The contribution of musculoskeletal disorders and multimorbidity to health-related job loss among older working-age adults: a population-based study

Thesis submitted in accordance with the requirements of the University of Liverpool for the degree of Doctor in Philosophy (PhD)

by Stephen John Duffield

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DECLARATION

This work has not been submitted in substance for any other degree or award at this or any other university or place of learning, nor is being submitted concurrently in candidature for any degree or other award. This thesis is being submitted in partial fulfilment of the requirements for the degree of PhD. This thesis is the result of my own independent work/investigation, except where otherwise stated. Other sources are acknowledged by explicit references. The views expressed are my own. I hereby give consent for my thesis, if accepted, to be available for photocopying and for interlibrary loan, and for the title and summary to be made available to outside organisations.

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THESIS ABSTRACT

THE CONTRIBUTION OF MUSCULOSKELETAL DISORDERS AND MULTIMORBIDITY TO HEALTH-RELATED JOB LOSS AMONG OLDER WORKING-AGE ADULTS: A POPULATION-BASED STUDY

BACKGROUND: Employment is the most important source of financial income and material well-being and therefore is the main driver of the social gradient in physical health, mental health, and mortality. In addition, good employment fulfils psychosocial needs and is fundamental for an individual's social status, societal participation, and identity. However, work participation is known to fall steeply after the age of 50 in women and 55 in men. In the EU, musculoskeletal disorders (MSDs) account for 50% of all absences from work lasting 3 days or longer and for 60% of all permanent work incapacity. However, in those aged over 50, MSDs also commonly co-occur with other health conditions, in what is known as multimorbidity.

AIMS: the overarching aims of this thesis are to investigate, among older working-aged people, a) the impact of common comorbid health conditions on work outcomes in people with MSDs, and b) the common patterns of multimorbidity and their contribution to health-related job loss.

METHODS: Chapter four is a systematic review of the impact of comorbidity on work outcomes in people with musculoskeletal disease. The chapters that follow describe results from a nested matched case-control study of working-age participants, over the age of fifty. Health and Employment After Fifty (HEAF) study participants with health-related job loss (HRJL) were matched 1:1 to working control participants for age, sex, and GP practice. Participants' health diagnoses at the time of HRJL were extracted using retrospective data from the Clinical Practice Research Datalink (CPRD). Chapter five describes a cohort of older workers with HRJL (case participants) for their known demographic, lifestyle, occupational, and health factors. Chapter six compares case participants to working controls for CPRD-defined health disorders to assess their association with HRJL. Chapter seven uses cluster analysis to describe common patterns of multimorbidity across the total study sample. In Chapter eight, these prominent clusters of health disorders were explored for their association with HRJL. Finally, in Chapter nine, multivariable conditional logistic models were constructed using purposeful selection to explore the population attributable fraction of HRJL for CPRD-defined health disorders.

CONCLUSIONS: Results supported the primary importance of common mental health problems and musculoskeletal disorders for health-related job loss in the older working-age population. However, multimorbidity (classified as two or more CPRD-defined health disorders) was strongly associated with HRJL and accounted for a significantly greater proportion of HRJL than any individual health disorder. Multimorbidity clusters formed by co-occurring musculoskeletal disorders and mental health problems appeared to have a particularly strong impact on HRJL.

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Many thanks to Professor Keith Palmer who I was lucky to work with just prior to his retirement. He helped me to get acquainted with the Health and Employment After Fifty (HEAF) study and Clinical Practice Research Datalink (CPRD) and taught me to think carefully about the research questions and methods of analysis that I proposed.

A great deal of thanks needs to go to the rest of the HEAF study team at the MRC-funded Lifecourse Epidemiology Unit in Southampton, who were willing to give me the opportunity and responsibility to decide and conduct my own statistical methods for this thesis using their data. Particularly deserving of thanks are Cathy Linaker and Philip Marshall-Cox and their charming family (Tim, Eleanor) who opened their very home to allow me to stay with them during my visits south.

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I am grateful to the patients who contributed their data to the Health and Employment After Fifty study and the Clinical Practice Research Datalink, without whom it would not have been possible to conduct the unique population-based research analysis presented in this thesis.

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Job 12:12

"Is not wisdom found among the aged?

Does not long life bring understanding?"

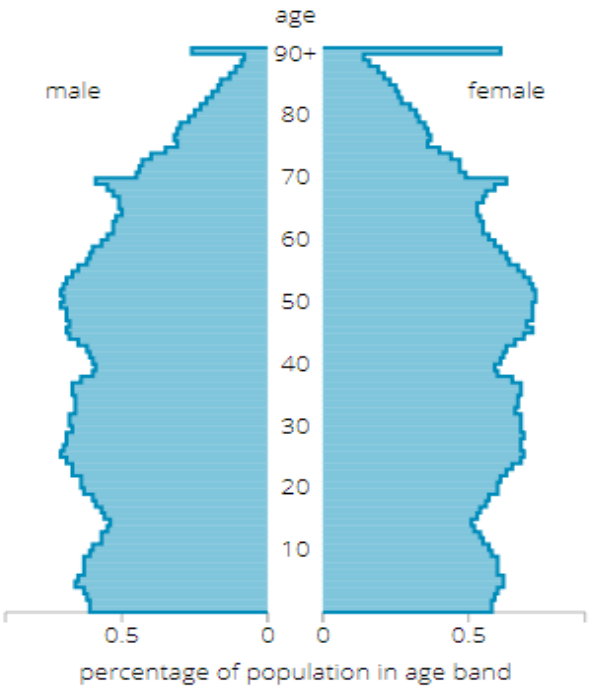
Chapter 1- Introduction

1.1 Work, ageing, and health

1.1.1 The ageing UK population

The population of the United Kingdom is getting older. Currently, 18% of the population is aged 65 years and older, with 2.4% aged 85 years and older.(1) In populations with high fertility and death rates, the traditional "population pyramid" actually resembles a pyramid shape, with larger numbers of youth at the bottom and fewer people reaching advanced age. In the UK however, the population pyramid flattens out at the bottom and broadens at the top, see Figure 1.(2) This reflects a combination of low national birth rates, particularly in the 1970's and early 2000s, and improvements in healthcare and lifestyle that have led to longer lifespans.(3) The successful lengthening of the average lifespan comes with economic challenges since the working-age group produce labour to support those who have retired (both in terms of care provided and taxes-rendered); and the ratio of working-age to retired is decreasing. In 2016 in the UK, there were as many as 285 persons aged over 65 years per 1000 working-age persons (16 – 64 years).(3)

Figure 1: Population pyramid (by age and sex) for UK, England and Wales, Scotland and Northern Ireland: mid-2016, Office for National Statistics. Total population 65,648,054.(2)



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1.1.2 Encouraging work to older ages: the ageing workforce

In order to address this population shift, member countries of the Organisation for Economic Co-operation and Development (OECD) have applied several changes in policy to encourage people to stay in work to a later age and to offset the fall in labour growth.(4) For example, the age at which public and private pensions can be claimed has been raised and governments have sought to address the employment disadvantages that result from age-discrimination due to negative age stereotypes. However, clear cases of age-discrimination are hard to find and measure.(5) In the UK, policy changes have included increasing state pension age, abolishing mandatory retirement ages, and legislation to remove age and disability discrimination in the workplace.(6)

As well as governmental intervention, other individual incentives to work until later in life are taking effect. Higher costs, taxation, and reduced return on savings and pensions have resulted in an increase in the numbers of people intending to work until later in life and the proportion of people working beyond the traditional retirement age.(6) In the UK, between 2004 – 10, the estimated average age of labour force withdrawal increased from 63.8 years to 64.6 years in men, and from 61.2 years to 62.3 years in women.(7)

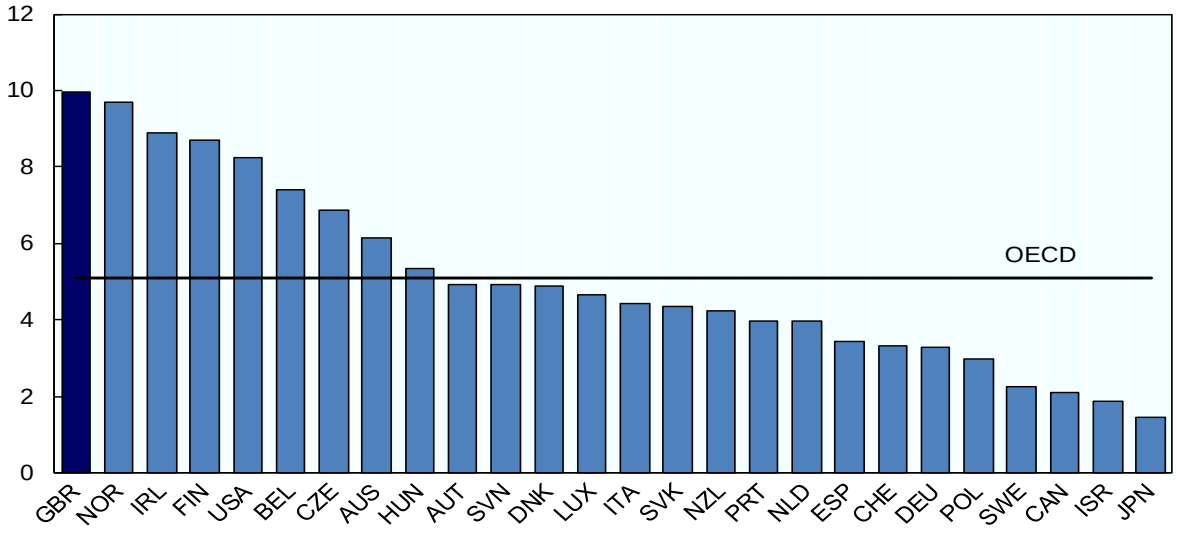
Encouraging people to work until later in life is a complicated solution as it increases the overall age of the workforce. As the age of the workforce increases, the prevalence of health problems rises concomitantly, along with rates of adverse work outcomes such as sickness absence and work disability.

1.1.3 Work disability in the UK

Under the Equality Act (2010), disability is defined as having a physical or mental impairment that has a “substantial” or “long-term” negative effect on a person’s ability to do normal daily activities.(8) Similarly, work disability can be defined as having a physical or mental impairment that has a substantial or long-term negative impact on a person’s ability to carry out the employee-role. However, work disability is not consistently defined. In the literature, work disability may be broadly classified by self-report, can sometimes include evidence of sickness absences, and sometimes requires that a person is certified work-disabled and receiving some kind of financial support.(9–14) While work disability has been used as an umbrella term for all health-related adverse work outcomes, it usually refers to a person who is no longer employed.

The cost of reduced work participation can be high for the individual, employer and society. Productivity loss, sickness absence, and time and resources dedicated to poor health in work, amount to £9 billion in costs, per year, for the employer, while the government pays an additional £13 billion per year on sickness-related benefits.(15) These figures featured in Dame Carol Black's influential review of sickness absence in health and work in 2008,(16) and are now likely to be an underestimate as, between 2013 – 2016, the number of disabled people of working age increased by over 400,000 taking the total to greater than 7 million.(17) In 2014, the UK was ranked first for new work disability claims of all OECD countries (see Figure 2).(18)

Figure 2: New disability benefit claims per 1,000 of the working-age population. (18)



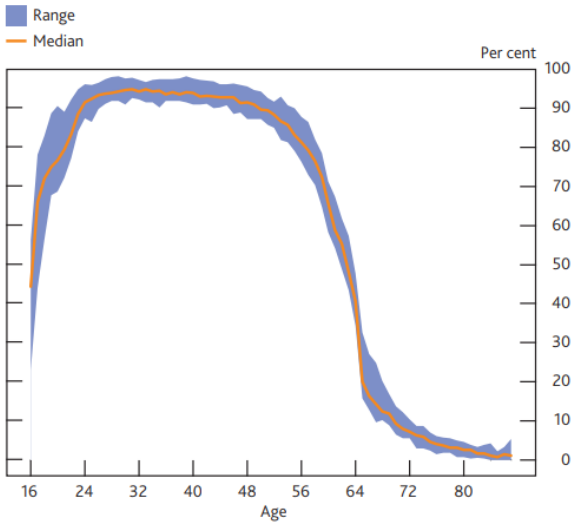
1.1.4 The relationship between age and work disability

As people age, they are more likely to become work disabled,(19–41) especially over the age of 50.(19) One systematic review concluded that age is related to work disability independently of diagnosed health problems.(42) This is likely because age correlates with multiple other health, lifestyle, and demographic risk factors for work disability. For example, reaction times and attention broadly decrease with age(43) and older people have fewer physical reserves.(44) Older people will generally have had chronic diseases for longer and, if the disease is progressive, will have more severe disease and a greater number of complications. In addition to health-related mechanisms, societal factors are impactful - including the exclusion of the elderly from the labour market due to discrimination and greater lenience with regard to certification of work disability in the elderly.(35,42)

The median rate of work participation falls steeply after the age of 50 in women and 55 in men and, among the working-age population, people over 50 account for the majority of work loss (see Figure 3).(45) As a result, the UK government is particularly interested in working-age people over 50 in its efforts to support people to remain in work. Understanding the health and demographic causes of work loss in this cohort holds most promise for developing targeted policy and healthcare interventions to support a longer working life. However, few UK-based studies of health-related job loss amongst the older working-age group have been conducted. To address this important research gap, people with health-related job loss between 50 - 64 years of age form the main focus of this thesis.

Figure 3: Participation rates over the life cycle in a) men and b) women in the UK. Participation rates at each age between 1984 and 2010. Based on data for the three months to June between 1992 and 2010 and the three months to May between 1984 and 1991. Data are non-seasonally adjusted.(46)

a)



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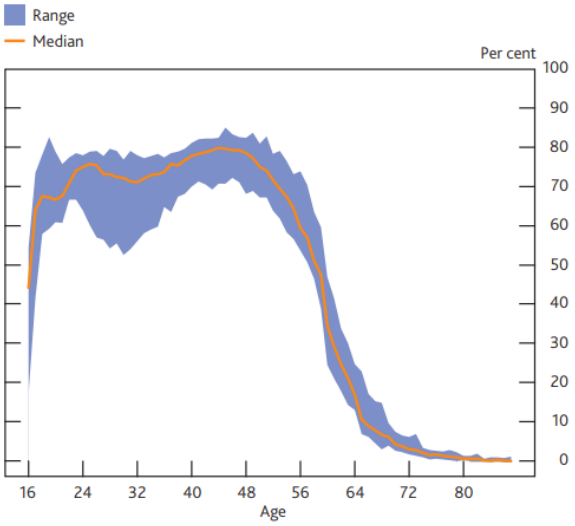

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1.1.5 Is work good for your health?

The effort to encourage people to work till later in life raises ethical issues, since work may be detrimental to health in some cases. This was particularly captured by the recent high-profile case of Stephen Smith who was mistakenly deemed "fit to work" despite his severe weight loss and chronic obstructive pulmonary disease (COPD), see Figure 4. In 2006, the Department for Work and Pensions conducted an independent review of scientific evidence to answer the question: "is work good for your health and well-being?"(47) It focussed on adults of working age, with a special interest in the health-conditions that account for two-thirds of sickness absence and long-term incapacity: mental health problems, musculoskeletal disorders, and cardio-respiratory conditions.(48)

Figure 4: Getting it wrong – the story of Stephen Smith, aged 64, weighing six-stone with severe COPD, who was deemed "fit to work" by the Department of Work and Pensions (DWP). Front page Liverpool Echo, February 4th, 2019.(49)

This review found that employment is the most important source of financial income and material well-being and therefore is the main driver of the social gradient in physical health, mental health, and mortality.(48) This is a key argument for the benefits of work for health. People who have low socioeconomic status endure many health disadvantages. For example, there is consistent evidence of higher prevalence of common mental health disorders among people with lower social status, regardless of measures of mental disorder or social class used.(50) Moreover, low income level, poor educational attainment, and neighbourhood low socioeconomic factors have been consistently associated with cardiovascular disease.(51) The financial gains that come with working may help to offset these disadvantages. Good employment additionally fulfils psychosocial needs and is fundamental for an individual's social status, societal participation, and identity.(52)

While work appears to be good for health in general, in some cases physical or psychosocial aspects of work could pose mental or physical health-hazards. For example, heavy physical work, such as construction work, is associated with lower back disorders,(53) and work around asbestos has led to cases of pleural plaques, bronchogenic carcinoma, and mesothelioma.(54) In addition, high work demands (increasing workload, long hours, time pressures) combined with low overall control (low decision authority, low skill discretion, low work-time control) may lead to the development of common mental health problems such as depression and anxiety.(55)

Unemployment, on the other hand, is clearly associated with higher mortality, poorer general health, longstanding illnesses, psychological morbidity, higher rates of healthcare consultations, higher number of drug prescriptions, and more hospital admissions for the unemployed individual.(48) Unemployment also appears to be devastating for the family. In the UK in 2004, children in families where neither parents were working were 2.5 times more likely to have emotional disorders compared to children in families where one parent was working, and three times more likely compared to children with both parents working.(56) Additionally, one cross-sectional study (n=10,317) found that children in families where neither parents had worked in the prior 6 months were more likely to have psychosomatic symptoms (OR 1.67 95%CI 1.16 to 2.40), chronic illness (OR 1.35 95%CI 1.00 to 1.84), and low wellbeing (OR: 1.47 95%CI 1.12 to 1.94).(57) Families without a working member are also much more likely to remain in a state of poverty.(58)

Re-employment appears to improve self-esteem, general health, and mental health and leads to reduced psychological or psychiatric morbidity.(48) This evidence of "reversibility

of effect" supports the hypothesis that work independently promotes health. One study found improvements in general distress, anxiety, and depression after re-employment were particularly strong among those of a lower social class.(59) Similarly, in another study, moving off social security benefits and into work improved income, mental health, and quality of life outcomes.(48)

Of course, interpreting all these findings can be challenging since the health of the employed and ill health of the unemployed may in part reflect a health-selection effect, whereby a person's initial health status later influences their work status. The problem of using broad group effects to make inferences about the individual (known as the "ecological fallacy") is another danger as the beneficial effects of work, identified at the population level, may not capture the severity and clinical features of an individual's health disorders, the nature and quality of their work, and their social context.

So is work good for a person with pre-existing illness? The consensus is that work for sick or disabled people, in general, can help to aid recovery and can be therapeutic, resulting in better health outcomes, quality of life, wellbeing, and reduced risk of long-term work disability. Moreover, much can be said for avoiding the pernicious effects of unemployment including deteriorating mental and physical health, the loss of independence, and reduced participation in society.(48) It should be noted that this consensus amounts to a summary of policy statements and guidance which lean heavily on evidence about the apparent positive effects of work *in general* and the clear detrimental effects of worklessness *in general*. In truth, there is little direct evidence about the physical or mental health benefits of employment for sick, disabled, or older people.

Of the existing evidence, one study on rehabilitation of people with musculoskeletal disorders who were on sick leave (full or partial) at baseline (n=91) found that participants who reduced their sick leave level had significantly lower pain intensity and frequency scores; lower disability, anxiety and depression scores; and higher reported quality of life at 5-year follow up than those who increased or maintained their sick leave.(60) For musculoskeletal disorders, evidence has also shown returning to work is usually safe and does not require full recovery.(61,62) Similarly, most employees with chronic diseases continue to work.(63) At the very least, results like these suggest that work is not harmful for many people with sickness or disability, and given the known benefits of work, this population should be supported to remain in work wherever desired and possible.

Unfortunately, the disability-employment gap (calculated as the difference in employment rate between people with and without Equality-Act-defined disability) has barely changed in more than a decade: an average of 31.1 percentage points between the disabled and non-disabled since 2008.(64) In recognition of the likely beneficial impact of work upon health and wellbeing, and the apparent stagnation of work opportunities for people with disability, there has been a push for work to be considered a health outcome from organisations both inside and outside of government.(65,66)

To close this disability-employment gap, a range of interventions may be effective such as stepped-support for people who are at risk of work disability, or early intervention following sickness absence or work loss.(67,68) Such interventions can be costly and economically impossible to offer to everyone with a health condition. Therefore, a targeted approach is needed that focusses on commonly occurring and disabling health conditions in the working-age population between 50 – 65 years old (the highest risk age-group). In this cohort, musculoskeletal disorders (MSDs) are key as they are both highly prevalent and, along with mental health disorders, are the leading cause of work disability. MSDs therefore form a focus of this thesis. I give an overview of the major MSD groups below, along with their relationship to work outcomes.

1.2 Musculoskeletal disorders

1.2.1 Clinical features and epidemiology

MSDs include inflammatory rheumatic diseases, such as rheumatoid arthritis and spondyloarthritis; degenerative conditions, such as osteoarthritis; fragility disorders, such as osteoporosis; regional pain syndromes, such as low back pain and neck pain; and widespread pain disorders, such as fibromyalgia. MSDs are common throughout the life course but become increasingly common at older ages (in particular, low back pain and osteoarthritis).

MSDs are markedly heterogeneous, ranging from highly disabling but fortunately less common conditions such as rheumatoid arthritis, ankylosing spondylitis, and systemic lupus erythematosus through to considerably more common but generally less disabling conditions such as low back pain and osteoarthritis. At older ages, osteoporosis also causes a substantial burden by increasing the risk of low-trauma fractures.(69)

1.2.2 Osteoarthritis

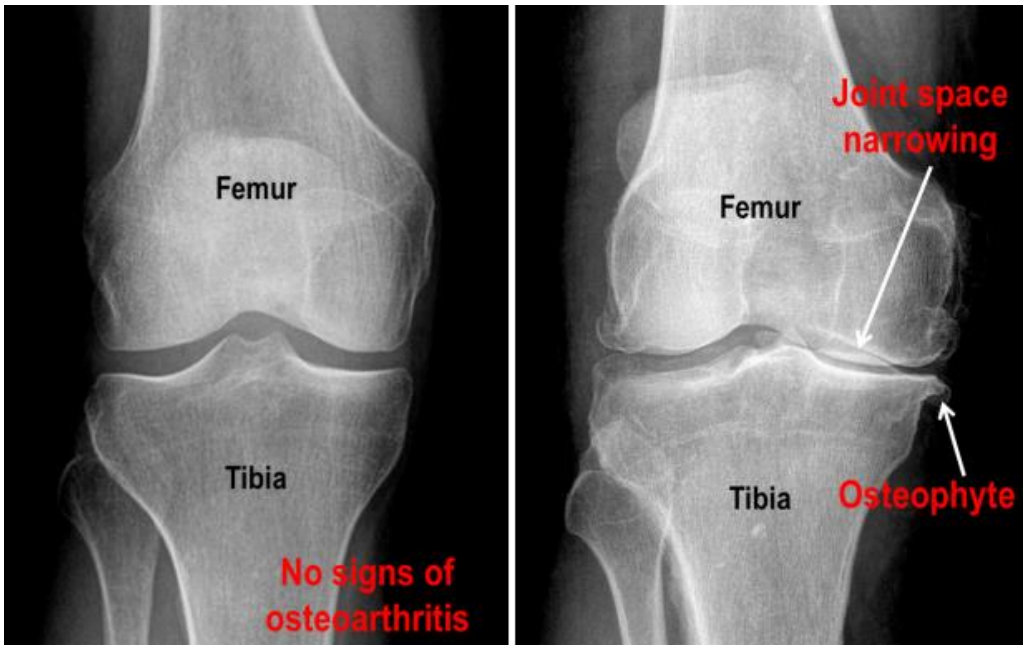
Osteoarthritis is both the most common type of arthritis and the leading cause of physical disability in older adults.(70) This condition occurs as a result of the deterioration of cartilage, the protective smooth connective tissue that covers the articulating surfaces of our joints. Once the cartilage has degenerated and worn away, this leaves underlying bony structures to rub on one another causing friction and symptoms of pain, aching, and stiffness. The condition is progressive and the development of bone spurs and osteophytes can occur within the joint which can worsen symptoms. The pathogenesis of osteoarthritis has traditionally been described as “wear and tear” of the joint over time, however more recent research has implicated a more dynamic disease process involving joint inflammation and synovitis.(71)

Diagnosis of osteoarthritis is often made on the basis of radiographic changes such as osteophytes, joint space narrowing, and sclerosis on x-ray of the joint, see Figure 5. However, substantial discordance may exist between those who report joint pain and those who have radiographic changes. For example, in one systematic review the proportion of participants over the age of 50 with knee pain who had radiographically defined osteoarthritis ranged from 15 – 76%, and similarly the proportion of participants with radiographic changes who had pain ranged from 15 – 81%.(72) Osteoarthritis is often reported as “symptomatic osteoarthritis,” which indicates the presence of symptoms as well as radiographic evidence, and “radiographic osteoarthritis” which only indicates radiographic signs, and may not require clinical management if asymptomatic.(73)

Osteoarthritis is common. However, estimates of prevalence vary greatly depending on the definition used (as well as by age, sex, and region studied).(74) In the UK, one third of people over the age of 45 have sought treatment for osteoarthritis, a total of 8.75 million.(75) The commonest regions affected by osteoarthritis are the knee and hip. In the UK, approximately 20% and 8% of people have sought treatment for osteoarthritis of the knee and hip, respectively. Less common are osteoarthritis of the foot and ankle and osteoarthritis of the hands and wrist which affect 7% and 6% of those over the age of 45. Of course, many people may also have osteoarthritis in two or more regions of the body known as multi-site or “generalised” osteoarthritis. In total, an estimated 1.76 million people (7% of those over the age of 45) have sought treatment for multi-site osteoarthritis.(75)

The risk factors for osteoarthritis are multifaceted. Firstly, there are a range of factors that make an individual susceptible, including older age, female sex, obesity, genetics and ethnicity, diet, and bone metabolism. At the level of the joint, repetitive joint use, load bearing, highly physical occupations, and prior injury may predispose to later development of osteoarthritis.(73) These factors may affect OA risk to a varying degree, for example, the risk of knee osteoarthritis is two times greater for men whose jobs required both carrying and kneeling/squatting in mid-life,(76) and those who are overweight or obese are nearly three times more likely to develop knee osteoarthritis than those of normal weight.(73) In the UK among those between the ages 45 – 64, approximately a third of women, compared to a quarter of men, have sought treatment for osteoarthritis.(75)

Figure 5: The radiographic features of knee osteoarthritis, including joint space narrowing, osteophyte formation, and subchondral sclerosis.(77)



(77)

1.2.3 Inflammatory arthritis

Inflammatory rheumatic disorders or inflammatory arthritis, classifies a group of conditions characterised by inflammation of the joints and sometimes other tissues. Most inflammatory arthritis is autoimmune, affecting the synovium, and leading to destruction of the bones and joint. The most common kinds of inflammatory arthritis are rheumatoid arthritis and spondyloarthropathies such as ankylosing spondylitis and psoriatic arthritis, however a range of other conditions are also described and include juvenile idiopathic arthritis and systemic lupus erythematosus. Gout is also a type of inflammatory arthritis; however, it is not autoimmune and is described separately, below. Symptoms of

inflammatory arthritis include pain, warmth, swelling and tenderness around the joint as well as morning stiffness (>1 hour). In addition, systemic symptoms may be apparent and, depending on the type of inflammatory arthritis, may include skin rashes, scleritis, and vasculitis.(78)

Rheumatoid arthritis is commonly diagnosed using a set of criteria that take into account the number and site of involved joints, symptom duration, serological evidence (e.g. rheumatoid factor positive), and inflammatory markers (erythrocyte sedimentation rate and C-reactive protein).(79) Spondyloarthritis is split into axial types, such as ankylosing spondylitis, and peripheral types, such as psoriatic arthritis. Axial spondyloarthritis is mainly diagnosed based on three or more months of symptomatic inflammatory back pain in a person younger than 45, with either evidence of sacroiliitis on imaging or an HLA-B27 positive blood test in combination with other features of spondyloarthritis. Peripheral spondyloarthritis is diagnosed using a combination of joint-based signs and broader clinical features. For example, psoriasis with arthritis and positive family history of spondyloarthritis would be sufficient for a diagnosis of psoriatic arthritis.(80)

Other than gout, rheumatoid arthritis is the most common kind of inflammatory arthritis affecting an estimated 400,000 people across the UK. This is followed by ankylosing spondylitis which affects approximately 200,000 people.(81) The occurrence and severity of rheumatoid arthritis is genetically influenced and is more common among women to a ratio of 2-3:1. Lifestyle factors such as smoking can also affect the development and course of this disease. Ankylosing spondylitis, the most common kind of axial spondyloarthritis, is more common in young men in whom it is most likely to start in late teens or early 20's. Once again this condition is genetically influenced and most patients have the HLA-B27 gene.(82) Psoriatic arthritis, the most common kind of peripheral spondyloarthritis, is common among people with psoriasis (around 6 – 41% of this group), and a family history is a risk factor, which also suggests a strong genetic component.(83)

1.2.4 Gout

Gout is a crystal arthropathy that is due to hyperuricaemia and deposition and build-up of urate crystals in peripheral joints and soft tissues. Clinically, this presents with severely painful acute synovitis which significantly impacts on function in acute attacks. Recurrent attacks occur in untreated gout and each attack may last for weeks before resolving. This can eventually lead to joint damage and deformity if uncontrolled.(84) Gout most commonly affects the first toe, ankle, knee, fingers, wrist and elbow joints.

