344	2.87%
Irritable bowel syndrome (IBS)	11,450	2.29%
Rheumatoid arthritis	10,978	2.19%
Anxiety	8,981	1.80%
Chronic obstructive pulmonary disease (COPD)	8,287	1.66%
Prostate disorders	8,236	1.65%
Osteoporosis	7,997	1.60%
Gout	6,969	1.39%
Diverticular disease of the intestine	5,389	1.08%
Glaucoma	5,285	1.06%
Inflammatory bowel disease	4,223	0.84%
Endometriosis	4,047	0.81%
Epilepsy	4,017	0.80%
Chronic sinusitis	3,094	0.62%
Chronic fatigue syndrome	2,162	0.43%
Schizophrenia and bipolar disorder	1,980	0.40%
Multiple sclerosis	1,756	0.35%
Pernicious Anaemia	1,509	0.30%
Meniere disease	1,369	0.27%
Viral Hepatitis	1,330	0.27%
Chronic kidney disease	1,300	0.26%
Bronchiectasis	1,133	0.23%
Chronic liver disease	970	0.19%
Parkinson's disease	853	0.17%
Alcohol problems	807	0.16%
Polycystic ovaries	623	0.12%
Shingles	411	0.08%
Treated constipation	401	0.08%

Anorexia or bulimia	368	0.07%
Trigeminal neuralgia	212	0.04%
Dementia	123	0.02%
Other psychoactive substance abuse	97	0.02%

Abbreviations: LTC, long-erm condition

Appendix 9 - Codebook (full version)

Themes	Categories	Sub-categories	Codes	Explanation
Comorbidity	Health conditions	Pain	Chronic widespread pain	Self-reported chronic pain all over the body
			Chronic pain	Self-reported pains more than 3 months/12 weeks
			Acute pain	Self-reported pain without a clear timeline or acute pain
		Cardiometabolic disease	Heart diseases	Self-reported angina, or other cardiovascular diseases
			Diabetes	Self-reported diabetes
			Hypertension	Self-reported hypertension or taking medication to high blood pressure
			Cardiometabolic disease	Self-reported cardiometabolic diseases
		Depression	Depression	Self-reported depression or taking antidepressants
	Relationship of the diseases	Relationship of the diseases	Relationship of the diseases	Diseases that led to development of other diseases, or made other diseases more severe

	Awareness	Health professionals	Holism	Health professionals being holistic and dealing with all conditions together
			Communication with other health professionals	Communication between health professionals about different conditions
		Patients	Communication with patients	Communication and understanding between the health professionals and patients
			Sources of the disease information	Internet, self-help book, leaflets and other sources of the information of patients
Treatment burden	Polypharmacy		Balancing the drugs	Co-prescribing multiple medications and finding the balance; different diseases restricted each other's treatment
			Side effects of drugs	Dependence and bad reactions of the medication
	Accessibility		Accessibility to health services	Navigation and accessibility to the clinic and facilities
			Diagnosis	Receiving enough inspections and the correct diagnosis
			Referrals	Referrals from primary care to secondary care
	Management		Appointments	Management and referral and other challenges of making appointments

			Investigations	Blood checks, body weight monitor and other uses of device
			Prescriptions	Prescription delivery and using dosset box to manage
			Routine of disease management	The routine workload of managing the medication and physiotherapist
	Financial burden	Direct financial burden	Medical cost	The cost of physiotherapy, drugs, devices, and private health services
			Outpatient cost	The cost of visiting different healthcare professionals
			Paid caring cost	The cost of hiring carers
		Indirect financial burden	Wage losses	The losses of wages and incomes
			Adaptation fees	The cost of adaptation and refurbishment of accommodations
			Transportation	The cost of transportation due to immobility
			Informal caring cost	The cost of family members offering the caring
			Accessing the financial support	The effort of applying for schemes and missing any eligible support due to lack of information or too much paperwork

			Inequity	Different policies of financial support in different countries
	Impact of life	Daily function	Diet	The change and restriction of diet
			Mobility	Immobility and inconvenience of mobility
			Capacity of ADL	Capacity of the essentail self-care activities like dressing, cleaning, eating, closing the door
		Impact on family	Marriage and relationship	Marriage, divorce, and the relationship between the patients and their partner
			Sexual life	The impact on sexual frequency and quality
			Pregnancy and parenting	Pregnancy, breastfeeding, babysitting and parenting
			Caring for someone	Caring for elder or family members with disability
			Diseases among the family	Family members sharing acute communicable diseases (like flu and cold) together and chronic diseases (like diabetes) due to family history
			Family social	The social and interaction within the family (like children visiting their grandparents)

		Impact on work	Employer	Responses from the employers
			Colleagues	Understanding from colleagues, and visibility of challenges to people
			Career development	The impact of productivity, promotion, restriction of working capacity, and being forced to quit job
		Impact on lifestyle	Physical activity	Doing housework and exercises
			Smoking and alcohol intake	Quit smoking and less alcohol intake
			Shopping	Accessing the supermarket and bringing back the groceries
			Social activities	Meeting friends, parties, voluntary work, and other social activities
Support	Outside home	Support from society	Social welfare, policies, financial support	Scheme of benefits, policies to help the disabilities
		Support from employer	Support from employer and colleagues	Flexibility working hours, accessible parking, understanding from colleagues
		Support from community	Social and network	Meeting friends and communicate with others
			Community-based mental support	Counsellors, nightlines

			Community-based support	Carer, parking support
	Inside home	Support from family	Family network	Mental support, visiting and accompany of family
			Caring from family	Family members help with the caring and management of the diseases
			The company of pets	The company and mental support of pets
		Support from accommodation	The adaptation of home facilities	The adaptation of toilet, stairs, door handles, and other facilities
			The change of the community	The change of flat to a house, or to somewhere with less noise
Feelings	Negative feelings		Desperation	Hopelessness and resignment of life
		Biographical disruption	Enslaved by the diseases	Reluctant to try new things, giving up struggling after the seesaw battle, feeling uncontrolled and just tolerating
			Dependence	Cannot accept the fact of becoming dependent from an independent person, cannot see one's value and meaning of life
			Stigma	Humiliating and embarrassment in front of others
	Positive feelings		Positive attitudes	Being faithful, stoicism, optimistic, proactive, facing the weakness and loss,

				focusing on what ones still have, motivated by pressure
			Impacts on positive attitudes	Encouraged by others, help from healthcare professionals