The criteria for gout diagnosis involves the occurrence of peripheral joint or bursal swelling, pain or tenderness, and the presence of urate monohydrate crystals in synovial fluid or tophus analysis.(85) Urate lowering treatment can prevent the formation of urate crystals and dissolve away existing crystals, meaning recurrent acute attacks and joint damage can be avoided with effective treatment.(86)

Gout is the most common kind of inflammatory arthritis, affecting around 4.5 million people in the UK (2.49% prevalence).(87) Hyperuricaemia is the key causal factor in developing gout and is linked to dietary factors (such as purine rich foods, alcohol, and fructose/sugar sweetened soft drinks), obesity, renal disease, and various medications such as diuretics and aspirin.(88)

1.2.5 Widespread pain syndromes

Chronic widespread pain is common in the population and characterised by long-lasting pain, in multiple sites often with additional symptoms such as fatigue and psychological distress.(89) A small proportion of those with chronic widespread pain will also have fibromyalgia syndrome, a complex neurosensory disorder characterised by a history of diffuse and persistent musculoskeletal pain, in conjunction with numerous discrete tender points elicited on clinical examination.(90,91) Additional symptoms such as fatigue, sleep disturbances, depression, and headache may also be apparent in this syndrome.(91,92) The cause of fibromyalgia is unclear, it is theorised that low-grade systemic inflammation could modify pain regulation, leading to increased pain sensitivity.(93) Alternatively, it has been suggested that psychological stress, perhaps caused by chronic disease, may play a role in generalisation of pain.(94,95)

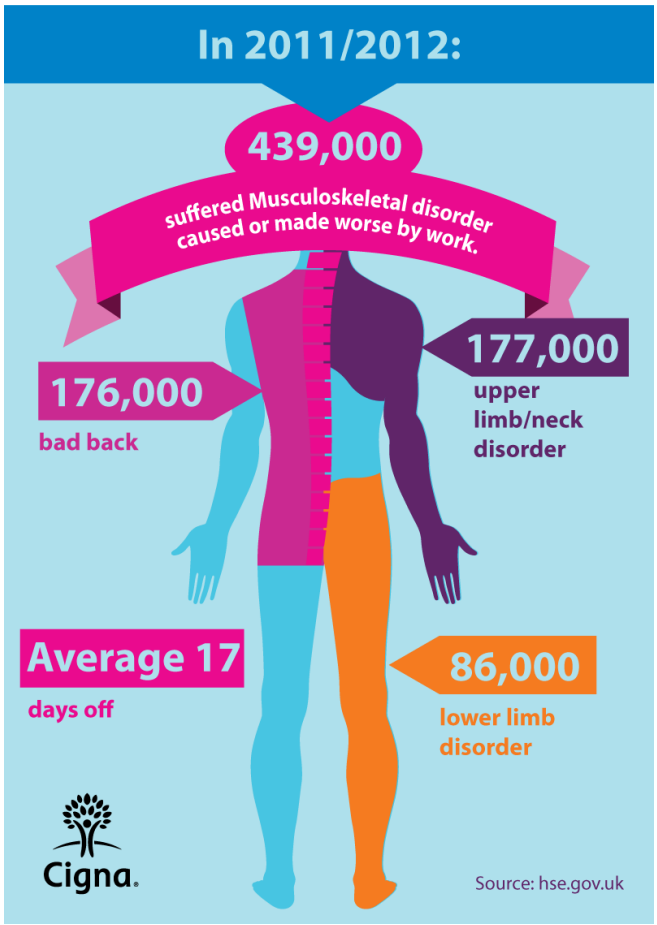
The American College of Rheumatology (ACR) classifies widespread pain as having pain in the left and right side of the body, pain above and below the wrist, and axial skeletal pain for at least three months. In addition to this, for a diagnosis of fibromyalgia, participants traditionally had to feel pain on palpation for 11, or more, of 18 potential tender point sites.(96)

Chronic widespread pain affects approximately 10 – 11% of the UK population while fibromyalgia has a prevalence of around 1-5%.(97,98) Both conditions are strongly associated with female gender(99) and increasing age.(100)

1.2.6 Regional pain, cumulative trauma disorders, and work-related musculoskeletal disorders

This section describes common musculoskeletal disorders which can be associated with certain work activities, including tendon inflammations, inflammation of the surrounding tissue (tenosynovitis, epicondylitis, bursitis), cumulative trauma disorders, and regional pain syndromes not attributable to known pathology, such as low back pain. These musculoskeletal conditions are common (see Figure 6) and have been associated with work factors such as rapid pace, repetitive motion actions; heavy lifting and forceful exertions; non-neutral body positions; regional or whole body vibrations; insufficient recovery time; and psychosocial factors related to job strain (high work demands and low control).(101) Specifically, higher-risk careers have been found to include nursing, mining, food processing, and heavy and light manufacturing.(102)

Figure 6: Cigna infographic showing the incidence of musculoskeletal disorders exacerbated by work in the UK (2011/2012)(103)



Upper limb conditions include tendon-related disorders, such as de Quervain's disease and trigger finger; nerve-related disorders, such as carpal tunnel syndrome; muscle-related

problems, such as tension neck syndrome, myalgia and muscle sprain/strains; circulatory problems such as Raynaud's syndrome; osteoarthritis; and bursa-related disorders.(104) These disorders are fairly common in UK general practice with an annual incidence of 25 first-time presentations with an upper limb disorder per 1000 person-years. Rate of presentation with upper limb disorders increases up to 45 years of age and then stays constant.(105) Along with the broadly higher-risk careers mentioned above, occupations in which the hands and arms are used intensively can be at increased risk for the development of upper limb disorders. These include clerical and administrative work, postal service, cleaning, and packaging.(102) However, non-work factors are also associated.

Neck musculoskeletal disorders can include neck strain, neck injuries, such as whiplash, degenerative disc disease and neurological pain from a pinched nerve or herniated disc. The most common neck MSD is non-specific neck pain. In one UK-based cross-sectional study, among the working age (16 – 64 years old), self-reported neck pain had a one-week period prevalence of 19.6% while self-reported neck pain in the prior year was as high as 33.7%.(106) Repetitive work involving continuous hand or arm movements affecting the muscles of the shoulder or neck, and extreme working postures leading to prolonged static loads on the neck musculature are thought to raise the risk of developing these conditions.(107) There is a higher risk of neck pain among women and risk peaks around age 35 – 49 years, after which the risk decreases.(108)

Regional back pain mostly refers to low back pain, which is usually idiopathic (85 – 95%) but may also be caused by injury, fracture, or degenerative changes in the back such as degenerative disc disease and osteoarthritis.(109) Back pain is common, an estimated 10 million people in England and Scotland report persistent back pain at any one time (around 17% prevalence).(110) Age is a risk factor with the prevalence of back pain increasing until ages 60 – 65 years and physical demands at work such as manual handling, bending, twisting, and whole-body vibration have been associated. For instance, one study found a prevalence of low back pain of 39% in male manual workers but only 18.3% in male sedentary workers.(111) Some employees appear particularly susceptible to back and lower limb disorders including, drivers, warehouse workers, baggage handlers, nurses, support workers, and operators of cranes and large machinery.(102) Low back pain is also associated with a number of psychosocial factors such as stress, anxiety, depression, job dissatisfaction, poor work relationships/support, and work monotony.(112)

Lower limb pain is mostly captured by hip pain and knee pain, which are largely caused by osteoarthritis in older adults, and are discussed above.(113)

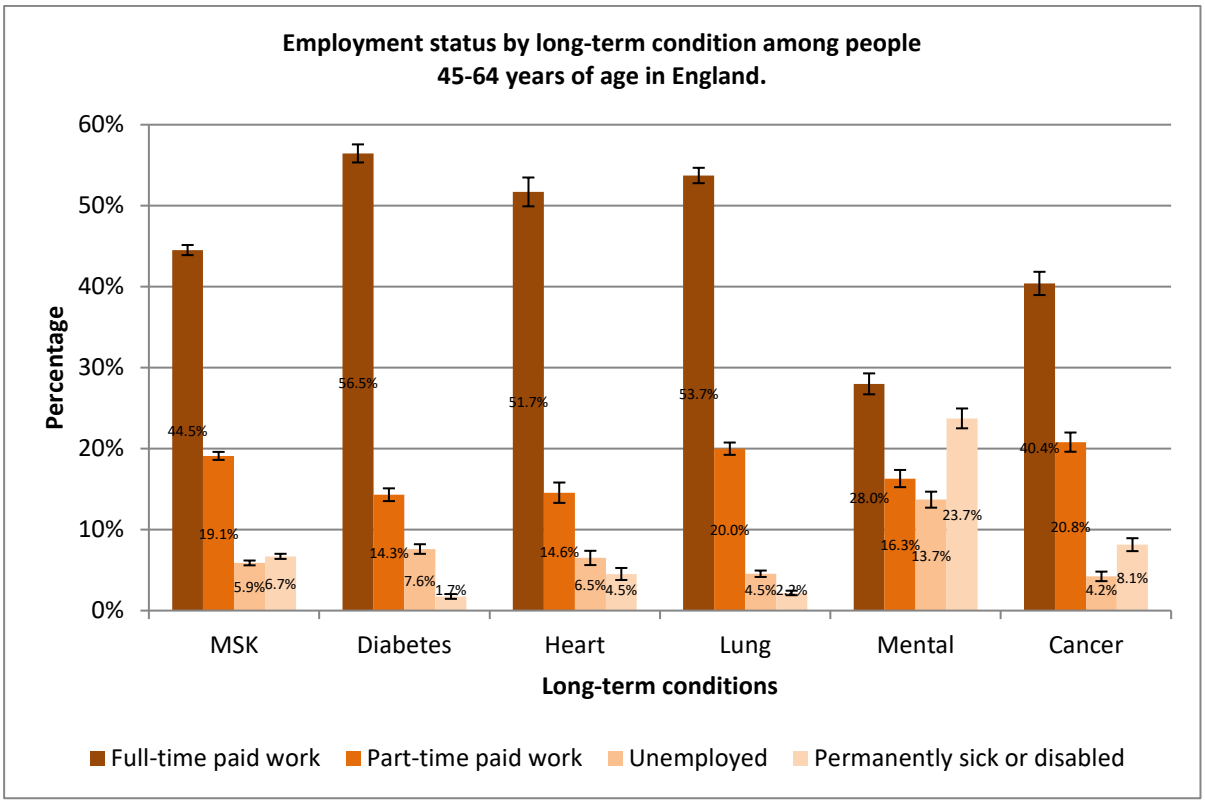
1.3 Musculoskeletal disorders and work

People with MSDs are less likely to be employed than people in good health, and are more likely to retire early.(114) In one systematic review and meta-analysis, MSDs were associated with double the risk of disability pension (RR 2.23 95%CI 1.93 to 2.59).(115) In the European Union and the United States, MSDs account for a higher proportion of sickness absence from work than any other health condition.(116,117)

Likewise, in the UK, MSDs are common and work-disruptive. One in eight of the working-age population reports having an MSD and the employment rate for people with MSDs is 59.7% compared with 73% in the general population.(118,119) In 2013, more days of sickness absence were attributed to back, neck and muscle pain than any other cause, which accounted for 30.6 million days of sickness absence (23% of all UK working days lost).(120) In addition, MSDs are responsible for a third of all UK long-term sickness absences; these have a poor long-term career prognosis and are particularly expensive for the individual and society.(120) Finally, in the UK, MSDs have the third lowest rate of full-time paid work (see Figure 7) and are the third highest-reported reason for being permanently sick or disabled, after mental health problems or a recent cancer experience.(121,122)

A synthesis of qualitative research on the experience of work in people with chronic musculoskeletal pain in the UK, found that people with musculoskeletal pain struggled to affirm themselves as good workers; struggled balancing life and work in the face of unpredictable symptoms; and sensed that their work colleagues didn't believe their symptoms, all of which had an adverse effect on their working life. Additionally, it was felt that the system did not facilitate return to work among those who fell out of employment.(123) Below, I review work outcomes among the major MSD subgroups.

Figure 7: Employment status by long-term condition among people 45-64 years of age in England.(121,122)



1.3.1 Osteoarthritis

Osteoarthritis is independently associated with an increased risk of work disability. In one recent longitudinal study, people with osteoarthritis had a 90% higher hazard of health-related job loss compared with non-osteoarthritis controls matched for age and sex, and after adjustment for BMI, number of chronic conditions, income, marital status, and degree of work stress (aHR: 1.90 95%CI 1.36 to 3.23).(124) Over one year, knee osteoarthritis has been found to have an approximately two-fold increased risk of one or more episodes of sick leave, and about 40 – 50% increased risk of requiring disability pension as compared with the general population (RR 1.54 95% 1.48 to 1.60 in women, 1.36 95%CI 1.28 to 1.43 in men).(125) One population-based cross-sectional study found a very strong association between hip osteoarthritis and needing to reduce or change work for health reasons, adjusting for age, sex, other conditions and socioeconomic status (aOR: 8.0 95%CI 4.6 to 14.1). This was a notably stronger relationship than found for those with knee osteoarthritis (aOR: 1.8 95%CI 1.2 to 2.7) and hand osteoarthritis (1.5 95%CI 0.9 to 2.8), in the same study.(126)

Risk of disability among people with osteoarthritis has been found to increase with age, lower attained education, being non-married, and presence of comorbidity. In one study of people with osteoarthritis younger than 65 years old, arthritis itself was found to explain less than one third of work disability after adjusting for these factors.(127) Disease-specific factors associated with an increased risk of disability in osteoarthritis included number of regions affected, duration of arthritis, and being underweight (BMI <20) or overweight (BMI ≥ 30).(128) Certain physical occupations have also been associated with disability due to osteoarthritis, particularly in weight bearing joints such as the hip. For example, compared to professional workers in one study, the hazard of disability retirement due to hip osteoarthritis was found to be much higher among male construction workers, electricians, and plumbers (HR 15.2 95%CI 7.5 to 30.8) and female professional drivers (HR 15.2 95%CI 7.5 to 30.8).(129)

1.3.2 Inflammatory arthritis

Rates of unemployment due to ill health or disability are high in participants with inflammatory rheumatic disorders: At baseline in the British Society for Rheumatology Biologics Registers (BSRBR), 49%, 41%, and 39% of rheumatoid arthritis, ankylosing spondylitis, and psoriatic arthritis patients were work disabled, respectively (self-reported and defined as not working due to ill health/disability).(130) Following first symptoms of rheumatoid arthritis, there is an estimated 80% chance (95%CI 78 – 82%) of remaining in work at two years, and an estimated 68% chance (95%CI 65% - 71%) of remaining in work at five years.(131) In Dutch patients with ankylosing spondylitis 13% had left the labour force by 5 years and 21% by 10 years, with risk for withdrawal 3.1 times higher (95%CI 2.5 to 3.7) than the general population.(11) In psoriatic arthritis, an estimated 22 – 23% left the workforce specifically as a result of their condition.(132)

Similarly, as among people with osteoarthritis, older age, physical job demands, low level of education attainment, and low functional capacity predict work disability in rheumatoid arthritis. Older age, manual work, lower social class, and worse function were predictive in ankylosing spondylitis.(133) In psoriatic arthritis, longer disease duration, manual work, low education level, worse physical function, and female sex have been associated with work disability.(132)

1.3.3 Gout

Rates of work disability among patients with gout are under-reported. However, there is some evidence to show that employees with gout take approximately 3 more days of sickness absence per year than employees without gout.(134) In a study among participants with chronic gout refractory to therapy, working participants reported a mean 25.1 days of work lost due to gout per year.(135)

1.3.4 Widespread pain

Fibromyalgia and, to a lesser extent, widespread pain conditions are strong predictors of work disability. One study compared fibromyalgia to widespread pain controls and general population controls. The prevalence of self-reported work disability was 31% among those with fibromyalgia (26.0% receiving disability pension), 10.5% among the widespread pain group (with 9.2% receiving disability pension) and 3% among the general population controls (2.2% receiving disability pension). A recent systematic review found that fibromyalgia symptom severity, and physically demanding jobs and work tasks were associated with higher risks of work disability, while perceived support of managers and colleagues helped people with fibromyalgia to manage the risk of work overload.(136)

The number of musculoskeletal pain sites is a known modifier of the impact of MSDs upon work. Multi-site musculoskeletal pain has been associated with an increased risk of low work ability,(137) sickness absence,(138,139) restrictions/limitations at work,(138) and work disability.(140–142) One longitudinal study examined the interaction between concomitant upper- and lower-body musculoskeletal pain and occupational exposures in relation to permanent work disability: Compared to people with low occupational mechanical stress and no pain, low mechanical exposures and combined pain had an adjusted hazard ratio of (HR 3.35 95%CI 1.74 to 6.45), high mechanical exposures and combined pain was associated with a higher relative hazard of permanent work disability (HR 4.59 95%CI 2.36-8.94).(143)

1.3.5 Regional pain

Low back pain is the leading cause of long-term disability worldwide.(144) In the UK, it is responsible for approximately 12.5% of all sick days (the largest single cause of absence from work in 1988 – 89)(145) and is responsible for an estimated £10 billion of indirect costs to the UK economy each year.(146) In 2004 – 05, people with work-related low back disorders took an average of 17.4 (95%CI 13.5 to 21.3) days off work due to their condition.

In the UK, musculoskeletal pain of the upper limbs or neck caused an estimated 4.7 million (95%CI 3.5 to 6.0 million) working days lost in 2004 – 05, amounting to an estimated 21.7 (95%CI 16.3 to 27.0) working days off annually for people with these conditions.(147)

Fewer working-age people have lower limb musculoskeletal disorders, however, of around 1 million people suffering a work-related disorder (i.e. a condition that is caused or made worse by work), approximately 18% reported MSDs mainly affecting the lower limb.(148) These conditions can be highly disabling, particularly affecting mobility, and in 2004 – 05 people with MSDs affecting the lower limb took an average of 26.4 (95%CI 18.6 to 34.5) days off work, per person, due to this health problem.(148)

Older age, delay between injury and first medical treatment, female gender, higher surrounding unemployment rate, and work related factors such as smaller firm size, and working in construction or logging was associated with prolonged work disability in US one study of workplace injuries.(149)

1.4 Multimorbidity

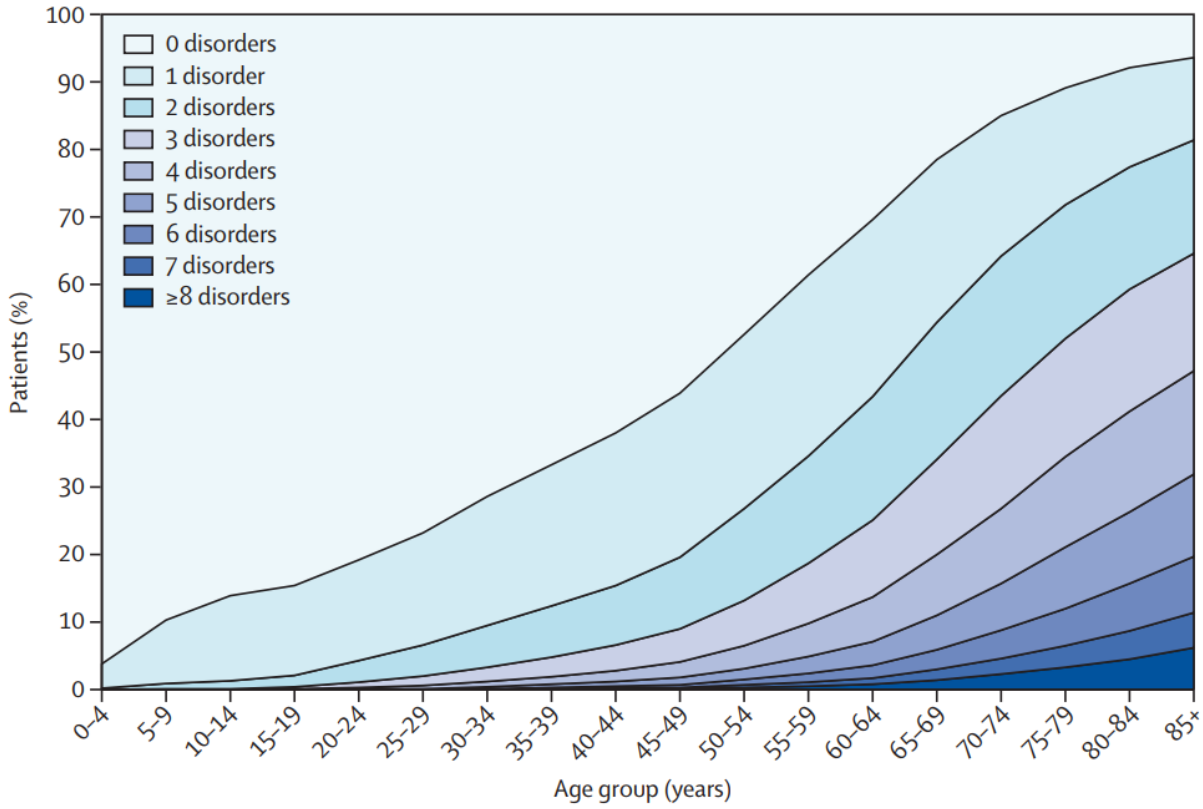
The co-existence of at least two different long-term health conditions in the same individual has been variously defined in the literature as “multimorbidity” or “comorbidity” but with a lack of clear consensus about the use of these definitions.(150) “Multimorbidity” is a broad term for the co-occurrence of multiple health problems in one person. The term “comorbidity” is generally used for any additional health disorder(s) occurring in an individual with an existing index health disorder. Importantly, these terms usually include long-term mental, as well as physical, health disorders.

The component health disorders used to classify multimorbidity are also inconsistent in the literature. For example, studies include: co-occurring long term conditions only; co-occurring long term conditions or acute conditions; or co-occurring long term conditions, acute conditions, or health-related risk factors.(150,151) Studies may also use completely different checklists of specific disorders to comprise a multimorbidity score. These difficulties with classification cause a particular problem when trying to summarise or compare prevalence estimates of multimorbidity.(152)

Reported levels of multimorbidity are especially high in the population of interest for this thesis, the older working-age between 50-65 years old. A UK based epidemiological study found that prevalence of multimorbidity correlates strongly with increasing age and was approximately 30-50% in those 50 – 65 years old (see Figure 8).(153) Therefore, to study

the impact and contribution of MSDs to health-related job loss among older workers, it is also important to consider the number and type of co-occurring health problems, i.e. the surrounding multimorbidity.

Figure 8: Number of chronic disorders by age-group.(153)



1.5 The relationship between musculoskeletal disorders and multimorbidity

Multimorbidity can occur for a number of reasons.(154) Firstly, the existing high prevalence of certain conditions mean that the likelihood of co-occurrence together in one person, by chance alone, is high, particularly for conditions which become more common with increasing age. For example, osteoarthritis and asthma may commonly co-occur but have no known etiological association. Shared risk factors between conditions can also increase the likelihood of clustering. For example, obesity increases the risk of developing both osteoarthritis and type 2 diabetes.(155,156) Finally, sometimes a pathogenic link between conditions means the risk of another developing is greater. For example, there is a known causal pathway between rheumatoid arthritis and cardiovascular disease.(157) Below, I will outline how these three mechanisms of multimorbidity relate to the common co-occurrence of MSDs and multimorbidity.

1.5.1 MSDs and multimorbidity are both highly prevalent

Due to their high prevalence, MSDs have higher odds of co-occurring with other long-term conditions, and therefore forming a component disorder in multimorbidity. In the European Union, chronic musculoskeletal pain is experienced by an estimated 100 million people;(117) back pain, has a mean estimated 1-year prevalence of 38%, worldwide;(158) and across the UK, an estimated 8.75 million people have sought treatment for osteoarthritis, the equivalent to a third of all people over 45 years of age.(75)

Similarly, evidence shows an endemic high prevalence of multimorbidity itself. In the European Union, there are an estimated 50 million people with multimorbidity and this number is expected to grow as the population ages.(159) Longitudinal evidence from various other countries also suggests that the number of people with multimorbidity is growing.(160–162) According to one estimate in England, by 2018, there will be 2.9 million people living with multimorbidity, as compared with 1.9 million in 2008.(162)

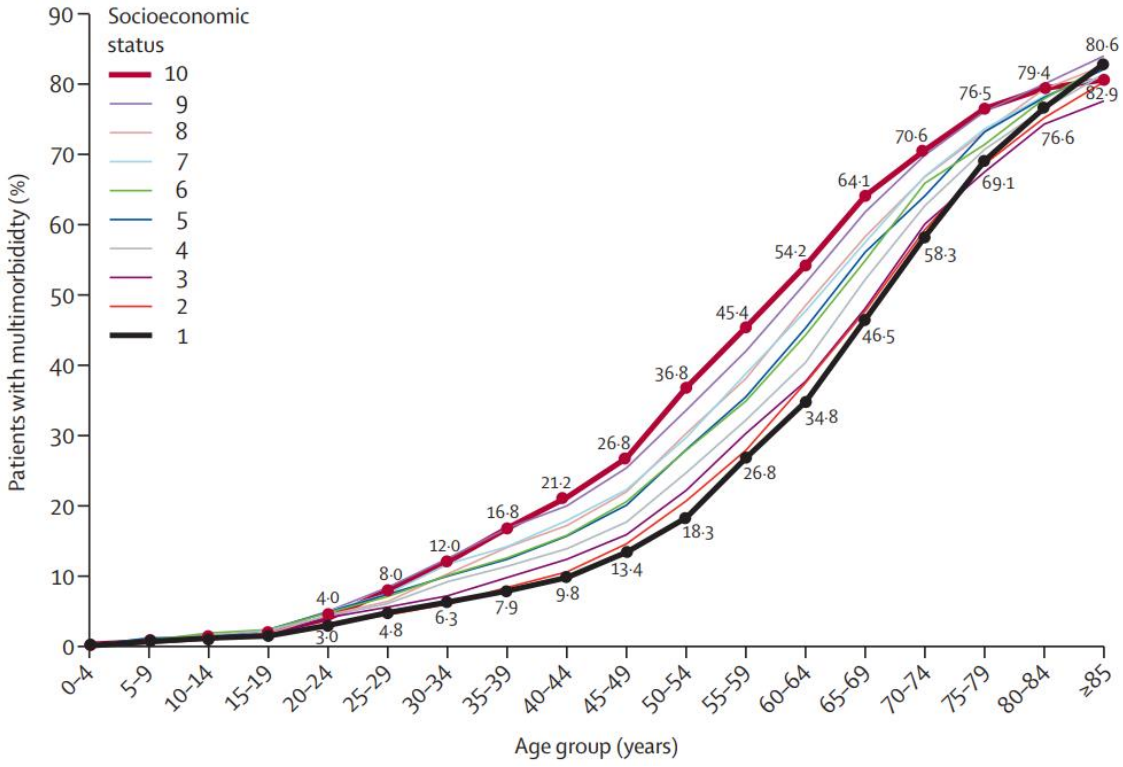
1.5.2 MSDs and multimorbidity share important risk factors

Many important risk factors for common MSDs show striking overlap with risk factors for multimorbidity, even where the definition of multimorbidity has not included MSDs. For example, age and female gender are two of the most important non-modifiable risk factors for MSDs (although this may not be true for specific conditions).(163) Likewise, there is a greater risk of multimorbidity among women as compared with men(164,165) and multimorbidity is also associated with increasing age.(152,164) The majority of people aged over 65 years are multimorbid;(153) for example, in Scotland, the estimated prevalence of multimorbidity was 64.9% amongst those aged 65-84 years and increased to 81.5% among those aged 85 years or over (see Figure 8).(153)

Modifiable risk factors such as physical inactivity and obesity are important in osteoarthritis and other regional pain syndromes, including low back pain.(155) Smoking is the main modifiable risk factor for inflammatory arthritis and lifestyle risk factors for osteoporosis include smoking, poor nutrition and low physical activity.(166) Multimorbidity has a similarly clear association with obesity,(167–171) and, while evidence about other modifiable risk factors for multimorbidity is scarce, there are parallels with those for MSDs. For instance, smoking,(169) physical activity in elderly males,(172) and nutrition(173) have been linked to multimorbidity in recent publications.

Social deprivation is associated with an increased likelihood of reporting chronic painful conditions, including arthritis and back pain.(174) For example, among English people of working age (45-64 years), the reported prevalence of arthritis was found to be more than double (21.5%) that observed in the least deprived areas (10.6%).(121) Multimorbidity also shows a strong association with social deprivation (see Figure 9);(152,153,164,165) people in the most deprived areas develop multimorbidity on average 10–15 years earlier than those living in the least deprived areas.(153) In particular, a higher risk of multimorbidity including a mental health condition has been demonstrated among people in the most deprived areas (11% versus 5.9% respectively).(153)

Figure 9: The prevalence of multimorbidity by age and socioeconomic status. On the socioeconomic scale, 1 is the most affluent and 10 is the most deprived.(153)



1.5.3 MSDs and long-term conditions may cause and exacerbate one another

Lastly, sometimes there are direct causal relationships between MSDs and other long-term conditions. For example, people with rheumatoid arthritis are at increased risk of developing several comorbid diseases including cardiovascular disease and osteoporosis because of shared aetiological pathways. In the UK, findings from the Early Rheumatoid Arthritis Study (ERAS) reported a 27.5% and 15.1% 15-year cumulative incidence of cardiovascular disease and osteoporosis in people with rheumatoid arthritis, respectively.(175)

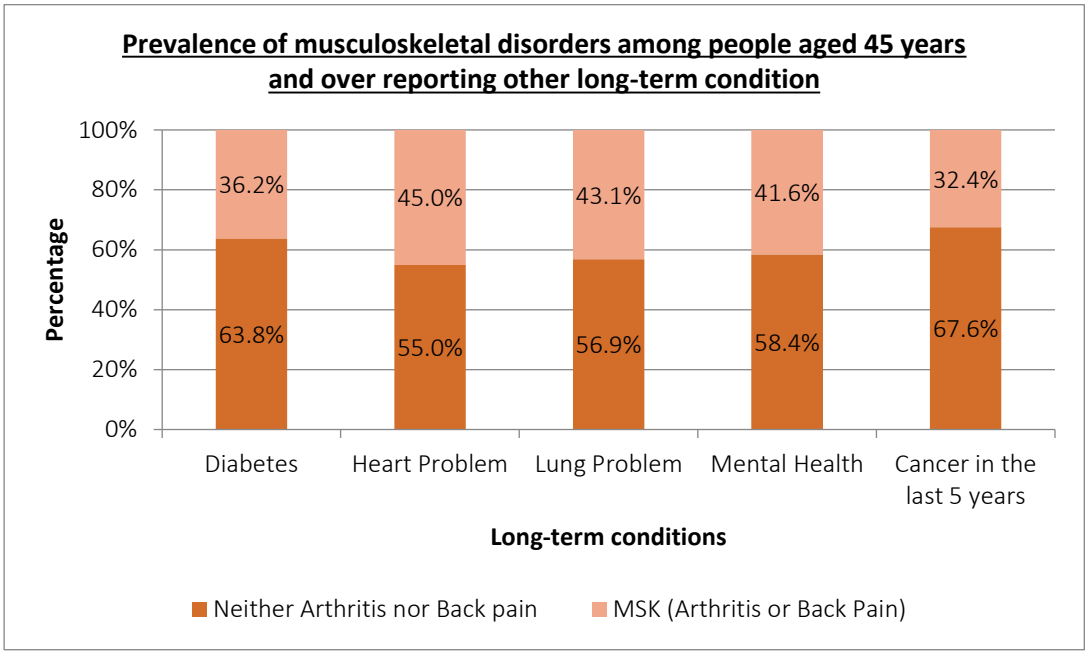
People with poor musculoskeletal health also carry a greater burden of mental health problems. MSDs, like many long-term conditions, are associated with an increased risk of mood, anxiety and substance use disorders. The association is even stronger in those with back pain or fibromyalgia.(176,177) Musculoskeletal disorders and mental health have a complex and reciprocal relationship, each exacerbating, or potentially causing, the other. Living with persistent pain can lead to depression and anxiety. Conversely, psychological distress and depression worsen the experience and reporting of pain.(178) A cycle can therefore develop, with ever-worsening pain and low mood leading to social withdrawal and isolation. People with mental health conditions may also delay seeking treatment, and clinicians may underestimate physical symptoms, attributing these to an individual's mental health condition.(179)

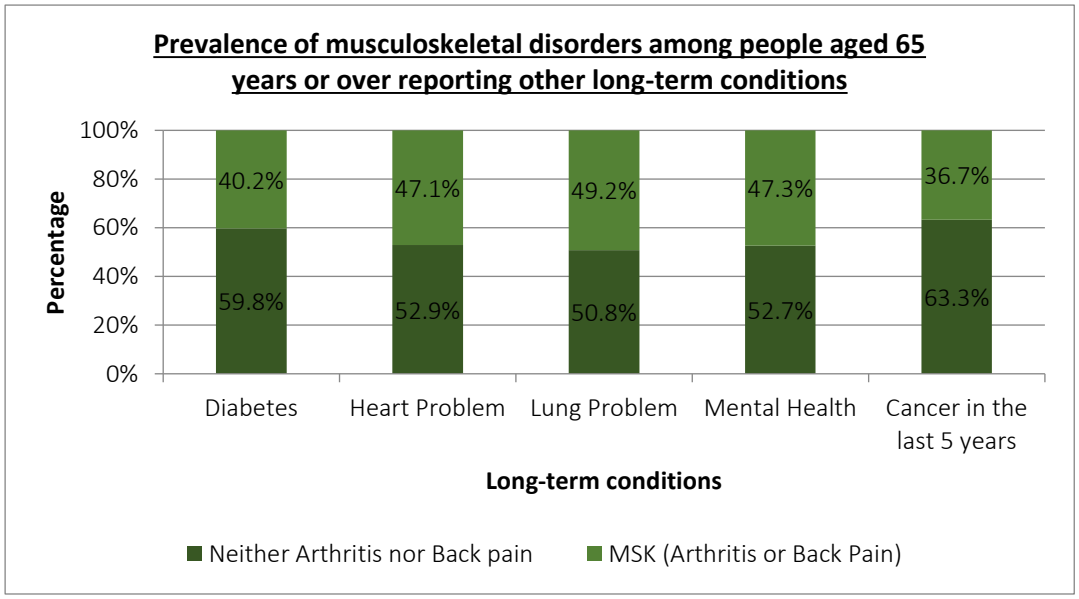
1.5.4 MSDs and multimorbidity frequently occur together

A combination of the factors discussed above explains the high prevalence of musculoskeletal disorders found alongside other long-term conditions as part of multimorbidity. For example, it has been shown that among English primary care patients (> 45 years of age) reporting living with a major long-term condition, almost a third also have a musculoskeletal condition.(121) Moreover, among those aged > 65 years, almost half of those with a heart, lung, or mental health problem also had an MSD (see Figure 10).(121) In the most deprived populations, painful conditions, such as osteoarthritis and back pain, are the most common multimorbidity among those already living with heart disease, diabetes, chronic obstructive pulmonary disease (COPD) or cancer.(153)

The converse is also true: people with an MSD have been shown to be more likely to have at least one other long-term condition. For example, according to the results of one study, four out of five people with osteoarthritis had at least one other long-term condition such as hypertension or cardiovascular disease.(180)

Figure 10: Prevalence of musculoskeletal disorders among English people a) aged 45 years and over and b) aged 65 years and over, reporting other long-term conditions.(121,122)

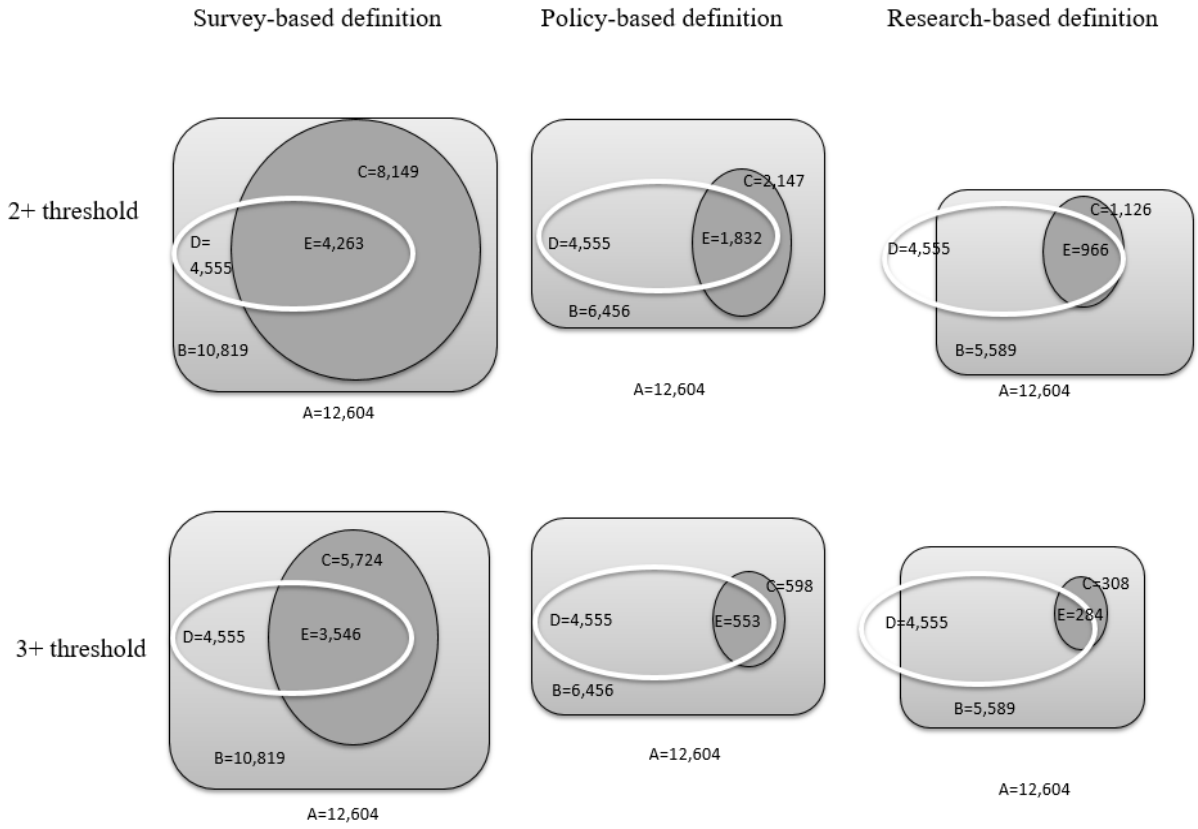




In order to visualise the relationship between MSDs and multimorbidity, and recognising the varying multimorbidity criteria used in the literature, a recent cross-sectional study used three definitions to define the prevalence of multimorbidity in working-age Australians. Two multimorbidity thresholds (i.e. minimum of 2+ or 3+ conditions) were compared, as well as three definitions of multimorbidity from three sources: a survey-based definition from the Australian National Health Survey; a policy-based definition from

the Australian National Health Priority Areas; and a research definition from a well-cited systematic review. They found that irrespective of how multimorbidity is defined, musculoskeletal disorders are a near-ubiquitous feature of multimorbidity (see Figure 11).(181)

Figure 11: Overlap between Australian populations with musculoskeletal disorders and multimorbidity as defined by different definitions and thresholds. A- total working-age sample population; B- sub-sample with at least one condition; C- sub-sample with multimorbidity; D- sub-sample with any musculoskeletal condition; E- musculoskeletal sub-sample considered multimorbid. Lowe et al. reproduced with permission from BioMed Central.(181)



1.6 MSDs and multimorbidity exacerbate one another

Beside the fact that MSDs and multimorbidity commonly co-occur, there is also strong evidence that MSDs and multimorbidity interact to exacerbate the health- and treatment-burden on patients, as outlined below.

1.6.1 MSDs and multimorbidity interact to worsen health-burden

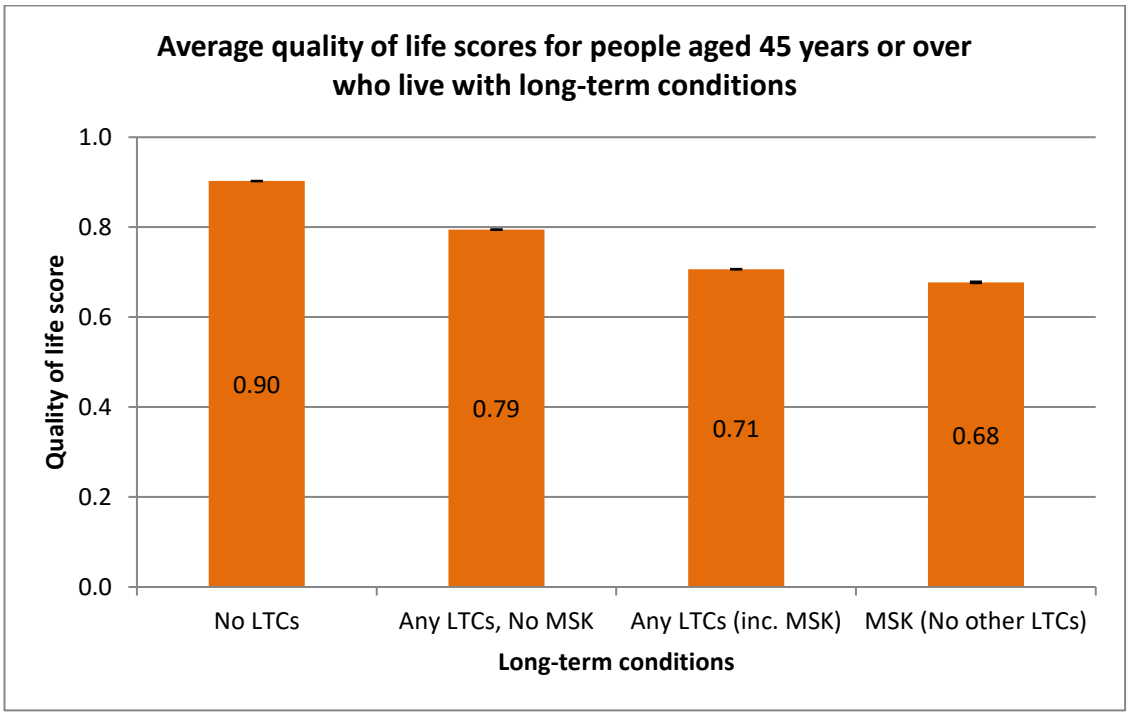
Morbidities tend to accrue in individuals. For example, as the number of physical comorbidities increase, so too does the likelihood of developing a mental health problem.(153) This accumulation of pathologies contributes to the complex and numerous

needs of people with multimorbidity. People with multimorbidity are less able to perform everyday tasks due to functional decline(182) and have worsened quality of life and health outcomes than those with one index condition.(183) For instance, across a range of index diseases, the presence of a comorbidity is consistently shown to increase mortality rates when compared to the index disease alone.(183)

MSDs play an important role in worsening the health-impacts of multimorbidity. They are the third largest cause of disability adjusted life years (DALYs) and the largest single cause of years lived with disability (YLD).(184) Pain is also a very common feature of most MSDs. For example, 78% of people with arthritis surveyed by Arthritis Research UK reported that they experience pain most days, with 57% experiencing pain every day.(185) Activities of daily living (ADLs or instrumental ADLs) such as bathing, dressing, getting out of bed or a chair, completing housework, preparing meals and shopping are frequently affected by the pain, along with other common MSD symptoms, such as stiffness, restricted mobility and impaired physical functioning.(186) People often need to make adaptations to their home to enable them to cope. Moreover, symptoms of MSDs, particularly those with an inflammatory cause, tend to fluctuate in severity over time so that their effects are unpredictable.(187–189) The pain, distress and functional limitations caused by MSDs greatly reduce independence and quality of life, and impair an individual's ability to participate in family, social and working life.(166) Arthritis and back pain, in particular, are amongst the most common causes of reduced health-related quality of life in the individual and, because of their high prevalence, the wider population.(165,178)

Self-reported Quality of Life (QoL) scores can be used to understand the personal impact of long-term conditions and to show the contribution of specific diseases to poor health in multimorbidity. In a national English survey, people living with one or more non-musculoskeletal long-term conditions reported substantially poorer quality of life than those without a long-term condition (QoL score 0.79 vs 0.90, respectively). However, quality of life was even more significantly reduced among those who had arthritis or back pain as part of their multimorbidity (QoL score 0.71). Notably, the impact of musculoskeletal disorders was significant enough that living with arthritis or back pain resulted in impaired quality of life irrespective of whether arthritis or back pain were the only condition (QoL score 0.68) or were one among multimorbidity (QoL score 0.71) (see Figure 12). This suggests that MSDs disproportionately reduce quality of life in multimorbidity, when compared to other long-term health disorders.(121)

Figure 12: Average Quality of Life scores for people aged 45 years and over who live with long-term conditions (LTCs). Long-term conditions are defined as conditions that cannot be cured but are controlled by medication and/or other treatment/therapies.(121,122)



1.6.2 MSDs and multimorbidity interact to worsen treatment-burden

Despite the proven effectiveness of many individual therapies commonly used in long term conditions, each additional therapy carries a 'treatment burden.' Treatment burden is a concept that encapsulates the physical effects of treatment, financial losses, and the psychosocial effects of time demands and dependence on others for assistance.(190) Predictably, the effects of treatment burden increase for a person receiving multiple treatments for multiple health problems. For example, a review of five UK disease-based clinical guidelines concluded that implementation of all individual disease best practice recommendations for a person with multimorbidity would result in polypharmacy.(191) Instead, recent clinical guidance recommends a person-centred approach to multimorbidity, prioritising treatments that improve quality of life while minimising overall treatment burden.(192)

MSDs can contribute significantly to the overall number of treatments a person receives. The management of MSDs aims to improve quality of life by reducing joint pain and stiffness, limiting progression of joint damage and maintaining or restoring functional ability,(193) but achieving this can necessitate the use of a range of interventions. This includes non-drug interventions, for example, physical activity, heat/cold or physiotherapy.

Additionally, drug therapies for MSDs may include topical or oral medication to ease joint pain and stiffness, and reduce inflammation. Amongst those severely affected, surgery may be required for people living in constant pain from arthritis, for example, osteoarthritis is responsible for over 90% of initial hip and knee joint replacements.(194,195)

1.6.3 MSDs and multimorbidity interact to impair self-management, leading to health and social decline

People with multiple long-term conditions are often required to carry out numerous tasks to maintain their health and administer their healthcare. This includes managing different tablets to be taken at specific times of day, or week, or only occasionally, keeping stock of their pills, creams, inhalers and injections, requesting repeat prescriptions on time, and visiting the pharmacy to collect items. Monitoring of treatment effectiveness with regular blood tests or physical tests (e.g. blood pressure measurement) may be required, and this may necessitate additional visits to the GP, or to the hospital, or may require an additional burden placed upon the individual (e.g. self-monitoring of blood glucose in diabetes mellitus).(190) As health systems are largely configured to treat individual diseases rather than support those living with multimorbidity,(153) managing multiple long-term conditions may require the attention of an array of separate health and care professionals at home, in the community and in hospitals. The time and effort required to remember and attend these appointments (including travel time and car parking or negotiating with hospital transport) contributes to the treatment burden.(190)

Having a musculoskeletal condition as part of multimorbidity makes all these activities more difficult. The Centres for Disease Control and Prevention's (CDC) Arthritis Program in the USA has identified nine functional limitations that people with arthritis report as being 'very difficult' or that they 'cannot do,' including grasping small objects, lifting or carrying, prolonged sitting or standing, walking ¼ mile, climbing stairs, and stooping, bending or kneeling.(196) As a result, comorbid arthritis or back pain substantially restrict the function and daily activities of people living with cardiovascular disease, diabetes and respiratory disease.(197) In addition, the unpredictable fluctuations in symptom severity that are a frequent feature of musculoskeletal disorders restrict mobility and can make attending hospital or GP appointments and planning ahead difficult, directly limiting people's ability to manage their health.

Therefore, for a person who is just managing despite their multiple long-term conditions, developing arthritis can take away their ability to cope with, or afford, treatment. This may

prevent effective self-management for other long-term conditions, which could then worsen. For example, people with painful osteoarthritis alongside their other long-term conditions have been shown to have increased risk of needing hospital admission.(198) Therefore, the co-occurrence of multimorbidity and an MSD may be a "tipping point", depriving people of their ability to maintain their health and independence, leading to a spiral of decline.

1.7 MSDs, multimorbidity, and the workforce

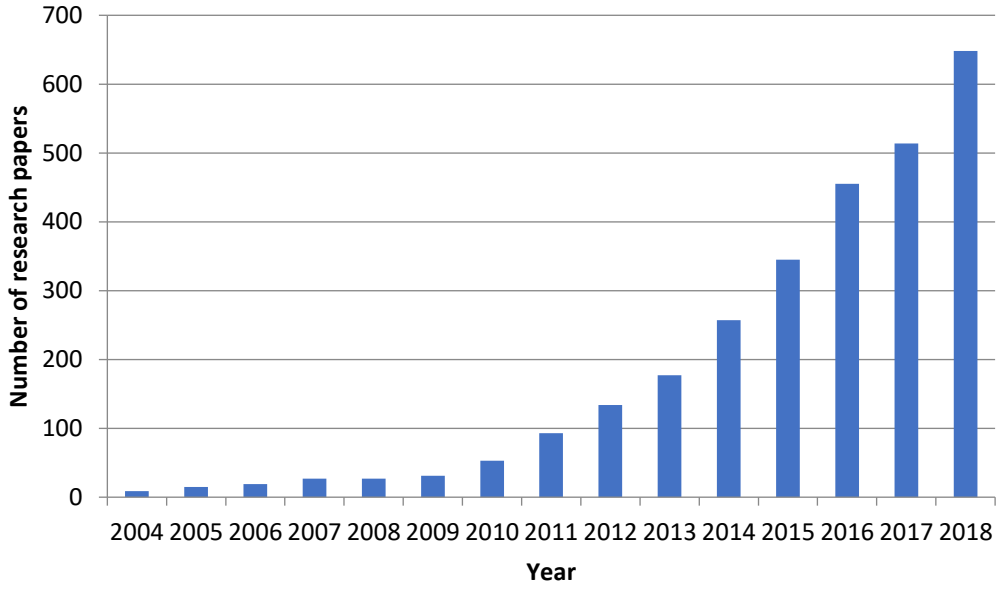
Musculoskeletal disorders and their impact upon work in the older working-age population has primarily been studied without consideration of the presence of co-occurring health disorders, or with only simple adjustment for presence or absence of comorbidity. This has left an important research gap since the overlap between MSDs and multimorbidity is significant and likely to be impactful, as outlined above. In addition, health disorders co-occurring with MSDs may interact in different ways to impact a person's ability to stay employed.

Multimorbidity-focused and work-focused research are two emerging fields which have both seen an increase in interest over recent years (see Figure 13). However, literature focused on both multimorbidity *and* work outcomes is scarce. Of the existing literature, it has been shown that the type of co-occurring long-term conditions, and not only the crude number of long-term conditions, is important for work outcomes.(199) However, there appears to be little research considering common patterns of co-occurring health disorders and the association of these common health disorder groups with work outcomes.

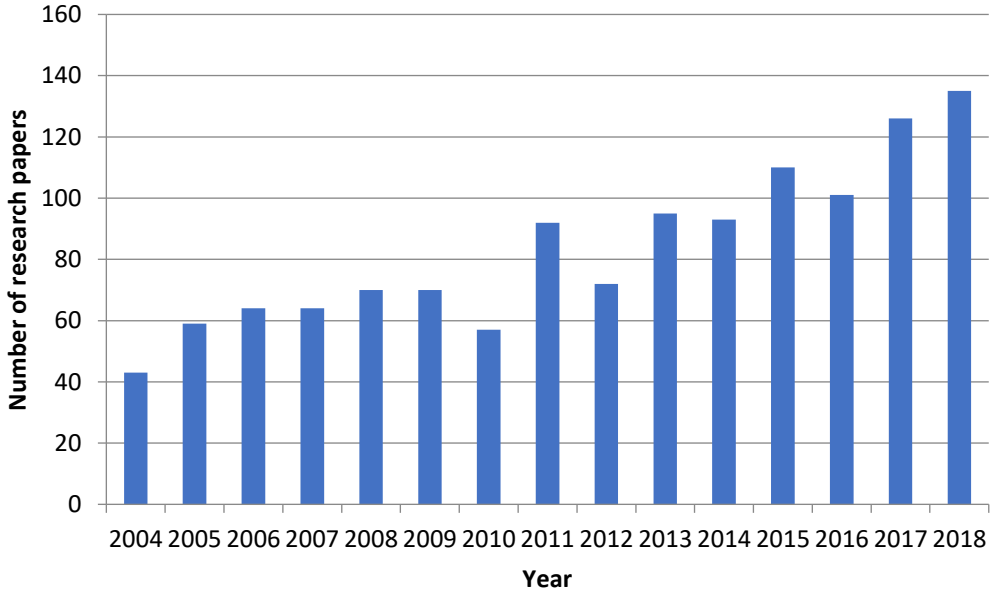
Given the recognised individual impact of MSDs on work outcomes, and their strong relationship with multimorbidity, it is likely that MSDs disproportionately contribute to the overall impact of multimorbidity upon work. To illustrate this, one recent cross-sectional study of a Dutch household survey among people of working age (18 – 65 years) showed that the effect of multimorbidity upon work disability, sickness absence, and unemployment, is significantly amplified when MSDs are included in the classification of multimorbidity.(200) However, these results have yet to be replicated in a study of the older working-age population in the UK.

Figure 13: Number of search results by year, from Pubmed using the following search terms a) "multimorbidity" and b) "work disability"

a) "multimorbidity"



b) "work disability"



1.8 Summary

There is a movement to encourage people to continue work to older ages. Of particular interest are the age group 50 – 65 years old in whom work participation drops off steeply in the UK. Much of this work loss appears to be health-related due to the proliferation of health problems in this age cohort. Employment appears to carry many benefits, even

among people with chronic health disorders, as it has advantages for personal finance, quality of life, mood, sense of identity, and for the health of the whole family. Therefore, people with chronic health problems who want to remain in work should be supported to do so. However, interventions to support work participation require person-centred, co-ordinated care involving healthcare professionals, patients, and employers. These can be expensive and time consuming. Targeting high-risk disease groups is therefore economically advantageous.

MSDs appear to be a key causal disease group for work disability; however, since they frequently co-occur with other health conditions in the older working-age population, research that explores the relationship between comorbidity and adverse work outcomes in musculoskeletal populations is needed. As MSDs are highly prevalent, such research would help to identify important sub-groups that are high-risk for poor work outcomes among the MSD population.

In addition, the impact of multimorbidity, in general, upon a person's ability to stay in work is also not well understood or characterised in the older working-age population. In exploring the relationship between multimorbidity and poor work outcomes, it is important to go beyond a crude count of the number of comorbid conditions to classifying multimorbidity, as the type of co-occurring conditions, not just the number, is likely to be important.

Chapter 2- Aims and Objectives

2.1 Research aims

Therefore, the overarching aims of this thesis are to investigate, among older working-aged people, a) the impact of common comorbid health conditions on work outcomes in people with MSDs, and b) the common patterns of multimorbidity and their contribution to health-related job loss.

2.2 Research objectives

1. To systematically review evidence for the impact of comorbidity upon work outcomes among people with musculoskeletal disorders

Among a sample of older workers (50 – 65 years old)

2. To describe a representative sample of participants with health-related job loss for their demographic factors, lifestyle factors, and health disorders
3. To explore the association between demographic factors, lifestyle factors, and health disorders and the occurrence of health-related job loss
4. To describe patterns of multimorbidity and which health disorders commonly co-present
5. To explore the association between common patterns of multimorbidity and the occurrence of health-related job loss
6. To explore the relationship between musculoskeletal disorders, with and without comorbidity, and health-related job loss
7. To estimate the population attributable fraction of health disorders and multimorbidity for health-related job loss in the English older working-age population

Chapter 3 – Methods

3.1 Introduction

In this chapter, the study population are introduced, and data collection and broad methodological techniques which will be used are discussed. This includes methods used for obtaining data relating to study participants' demographics and employment history and for estimating clinical disease burden and multimorbidity. In addition, the main statistical techniques applied in this thesis are described. Other methodological techniques relevant only to specific research questions will be detailed within their respective chapters.

3.2 The study population and data sources

One population of study participants, and two sources of primary data were explored in this thesis. Study participants were from the Health and Employment After Fifty (HEAF) study, which is a prospective cohort of a representative sample of primary care patients, in England. These participants were recruited from 24 selected GP practices between 2013 and 2014 and provided data from postal questionnaires and their electronic clinical records. As part of the HEAF study, participants received a baseline questionnaire which contained items relating to demographics, employment, and health. Participants also gave written consent that their clinical records, pharmaceutical and diagnostic information could be accessed from the Clinical Practice Research Datalink (CPRD).(201) These data sources will be described in more detail in the following sections.

3.3 Ethical approval

The HEAF study received ethical approval from National Research Ethics Service Committee North West-Liverpool East. While no ethical approval is required for research using CPRD primary care data with selected established data-linkages, proposed studies with patient involvement require separate ethical approval, for example, where CPRD data is being linked to questionnaire responses. The HEAF study link to CPRD data received ethical approval from the Independent Scientific Advisory Committee of the Clinical Practice Research Datalink.

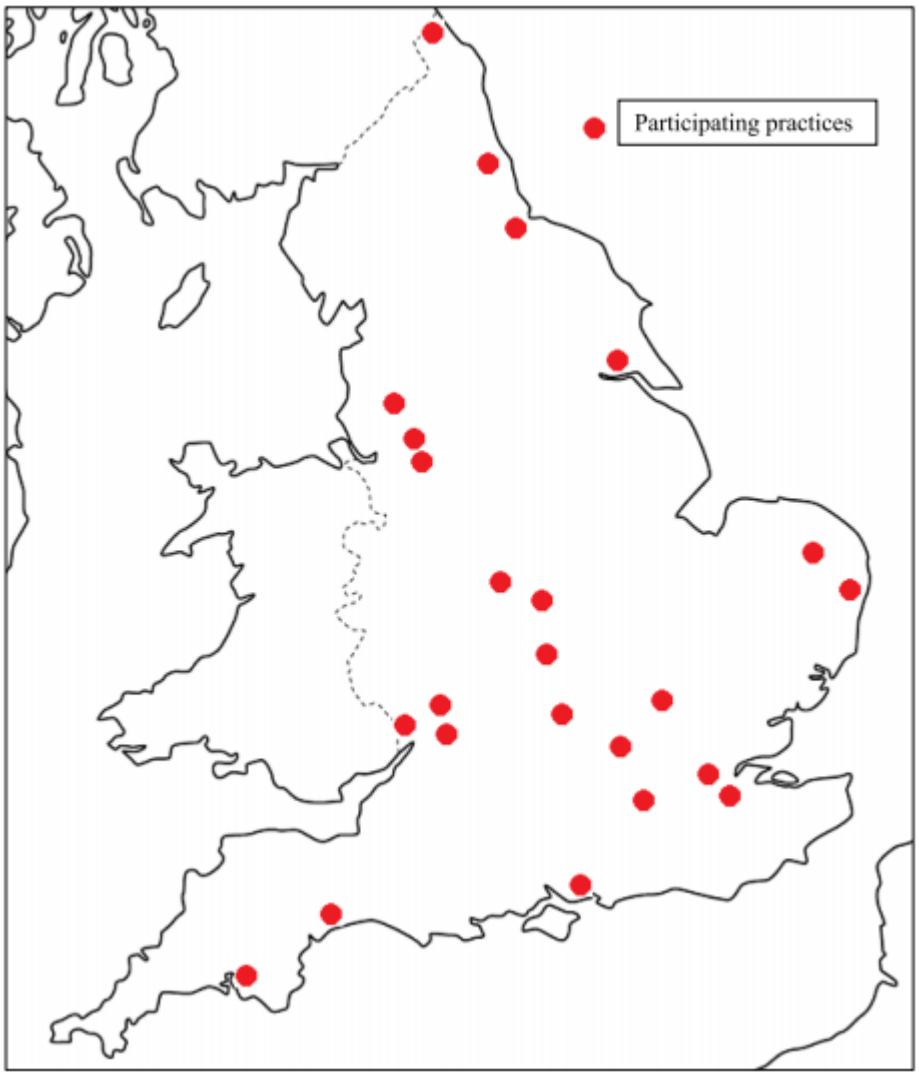
3.4 The HEAF study

3.4.1 Background

The HEAF study is a large prospective cohort study recruiting older working-age adults, between 50 – 64 years of age, from primary care settings (GP practices).(201) The HEAF cohort was established in 2013 Professor Keith Palmer and Professor Karen Walker-Bone based at the Medical Research Council Lifecourse Epidemiology Unit (MRC-LEU) in Southampton. The cohort was set up to examine the relationship between work, health and wellbeing, particularly: i) to assess the health benefits and risks of remaining in work to older ages; and ii) to assess how health itself impacts on employment outcomes, such as job-loss and sickness absence using prospective follow up of these participants. The sampling frame comprised the registers of 24 general practices (GPs) across England. These practices responded to an advert inviting CPRD-contributing practices to take part in the study. GPs were based in England to allow later linkage with other English based databases such as the Hospital Episode Statistics. Although there was no requirement that the distribution of included participants' occupations be nationally representative, GPs contributing to the sampling frame did provide a broad geographical spread which allowed recruitment from the North, Midlands, and South of England (see Figure 14). This was advantageous since rates of population work participation, types of health disorders, and interactions with healthcare are likely to differ between regions.(201)

A full-time team of clinical, database, and information managers, data entry and administrative staff, and statisticians oversee the continued running of the HEAF study as well as the initial processing of HEAF study participant data. This takes place in the MRC-LEU, which is based on the grounds of Southampton General Hospital.

Figure 14. location of GP practices participating in the HEAF study.(201)



3.4.2 Eligibility and contacting participants in the HEAF study

Eligible participants were registered at one of the participating GPs and were born between 1948 and 1962, in order to recruit from the target age band of 50 – 64 years of age. General practitioners, in the participating practices, were asked to review the list of eligible participants and exclude those patients whom they considered would be inappropriate to approach, e.g. because of recent bereavement or terminal illness. Initially, the participating practices mailed a single invitation to the study, without reminder. Participants' contact details were not given to researchers unless the participants gave this information voluntarily to the team by returning the baseline questionnaire and signed consent form to the MRC-LEU. The consent form also gave an opportunity for participants to give or decline access to their CPRD data. Those who declined CPRD linkage were not included in this thesis.(201)

3.4.3 The HEAF baseline questionnaire

Although the HEAF study is a prospective study, with annual questionnaire follow up, data used in this thesis was derived from the initial HEAF baseline questionnaire, distributed in 2013 – 2014. As mentioned, this questionnaire contained detailed information about employment, health and wellbeing. The cover page and an example of one of the data entry forms is displayed in Figure 15, below. Of the items that were relevant to this thesis, participants responded to questions about their date of birth, gender, ethnicity, marital status, education, employment status, and occupation. The work of this thesis mostly depended on CPRD records to define health exposures. However, the HEAF baseline questionnaire was also used to extract information about a participant's smoking habits. These questionnaire-derived variables are described in more detail below.

3.4.4 Data cleaning

HEAF participant data was extracted and cleaned by the MRC-LEU team in Southampton before being used for research. Following the return of the study questionnaires by post, information was independently extracted into an electronic database by two data entry personnel. To minimise the risk of transcription error, any disagreements were highlighted and compared to the original questionnaire entry for accuracy. Following extraction, electronic participant data was cleaned. Initially, the dataset was cleaned of any remaining formatting or transcription errors by a database manager. Following this, a statistician looked for any incongruent data patterns across individual participants, for example, in the case of a participant who initially described himself as unemployed but went on to describe the qualities of his current job. For events such as these, an investigation of the original questionnaire was once again performed to derive the most likely meaning. Where erroneous data was unreconcilable, the information was not used for research. Once these processes were complete, electronic data was available for my use.

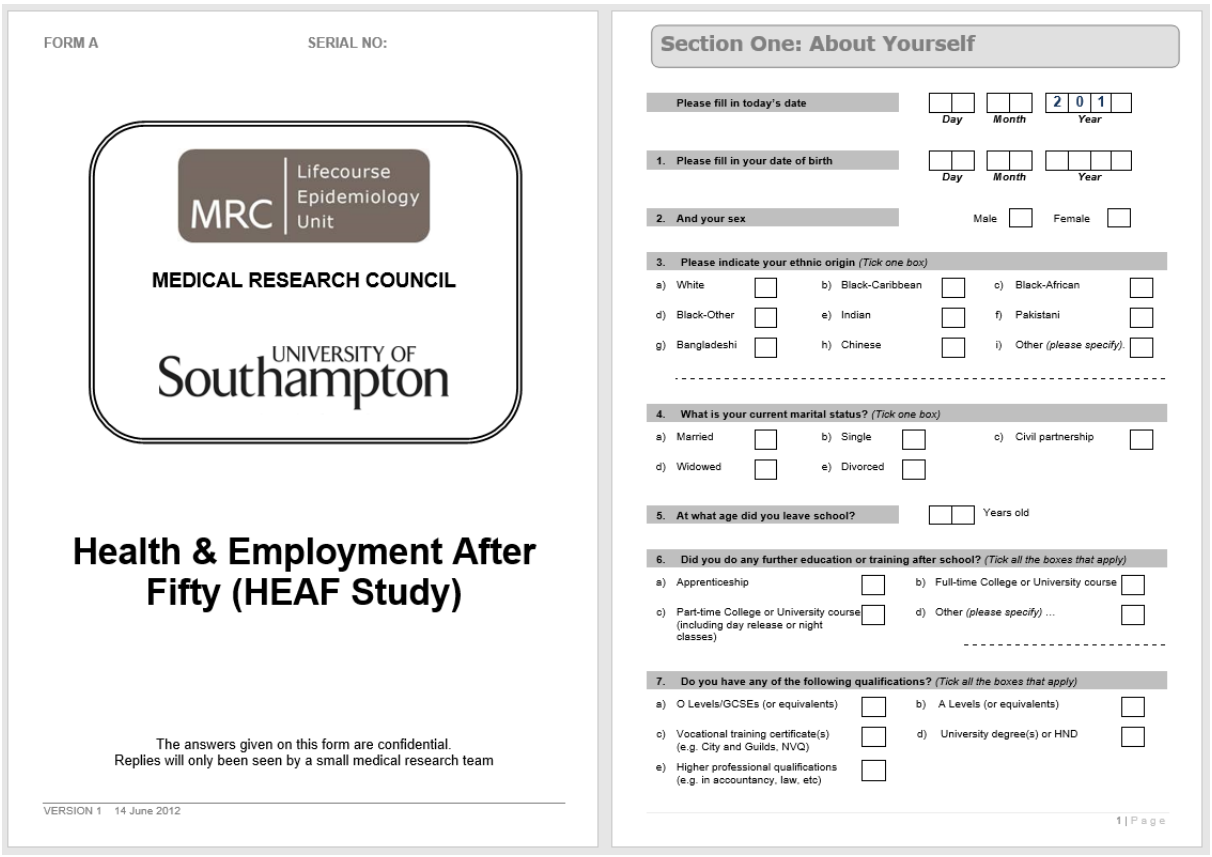
3.4.5 Variables derived from the HEAF baseline questionnaire for this thesis

For the main demographic variables, participants reported both their date of birth and the date of questionnaire completion; age was therefore derived by calculating the number of years between these two dates. Participants indicated their sex as being either "male" or "female" and their ethnicity as being one of the following categories: "White", "Black-Caribbean", "Black-African", "Black-other", "Indian", "Pakistani", "Bangladeshi", "Chinese", or "other", which could be specified in a free text space. Additionally, participants indicated

their marital status and could specify one of the following categories: “married”, “single”, “civil partnership”, “widowed”, or “divorced”.

To derive information about level of education, participants were asked to indicate whether they had any of the following qualifications: “O levels/GCSEs”, “A levels”, “vocational training certificates”, “university degree(s) or HND” (Higher National Diploma), or “higher professional qualifications”. From these responses I could derive a person’s highest qualification level. For analysis, these categories could be viewed at different levels of resolution. For example, there were few participants for whom A-level was the highest qualification level, likely because people completed their A-levels with a view to entering higher education. Therefore, I combined O level/GCSE and A level categories to form a “high school and sixth form” level of qualifications. In addition, I observed that many HEAF participants had indicated obtaining higher professional qualifications but not university degree level qualifications. This suggests that the “higher professional qualifications” were unlikely to be masters or PhD-level qualifications. I therefore considered university level qualifications the highest strata of education, followed by vocational and higher professional qualifications, then high school and sixth form, and finally, no qualifications.

Figure 15. Cover page and page one (of 15) from the HEAF study baseline questionnaire.



FORM A SERIAL NO:

MRC Lifecourse Epidemiology Unit

MEDICAL RESEARCH COUNCIL

UNIVERSITY OF Southampton

Health & Employment After Fifty (HEAF Study)

The answers given on this form are confidential.
Replies will only been seen by a small medical research team

VERSION 1 14 June 2012

Section One: About Yourself

Please fill in today’s date — Day / Month / Year: 2 0 1

1. Please fill in your date of birth — Day / Month / Year

2. And your sex — Male ☐ Female ☐

3. Please indicate your ethnic origin *(Tick one box)*

a) White ☐ b) Black-Caribbean ☐ c) Black-African ☐
d) Black-Other ☐ e) Indian ☐ f) Pakistani ☐
g) Bangladeshi ☐ h) Chinese ☐ i) Other *(please specify)*. ☐

4. What is your current marital status? *(Tick one box)*

a) Married ☐ b) Single ☐ c) Civil partnership ☐
d) Widowed ☐ e) Divorced ☐

5. At what age did you leave school? ☐☐ Years old

6. Did you do any further education or training after school? *(Tick all the boxes that apply)*

a) Apprenticeship ☐ b) Full-time College or University course ☐
c) Part-time College or University course (including day release or night classes) ☐ d) Other *(please specify)* ... ☐

7. Do you have any of the following qualifications? *(Tick all the boxes that apply)*

a) O Levels/GCSEs (or equivalents) ☐ b) A Levels (or equivalents) ☐
c) Vocational training certificate(s) (e.g. City and Guilds, NVQ) ☐ d) University degree(s) or HND ☐
e) Higher professional qualifications (e.g. in accountancy, law, etc) ☐

1 | Page

Study participants also responded to questions about employment status and occupation, indicating their current employment status as either “employed”, “self-employed”, “unemployed”, or “retired”. Participants who stated that they were currently in paid work gave their job title and indicated the industry in which they worked. Likewise, participants who were not currently in paid work indicated the job title of their last paid occupation and the date at which they left this job. These participants were also asked whether they left work because of a health problem and could respond “no, not at all”, “yes, a health problem was the main reason for leaving”, or “yes, a health problem was part of the reason for leaving”. For those who considered a health problem to be a factor in their leaving work, an additional question about the type of health problem was asked, and response options included: “a problem with your back, neck, arm, shoulder or leg”, “a mental health problem or stress”, “a problem with your heart or lungs”, or “another type of health problem.”

Lastly, the HEAF questionnaire included participant’s smoking history. Participants were asked: if they had ever smoked regularly; how old they were when they first started smoking regularly; whether they still smoked regularly; and, if no, their age when they last smoked regularly. Using this information, and the participant’s date of birth, I could derive a person’s smoking status at any point in time prior to the baseline questionnaire.

3.4.6 Deriving classifications of work and socioeconomic class from a participant’s self-reported job title in HEAF

3.4.6.1 The Standard Occupational Classification system

The Standard Occupational Classification 2010 system (SOC-10) is a commonly used UK-based system, developed by the Office of National Statistics (ONS).(202) In the HEAF study, this system was used to group jobs according to their skill specialisation and skill level. Firstly, the SOC-10 four-digit codes split occupations into major, sub-major, minor, and unit occupation groups based on specialisation type. For example, the SOC-10 code 2112 corresponds to: major category 2 (professional occupations); sub-major category 1 (science, research, engineering and technology professionals); minor category 1 (natural and social science professionals and unit occupation group); and unit category 2 (biological scientists and biochemists). The SOC-10 separation of occupations by the major specialisation groups is outlined in Table 1, below.(202)

Table 1: General nature of qualifications, training and experience for occupations in SOC-10 major groups as described in "Standard Occupational Classification 2010: Volume 1 Structure and descriptions of unit groups" (202)

Code	Major SOC-10 group	General nature of qualifications, training, and experience required for occupations in the major group
1	Managers, directors and senior officials	A significant amount of knowledge and experience of the production processes and service requirements associated with the efficient functioning of organisations and businesses.
2	Professional occupations	A degree or equivalent qualification, with some occupations requiring postgraduate qualifications and/or a formal period of experience-related training.
3	Associate professional and technical occupations	An associated high-level vocational qualification, often involving a substantial period of full-time training or further study. Some additional task-related training is usually provided through a formal period of induction.
4	Administrative and secretarial occupations	A good standard of general education. Certain occupations will require further additional vocational training to a well-defined standard (e.g. office skills).
5	Skilled trades occupations	A substantial period of training, often provided by means of a work-based training programme.
6	Caring, leisure and other service occupations	A good standard of general education. Certain occupations will require further additional vocational training, often provided by means of a work-based training programme.
7	Sales and customer service occupations	A general education and a programme of work-based training related to Sales procedures. Some occupations require additional specific technical knowledge but are included in this major group because the primary task involves selling.
8	Process, plant and machine operatives	The knowledge and experience necessary to operate vehicles and other mobile and stationary machinery, to operate and monitor industrial plant and equipment, to assemble products from component parts according to strict rules and procedures and subject assembled parts to routine tests. Most occupations in this major group will specify a minimum standard of competence for associated tasks and will have a related period of formal training.
9	Elementary occupations	Occupations classified at this level will usually require a minimum general level of education (i.e. that which is acquired by the end of the period of compulsory education). Some occupations at this level will also have short periods of work-related training in areas such as health and safety, food hygiene, and customer service requirements.

The sub-major specialisation categories of SOC-10 have also been arranged by skill level, which was defined in relation to the content of, and time taken to attain, qualifications, training, and work experience to be able to perform the work. The first skill level comprises

occupations suitable for a person who had completed compulsory education and requiring only short periods of work-related training, for example cleaning and catering assistants; the second skill level includes occupations of a similar level of education but involving longer work-related training or experience, such as driving, caring, or secretarial work; the third level contains occupations that normally involve a knowledge base requiring qualifications at a sub-degree level and potentially a long period of work experience; and the fourth skill level includes "professional" occupations that usually require degree-level education or an equivalent period of work experience.(202) The separation of sub-major specialisation groups by skill level can be observed in Table 2, below.

Table 2: the sub-major groups of SOC-10, by skill level. as described in "Standard Occupational Classification 2010: Volume 1 Structure and descriptions of unit groups" (202)

Skill level	Code	Sub-major group of SOC-10
Level 4	11	Corporate managers and directors
	21	Science, research, engineering and technology professionals
	22	Health professionals
	23	Teaching and educational professionals
	24	Business, media and public service professionals
Level 3	12	Other managers and proprietors
	31	Science, engineering and technology associate professionals
	32	Health and social care associate professionals
	33	Protective service occupations
	34	Culture, media and sports occupations
	35	Business and public service associate professionals
	51	Skilled agricultural and related trades
	52	Skilled metal, electrical and electronic trades
	53	Skilled construction and building trades
	54	Textiles, printing and other skilled trades
Level 2	41	Administrative occupations
	42	Secretarial and related occupations
	61	Caring personal service occupations
	62	Leisure, travel and related personal service occupations
	71	Sales occupations
	72	Customer service occupations
	81	Process, plant and machine operatives
	82	Transport and mobile machine drivers and operatives
Level 1	91	Elementary trades and related occupations
	92	Elementary administration and service occupations

3.4.6.2 Assigning SOC-10 occupational classifications in HEAF

Each participant included in HEAF was assigned a four-digit SOC-10 code, based on their reported job title and industry. These codes were assigned by two personnel using the Computer Assisted Structured Coding Tool (CASCOT), a computer programme which facilitates the conversion of text information to standard classifications.(203) CASCOT automatically assigned a SOC-10 code to each participant's self-reported job title along with a percentage score representing the certainty of the match between the given job title and the specific SOC-10 category. The Warwick Institute for Employment Research recommends an optimal match certainty threshold of 64%, above which text can be automatically assigned to occupational codes by CASCOT.(204) Therefore, initially, all participant's occupations were automatically assigned SOC-10 codes, then those codes to which CASCOT had assigned a match certainty greater than 64% kept their assigned SOC-10 codes. Finally, those with match certainty lower than 64% were manually reviewed by two HEAF study personnel for accuracy. Those job titles for which the automatically assigned SOC-10 code appeared inappropriate were manually reassigned new SOC-10 codes using the most likely alternative occupational code.

3.4.6.3 Defining socioeconomic status using the National Statistics Socio-economic Classification

The SOC-10 information was mapped onto the National Statistics Socio-economic Classification (NS-SEC) which is also a UK-based classification system developed by the ONS.(205) The NS-SEC organises occupations into socioeconomic strata by considering aspects of a person's labour market situations and work situations. "Labour market situations" relates to source of income, economic security, and prospects of economic advancement, while "work situations" refers to a person's location in authority structures at work and their degree of autonomy/control at work. As such, SOC-10 codes can be arranged into a socio-economic hierarchical classification system with never worked and long-term unemployed at the bottom, and employers in large establishments at the top.

The NS-SEC can be derived from SOC-10 using a full (gold-standard), reduced, or simplified method. Since the HEAF questionnaire did not collect information about a participant's supervisory roles or whether the employing organisation employed 25 or more employees, I used the simplified method, which relies entirely on a participants SOC-10 code and has been found to correctly allocate 88% of participants, compared with the full method.(205)

3.4.6.4 Deciding on an appropriate level of resolution for the NS-SEC

In the NS-SEC, there are as many as 14 possible socioeconomic strata including: employers in large establishments; higher managerial occupations; higher professional occupations; lower professional and higher technical occupations; lower managerial occupations; higher supervisory occupations; intermediate occupations; employers in small establishments; own account workers; lower supervisory occupations; lower technical occupations; semi-routine occupations; routine occupations; and never worked or long-term unemployed. Depending on the requirements of the researcher, different resolutions of the NS-SEC are possible ranging from a 14- to three-category system, see Table 3.(206,207) Insufficient information about the size of the employing organisation was available from HEAF, so it was not possible to distinguish employers in large establishments from higher managerial occupations in the 14 tier classification. Therefore, the nine-level NS-SEC categorisation which combined employers in large establishments with higher managerial occupations in the top socio-economic stratum was used and retained a high degree of detail, overall.

Table 3: Different resolutions of the NS SEC classification system (207)

Operational categories (14 levels)	Nine categories	Eight categories	Five categories	Three categories
1. Employers in large establishments	1.1 large employers and higher managerial occupations	1. Higher managerial and professional occupations	1. Managerial and professional occupations	1. Managerial and professional occupations
2. Higher managerial occupations				
3. Higher professional occupations	1.2 higher professional occupations			
4. Lower professional and higher technical occupations	2. lower managerial and professional occupations	2. lower managerial and professional occupations		
5. Lower managerial occupations				
6. Higher supervisory occupations				

7. Intermediate occupations	3. Intermediate occupations	3. Intermediate occupations	2. Intermediate occupations	2. intermediate occupations
8. Employers in small establishments	4. Small employers and own account workers	4. Small employers and own account workers	3. Small employers and own account workers	
9. Own account workers				
10. Lower supervisory occupations	5. lower supervisory and technical occupations	5. lower supervisory and technical occupations	4. lower supervisory and technical occupations	3. Routine and manual occupations
11. Lower technical occupations				
12. Semi-routine occupations	6. semi-routine occupations	6. semi-routine occupations	5. semi-routine and routine occupations	
13. Routine occupations	7. routine occupations	7. routine occupations		
14. Never worked and long-term unemployed	8. never worked and long-term unemployed	8. never worked and long-term unemployed	Never worked and long-term unemployed	Never worked and long-term unemployed

3.5 The Clinical Practice Research Datalink

Other than the data retrieved from the HEAF study questionnaire, the primary source of health data for this thesis was the CPRD.

3.5.1 Background

While electronic health records have existed since the 1970s, it wasn't until the 1980s that electronic medical record systems were being introduced among individual UK general practices. Particularly, the work of two general practitioners was influential. First was Dr James Read who pioneered a hierarchical coding system for clinical events, ushering in the use of the comprehensive, intuitive and eponymous "Read codes." In 1988, the Royal College of General Practitioners (RCGP) and the British Medical Association (BMA) recommended the adoption of these codes nationally, which were used by almost all GPs in the UK since the mid-1990s.(208) They remain the standard vocabulary for clinicians to record clinical findings and procedures, across health and social care IT systems, to this day.(209)

Also in the 1980s, Dr Alan Dean, with a team of software developers, formed the VAMP Health company to produce a computer-based tool for recording electronic routine medical information, in order to replace the paper records historically used by general practitioners. The Clinical Practice Research Datalink (CPRD) was the eventual result of this work, and was established in London, in 1987. Originally, the smaller Value Added Medical Products (VAMP) dataset, this became the larger General Practice Research Datalink in 1993, before eventually growing to become the CPRD in 2012.(210) It is now one of the largest databases of longitudinal primary care medical records in the world and has been collecting data for over 30 years. Currently, this not-for-profit service is primarily government-funded through the National Institute for Health Research (NIHR) and the Medicines and Healthcare products Regulatory Agency (MHRA).(211) The main purpose of the CPRD is to offer high quality primary-care clinical data to support retrospective and prospective public health and clinical studies.(212)

3.5.2 Size and representativeness of CPRD

Approximately one in 10 general practices across England, Wales, Scotland, and Northern Ireland have contributed deidentified data to CPRD. This includes over 1,200 UK primary care practices and data from 35 million patients, with 10 million patients currently registered and active; although the number of patients and general practices has varied since the establishment of CPRD.(212) As of 2014, there were 674 contributing practices covering approximately 6.9% of the UK population, and participants were found to be broadly representative of the general population in terms of age, sex, and ethnicity. The distribution of the contributing practices is mapped in Figure 16.(211)

Figure 16: Distribution of 674 CPRD practices by region in England, and in Wales, Scotland and Northern Ireland. Note: practices mapped are those contributing up to standard data to the dataset on 2 July 2013, based on the January 2014 dataset build.(211)

3.5.3 Available data from the CPRD

A complete electronic record of a patient's primary care events is captured in real time by practice staff for the duration of a general practice's participation in CPRD and a patient's registration at a contributing general practice. Although it is possible for a patient to opt out of sharing information from their health record, this rarely occurs.

CPRD captures routine information on all care events that a GP has recorded as part of their usual clinical care, these include: demographic data (e.g. age, sex, and patient registration date); clinical diagnoses and symptoms (e.g. heart failure or painful knee); assessment of lifestyle and risk factors (such as BMI recordings, smoking, and alcohol intake); prescribed drugs and vaccinations (issued at a primary care level); laboratory and diagnostic testing (e.g. HbA1c); and referrals to hospital and secondary care (e.g. referrals to mental health crisis teams).(212) General practitioners and other health care professionals will code these data using the Read code system and British National Formulary (BNF) codes for

prescription data. At the same time, linkage to other secondary care data sources (for example, Hospital Episode Statistics (HES) and mortality data from the ONS) is possible and data is date-stamped so that the time of event/diagnosis can be retrieved.(212)

The data is suitable for longitudinal analysis as at least 20 years of follow up is available for 25% of contributing patients. CPRD-supported clinical research requires that patients consent to the use of their data for CPRD, then CPRD agree to share this anonymised data if and ethics approval and payment of licence and administration fees allow.

3.5.4 Quality of CPRD data

The quality of CPRD data is variable across time and somewhat dependent upon the participating general practice and practitioner. However, CPRD undertakes internal data-quality assessments both at the patient and practice level.(213) “Unacceptable” patients are those for whom there is non-contiguous follow up or poor data recording (e.g. missing vital information such as first registration date, or errors such as age >115 years). Across CPRD approximately 11.89% of patients are unacceptable, 10.44% of whom are temporary patients, with only 1.45% unacceptable due to inconsistent data.(213) “Up to date” GP practices are those which record a minimum of 95% of prescribing events and patient-consultations. Practices are routinely validated by internal checks and sent a validation report after submission of data. These checks look at completeness of prescribing, demographic, registration, referrals, and cause of death data. Practices not meeting CPRD standards are removed from the database.(214) Possibly because of these quality assessments, the recording of most clinical events has improved over time, although large inter-practice variation in data quality remains.(215)

Other factors affect the quality of recorded clinical data in CPRD. For instance, since 2004, English general practices also began to participate in the Quality and Outcomes Framework (QOF) which is a voluntary annual incentive programme, requiring GP practices to record several indicators of quality of care in return for financial reward. For example, a practice may be scored based on the percentage of patients with asthma between the age of 14-20 years old who have had their smoking status recorded in the last 12 months; or the percentage of patients with a diagnosis of heart failure who have had their heart failure confirmed using an echocardiogram.(216) Following the introduction of QOF, the completeness in recording of many variables improved.(211)

CPRD has shown a high positive predictive value for certain clinical diagnoses and incidence figures derived from CPRD appear to be comparable to other UK-based data sources.(211) However, few studies reporting validation outcomes have reported sensitivity and specificity outcomes for CPRD diagnostic data. This may be a limitation as the absence of a Read code for a particular disease is usually interpreted as the absence of the disease itself. However, diseases may be missed, such as those diagnosed in secondary care which have to be transcribed into the patient's primary care record. There are also no standard definitions for clinical diseases in CPRD and miscoding is possible, particularly for poorly defined conditions. To combat this, researchers use lists of possible Read codes for a particular disease of interest with selective algorithms to improve internal validation wherever possible.(211)

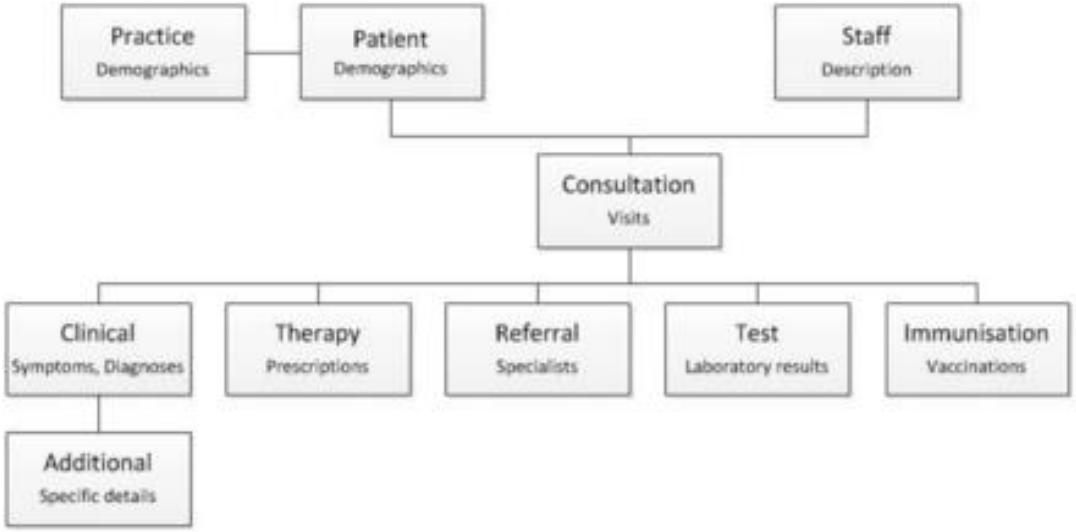
3.5.5 Deidentification of CPRD data

The NHS is the single provider of healthcare in the United Kingdom. As all participating CPRD practices are under the NHS this means that each individual patient contributing data has a unique patient identifying number, the NHS number. This is a trusted identifier that can be used for valid linkage of health data from various sources. The NHS number is used to produce an "encrypted linker key," this is performed by a third party (NHS Digital) and CPRD does not receive or distribute patient-identifiable data. Instead, patients are ascribed a new unique CPRD number. Using such identifiers CPRD data can be linked to questionnaire data for observational research, as was implemented for the HEAF study.(212)

3.5.6 Structure of CPRD data

Data in the CPRD can be separated into clinical, referral, immunization, test, and therapy data. When an entry of data to a patient's clinical record occurs, this is considered a "consultation," which is recorded against practice, patient, and staff pseudo-identifiers. Within a consultation, "events" can be recorded which can include demographic information, drug prescriptions, clinical diagnoses and symptoms, hospital admissions and the clinical outcome of hospital admissions, referrals to specialist care, provided preventative care, diagnostic and monitoring tests, immunisations, and details of death. Each event is recorded with an associated date. Figure 17 below gives a conceptual diagram of CPRD data.(211)

Figure 17: the structure of the CPRD dataset. Patients consult with practice staff, where clinical, therapy, referral, test, and immunisation information is coded in the medical record.(211)



3.5.7 Request and retrieval of CPRD data

There over 96,000 codes corresponding to "events" in the entire Read code hierarchical classification system. In this system, codes are organised into broader diagnostic categories such as "N: Musculoskeletal and connective tissue diseases" and within those, narrower divisions of clinical diagnostic codes such as "N211: rotator cuff syndrome" or related symptomatic codes such as "N131: chronic/recurrent neck pain." Similarly, BNF prescription codes contain broad categories (such as "10.3: Drugs for the relief of soft-tissue inflammation") and specific codes relating to drug names, doses, and formulations. Given that it was possible to request an unmanageable amount of CPRD data for study participants, it was desirable to refine the request according to HEAF study research objectives.(201) To achieve this, members of the HEAF research team searched CPRD disease and drug code dictionaries to compile a list of relevant codes, which were requested from CPRD. The following items of CPRD data were prioritised:

- All hospital admissions, including discharge diagnoses and procedures
- All GP consultations for: musculoskeletal disorders (MSDs); mental health problems; cardiovascular problems; asthma; chronic obstructive pulmonary disorder (COPD); diabetes; and epilepsy
- All prescriptions related to these health problems

- All injuries likely to be occupational
- Frequency of GP consultations for all reasons combined
- Records of height, weight, BMI, smoking habits, and alcohol consumption

10,825 BNF codes and 11,316 Read codes relating to the above items were requested from CPRD. If these events had been previously coded in the electronic clinical record of HEAF study participants, data were returned to the research team. For example, if a study participant had been diagnosed with COPD and the event was coded, this information would have been returned along with the date of diagnosis and a unique identification number for linkage with questionnaire data.

3.5.8 Development of health disorder variables using CPRD codes

The returned CPRD data were already grouped by body system (e.g. musculoskeletal, mental health, cardiovascular), however no further grouping had been performed. Two researchers with medical training (myself and Professor Keith Palmer) independently went through the clinical codes and assigned them into disease groups. Codes were grouped into the smallest possible distinct disorders or events. For example, two codes were found relating to people who had had a heart transplant: “other transplantation of heart”; and “other transplant of heart NOS.” These were grouped together to form a heart transplant category. Read codes were excluded from further analysis if 1) they were considered too vague, or not relating to clinically recognised health problems, for example “Sibling Jealousy,” 2) they referred to a health problem that had not been requested from CPRD (as these codes would be unlikely to capture all participants in the study sample with the specific health problem). For example, Table 4 lists the excluded musculoskeletal Read codes; a full list of excluded codes is available in Table 1, Appendix. In the event of disagreements between the two researchers a third clinician was sought out to adjudicate (Dr Nicola Goodson or Prof. Karen Walker-Bone).

Once codes were organized into health problem groups at the highest possible degree of resolution, distinct groups were combined into larger clinical disorder groups where appropriate. This was desirable in order to increase the available statistical power for analysis. However, maintaining a high resolution of the clinical disease groups was also desirable, since clinical disease groups become less meaningful as they become less distinct. The grouping process is outlined, below.

Table 4: Excluded musculoskeletal Read codes

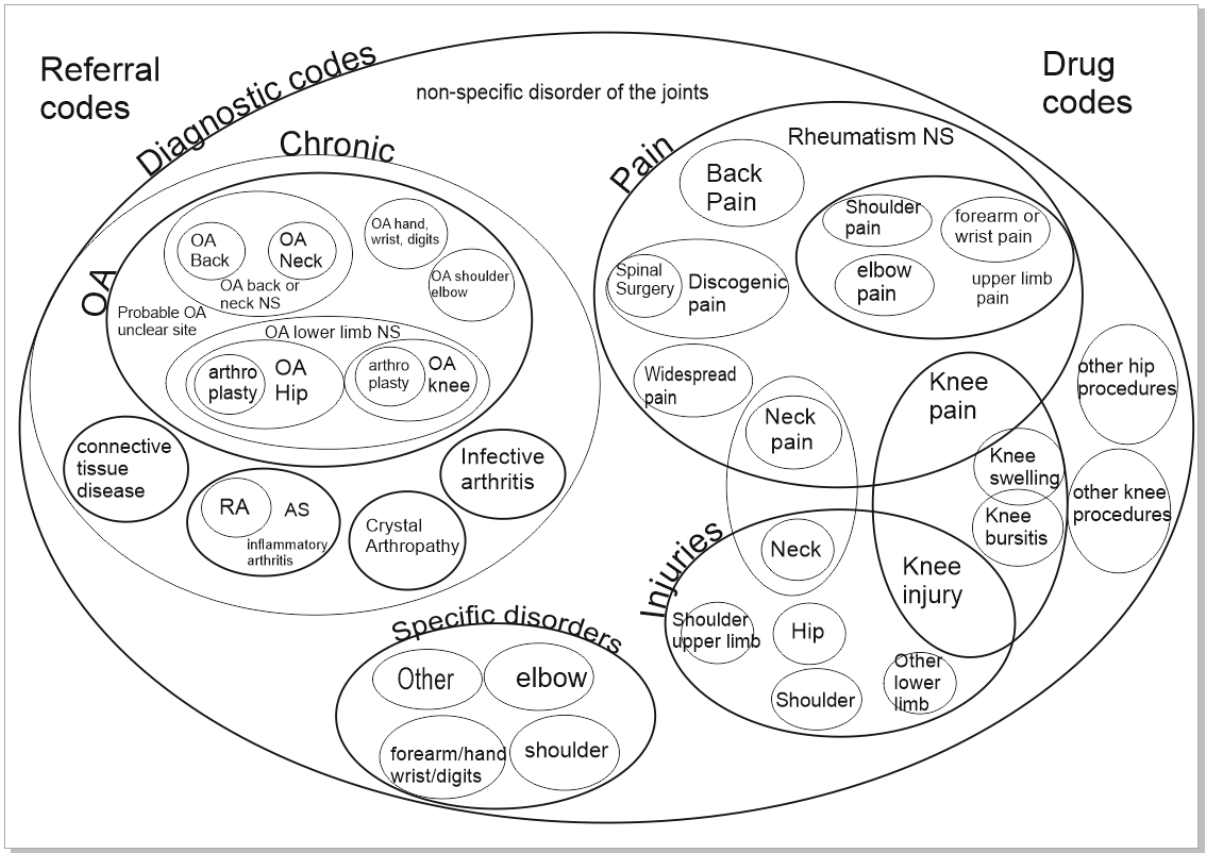
Body system	Excluded Read codes
Musculoskeletal disorders	Acute rheumatic fever
	O/E - knee joint abnormal
	O/E - shoulder joint abnormal
	H/O: rheumatic fever
	O/E - finger joint abnormal
	O/E - wrist joint abnormal
	O/E - elbow joint abnormal
	O/E - joint abnormal
	O/E - neck joint abnormal
	O/E - toe joint abnormal
	O/E - hip joint abnormal
	O/E - hand joint abnormal
	Rheumatoid factor
	Back X-ray
	Adverse reaction to analgesics, antipyretics, antirheumatics
	[D]Head and neck symptoms
	O/E - ankle joint abnormal
	[X]Cervicogenic headache

3.5.8.1 Musculoskeletal disorders

At the end of categorisation, 51 distinct musculoskeletal disorder sub-groups were identified. These included: 1) rheumatoid arthritis 2) inflammatory arthritis or juvenile arthritis 3) probable osteoarthritis (OA) unclear site 4) OA back 5) OA neck 6) OA shoulder and elbow 7) OA hip 8) OA knee 9) OA lower limb, not specified or other than hip or knee 10) OA back or neck, not specified (NS) 11) OA hand, wrist, digits 12) OA pelvis 13) crystal arthritis 14) infective arthritis/arthropathy 15) NS disorder of joints 16) back pain 17) discogenic/nerve root pain 18) spinal surgery 19) neck pain 20) hip pain 21) knee pain 22) lower limb pain unspecified or other than hip or knee 23) knee bursitis 24) knee joint swelling or effusion 25) widespread pain 26) connective tissue disease 27) shoulder pain 28) elbow pain 29) wrist/hand or forearm pain 30) specific disorders of the shoulder & shoulder girdle (not OA) 31) specific disorders of the elbow (not OA) 32) specific disorders of forearm, hand, wrist or digits (not OA) 33) shoulder surgery & other procedures 34) procedures relating to elbow 35) procedures relating to wrist 36) other procedures upper limb (not shoulder) 37) upper limb pain not specified 38) non -specific sprain/injury group 39) neck injury 40) back injury 41) shoulder/upper limb injury 42) hip injury 43) knee injury (including ligament tears) 44) other lower limb injury 45) specific disorder that does not fit

anywhere 46) arthroplasty of hip 47) other hip procedures 48) arthroplasty of knee 49) other knee procedures 50) other musculoskeletal referral codes 51) 'rheumatism' NS. See Table 2, Appendix, for a description of the specific Read codes that comprised these groups. These sub-groups were arranged into related broader groups, see Figure 18.

Figure 18: Concept map showing related groups of musculoskeletal disorders



Of the chronic musculoskeletal disorders identified, by far the most prevalent condition was osteoarthritis. The low prevalence of the other chronic musculoskeletal disorders, such as inflammatory rheumatic disorders, limited the power available for undertaking a subgroup analysis of these conditions. Therefore, all chronic musculoskeletal disorders were grouped together for analysis including all osteoarthritis, inflammatory arthritis, and chronic tissue disease groups. Crystal arthropathies were also considered chronic musculoskeletal disorders, providing that the person was still being treated for the condition at the point of analysis.

Many other musculoskeletal code groups referred to musculoskeletal pain conditions, or short-term musculoskeletal injuries, for example back pain or knee injury. These groups were combined to form a broad musculoskeletal pain group. Unlike chronic musculoskeletal disorders, these conditions may be short-term or heal completely.

Therefore, for these musculoskeletal codes, the proximity in time to the work outcome of interest was important.

Four sub-groups were considered too non-specific to classify the presence of a musculoskeletal pain or chronic musculoskeletal disorder and these subgroups were dropped from any further analysis in this thesis. These included, "procedures relating to the elbow", "procedures relating to the wrist", "procedures relating to the upper limb (not shoulder)", and "other musculoskeletal referral codes". See Table 5, below, for the final grouping of musculoskeletal code sub-groups for analysis.

Table 5: Musculoskeletal disorder sub-groups arranged into broader groups for analysis

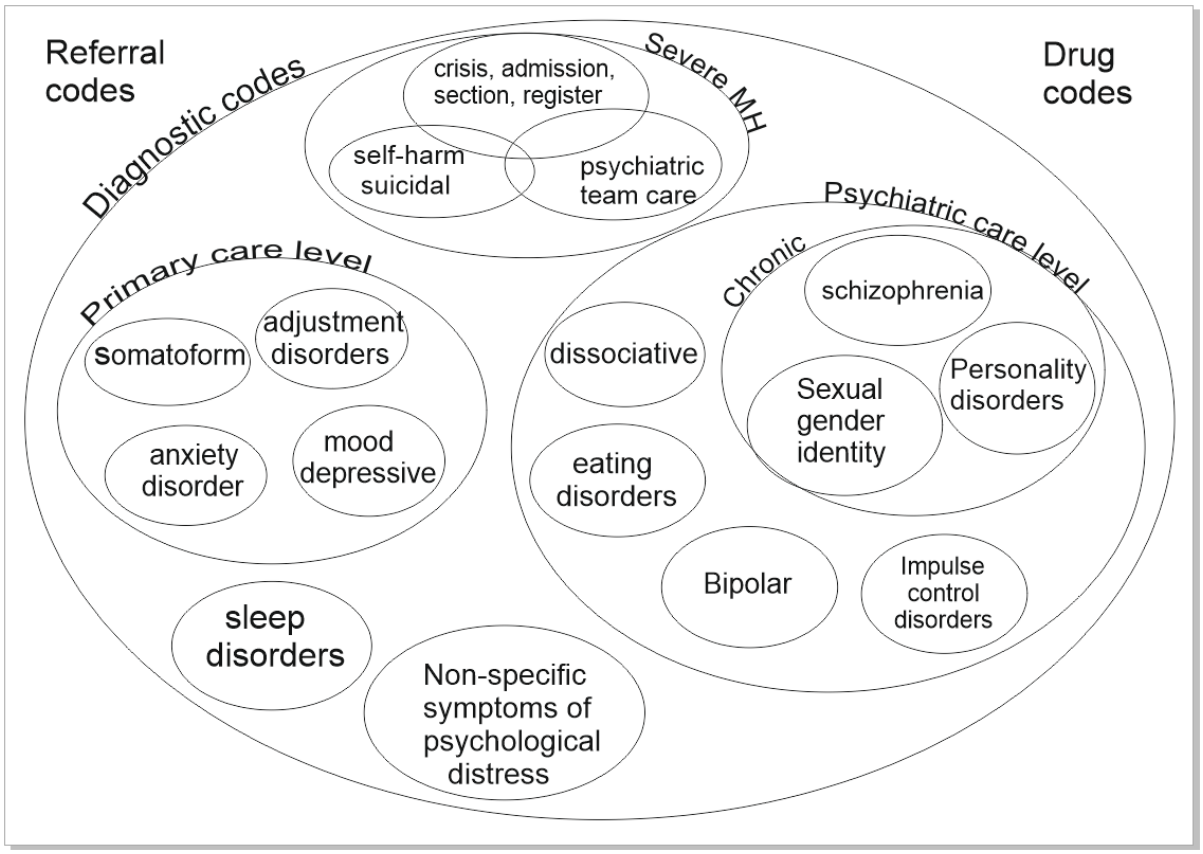
Broad musculoskeletal group	Musculoskeletal sub-groups
Chronic musculoskeletal disorders	Rheumatoid arthritis Inflammatory arthritis/juvenile arthritis Probable osteoarthritis (OA) unclear site OA back OA neck OA shoulder and elbow OA hip OA knee OA lower limb, not specified or other than hip or knee OA back or neck, not specified OA hand, wrist, digits OA pelvis Crystal arthritis Connective tissue disease Arthroplasty of hip Arthroplasty of knee
Musculoskeletal pain disorders	Infective arthritis/arthropathy NS disorder of joints Back pain Discogenic/nerve root Spinal surgery Neck pain Hip pain Knee pain Lower limb pain unspecified or other than hip or knee Knee bursitis Knee joint swelling or effusion Widespread pain Shoulder pain

	Elbow pain Wrist/hand or forearm pain Specific disorders of the shoulder & shoulder girdle (not OA) Specific disorders of the elbow (not OA) Specific disorders of forearm, hand, wrist or digits (not OA) Shoulder surgery & other procedures Upper limb pain not specified Non -specific sprain/injury group Neck injury Back injury Shoulder/upper limb injury Hip injury Knee injury (including ligament tears) Other lower limb injury Specific disorder that does not fit anywhere Other hip procedures Other knee procedures 'Rheumatism' NS

3.5.8.2 Mental health disorders

At the end of categorisation, 22 different mental health disorder sub-groups were identified. These included: 1) disorders usually first diagnosed in infancy, childhood, or adolescence 2) delirium, dementia, and amnestic and other cognitive disorders 3) mental disorders due to a general medical condition not elsewhere classified 4) substance-related disorders 5) schizophrenia and other psychotic disorders 6) mood disorders or depressive disorders 7) bipolar disorders 8) anxiety disorders 9) somatoform disorders 10) factitious disorders 11) dissociative disorders 12) sexual and gender identity disorders 13) eating disorders 14) sleep disorders 15) impulse-control disorders, not elsewhere classified 16) adjustment disorders 17) personality disorders (axis II) 18) self-harm, suicidal actions, or ideations 19) referral to a support service 20) under the psychiatrist's team 21) crisis admission, section, on a severe mental health register 22) symptoms of psychological distress (with no diagnosis specified). See Table 3, Appendix, for the specific Read codes that comprised these distinct groups. I arranged these sub-groups into related broader groups, see Figure 19.

Figure 19: Concept map showing related groups of mental health problems



Mental health disorder sub-groups referring to disorders usually diagnosed at the primary-care level were grouped together: these included adjustment disorders, somatoform conditions, and mood disorders (anxiety and depression). This was considered appropriate, since a person presenting with anxiety or depression in general practice may be coded as having a mood disorder or an adjustment disorder, which may depend as much on the general practitioner as on the participant's clinical history.

Sleep disorders were also considered separately for analysis, since there was a greater possibility that these had manifested because of some other organic cause. For example, sleep apnoea or pain are common causes of sleep disturbance.

Disorders for which diagnosis and care required psychiatric oversight were grouped together, these included the following subgroups: schizophrenia and other psychotic disorders, bipolar disorders, dissociative disorders, sexual and gender identity disorders, eating disorders, impulse-control disorders not elsewhere classified, and personality disorders (Axis II). These sub-groups also described disorders that were relatively rare, and therefore there was incentive to combine into one group in order to allow enough power

for analysis. However, clinical features were more heterogeneous between sub-groups in this case.

Lastly, certain subgroups indicated a history of a severe mental health problems and were combined for the purposes of this study. These included: self-harm, suicidal actions or ideations; under the psychiatrist's team; crisis admission, section, on a severe mental health register.

At this stage, certain subgroups were excluded from further analysis. These included: "disorders usually first diagnosed in infancy, childhood, or adolescence", which included several Read codes relating to speech disorders such as stammering; "Substance-related disorders" which contained one code relating to alcohol withdrawal-induced seizure; "delirium, dementia, amnestic and other cognitive disorders", "Referral to a support service", "symptoms of psychological distress" for which Read codes did not define a clinically distinct health problem; and "mental disorders due to a general medical condition not elsewhere classified", for which the underlying cause was not described. In addition, the study sample contained no participants with "Factitious disorders". See Table 6, below, for the final grouping of mental health problem code groups for analysis.

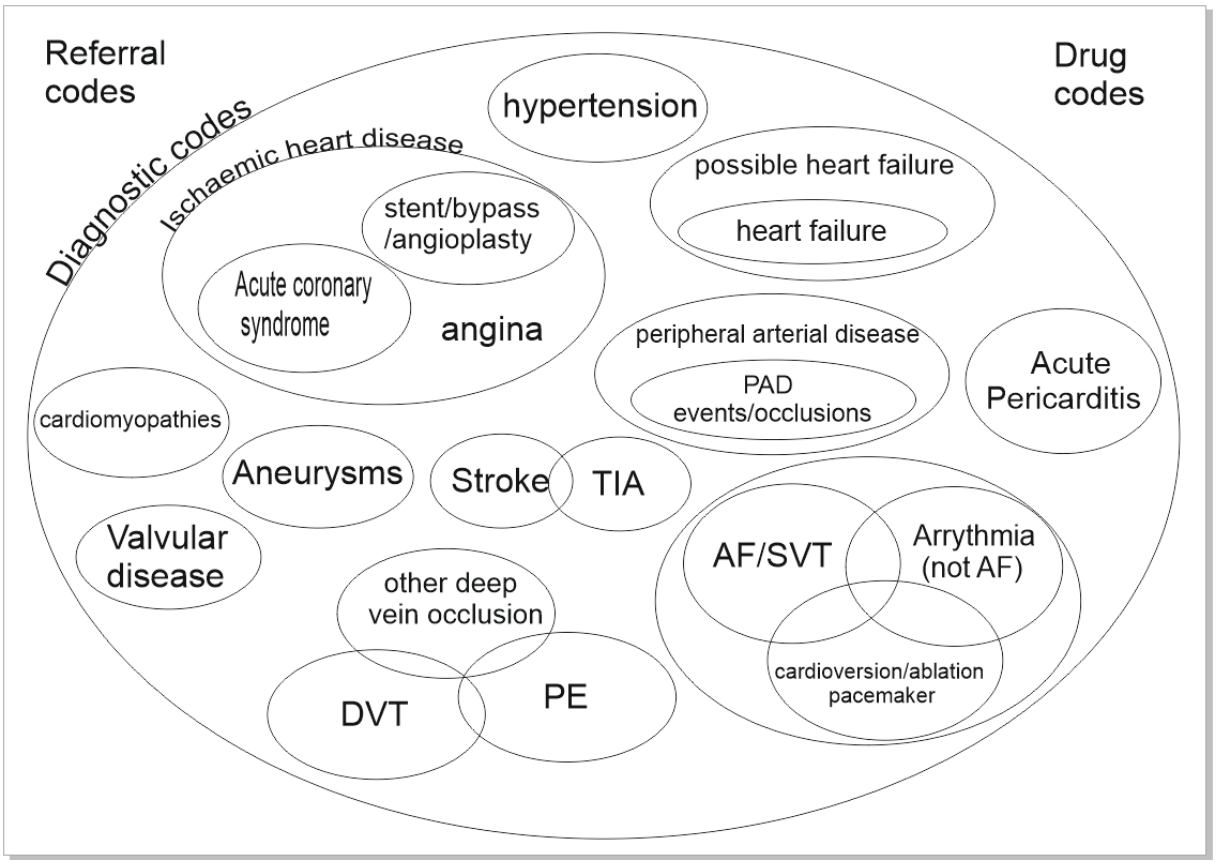
Table 6: Mental health problems sub-groups arranged into broader groups for analysis

Broad mental health problem group	Mental health problem sub-groups
Primary-care-level mental health problems	Mood disorders or Depressive disorders Anxiety disorders Somatoform disorders Adjustment disorders
Sleep disorders	Sleep disorders
Psychiatric-care-level mental health problems	Schizophrenia and other psychotic disorders Bipolar disorders Dissociative disorders Sexual and gender identity disorders Eating disorders Impulse-Control Disorders Not Elsewhere Classified Personality disorders (Axis II)
Severe mental health problems	Self-harm, suicidal actions or ideations Under the psychiatrist's team Crisis admission, section, on a severe mental health register

3.5.8.3 Cardiovascular disorders

At the end of categorisation, 28 different cardiovascular sub-groups were identified. These were 1) myocardial infarction or unstable angina 2) myocardial ischaemia, atherosclerosis, or angina 3) cardiology and vascular investigations 4) coronary angioplasty, bypass, or stent 5) non-specific cardiovascular problem 6) pulmonary embolism 7) referrals, cardiac clinic follow up, cardiovascular surgeon, GP with cardiovascular interest and other cardiovascular follow up and monitoring codes 8) heart failure 9) probable or possible heart failure 10) diseases of the endocardium and valves 11) arrythmia other than AF 12) cardiomyopathies 13) pericardial diseases 14) possible and probable acute coronary syndrome 15) non-coronary vascular, atherosclerotic, and peripheral arterial disease 16) aneurysms (all body) 17) heart transplant 19) hypertension 20) deep vein thrombosis 21) stroke or cerebrovascular disease 22) cardiac arrest or cardiopulmonary resuscitation 23) superficial vein thrombus 24) atrial fibrillation or supraventricular tachycardia 25) ectopics 26) arrhythmia requiring cardioversion, ablation, or a pacemaker 27) non-coronary vascular atherosclerotic events, occlusions, or cardiovascular surgery 28) secondary hypertension including gestational hypertension and pre-eclampsia 29) transient ischaemic attack (TIA) 30) other non-superficial venous occlusions. See Table 4, Appendix, for the specific Read codes that comprised these distinct groups. I arranged these sub-groups into their related broader groups, see Figure 20.

Figure 20: Concept map showing related groups of cardiovascular disorders



Using the generated sub-groups it was possible to create several clinically distinct but broader cardiovascular variables. An ischaemic heart disease variable was constructed using angina and myocardial infarction-related subgroups as well as a sub-group referring to cardiac surgery for these problems. It was also possible to define severe ischaemic heart disease using one sub-group relating to acute coronary syndrome events. A heart failure variable was defined using two sub-groups containing heart failure specific codes and heart transplant codes. Structural heart disease was comprised of two sub-groups relating to diagnoses of cardiomyopathy and diseases of the endocardium and valves. An arrhythmia variable brought together sub-groups containing diagnostic codes for supraventricular tachycardias and surgical procedures to treat cardiac arrhythmias. Hypertension was defined using only one sub-group of hypertension specific diagnostic codes. A venous thrombosis variable was comprised of two sub-groups containing pulmonary embolism and deep vein thrombosis codes. A peripheral atherosclerosis variable was defined using two sub-groups containing diagnostic codes relating to peripheral atherosclerotic disease and related events. Lastly, Stroke and TIA groups were combined for analysis to form a cerebrovascular accident variable. However, it was noted that the clinical sequela of stroke and TIA may be dramatically different. Since TIAs, by nature, leave no residual damage,

their occurrence may primarily impact work if occurring in proximity to the adverse work outcome of interest.

At this stage, certain subgroups were excluded from further analysis. These included: "cardiology or vascular investigations", "non-specific cardiovascular problems", "referrals or follow up in cardiac clinic and other cardiac monitoring" which did not define distinct cardiovascular disorders. "probable/possible heart failure" which was excluded since more specific heart failure sub-groups were available; "pericardial diseases" which described uncommon short term cardiovascular disorders; "possible/probable acute coronary syndrome" for which no codes were identified in the study sample; "aneurysms" for which only one study participant reported a rupture code; "cardiac arrest, cardiopulmonary resuscitation" which may be as a result of underlying non-cardiovascular causes; "superficial vein thrombus" which contained codes relating to relatively benign disorders such as thrombophlebitis; "ectopics" which contained codes relating to benign cardiac arrhythmias which may occur in health individuals; "secondary hypertension including gestational/pre-eclampsia" which described typically transient conditions, in younger populations, often followed by pre-planned maternity leave from paid employment; and "venous occlusions" which was a heterogenous group of other venous thrombotic events. See Table 7, below, for the final grouping of cardiovascular code groups for analysis.

Table 7: Cardiovascular disorder sub-groups arranged into broader groups for analysis

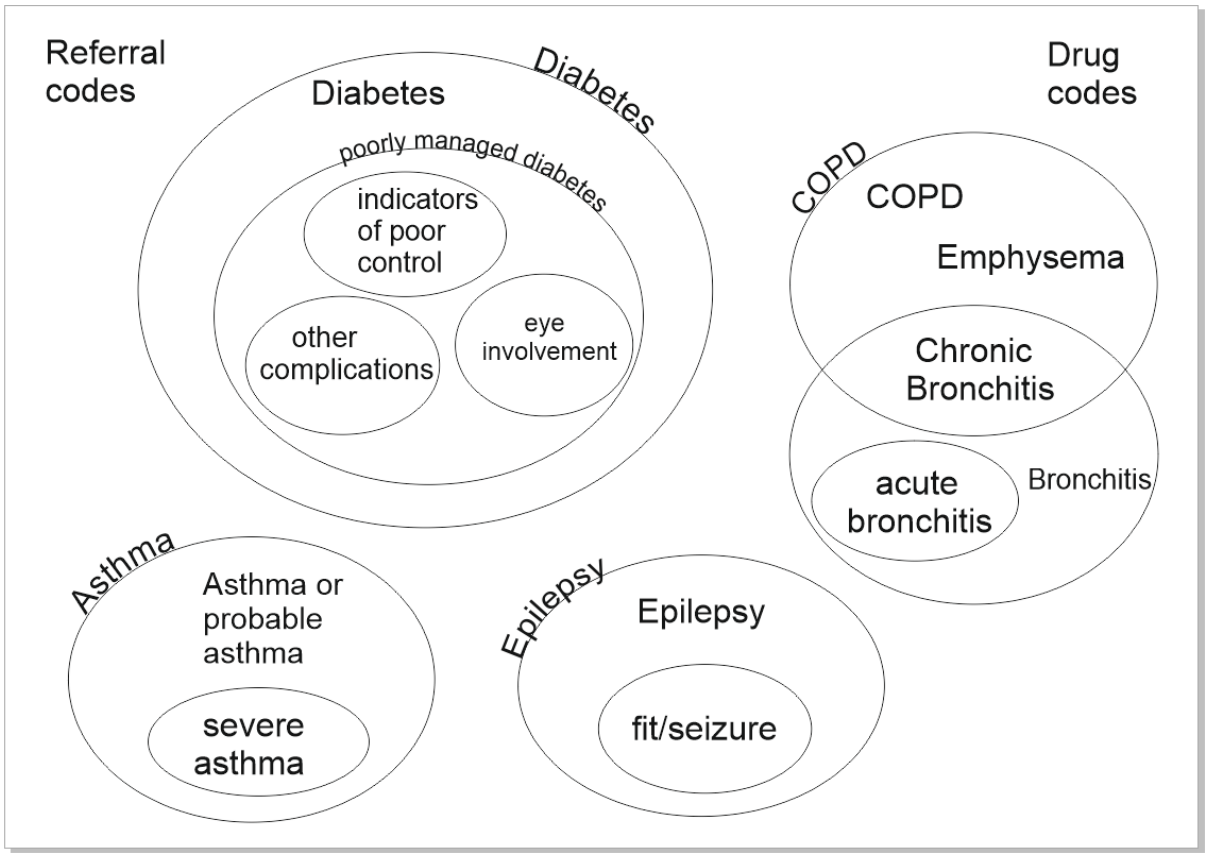
Broad cardiovascular disorder group	Cardiovascular disorder sub-groups
Ischaemic heart disease	Myocardial infarction/unstable angina Myocardial ischaemia/atherosclerosis/angina Coronary angioplasty/bypass/stent
Severe ischaemic heart disease	Myocardial infarction/unstable angina
Heart failure	Heart failure Heart transplant
Structural heart disease	Diseases of the endocardium and valves Cardiomyopathies
Arrhythmias	Arrhythmia other than AF or treated AF, SVT Arrhythmia requiring cardioversion/ablation/pacemaker
Hypertension	Hypertension
Venous thromboembolism	Pulmonary embolism DVT
Peripheral Atherosclerosis	Vascular atherosclerotic events/occlusions/surgery (non-coronary)

	Vascular/atherosclerotic/peripheral arterial disease (non-coronary)
Cerebrovascular accident	TIA Stoke/CVA

3.5.8.4 Asthma, COPD, Diabetes, and Epilepsy

Following categorisation, six respiratory subgroups were identified. These included 1) asthma or probable asthma 2) severe asthma 3) acute bronchitis 4) chronic bronchitis 5) bronchitis NOS 6) COPD or emphysema. Two subgroups relating to epilepsy were identified, these included 1) epilepsy 2) fit/seizure (non-specific). Four subgroups relating to diabetes were identified, these included 1) diabetes 2) diabetes with eye involvement 3) diabetes with indicators of poor control 4) diabetes with other complications. See Table 5, Appendix, for the specific Read codes that comprised these groups. I arranged these sub-groups into their related broader groups, see Figure 21.

Figure 21: Concept map showing related groups of respiratory, diabetes, and epilepsy codes



An asthma variable was constructed using the "asthma or probable asthma" sub-group. In addition, I defined severe asthma using the "severe asthma" sub-group which contained

Read codes indicating more debilitating disease, for example "Emergency admission, asthma." A COPD variable was constructed using two sub-groups which contained diagnostic codes for COPD, emphysema, and chronic bronchitis. A diabetes variable was constructed from one sub-group containing general diabetes codes. It was also possible to identify poorly controlled diabetes using three subgroups containing Read codes for diabetic eye disease, diabetic complications, and other indicators of poor diabetic control, for example "diabetes mellitus with ketoacidosis". An epilepsy variable was defined using a sub-group of epilepsy-specific codes and a sub-group containing fit or seizure events. While fit or seizure codes were often specific to epilepsy, certain codes could have described fits or seizures with other underlying causes.

At this stage, certain sub-groups were excluded from further analysis. These were "acute bronchitis", and "bronchitis non-specific" which were removed as they were non-specific to COPD. Of the respiratory conditions, only COPD- and Asthma-related codes had been requested from CPRD, therefore, codes pertaining to other respiratory conditions were excluded, since they were not adequately measured. See Table 8, below, for the final grouping of these health problem code groups for analysis.

Table 8: Other health disorders arranged into broader groups for analysis

Broad health disorder group	Health disorder sub-groups
Respiratory disorders	
Asthma	1 Asthma or probable asthma
Severe Asthma	2 Severe asthma
COPD	4 Chronic bronchitis 6 COPD or emphysema
Diabetes	
Diabetes	1 Diabetes
Diabetes with complications	2 Eye involvement 3 Poor control 4 Other complication
Epilepsy	
Epilepsy	1 Epilepsy 2 Fit or seizure (non-specific)

3.5.8.5 History of heavy alcohol intake

CPRD also contained clinical codes relating to a history of heavy alcohol intake. Following separation of these codes from other alcohol and lifestyle-related Read codes, two subgroups were identified. These included 1) codes pertaining to heavy alcoholism, for

example, “hazardous alcohol use” or “replaces meals with drinks” 2) codes relating to previous alcoholism e.g. “ex-heavy drinker – (7-9u/day)” and “ex-very heavy drinker” – (>9u/day). A “history of heavy alcohol intake” variable was constructed using these sub-groups. See Table 6, Appendix, for the specific Read codes that comprised these sub-groups.

3.6 Study design and methods

3.6.1 Outcome of interest

This thesis primarily focusses on one work outcome: health-related job loss (HRJL). As described above, participants who were not currently in paid work were asked whether they left work because of a health problem and could respond “no, not at all”, “yes, a health problem was the main reason for leaving”, or “yes, a health problem was part of the reason for leaving”. In general, HRJL was defined as job loss in which a health problem was either part of or the main reason for leaving. However, some sensitivity analysis was undertaken to explore the differences between those who answered that a health problem was “part of the reason” and those who answered that health was “the main reason” for job loss.

3.6.2 Methods- case control

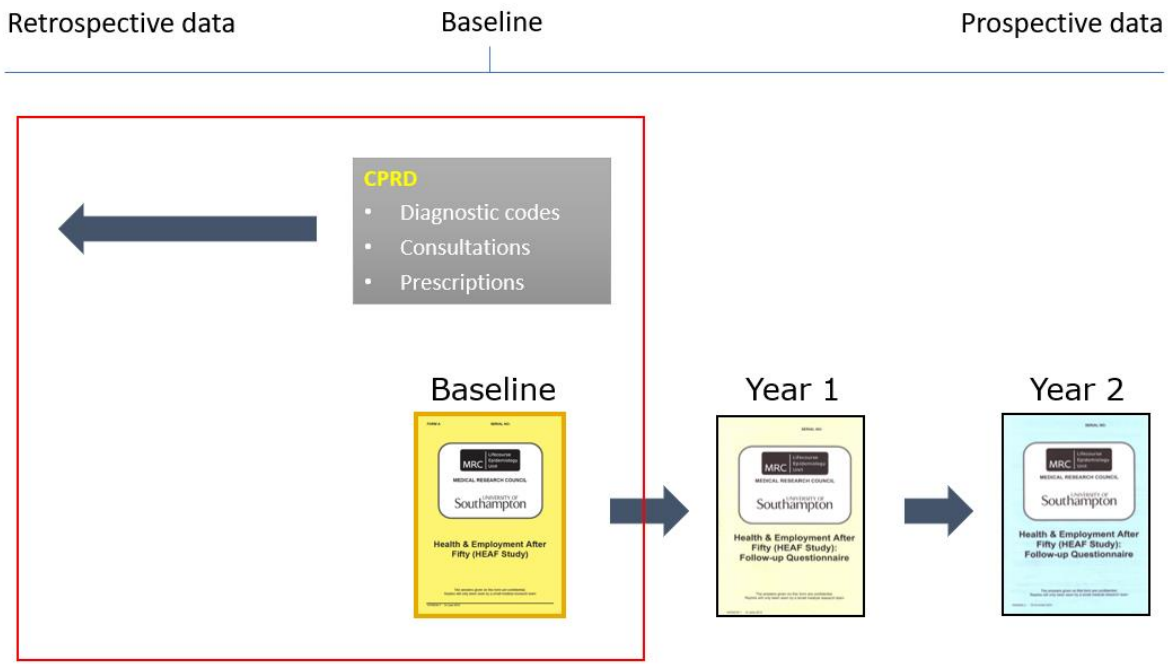
A matched retrospective case-control study design was used for this observational, epidemiological study. Briefly, this investigative design involves the selection of cases (participants with a certain disease or health outcome of interest) and matches them with control participants who are similar in many respects, but do not have the outcome of interest. Cases and controls are matched for important confounding factors associated with both the exposures being studied and the outcome of interest. Following matching, cases and controls can be compared for the presence of certain exposures that, if unevenly distributed across groups, may constitute evidence of association.

3.6.3 Time period covered by this study

CPRD data were linked to data from the HEAF baseline questionnaire. This supplied clinical diagnostic information covering the time period prior to HEAF study participant’s completion of the questionnaire, between 2013 – 2014 (see Figure 22). For cases, it was important to know if any CPRD-defined health disorders had occurred prior to the occurrence of HRJL. Likewise, for working controls, it was important to know whether any

CPRD-defined health disorders had occurred prior to the point of HRJL *of their matched controls.* Proximity to the work outcome of interest was also important. For example, in the case of chronic health problems like osteoarthritis, a diagnosis could be made any time prior to the index date, since these conditions do not resolve. For shorter-term conditions, it was imperative that there was evidence of a recent clinical event in the year prior to job loss.

Figure 22: Data used in this thesis and the time period covered (red square)



3.6.4 Case definition

Cases were participants of the HEAF study who reported that they had HRJL, as defined above. Since HEAF participants had variable retrospective CPRD coverage, it was necessary that retrospective CPRD data extended back prior to a case's HRJL. Therefore, cases were included in the present study if they had CPRD coverage for a minimum of a year prior to the date of their health-related job loss. Cases were those who reported HRJL at HEAF baseline, however, a HEAF participant who had previously stopped work for a health reason, but were subsequently reemployed before HEAF baseline, would not be identified as a case for the current study.

3.6.5 Matching Controls

Control participants were selected from the remaining HEAF study participants who did not report that they had experienced HRJL. Good comparability between cases and controls is

the primary issue in the design of a case-control study, besides accuracy and completeness of the data. The controls do not need to be generalizable to the broader population of people without health-related job loss. Rather, they must represent, as closely as possible, their cases, but without being matched for the exposure under study or the outcome of interest.(217) Below is a discussion of the process of selecting confounding factors to match for.

The first, and most well-known, assumption of matching is that the proposed confounder is associated with both the exposure and the outcome of interest.(218–220) However, inappropriately matching for an intermediate variable between the exposure and the outcome on the causal pathway could threaten a study's validity. For example, matching based on number of GP consultations when considering the relationship between multimorbidity and work disability would be to adjust for the downstream effect of the health problem itself and may obscure any observable statistical association. Strength of association also appears to be important and it is recommended that the matched variable must have a strong, or at least moderate, association with both the exposure of interest and the outcome of interest.(219)

In selecting matching variables, several possible confounding factors were identified, including: age(19–41), gender(19,21–24,28,30,31,33,39,41,132), education(19–24,28,32,36,132,221–224), low socioeconomic status or social class(21–23,32,40,222,225–230), types of work(19–21,24–28,30,33,35,40,132,136,222,224,226,231,232), regional differences(21,23,221,223,233,234), ethnicity(21–23,32), and marital status(21,23–25). However, it was not practically possible to match for each of these exposures as the more specific the criteria, the greater the risk of over-matching and the less likely that enough controls can be found for analysis. Therefore, a trade-off was necessary, and controls were matched for both important and common confounders. Any remaining important confounders were statistically adjusted for in later analysis.

Cases were matched to control participants for age. Age is an important non-modifiable risk factor for of work disability,(19–41) and increasing age is also known to correlate with multimorbidity.(153) Apart from health-associations, the relationship between age and reduced work participation is likely to be driven by increasing availability of options such as early retirement or other factors such as age discrimination in employment. Therefore, it was desirable to adjust for the effect of age in analysis. Since participants of HEAF were

recruited within a narrow age band (50 – 65 years old) it was possible to match cases to controls to within one year of age.

Gender has been shown to drive the risk of certain health disorders such as mental health problems and cardiovascular disease.(235,236) Female gender was also associated with risk of work disability across a variety of health problems in the literature.(19,21–24,28,30,31,33,39,41,132) The strength of this association is debatable and the large number of women available for most research studies means that small effects can often be detected as statistically significant. I could not rule out the important role played by gender, and since many male and female participants were available for matching, little was lost by controlling for this common variable. Therefore, cases were matched to controls for gender.

There were sufficient participants within each general practice to make matching by general practice possible. This would allow adjustment for a participant's local levels of deprivation as well as accounting for factors such as regional job market, since most people live near to their general practice. Local levels of deprivation are related to an individual's socioeconomic status, which is a strong driver of health(153) and work disability in the literature.(21–23,32,40,222,225–230) Regional differences also appear to be important influencers of health(237,238) and work disability.(21,23,221,223,233,234) As such, cases and controls were matched by GP practice.

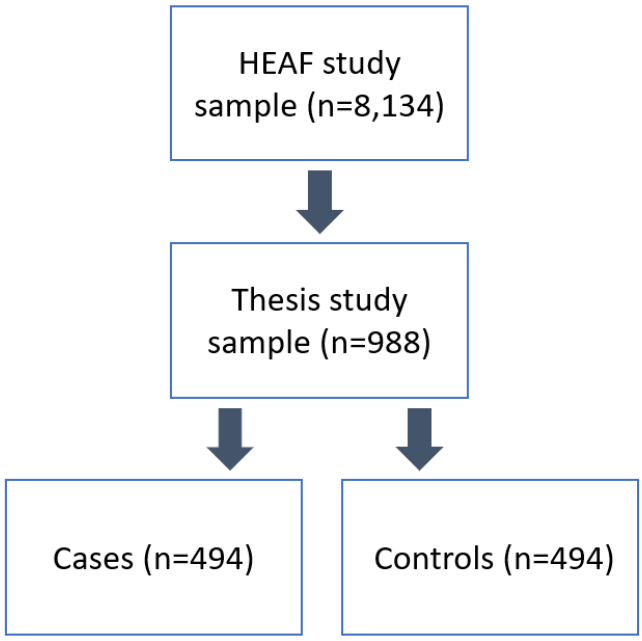
3.6.6 Control definition

In summary, therefore, control participants were selected from the remaining HEAF study participants who had not reported HRJL in the HEAF baseline questionnaire. Matched controls were required to be at risk of HRJL at the point of observation, i.e. were working when their matched case experienced HRJL. Therefore, HEAF participants who had been retired or unemployed at the time of a case's HRJL were ruled out as controls; this was possible as HEAF study participants reported the date at which they had stopped working for any reason. As described, control participants were also matched for three key confounding factors: age, sex, and GP practice. All control participants were within 1 year of age of their matched cases, of the same sex, and from the same GP practice. Finally, control participants were included in the present study if they had CPRD coverage for a minimum of a year prior to the date of health-related job loss of their matched case.

3.6.7 Sample size

Of the total number of participants in the HEAF study (n=8,134), 494 HEAF participants with HRJL met eligibility criteria and were included as case participants. These were matched 1:1 with eligible control participants. Therefore, in total, 988 participants were included in the thesis study sample, see Figure 23.

Figure 23: Flowchart of the study populations included in this thesis



3.7 Using and validating CPRD-defined health exposures in analysis

In their current format, CPRD-defined health disorder variables were unsuitable for analysis. This was primarily because it was not yet clear whether the health problem had occurred prior to the HRJL event. CPRD offers time-stamped data on drugs prescriptions and diagnoses, meaning that it was possible to determine whether exposure preceded the event of health-related job loss. CPRD-defined health disorders were therefore limited to those that had occurred prior to the date of a case's HRJL, or, for control participants, the date of the matched case's HRJL.

Although high positive predictive values of CPRD diagnoses have been reported in the literature,(239) there are numerous ways in which a diagnostic Read code can be misapplied or misspelled by a general practitioner, leading to measurement error. I therefore reviewed studies identified by one well-cited systematic review of studies reporting validation outcomes for CPRD/GPRD-defined health disorders.(239) Included studies used a variety of methods to validate this data including internal validation methods

(e.g. manual review of computerised records, sensitivity analysis) or external methods (comparison of rates/prevalence with other studies, questionnaire or record request sent to GP). Many of these studies also employed algorithms that made use of a combination of clinical diagnostic codes and pharmaceutical data, although clinical referral codes and investigative codes were sometimes also used. A discussion of this literature and comparison with the algorithms used in this thesis for defining health disorders follows.

3.7.1 Musculoskeletal disorders

3.7.1.1 Chronic musculoskeletal disorders

Numerous studies reporting validation outcomes for CPRD-defined diagnoses measured chronic musculoskeletal disorders using disease-specific Read codes and sometimes other criteria, see Table 9. Most studies used diagnostic Read codes and required no further evidence, specifically these were studies of musculoskeletal disorders,(240) rheumatoid arthritis,(241,242) osteoarthritis,(243) childhood-onset arthritis,(244) hip and knee arthroplasty,(245–247) systemic lupus erythematosus, (248) and gout populations.(249) For inflammatory rheumatic disorders, some studies required one or more further pieces of evidence, such as multiple disease codes for RA, codes suggesting systemic involvement, evidence of fulfilled diagnostic criteria in clinical notes, or specific drug treatments (e.g. disease modifying anti-rheumatic drugs or the prescription of anti-inflammatory drugs).(250–254) One study in gout required a concomitant prescription of allopurinol, colchicine, probenecid, indomethacin, or other non-steroidal anti-inflammatory agent.(254) The studies that applied strict criteria were mostly of inflammatory rheumatic conditions.

For chronic musculoskeletal disorders I chose to be inclusive for the following reasons: In primary care, inflammatory rheumatic disorders contribute to a small percentage of the overall number of people with chronic musculoskeletal disorders, which is mostly comprised of people with osteoarthritis. For the work of this thesis, it was also not necessary to distinguish certain types of inflammatory rheumatic disorder from other similar diseases, such as was necessary for the rheumatoid arthritis research papers. Lastly, the prevalence of musculoskeletal disorders has been reported as underestimated by CPRD when compared to other general practice databases.(240)

Gout can be considered a chronic condition;(255) however, a person may fully recover from gout and no longer need to think about it, or they may require regular treatment to

manage this condition. It was therefore necessary to distinguish people for whom gout appears to be a problem that could be affecting their work.

People with chronic musculoskeletal disorders were therefore defined as:

1. Participants with a diagnostic code for chronic musculoskeletal disorders, excluding gout, diagnosed any time prior to HRJL.

OR

2. Participants with a diagnostic code for gout diagnosed in the year prior to HRJL

OR

3. Participants with a diagnostic code for gout received more than a year prior to HRJL, who were receiving treatments for gout in the year prior to HRJL.

3.7.1.2 Musculoskeletal pain

Fewer studies reporting validation outcomes for the use of CPRD data in musculoskeletal pain disorders were identified. Some examples included papers studying carpal tunnel syndrome(256) and polymyalgia rheumatica.(257) Geoghegan et al. accepted any carpal tunnel diagnostic code that had occurred in the observation period,(256) whereas Smeeth et al required that polymyalgia rheumatica codes have concomitant codes showing two prescriptions for oral corticosteroid use over six months.(257) See Table 9, below.

In defining the musculoskeletal pain group, the exact diagnosis of the musculoskeletal pain was considered less important than the experience of musculoskeletal pain within a time frame that might influence a person's risk of HRJL. Restriction of the musculoskeletal pain group to only those who were prescribed pain medications was a possibility. However, pain is managed in a variety of ways such as massage, CBT, or alternative medicines. Alternatively, participants could be taking over the counter pain medication which is not observed in CPRD. Since musculoskeletal pain conditions may be short-lasting, codes that occurred in the prior year were considered.

People with recent musculoskeletal pain were therefore defined as:

Participants with a diagnostic code for musculoskeletal pain, received in the year prior to HRJL

Table 9: Identified research studies reporting validation outcomes and using CPRD/GPRD criteria for musculoskeletal disorders

Health problem	Populations studied	Criteria used
Chronic MSD	Musculoskeletal disorders (240) Rheumatoid arthritis (241,242) Osteoarthritis (243) Childhood-onset arthritis (244) Hip and knee arthroplasty (245–247) Systemic lupus erythematosus (248) Gout (249)	Disease-specific Read codes with no further evidence required
	Systemic lupus erythematosus (250,251) Rheumatoid arthritis (252,253)	Disease-specific Read codes AND one or more pieces of evidence, such as: - Evidence of systemic involvement - Multiple disease codes - Written evidence of fulfilled diagnostic criteria - Drug prescriptions (e.g. disease modifying anti-rheumatic drugs or prescriptions for anti-inflammatory drugs)
	Gout (254)	Disease-specific Read codes AND evidence of treatment with allopurinol, colchicine, probenecid, indomethacin, or other non-steroidal anti-inflammatory agent.
MSD pain	Carpal tunnel syndrome (256)	Disease-specific Read codes with no further evidence required
	Polymyalgia rheumatica (257)	Disease-specific Read codes AND two prescriptions for oral corticosteroid use over six months

3.7.2 Cardiovascular disease

3.7.2.1 Ischaemic heart disease

In the literature, some studies reported validation outcomes for CPRD-defined ischaemic heart disease, defined using CPRD read codes alone. They searched for codes indicating

ischaemic heart disease or surgery indicating heart disease.(258,259) This simpler approach yielded a high positive predictive value for myocardial ischaemia codes, which was greater than 90% when compared to hospital-discharge letters.(259) Other studies were more careful, favouring a combination of diagnostic codes and one extra item of evidence, for example hospital discharge letters, symptomatic codes, evidence of raised troponin, or treatment with fibrinolytic or antiplatelet drugs for the diagnosis of myocardial infarction.(260–263) In a prevalence study for the Office of National Statistics, a similar approach was used for ischaemic heart disease where the definition was the presence of a diagnostic code for the disease in combination with treatment with aspirin or a drug in BNF Chapter 2 (cardiovascular system).(264)

Although CPRD Read codes for myocardial infarction were found to have high positive predictive value when used alone, prescription data for drugs used in cardiovascular disorders was readily available from CPRD and participants with known ischaemic heart disease would be expected to be receiving medication. It was therefore required that participants with Read codes relating to ischaemic heart disease should also have received a prescription from the BNF chapters relating to treatments used in lipid control or atherosclerotic disease. Since ischaemic heart disease is generally a long-standing condition, these codes could occur any time prior to HRJL.

People with ischaemic heart disease were therefore defined as:

Participants who had received a diagnostic code for ischaemic heart disease and a prescription for treatments used in lipid control or atherosclerotic disease, prior to HRJL.

People with severe ischaemic heart disease were defined as:

Participants who had received a diagnostic code for myocardial infarction or unstable angina and a prescription for treatments used in lipid control or atherosclerotic disease, prior to HRJL.

3.7.2.2 Heart failure

Among studies reporting validation outcomes, a couple defined heart failure using CPRD read codes alone, i.e. searching for codes indicating heart failure such as “cardiac failure”, “left ventricular failure.”(265,266) In one study, these codes were found to have a high positive predictive value with 83.4% of the cases confirmed by the patient’s general practitioner.(266) One ONS prevalence study required a combination of diagnostic codes

for heart failure with a prescription for either a diuretic or ACE-inhibitor in the same year.(267)

Participants with heart failure would be expected to be receiving drug therapy. Therefore, to improve validity, participants with heart failure were required to have received drugs used in BNF chapters relating to the treatment of heart failure. Participants who had a history of heart transplant were clinically distinct from the broader group of participants with heart failure, however since these were rare, they were grouped with the other heart failure participants. Since heart failure is a chronic condition, these codes could occur any time prior to HRJL.

People with heart failure were defined as:

Participants who had received a diagnostic code for heart failure and a prescription for treatments used in heart failure, prior to HRJL.

3.7.2.3 Hypertension

Only one study reporting validation outcomes studied hypertension classified using CPRD data. This was an ONS study that classified hypertension using a combination of hypertension-specific diagnostic codes with a prescription for hypertension related-drugs in the year of analysis.(268)

In this thesis, in concordance with the ONS study, a person with hypertension was required to have both diagnostic codes for hypertension and to have been treated with drugs used in hypertension. Again, it was reasonable to assume that people with recognised hypertension would have received drug treatment for this problem. Since hypertension is generally a chronic condition, these codes could occur any time prior to HRJL.

People with hypertension were defined as:

Participants who had received a diagnostic code for hypertension and a prescription for treatments used in hypertension, prior to HRJL.

3.7.2.4 Structural heart disease

Structural heart disease included people with diseases of the endocardium and valves, and cardiomyopathies. This was a heterogeneous group of rarer conditions. In the literature, two studies reporting validation outcomes defined valvular disease using CPRD Read codes in addition to one other item of evidence, for example echocardiography, heart

catheterisation, or clinical examination codes. They searched for codes indicating valvular disease such as “valve regurgitation” or “valve incompetence,” and confirmed the diagnosis if there was also further documented evidence of the diagnosis.(269,270)

Access to hospital records to help validate the read codes for structural heart disease was not possible for this thesis. In addition, none of the drug prescriptions were disease-specific enough to restrict the classification of structural heart disease. Finally, these conditions were rare and likely to be important on the individual level, so it was desirable to err on the side of inclusivity. Since these structural heart problems are generally chronic, codes were permitted to occur any time prior to HRJL.

People with structural heart disease were defined as:

Participants who had received a diagnostic code for structural heart disease prior to HRJL.

3.7.2.5 Arrhythmias

Multiple studies reporting validation outcomes for CPRD-defined cardiac arrhythmia were identified. The majority of these studies also confirmed the diagnosis using hospital records, questionnaires sent to the GP, or death certificates.(271–275) One study found that CPRD codes for ventricular arrhythmias alone had a positive predictive value of 80% (4 of 5), with the remainder unclear because of poorly written notes.(258) Another article studying atrial fibrillation (AF) (paroxysmal or chronic) sought GP validation and found that AF codes had an accuracy of 93.4%.(274) Similarly, 95.9% of CPRD AF codes were GP-confirmed in another study.(275)

It was not possible to write to the general practitioners to validate disease codes in this thesis. However, given the reported high positive predictive values of these codes, it was considered valid to use them alone. While I had access to data about antiarrhythmic drug prescriptions, certain arrhythmias may be controlled using non-medical means such as cardioversion and, therefore, arrythmia codes were not validated based on concurrent drug treatment. Cardiac arrhythmias may be brief or short-lasting, so only codes that occurred in the prior year were considered.

People with cardiac arrythmias were defined as:

Participants who had received a diagnostic code for cardiac arrythmia in the year prior to HRJL.

3.7.2.6 Venous thromboembolic disease

In the literature, multiple studies reporting validation outcomes for CPRD-defined venous thromboembolism (VTE) were identified. Most also required a confirmation of this diagnosis using one further item of evidence. For example, Meier et al. looked into hospital records and death certificates for confirmation of PE, and required ultrasound or venogram confirmation of DVT.(276) Other identified studies reinforced the diagnosis of VTE with evidence of anti-coagulation prescription.(277–280) One study looked at codes for hospital admission for PE or DVT and found that around 96% of the codes could be confirmed by writing to the GP.(281) Another study showed that for 99% of read code diagnoses of VTE the GP confirmed hospitalisation and 83% also had confirmatory evidence of venogram, doppler ultrasound, or VQ scan.(279)

For this thesis people with deep vein thrombosis were grouped with pulmonary embolism. These describe two clinically distinct groups of patients with potentially very divergent clinical presentations. However, the survivor bias inherent in this retrospective study would mean that anyone who had died from pulmonary embolism would not have been included in this study. Therefore, the expected low prevalence of pulmonary embolism in this sample suggested combination with deep vein thrombosis would be expedient. Since pulmonary embolism is also a clinical sequela of DVT, this also seemed appropriate. Once again it was not possible to write to the general practitioners to validate VTE codes in this study, however VTE codes were required to co-occur with evidence of anti-coagulation drug prescriptions. Since VTE codes in this study are likely to describe deep vein thrombosis or pulmonary embolism with full recovery, CPRD-defined VTE was considered a short-term condition. As such, codes were restricted to those used for analysis that occurred in the prior year.

People with venous thromboembolic disease were defined as:

Participants who had received a diagnostic code for venous thromboembolic disease and a prescription for treatments used in anticoagulation, in the year prior to HRJL.

3.7.2.7 Peripheral arterial disease (PAD)

No studies reporting validation outcomes that used CPRD to identify peripheral arterial disease were identified. However, since prescription data was available showing whether a person had received treatments for lipid control or anti-coagulation, I validated peripheral

arterial disease codes using this information. Since these health disorders are generally chronic, codes were included that occurred at any time prior to HRJL.

People with peripheral arterial disease were defined as:

Participants who had received a diagnostic code for peripheral arterial disease and a prescription for treatments used in lipid control, atherosclerotic disease, or anticoagulation therapy, prior to HRJL.

Table 10: Identified research studies reporting validation outcomes and using CPRD/GPRD criteria for cardiovascular disorders

Health problem	Populations studied	Criteria used
Ischaemic heart disease	Ischaemic heart disease (258,259) Myocardial infarction (259)	Disease-specific Read codes with no further evidence required
	Ischaemic heart disease (264)	Disease-specific Read codes AND evidence of treatment with aspirin or a drug in BNF Chapter 2
	Myocardial infarction (260–263)	Disease-specific Read codes AND one or more pieces of evidence, such as: - Hospital discharge letters - Symptomatic Read codes - Raised troponin - Treatment with fibrinolytic or antiplatelet drugs
Heart failure	Heart failure (265,266)	Disease-specific Read codes with no further evidence required
	Heart failure (267)	Disease-specific Read codes AND prescription for either a diuretic or ace-inhibitor in the same year
Hypertension	Hypertension (268)	Disease-specific Read codes AND prescription for a hypertension-related drug in the same year
Structural heart disease	Valvular disease (269,270)	Disease-specific Read codes AND one or more pieces of evidence, such as:

		- Echocardiography - Heart catheterisation - Clinical examination
Arrhythmias	Cardiac arrhythmias (272,273) Ventricular arrhythmias (258,271) Atrial fibrillation (274,275)	Disease-specific Read codes with no further evidence required
Venous thromboembolic disease	Venous thromboembolism (277–280)	Disease-specific Read codes AND treatment with an anti-coagulant
	Venous thromboembolism (276,281)	Disease-specific Read codes AND one or more pieces of evidence, such as: - Doppler - Ventilation perfusion scan - Angiography - Hospitalisation (excluding other causes)
Peripheral arterial disease	No studies identified	No studies identified

3.7.3 Mental health problems

3.7.3.1 Primary-care-level mental health problems

There was one study reporting validation outcomes and using CPRD codes to analyse the prevalence of mental health problems and drug addiction.(282) This study used disease codes with no other form of evidence.

While it was possible to use prescription data to classify mental health problem exposures, a participant may choose other options for the treatment of mood disorders such as CBT, counselling, or even hypnosis. Therefore, in this thesis, prescriptions related to mental health problems were not used to validate the disease codes. Mental health problems may also improve and are often short term. For this reason, mental health codes that had occurred in the year prior to health-related job loss were included. In addition, a person may have been diagnosed for a mental health problem earlier but be continuing medication, such as selective serotonin reuptake inhibitors (SSRIs), to control symptoms. These participants were also included in analysis.

People with primary care level mental health problems were defined as:

Participants who had received a diagnostic code for a primary-care-level mental health problem in the year prior to HRJL.

OR

Participants who had received a diagnostic code for a primary-care-level mental health problem earlier than a year prior to HRJL and received a prescription code for treatments used in mood disorders or treatments used in insomnia and anxiety, in the year prior to HRJL.

3.7.3.2 Sleep disorders

No studies reporting validation outcomes for the use of CPRD codes to classify sleep disorders were identified. Similarly to primary-care-level mental health problems, prescription data can be used to validate sleep disorder diagnostic codes, although a participant may choose other non-pharmacological options for treatment. Sleep disorders may also improve and are often short term. For this reason, sleep disorder codes that had occurred in the year prior to health-related job loss were included. In addition, a person may have been diagnosed for a sleep disorder earlier but may still be receiving medication, such as zolpidem, to control symptoms. These participants were also included in analysis.

People with primary care level mental health problems were defined as:

Participants who had received a diagnostic code for a sleep disorder in the year prior to HRJL.

OR

Participants who had received a diagnostic code for a sleep disorder earlier than a year prior to HRJL and received a prescription code for treatments used in mood disorders or treatments used in insomnia and anxiety, in the year prior to HRJL.

3.7.3.3 Psychiatric care diagnosed mental health problems

Several studies that used CPRD-derived diagnostic codes to classify psychotic disorders, including schizophrenia, were identified. Howard et al, in three studies, included participants with CPRD codes for a psychotic disorder or had prescription codes for lithium or a neuroleptic or antipsychotic drug.(283–285) In the diagnosis of schizophrenia, some

studies required only the relevant CPRD disease codes.(286–288) One study reported the diagnostic accuracy of CPRD-defined schizophrenia, comparing to case notes to see whether such patients met International Classification of Disease criteria(289) and the Diagnostic and Statistical Manual of the American Psychiatric Association.(290) The sensitivity and positive predictive value of schizophrenia diagnostic codes was found to be 88% (95%CI 62 to 98%) and 71% (95%CI 48% to 88%), respectively. For non-organic psychosis, sensitivity and positive predictive value was 91% (95%CI 74% to 97%) and 91% (95%CI 74% to 98%), respectively.(287) No other research studying the use of CPRD for bipolar disorders, dissociative disorders, sexual and gender identity disorders, eating disorders, impulse control disorders, or personality disorders were identified.

Since identified studies reported high diagnostic accuracy for CPRD-defined schizophrenia, it was considered acceptable to use schizophrenia codes alone, with no further evidence required. Diagnostic codes for longer lasting psychiatric disorders, such as personality disorders or sexual and gender identity disorders were also used alone. For these conditions, a participant was permitted to receive a diagnostic code any time prior to health-related job loss. Other psychiatric conditions such as dissociative disorders, eating disorders, impulse-control disorders, bipolar disorders, and psychosis were conditions that could completely resolve. For these conditions, a participant was required to also have evidence of a continuing mental health problem into the year prior to health-related job loss.

People with psychiatric-care-level mental health problems were defined as:

Participants who had received a diagnostic code for schizophrenia, personality disorders, or sexual and gender identity disorders, prior to HRJL.

OR

Participants who had received a diagnostic code for dissociative disorders, eating disorders, impulse-control disorders, bipolar disorders, and psychosis in the year prior to HRJL

OR

Participants who had received a diagnostic code for dissociative disorders, eating disorders, impulse-control disorders, bipolar disorders, and psychosis earlier than a year prior to HRJL and received a prescription for treatments used in mood disorders, treatments used in

mania and hypomania, treatments used in psychoses, or treatments used in insomnia and anxiety, in the year prior to HRJL.

3.7.3.4 Severe mental health disorders

In the literature, several studies reporting validation outcomes for CPRD-defined suicide and self-harm were identified. Two studies used diagnostic codes for suicide with no further evidence required.(291,292) Two other studies used diagnostic codes for suicide or self-harm combined with a review of the GP notes or death certificates.(293,294)

In this thesis, severe mental health problems included codes relating to self-harm, suicidal actions or ideations and refers to people with crisis admission, section, on a severe mental health register or under psychiatric care. It was considered that such events were unlikely to be misclassified; therefore, any code relating to these events was included in analysis. These codes represent serious life events which may have fallout for years to come. Therefore, I was interested the occurrence of these codes any time prior to HRJL.

People with psychiatric-care-level mental health problems were defined as:

Participants who had received a diagnostic code for a severe mental health event prior to HRJL

Table 11: Identified research studies reporting validation outcomes and using CPRD/GPRD criteria for mental health problems

Health problem	Populations studied	Criteria used
Primary-care-level mental health problems	Mental health problems in general practice (282)	Disease-specific Read codes with no further evidence required
Sleep disorders	No studies identified	No studies identified
Psychiatric-care-level mental health problems	Schizophrenia (286–288)	Disease-specific Read codes with no further evidence
	Schizophrenia (283–285)	Disease-specific Read codes AND prescriptions for a neuroleptic, antipsychotic or lithium
Severe mental health problems	Suicide and self-harm (291,292)	Disease-specific Read codes with no further evidence

	Suicide and self-harm (293,294)	Disease-specific Read codes AND a review of the GP notes or death certificates

3.7.4 Neurological disorders: epilepsy and cerebrovascular accident

3.7.4.1 Epilepsy

In the literature, studies reporting validation outcomes for CPRD-defined epilepsy used a combination of diagnostic codes with epilepsy-specific drug codes.(295–297) Epilepsy is a condition with a relatively specific and sensitive set of drugs for which it is treated. This makes the use of prescription data ideal, as a person is unlikely to have epilepsy if they are not also being managed by an epilepsy drug, see NICE guidelines for diagnosed epilepsy.(298) As such, in this thesis, epilepsy codes were only included for analysis if they occurred with concomitant epilepsy-specific prescriptions. The use of fit and seizure codes was more complicated: in clinical practice, a diagnosis of epilepsy is made carefully, and may not be made for some time following a seizure, as long-term treatment with epilepsy drugs has considerable consequences for the patient. Therefore, participants with fits and seizures who were later diagnosed with epilepsy (even after HRJL) were also included.

People with epilepsy were defined as:

Participants who had received a diagnostic code for epilepsy prior to HRJL and had ever received a prescription for treatments used in epilepsy

OR

Participants who had received a diagnostic code for fits or seizures prior to HRJL, and had ever received a diagnostic code for epilepsy and a prescription for treatments used in epilepsy

3.7.4.2 Cerebrovascular accident

Several studies reporting validation outcomes used CPRD data to classify stroke and TIA. In several studies these clinical codes were used with one further piece of evidence, such as the use of antiplatelet drugs, new epilepsy, hospitalisation discharge letters and referrals, or neuroimaging results.(299–303) Other studies combined TIA and stroke codes to form a cerebrovascular accident (CVA) group.(258,304) Importantly, one study found the

diagnostic accuracy of TIA and stroke diagnostic codes was quite low: overall agreement between stroke and TIA codes and hospital specialist notes was 66%. This was largely due to misdiagnosis between strokes and TIA codes. However, if the two groups were merged to form CVA, agreement increased to 80%.

In accordance with the methods outlined in the literature, I reinforced diagnostic codes for these conditions with one further piece of evidence: participants were also required to have been prescribed antiplatelet drugs. Since TIA is a condition from which full recovery is expected, these codes were restricted to those that had occurred in the year prior to HRJL. In consideration of the disparity between GP diagnosis of stroke/TIA and specialist diagnosis of stroke/TIA in the literature, I also merged these two groups to form a CVA group for analysis.

People with CVA were defined as:

Participants who had received a diagnostic code for stroke prior to HRJL and had ever received a prescription for antiplatelet treatment

OR

Participants who had received a diagnostic code for TIA and received a prescription for antiplatelet treatment in the year prior to HRJL

Table 12: Identified research studies reporting validation outcomes and using CPRD/GPRD criteria for neurological disorders

Health problem	Populations studied	Criteria used
Epilepsy	Epilepsy (295–297)	Disease-specific Read codes with AND drugs used in epilepsy
Cerebrovascular accident	Cerebrovascular accident (258,304)	Disease-specific Read codes with no further evidence required
	Stroke or TIA (299–303)	Disease-specific Read codes AND one or more pieces of evidence, such as: - Antiplatelet drug treatment - New diagnostic epilepsy code - Hospitalisation

- Neuroimaging

3.7.5 Respiratory disorders: asthma and COPD

3.7.5.1 Asthma

A few studies were identified in the literature that reported validation outcomes and used CPRD diagnostic codes for asthma in their analysis. Two studies used the asthma codes alone,(305,306) while another required both asthma codes and prescription codes.(307) Two studies reported good agreement between CPRD and other databases or coding systems for asthma, with or without the use of prescription data.(305,307)

The use of prescription inhalers in asthma is ubiquitous enough that a person who was not prescribed such medication would have a doubtful diagnosis of asthma. It was also desirable to exclude participants with a previous diagnosis of asthma but who had not needed treatment for some time (e.g. over a year).

People with asthma were defined as:

Participants who had received a diagnostic code for asthma prior to HRJL and had received a prescription for treatments used in asthma or COPD in the year prior to HRJL

People with severe asthma were defined as:

Participants who had received a diagnostic code for severe asthma prior to HRJL and had received a prescription for treatments used in asthma or COPD in the year prior to HRJL

3.7.5.2 COPD

In the literature, one study of CPRD-defined COPD used diagnostic codes alone in analysis and found similar prevalence rates to those found in the Morbidity Survey in General Practice.(307) Other identified studies used a combination of disease codes and prescription data.(307–309) Soriano et al. used a system of COPD prescriptions to devise a severity ladder: those on at least two prescriptions of inhaled or oral bronchodilators, xanthines, cromones, steroids, or combinations were considered as having moderate COPD; those on oxygen or nebulised therapy were considered as having severe COPD; while everyone else was defined as having mild COPD.(309) When comparing COPD diagnosis to GP-recorded diagnosis, the positive predictive value was surprisingly low: one study

reported that only 57.8% of cases were confirmed by the GP. This appeared to be because the remaining participants had had asthma which was erroneously coded as COPD.(309)

The expected number of people with diagnosed COPD in this working-age study sample was likely to be very low and therefore I did not attempt to derive the severity of COPD using prescription codes. However, given the low diagnostic accuracy of COPD Read codes reported in one study, COPD disease codes were restricted to those that occurred prior to HRJL alongside prescriptions for COPD treatments in the year prior to HRJL. In interpreting analysis using asthma and COPD variables, it was also important to remain mindful of possible misdiagnosis between these two conditions in study participants.

People with COPD were defined as:

Participants who had received a diagnostic code for COPD prior to HRJL and had received a prescription for treatments used in asthma or COPD in the year prior to HRJL

Table 13: Identified research studies reporting validation outcomes and using CPRD/GPRD criteria for asthma and COPD

Health problem	Populations studied	Criteria used
Asthma	Asthma (305,306)	Disease-specific Read codes with no further evidence required
	Asthma (307)	Disease-specific Read codes AND prescriptions for asthma drugs
COPD	COPD (307)	Disease-specific Read codes with no further evidence required
	COPD (307–309)	Disease-specific Read codes AND two prescriptions for COPD drugs

3.7.6 Endocrine disorders

3.7.6.1 Diabetes

The use of CPRD-derived disease codes for diabetes varied significantly in the literature. Two studies were identified that used disease codes alone,(310,311) one study that required a combination of disease codes and prescription codes,(312) and three studies that based identification of diabetes solely on the basis of treatment with diabetic drugs in

the past 12 months.(313–315) Additionally, several studies split by type 1 or type 2 diabetes using an algorithm which took into account age at diagnosis and type of treatment.(266,303,316–318)

For the work of this thesis, the distinction between type 1 and type 2 diabetes was not as important as whether diabetes was well-managed and whether there were complications. Severe diabetic problems would be likely to have a greater impact on work. Moreover, to restrict diabetes codes based on diabetic prescriptions would be to exclude many people managing their diabetes without drugs. Since diabetes is a chronic condition, codes were included that had occurred prior to the point of health-related job loss.

People with diabetes were defined as:

Participants who had received a diagnostic code for diabetes or severe diabetes prior to HRJL

People with severe diabetes were defined as:

Participants who had received a diagnostic code for severe diabetes prior to HRJL

Table 14: Identified research studies reporting validation outcomes and using CPRD/GPRD criteria for diabetes

Health problem	Populations studied	Criteria used
Diabetes	Diabetes (310,311)	Disease-specific Read codes with no further evidence required
	Diabetes (312)	Disease-specific Read codes AND prescription for diabetes
	Diabetes (313–315)	Diabetes treatment in the prior 12 months
	Type 1 and type 2 diabetes (266,303,316–318)	Type 1 and type 2 diabetes were distinguished using an algorithm that separated diabetes based on age at diagnosis and type of treatment (e.g. treated with insulin and <35 years old at diagnosis = type 1 diabetes)

3.8 Statistics

This section describes the statistical methods used throughout the thesis and how they will be applied to answer the research objectives. This includes a discussion of the use of descriptive statistics, conditional logistic regression, and cluster analysis. Statistical analyses were performed using STATA-13.

3.8.1 Descriptive statistics

Percentages were used to describe proportions for categorical data. For measures of central tendency and scatter, means and standard deviations were used for continuous data, and medians and interquartile ranges for ordinal data and skewed continuous data.

The Wilcoxon rank-sum test, also known as the Mann-Whitney U test was used to compare independent sample, continuous variables between groups. This test was used where data was not normally distributed and tested the null hypothesis that a randomly selected value from one group is equally likely to be larger or smaller than a randomly selected value from a second group. Since independence is a requirement, this test was run on unmatched data only.

The chi-squared test was used for categorical data, to determine whether differences in proportions were statistically significant. Where expected values in cells of the generated contingency table were below 5, Fisher's exact test was used instead.

3.8.2 Conditional logistic regression

Logistic regression analysis is a commonly used statistical approach in which a logistic function is used to predict the probability of a categorical dependent variable (outcome of interest) using a set of explanatory variables (exposures of interest). Binomial logistic regression is used to predict the probability of a binary dependent variable (outcomes where only two values are possible) e.g. living vs dead or diabetes vs no diabetes. While in linear regression a straight line is used to describe the relationship between one or several explanatory variables and a continuous outcome, in logistic regression it is not possible to apply a linear equation to predict probabilities. Instead, the log odds of the event of interest are predicted, which may follow a linear relationship with the explanatory variables of interest and therefore can be predicted using a linear equation. The coefficients (beta values) produced by the logistic model describe the relationships between the explanatory variables of interest and the log odds of the event of interest. By exponentiating these

coefficients, it is possible to calculate odds ratios (OR) which are a measure of the association between the variables of interest and the outcome of interest.

Conditional logistic regression is a specialised version of logistic regression that takes case and control matched pairs into account. In this kind of analysis, cases are compared to their matched controls for a certain set of explanatory variables. Interestingly, this analysis predicts (or "retrodicts") how the value of the explanatory variables of interest vary based on the fixed value of the outcome of interest. The coefficients (and thus odds ratios) produced by this model can be interpreted the same as for a logistic regression, except that all observed associations are independent of the variables for which case and control participants were matched. Using the proposed case control analysis above as an example, this means conditional logistic regression analysis will account for age, gender, and GP practice in this thesis.

Matched case control studies are advantageous as they require fewer study participants than regular case control studies to achieve sufficient statistical power. Matching for known confounding factors means that further statistical adjustment is not required for the variables used in the matching process. However, once matched for, such variables cannot be examined for their association with the outcome of interest in regression analysis.

In this thesis, conditional logistic regression was used to assess the association between demographic, lifestyle, and health-related exposures and the occurrence of HRJL. As described above, the number of variables on which a participant can be matched is limited as the greater the number of matching variables the less likely suitable controls can be found for analysis. However, other factors may confound the relationship between a health exposure and HRJL, and, where appropriate, these were statistically adjusted for as co-variables in multivariable logistic regression analysis.

To make appropriate adjustment in multivariable analysis there should be strong reason to believe a variable is associated with both the exposure and outcome of interest. Adjusting for a factor that is associated with the exposure of interest alone, or the outcome of interest alone, constitutes an *unnecessary adjustment* leading to reduced precision in estimating effect. If a factor is associated with both the exposure and outcome of interest one must also be careful that it is not a mediator between the exposure and outcome: adjustment for a mediating variable amounts to an *over-adjustment* which may lead to underestimates of true effect.(319) Throughout the thesis, I considered potential confounding factors for their association with the outcome of interest (HRJL) and the

exposure under study, before their use in multivariable conditional logistic regression analysis.

3.8.3 Cluster analysis

Cluster analysis is used to describe common groupings, or patterns, of variables in a study population. In this thesis, cluster analysis was used to define common groups of health disorders among study participants with multimorbidity. Several methodological considerations are required for planning cluster analysis. In the first stage, the variables on which to base the cluster analysis are selected and it is important that these variables characterise the phenomenon under study. For example, age does not constitute a useful cluster-defining variable for multimorbidity as it does not characterise multimorbidity well. Instead, variables describing distinct health disorders are appropriate.

Cluster analysis groups individuals based on their mathematical "similarity" for selected variables. In practice, there are several techniques that can be used to describe the degree of similarity. One approach used involves correlation between groups, where large values of Pearson's correlation statistic *r*, for example, may indicate strong similarity between two individuals for certain variables and initiate their clustering together. However, in the literature, geometric distances are more commonly used for cluster analysis. Similarity statistics are derived from these geometric distances with higher values representing greater levels of similarity. There are multiple similarity statistics that use geometric distances and their selection depends upon the objectives of the research and the data available.(320) In this thesis, the clustering of health disorders among participants with multimorbidity was described, and clustered variables were all binary (since the participant either had the disorder or did not). In this situation, an appropriate similarity measure is the Jaccard coefficient.(321) This coefficient is advantageous as it's easily understood and defines similarity between two individuals using a count-based algorithm which considers the proportion of variables that are present in two individuals over those that are present in both or only in one person, $J = M_{11} / M_{01} + M_{10} + M_{11}$, see Figure 24. For the purposes of this thesis, it was also advantageous because it did not lend weight to negative matches (i.e. grouping participants based on diseases that they did not have), as for most study participants many CPRD-defined disorders will not be present. The Jaccard coefficient contrasts with the simple matching coefficient, for example, that lends weight to negative matches, including M_{00} in its numerator and denominator $SMC = M_{11} + M_{00} / M_{01} + M_{10} + M_{11} + M_{00}$.

Figure 24: binary variables used in calculating the Jaccard similarity coefficient and the simple matching coefficient

	Disease absent (0)	**Disease present (1)**
Disease absent (0)	M_{00}	M_{10}
Disease present (1)	M_{01}	M_{11}

Cluster analyses can take hierarchical or non-hierarchical approaches. Non-hierarchical cluster analysis requires the user to pre-specify the number of clusters they wish to examine. The algorithm (k-mean or k-median) assigns each participant or observation to one of the cluster seeds with the nearest mean or median similarity. Non-hierarchical cluster analysis is useful in that the results are less susceptible to outliers and as it can analyse extremely large datasets. However, this method can be susceptible to high variability in output, depending on the number of clusters that have been specified. Therefore, non-hierarchical methods tend to be used when analyses are less explorative and when the researcher has validated information about the underlying structure of the data that will help them to select an appropriate number of cluster points. A more explorative approach was undertaken in this thesis since patterns of multimorbidity had not yet been described in the older working-age population, and it was preferable to be led by the available data. In addition, to visualise how health disorder clusters merged at different levels of similarity was only possible with the use of a generated dendrogram in hierarchical cluster analysis.

Hierarchical methods include agglomerative and divisive methods. In agglomerative cluster analysis participants start the process as individuals that are subsequently clustered one by one based on their similarity to other groups of participants, so that eventually all participants form one cluster. The opposite process happens in divisive methods where participants start in one cluster and are separated out by an individual's dissimilarity to other members of that cluster. In this process, all individuals end up on their own or in a group of identical participants for the variables specified. For the purposes of this work, analysis was performed in STATA-13, which takes an agglomerative approach to hierarchical cluster analysis, since the computational time required for divisive methods is greater.(322)

Similarity measures, such as the Jaccard coefficient, may be employed in different clustering algorithms, which decide which groups of individuals should be grouped together at each step in the clustering solution. Some of the more well-known methods include:

- Single linkage: which computes dissimilarity as the dissimilarity between the most similar pair of observations between two groups. This technique has low resistance to measurement error and outliers and tends to form unbalanced clusters where members have little in common and are mostly grouped together based on intermediate observations.(323,324)
- Complete linkage: which is like single linkage except it uses the furthest pair of observations between two clusters to calculate dissimilarity. This technique is less sensitive to outliers but tends to clump observations into many tight compact clusters which are resistant to merging.(324)
- Average linkage: uses the average dissimilarity between two clusters and therefore has properties intermediate between single and complete linkage. These algorithms are commonly used, reasonably robust, and produce more stable dendrograms.(324,325)
- Wards linkage: uses the similarity between two clusters based on the minimum increase in the error of sum of squares within the clusters, summed over all variables.(324) Wards method is strongly biased towards producing clusters with similar numbers of participants and groups that are multivariate normal. This method is appropriate in situations when it is reasonable to assume that clusters should be of similar sizes.

I used average-linkage algorithms to cluster since these produced a more stable solution and because finding clusters of similar sizes was not a necessity for the purposes of this thesis.

During hierarchical cluster analysis, the researcher must consider at what point clusters are most meaningful i.e. when individuals within each cluster are similar enough for their selected characteristics but the total number of clusters is also small enough to allow for intelligible comparison. This process is facilitated by the production of a tree-like dendrogram which allows the researcher to observe the overall similarity measure (the average within-cluster distance) at each point in the stepwise process. For the purposes of this thesis, I observed points at which there were large leaps in the within-cluster dissimilarity between cluster steps, reflecting the algorithm's "reluctance" to join two

clusters together, as occurs when there appears to be substantial inter-cluster differences. This is visualised by long drawn out vertical lines on the generated dendrogram. When such leaps were visible, the process was stopped, and the comparative disease and demographic profiles of the developed clusters were examined. To compliment this process, I used the variance ratio criterion, or pseudo F-statistic, which was calculated to suggest the optimum number of clusters.(326) When the F-statistic was similar at different stop points, the dendrogram was observed to make a final decision regarding number of clusters.

As part of this process, outlying clusters were identified and described. Such clusters were usually composed of few or single individuals with marked differences to the majority (e.g. participants with rarer disorders or unusual pairings). Outlying clusters were defined as those composed of less than 10 participants and were discarded from further analysis.

3.8.4 Statistical power calculations

For the analyses conducted in this thesis, recruitment had already occurred, and the number of participants was set. Therefore, I estimated the statistical power available for planned analyses using the available sample size. Statistical power describes the probability of finding a statistically significant effect (rejecting the null hypothesis) if there is an effect to be found (the alternative hypothesis is true). In other words, the higher the statistical power the lower the chance of committing a type II error. In this section, for a range of planned analyses, I considered the minimum detectable odds ratio that could be achieved with a statistical power of 80%. To calculate statistical power, a well-cited method for matched case-control studies using 1:1 matching was applied (Schlesselman 1982).(327,328) This method required information about the number of case participants available (maximum 498 for this thesis), the number of controls per case (1:1 for all analyses), the alpha significance level (set by convention at 5%), and, lastly, the likely prevalence of the exposure of interest among control participants – which was estimated using previously reported prevalence figures in a comparable population and age group.

Since this thesis employed a novel classification system to define health exposures, the prevalence of these exposures could not be estimated from pre-existing publications using the same classification system. Instead, I used prevalence figures from the Age UK Almanac of disease profiles in later life.(329) This paper used a sample representative of the English population, born before 1954, from a complete dataset of GP practices participating in CPRD. As such, it provided UK-based and similarly sourced reference figures for disease prevalence. However, it should be emphasised that power calculations performed using

these figures were estimates only, since the prevalence study retrieved additional diagnostic information from HES data and was likely to have used different Read codes to classify health exposures. In addition, prevalence figures were not available for ages below 60-64 years, meaning the estimated prevalence of certain conditions may have been slightly higher than in this sample for some age-associated health problems.

Using the Age UK prevalence figures, I considered the statistical power available to complete the main aims of this thesis. Firstly, I considered the statistical power to assess the association between HRJL and the major musculoskeletal, mental health, cardiovascular, neurological, and endocrine disorders studied in this thesis. Then, I considered the statistical power available to assess the relationship between multimorbidity and HRJL.

Age UK reported the prevalence of osteoarthritis to be 17.1% among those aged 60-64 years. Osteoarthritis is the most common musculoskeletal disorder in this age group and the major contributor to chronic musculoskeletal disorders. Therefore, for chronic MSDs and HRJL, a conservative estimate was made, using this prevalence figure, that the total sample size in this thesis was sufficient to detect a minimum association of 1.56 OR at a statistical power of 80%.

Age UK reported the prevalence of diagnosed depressive disorders to be 22.3% and the prevalence of severe mental health problems to be 1.9% among those aged 60-64 years old. Depressive disorders are the most common mental health problems diagnosed in primary care, therefore, a conservative estimate was made that the total sample size in this thesis was sufficient to detect a significant association between HRJL and primary care-level mental health problems, at a minimum OR of 1.50 and a statistical power of 80%. In addition, the sample size was sufficient to detect a minimum OR of 2.7 for severe mental health problems, according to the Age UK figures.

Concerning cardiovascular disorders, Age UK reported the prevalence of ischaemic heart disease to be 7.6%, heart failure to be 1.4%, and hypertension to be 32.4% among those aged 60-64 years old. At a statistical power of 80%, the total sample size in this thesis was sufficient to detect an association between these exposures and HRJL at a minimum OR of 1.81 for ischaemic heart disease, a minimum OR of 3.1 for heart failure, and a minimum OR of 1.45 for hypertension. The remaining cardiovascular conditions (structural heart disease, cardiac arrhythmias, venous thrombus and peripheral atherosclerosis) represented a mix of rarer diagnoses for which it was harder to find UK- and age-specific reference values. Since

these conditions are rarer it may be difficult to detect a significant association with HRJL using the available sample size, unless the strength of association is large.

Age UK reported the prevalence of asthma to be 11.7% and of COPD to be 4.8% among those aged 60-64 years old. At a statistical power of 80%, the total sample size in this thesis was sufficient to detect an association between these respiratory exposures and HRJL at a minimum OR of 1.66 for asthma, and a minimum OR of 2.03 for COPD, according to the Age UK figures.

Age UK reported the prevalence of stroke to be 2.8% and of epilepsy to be 1.8% among those aged 60-64 years old. At a statistical power of 80%, the total sample size in this thesis was sufficient to detect an association between these neurological exposures and HRJL at a minimum OR of 2.40 for stroke, and a minimum OR of 2.82 for epilepsy, according to the prevalence figures reported by Age UK.

Age UK reported the prevalence of diabetes to be 10.6% among those aged 60 – 64 years old. Therefore, at a statistical power of 80%, the total sample size in this thesis was sufficient to detect an association between diabetes and HRJL at a minimum OR of 1.69.

Next, I considered what statistical power was available to assess the association between multimorbidity and HRJL. Age UK looked at 22 conditions (hypertension, atrial fibrillation, coronary heart disease, heart failure, stroke, dementia, depression, epilepsy, mental health, asthma, COPD, diabetes, hypothyroidism, chronic kidney disease, cancer in the past 5 years, anaemia, osteoporosis, falls, fragility fractures, incontinence and skin ulcers). They found that the prevalence of participants with no morbidity, one morbidity, two morbidities, three morbidities, four morbidities, or five morbidities were 38.1%, 31.1%, 17.3%, 8.0%, 3.3% and 2.2% respectively, among those aged 60 – 64 years. Although the Age UK classification of multimorbidity could not be replicated here, these prevalence figures were used as rough estimates. At a statistical power of 80%, the total sample size in this thesis was sufficient to detect an association between multimorbidity and HRJL at a minimum OR of 1.55 for two morbidities, OR of 1.79 for three morbidities, OR of 2.28 for four morbidities, and OR of 2.60 for five morbidities, according to the prevalence figures reported by Age UK.

Based on the power calculations above, it appeared that statistical power was sufficient to observe, at minimum, a small to moderate association with HRL for the majority of health exposures of interest in this thesis. However, for subgroup analyses, it was recognised that

the overall number of case-control pairs available would drop, meaning reduced statistical power. Using depression as an example, if the association between depression and HRJL was considered, and analysis was restricted to male participants only in order to look for effect modification by gender, the number of available case-control pairs would drop to 220 instead of 494. In this case, at the prevalence of depression reported by Age UK (22.3%) and a statistical power of 80%, the sample size was still sufficient to detect a minimum OR of 1.82 (a weak association) among men. However, for rarer conditions, for example stroke, using the prevalence of stroke reported by Age UK (2.8%) at a statistical power of 80%, the sample size was only sufficient to detect a strong association (minimum OR 3.35) among men. This drop in power was appreciated when interpreting results from subgroup analysis. It must be stressed that where effect estimates suggested an important relationship, but analysis was underpowered to show a statistically significant result, this was not interpreted as evidence of no association.

3.9 Summary

3.9.1 Data sources

- Data was derived from two sources for this thesis:
    - The baseline HEAF study questionnaire, which was a postal questionnaire including items relating to date of birth, gender, ethnicity, marital status, education, employment status, and occupation (responses collected 2013 – 2014).
    - The CPRD, which was an electronic medical record system used to derive retrospective primary-care clinical data in the form of date-stamped diagnostic “Read” codes and BNF prescription codes (CPRD data was available from a participant’s initial registration at a CPRD-contributing GP practice to the point of completion of the HEAF baseline questionnaire).
    - As only CPRD-contributing GP practices were recruited to the HEAF study, it was possible to link questionnaire data to CPRD data for all HEAF study participants.

3.9.2 Study design and participants

- A matched retrospective case-control study design was used, involving the selection of “cases” (with the outcome of interest) and matched “controls”

(participants who are similar for important confounders, but do not have the outcome of interest). These are defined below:

- Cases were participants of HEAF who were unemployed at baseline and reported that a health problem was “part of the reason” or “the main reason” reason for dropping out of work. Cases were included if they had CPRD coverage for a minimum of a year prior to the date of their health-related job loss (HRJL).
- Control participants were participants of HEAF who did not report HRJL at baseline. Controls were employed when their matched case participant experienced HRJL. All control participants were within 1 year of age of their matched cases, of the same sex, and from the same GP practice. Control participants were included if they had CPRD coverage for a minimum of a year prior to the date of HRJL of their matched case.

3.9.3 Categorising CPRD-defined health exposures

- Returned CPRD data grouped initially by body system. Two researchers with medical training independently organised the clinical codes into disease groups. Codes were grouped into distinct disorders or events.
- Read codes were excluded from further analysis if:
  - non-specific or not relating to clinically recognised health problems
  - referring to a health problem that had not been requested from CPRD.
- Distinct groups were combined into larger clinical groups when:
  - Clinical conditions were similar enough
  - When existing groups were likely to be too small for meaningful analysis

3.9.4 Use of CPRD-defined health exposures in analysis

- Use of CPRD diagnostic codes were restricted based on the date at which they occurred:
  - Codes for chronic or long-lasting disorders were used if they occurred any time prior to the date of HRJL
  - Codes for short-term or probable short-term disorders were used if there were evidence of them occurring in the year prior to HRJL

- Where appropriate for certain clinical conditions, use of CPRD diagnostic codes were restricted based on BNF prescription codes, if:
    - available pharmaceutical codes were for drugs used in that clinical condition
    - all people with that clinical condition would be expected to have been prescribed a drug in the specified drug class

3.9.5 CPRD-defined health exposures

- The following CPRD-defined health exposures were explored in this thesis:
    - Chronic musculoskeletal disorders
    - Musculoskeletal pain disorders
    - Ischaemic heart disease
    - Heart failure
    - Hypertension
    - Structural heart disease
    - Cardiac arrythmias
    - Venous thromboembolic disease
    - Peripheral arterial disease
    - Primary-care-level mental health problems
    - Psychiatric-care-level mental health problems
    - Severe mental health problems
    - Epilepsy
    - Cerebrovascular accident
    - Asthma
    - COPD
    - Diabetes

3.9.6 Statistics

- For descriptive analysis, percentages were used to describe proportions for categorical data; means and standard deviations were used for continuous data; and medians and interquartile ranges were used for ordinal data and skewed continuous data.

- Wilcoxon rank-sum test was used to compare non-parametric independent continuous variables between groups. The chi-squared test was used for categorical data to assess differences in proportions. Where expected values in a cell of the generated contingency table were below 5, Fisher's exact test was used for categorical data.
- Conditional logistic regression analysis was used to study the association between independent exposures of interest and HRJL, taking into account case and control matched pairs and thereby controlling for age, gender, and GP practice.
- Cluster analysis was used to describe common groups, or patterns, of co-occurring CPRD-defined health problems in study participants with multimorbidity.
- Power calculations, based on prevalence figures reported by the Age UK almanac of disease profiles, estimated that statistical power was sufficient to observe a small to moderate association with HRJL for the majority of health exposures of interest. However, for subgroup analysis, the overall number of case-control pairs was fewer and statistical power was reduced, meaning power was only sufficient to detect a strong association for rarer conditions.

Chapter 4: How does comorbidity impact work outcomes in musculoskeletal disease? a systematic review

4.1 Introduction

In this chapter, the first research objective (see Chapter 2) is addressed: to systematically review evidence for the impact of comorbidity upon work outcomes among people with musculoskeletal disorders. Throughout this review, people with MSDs and no known comorbidities comprised the reference group. Only two other systematic reviews on the topic were identified: one reviewed the effect of co-presenting mental health problems on return to work and sickness absence in a low back pain population; the other, the effect of depression on return-to-work rates in MSD populations.(330,331) To my knowledge, this is the first review to consider impact of all reported comorbidities on work, and the first to consider all major employment outcomes, according to their definitions in the identified literature, including: work disability; sickness absence; unemployment; job loss; return-to-work time; and productivity loss.

4.2 Methods

A broad systematic review was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).(332) Cochrane library, MEDLINE, Psychinfo, PubMed, and Web of Science were searched independently by two reviewers on 12/12/2018 applying important search terms in the following algorithm: (((disease* or illness* or disorder* or health or pain) AND (musculoskeletal or rheum*)) OR (osteo* or arthrit* or spondyl* or rheum* or frail*)) AND (employ* or work or job* or productivity) AND (comorbid* or multimorbid*). Similar terms were accounted for by using the wildcard function. The protocol was registered in PROSPERO in advance of completion of this work (registration number CRD42016038756).

Studies were included if they: (1) were published in the English language; (2) compared patients with an MSD and comorbidity to MSD alone as the reference group; (3) reported

adjusted measures of association between comorbidity and work outcomes (there was no requirement for a study to adjust for any specific covariable); (4) report measures of error or report enough information to impute or calculate confidence intervals; and (5) were available in full text. Comorbidity was defined as a co-presenting long-term health condition in a person with an MSD, excluding those for which the long-term conditions could be sequelae or complication of their index MSD condition. The additional impact of comorbidity over and above that of having an MSD alone was the focus of this review. Fully published papers were included only, since it was not possible to critically appraise study methods from the abstract alone. Reviews, comments, and editorials were excluded. It was accepted that included studies may define work outcomes of interest in different ways. However, for the purposes of this review, the work outcomes of interest were broadly categorised as in Table 15, below.

Table 15: Categorisation of included work outcomes

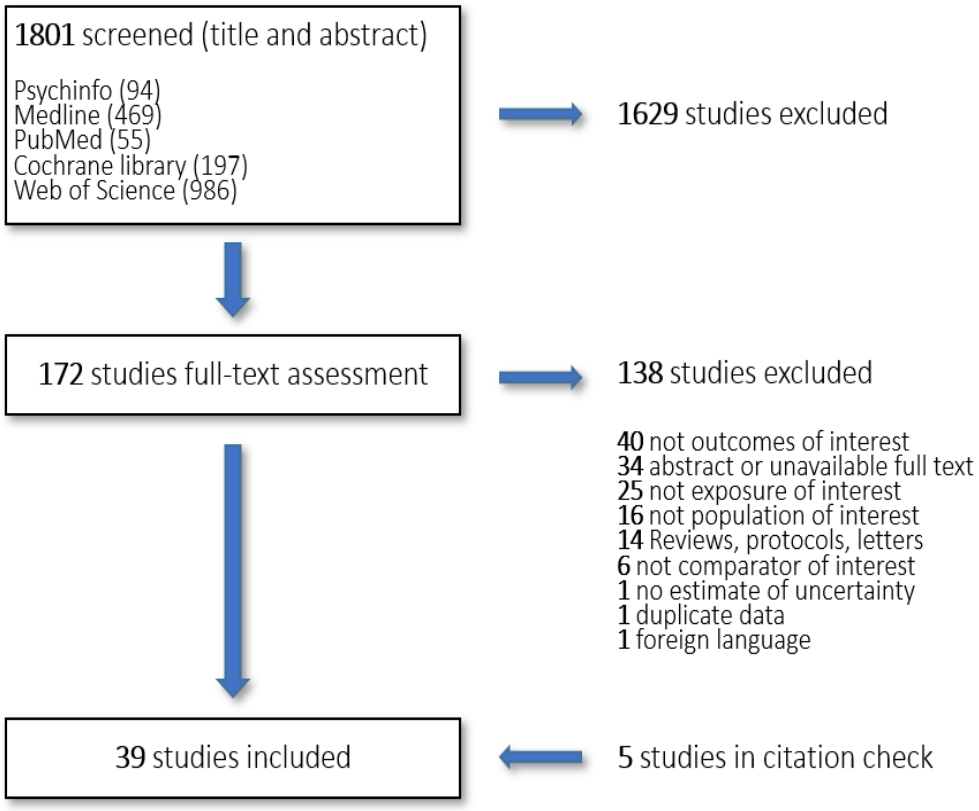
Work outcome	Definition
Work disability	Work outcomes included those in which participants described themselves as unable to work due to health problems; where certified or official disability was apparent; or participants were receiving disability pension
Return to work following disability	Work outcomes included those in which previously disabled or out-of-work participants with health problems were assessed for return to employment, or time taken to return to work
Sickness absence (absenteeism)	Work outcomes included those which described absence from work over a matter of hours or days in an employed individual, with no indication of the receipt of disability pension
Reduced productivity and presenteeism	Work outcomes included those which included some assessment of impaired productivity at work e.g. working longer hours, reduced output, and longer breaks. Presenteeism refers to reduced productivity as a direct result, or in part, due to a health problem
Employment status and job loss	Work outcomes included those which assessed odds of being unemployed (or employed). Job loss referred to loss of employment for any reason, while health-related job loss is

	that which is as a direct result, or in part, due to a health problem
Work transition	Included changing work or type of work for any reason

Data were extracted from the included papers into predefined tabulated summaries. These data included: study design; classification used for the index condition and comorbidity; important characteristics of the study population (number (n) and average age/gender); definition of the work outcome(s) considered; factors used in statistical adjustment for final analysis; and measure of association (see Tables 7 – 12, Appendix). Risk of bias was assessed using three versions of the Newcastle-Ottawa Scale (NOS) for case-control studies, cohort studies, and an adapted version for cross-sectional studies.(333) In assessment of quality, studies were judged based on three broad categories: risk of selection bias, comparability of the exposed and non-exposed groups, and quality of measurement of the exposure and outcome variables. Studies could score up to nine points for cohort studies or case control studies, and ten points for cross-sectional studies. Studies were also rated downwards for quality if they had not adjusted or stratified for age, gender, or socioeconomic status (education was also accepted as a proxy for socioeconomic status) as a minimum in their final analyses (see Tables 13 – 15, Appendix).

Given the highly variable MSD populations and classifications of comorbidity observed across included studies, it was not appropriate to attempt meta-analysis. Therefore, a narrative summary of the evidence was completed, and results were displayed graphically (see Figures 26 and 27).

Figure 25. Flowchart showing selection of suitable articles



4.3 Results

The search strategy identified 1801 publications, the titles and abstracts of which were screened for inclusion. The full text of 172 articles were retrieved, of which 39 studies met the pre-stated inclusion criteria (see flowchart, Figure 25).(9–13,199,334–366) Common reasons for exclusion were: no work outcomes of interest reported; abstract alone or no full text published; no exposure of interest studied (i.e. comorbidities); no population of interest (i.e. musculoskeletal disorders); inappropriate study design, such as review articles; and inappropriate reference group (which must be MSD alone to outline the *additional* risk posed by comorbidities). Some excluded studies examined the exposure of multiple comorbid MSDs (e.g. back pain and neck pain). However, it was not clear if these articles were reporting true comorbid diseases, or simply additional musculoskeletal manifestations arising from a single index condition.

Twenty cohort studies were included,(10,11,343–357,359,360,362) 18 cross-sectional studies,(9,12,13,199,334–341,358,361,363–366) and one case-control study.(342) These papers were entirely from developed nations, including 11 from the USA, (10,12,199,334,338,339,345,346,348,350,365), ten from Netherlands,

(9,11,340,341,347,349,354,361,362,364) six from Canada,(13,334,337,344,356,358) three from Australia,(343,352,363), two from Denmark,(357,360) and one each from Norway,(359) Sweden,(351) Germany,(336) Argentina,(342) Switzerland,(355) and UK.(353)

Classification of musculoskeletal disorders

The MSD study populations varied, and included: non-specific musculoskeletal disorder (MSD), musculoskeletal pain, or rheumatism,(337,340,360,364) back pain and/or neck pain,(350,358,364) knee pain or knee arthroplasty,(343,347,363) inflammatory rheumatic disorders (IRDs),(336,354) rheumatoid arthritis (RA),(339,341,349,351,357) ankylosing spondylitis (AS),(9–11,342,362), spondyloarthritis (SpA),(361) psoriatic arthritis (PsA),(334) systemic lupus erythematous (SLE),(338,344) scleroderma,(13) arthritis non-specific,(12,199,352,358,365) osteoarthritis (OA),(353) occupational muscular injury,(346) whiplash,(356) and spinal surgery, discectomy, or disc disorders.(345,348,355,359,366)

The classifications used for these MSDs were heterogeneous and varied according to the disorder considered. For example, the presence of non-specific musculoskeletal disorders, musculoskeletal pain, osteoarthritis, or non-specific arthritis, was usually self-reported and determined through the use of a questionnaire or structured interview.(12,199,337,340,352,353,356,358,360,364,365) However, for disorders that are primarily managed by specialists, e.g. inflammatory rheumatic disorders, the majority met pre-specified clinical criteria, often assessed by a rheumatologist.(9–11,13,334,336,338,339,341,342,344,347,349,351,354,355,359,361,362) In some studies, the presence of an MSD was derived through the use of electronic medical coding, for example, from administrative insurance databases.(336,345,349,357,364,366) Included studies and the classifications used for their MSD populations are outlined below, see Table 16.

Table 16: Classifications used for each musculoskeletal disorder

Included study	MSD classification used in study
Non-specific musculoskeletal disorder (MSD), musculoskeletal pain, or rheumatism	
Buist-Bouwman (2005) (364)	Rheumatism- survey interview data (self-report). Participants indicated they had experienced rheumatism or inflammation of joints in past 12m and had been treated for the condition by a healthcare professional or if medication had been prescribed.

van den Berg (2017) (340)	Musculoskeletal disorders – online questionnaire (self-report). Presence of diseases was assessed using the Work Ability Index,(367) in which participants were asked to indicate across a list of 13 broad disease categories whether they currently had a health disorder which had been diagnosed by a physician (yes/no). Specific musculoskeletal disorders included: disorder of the upper back or cervical spine; disorder of the lower back; pain radiating from the back into the leg (sciatica); musculoskeletal disorder affecting the limbs (hands, feet); rheumatoid arthritis; other musculoskeletal disorder. Participants were classified as having an MSD if they indicated any of the above.
Melkevik (2018) (360)	Musculoskeletal pain – survey questionnaires (self-report). Participants were asked to rate the average levels of musculoskeletal pain in low back, neck/shoulders and knees over the last three months. The response scale ranged from 0 to 9: 0 was "no pain" and 9 was "worst imaginable pain." A drawing from the Nordic Questionnaire defined the three respective body part regions.(368) A cut-off of 3 points on each scale was used to indicate whether participants had substantial levels of pain in the low back, in the neck/shoulders, or in the knees.
Munce (2007) (337)	Chronic pain condition – survey questionnaire (self-report). Participants reported that they had a chronic pain condition, diagnosed by a health care professional and present for at least 6 months. Included chronic pain conditions were: fibromyalgia, arthritis, rheumatism, back problems and migraine.
Back pain and/or neck pain	
Buist-Bouwman (2005) (364)	Chronic back trouble- survey interview data (self-report). Participants indicated they had experienced chronic back trouble in the past 12m and had been treated for the condition by a healthcare professional or medication had been prescribed.
Nordin (2002) (364)	Non-specific low back pain (NSLBP) – data obtained from occupational health administrative clinical records held by two utility and transportation companies. Clinical data was held as ICD-9 codes. NSLBP included the following ICD-9 codes after an index visit to the occupational health physician: lumbago (724.2) and sprains of the lumbosacroiliac region (846.0–3/8–9, 847.2–3). To prevent inclusion of specific back pain, analysis was limited to those cases in which the primary diagnosis was "sprains and strains of the lumbo-sacroiliac region."
Csupak (2018) (358)	Back problems – survey interview data (self-report). Participants were asked to report back problems (excluding fibromyalgia and arthritis) diagnosed by a health professional that lasted (or were expected to last) for at least 6 months.
Knee pain or knee arthroplasty	
Agaliotis (2013) (343)	Knee Pain – participants reported knee symptoms for more than 6 months, had knee pain or were taking non-steroidal anti-inflammatory drugs or analgesia for knee pain on most days of the past month and rated their knee pain ≥4 out of 10 for most days of the past week. A symptomatically eligible knee needed to demonstrate medial tibio-femoral joint space narrowing on X-ray but retain more than 2 mm joint space.
Agaliotis (2017) (363)	Knee Pain – defined as for Agaliotis (2013), above.

Kuijer (2016) (347)	Participants had received a total knee arthroplasty at one of two Dutch hospitals
Inflammatory rheumatic disorders (IRDs)	
Lowe (2004) (336)	Participants with inflammatory rheumatic disorders from a rheumatology outpatient clinic, diagnosed by their physicians according to ACR 1987 criteria for RA,(369) Tan et al criteria for SLE,(370) and using ICD-10 codes for other inflammatory rheumatic disorders.
de Buck (2006) (354)	Rheumatologist diagnosed RA, AS, SLE, or scleroderma. RA according to the American Rheumatism Association (ARA) classification criteria (Arnett et al. 1988);(369) AS according to the modified New York classification criteria (Van der Linden et al. 1984),(371) reactive arthritis or psoriatic arthritis; systemic lupus erythematosus (SLE) according to the ARA classification criteria (Tan et al. 1982),(370) or scleroderma.
Rheumatoid arthritis	
Callahan (1992) (339)	Rheumatologist diagnosed RA according to the ARA criteria, 1987.(369)
Hansen (2016) (357)	Patients with RA identified through the nationwide DANBIO Registry(372) and the Danish National Patient Registry (NPR).(373) Rheumatoid arthritis was identified using the following codes from the ICD-8 and ICD-10: 712.19 (Syndroma Felty), 712.39 (Arthritis rheumatoides alia et non specificata), 712.59 (Fibrositis rheumatoides chronica nodularis), DM05 (Arthritis rheumatoides seropositiva), and DM06 (Arthritis rheumatoides alia).
Manders (2014) (349)	Rheumatoid arthritis data from the biologic register of the Dutch Rheumatoid Arthritis Monitoring (DREAM) project.(374) Participants were diagnosed according to the 1987 ACR classification criteria,(369) had moderate to high disease activity [28-joint Disease Activity Score (DAS28) > 3.2], and were on TNF-inhibitor treatment.
Olofsson (2017) (351)	Participants starting treatment with their first TNF-inhibitor from the Swedish Rheumatology Quality Register.(375) A national register comprising the Swedish biologics register (Anti-Rheumatic Treatment In Sweden (ARTIS), covering 87–95% of all biologics-treated patients with RA in Sweden, and the register for follow-up of incident RA (according to 1987 ACR criteria).
Van der Zee-Neuen (2017) (341)	Rheumatoid arthritis patients diagnosed according to the 1987 American College of Rheumatology classification criteria.(369)
Ankylosing spondylitis	
Boonen (2001) (11)	Patients selected from the nationwide Dutch Standard Diagnosis Register of Rheumatic Diseases (SDR).(376) Selected patients had to have definite rheumatologist-diagnosed ankylosing spondylitis.
Castillo-Ortiz (2016) (9)	Rheumatologist-diagnosed patients with ankylosing spondylitis recruited from a rheumatology outpatient clinics.
Marengo (2008) (342)	Patients attending a rheumatology clinic diagnosed according to the modified New York criteria for ankylosing spondylitis, 1984.(371)

Ward (2001) (10)	Patients attending a rheumatology clinic diagnosed according to the modified New York criteria for ankylosing spondylitis, 1984.(371)
Webers (2018) (362)	Patients diagnosed according to the modified New York criteria for ankylosing spondylitis, 1984.(371)
Spondyloarthritis	
Nikiphorou (2018) (361)	Patients with a clinical diagnosis of spondyloarthritis, either axial or peripheral, fulfilling the ASAS criteria for spondyloarthritis.(377)
Psoriatic arthritis	
Kennedy (2014) (334)	Patients recruited from a psoriatic arthritis clinic with a rheumatologist-confirmed diagnosis of PsA (99% fulfilling CASPAR criteria).(378)
Systemic lupus erythematosus	
Dhanhani (2009) (344)	Patients diagnosed with SLE according to the ACR classification criteria (Tan et al, 1982),(370) with the presence of at least 4 criteria or the presence of 3 criteria and evidence of SLE on tissue biopsy sample, who joined the University of Toronto Lupus Clinic and Registry. Patients were limited to those who were seen within 1 year of their diagnosis.
Panopalis (2007) (338)	All participants met at least 4 of the 11 ACR revised criteria for the classification of SLE.(370) after chart review by a rheumatologist or a registered nurse working under the supervision of a rheumatologist.
Scleroderma	
Hudson (2009) (13)	Study subjects consisted of those enrolled in the Canadian Scleroderma Research Group Registry (CSRG).(379) Patients must have a diagnosis of scleroderma made by a rheumatologist.
Arthritis, non-specific	
Csupak (2018) (358)	Arthritis – survey interview data (self-report). Participants reported arthritis (excluding fibromyalgia) diagnosed by a health professional that lasted (or was expected to last) for at least 6 months.
Joshi (2015) (365)	Arthritis – telephone interview data (self-report). Patients responded ‘‘yes’’ to the question, ‘‘Have you been told by a doctor, nurse, or other health professional that you have some form of arthritis, rheumatoid arthritis, gout, lupus, or fibromyalgia?’’
Kessler (2001) (199)	Arthritis – telephone interview and self-administered questionnaire data (self-report). Arthritis was assessed by a standard checklist (of several chronic conditions) preceded by the question, “In the past 12 months, have you experienced or been treated for any of the following?”
Kessler (2003) (335)	Arthritis – defined as in Kessler (2001), above.
Schofield (2014) (352)	Arthritis – survey data (self-report). People who reported having ‘arthritis and related disorders’ (ICD10 code M00-19) were classified as having ‘arthritis’.
Abraido-Lanza (2006) (12)	Arthritis – interview survey data (self-report). Each self-reported condition was assigned an ICD-9 code. Respondents with “arthritis” had ICD-9 diagnostic codes for rheumatoid arthritis, juvenile rheumatoid arthritis, other forms of inflammatory arthritis, osteoarthritis, ankylosing spondylitis and other forms of spondylosis, or rheumatism.

Osteoarthritis	
Wilkie (2013) (353)	Osteoarthritis – postal questionnaire data (self-report). “Osteoarthritis” was defined as hip, knee or foot pain for 1 day or more during the past year.
Occupational muscular injury	
Brede (2013) (346)	Occupational musculoskeletal injury - referred to a rehabilitation centre after an occupational musculoskeletal injury and enrolled in the treatment program. Participants were work disabled as a result of their injury for at least 4 months and completed rehabilitation.
Whiplash	
Cote (2001) (356)	Whiplash – postal questionnaire data (self-report). To be classified as whiplash, a claimant had to be injured in an automotive collision, not have been hospitalized for more than 2 days, and answered ‘yes’ to the two following questions: “Did the accident cause neck/shoulder pain?” and “Have you felt neck/shoulder or reduced/painful neck movement pain since the accident?”
Spinal surgery, discectomy, or disc disorders	
Anderson (2016) (345)	Participants were identified through a workers’ compensation claims from the Ohio Bureau of Workers’ Compensation administrative database. ICD-9 codes were used to identify patients who underwent anterior, posterior, or 360° lumbar fusion for spondylolisthesis.
Kausto (2017) (366)	Participants were identified through the Sickness Insurance Register and Hospital Discharge Register administrative databases in Finland. ICD-10 codes were used to identify patients with intervertebral disc disorders (ICD-10 M51).
Schade (1999) (355)	Patients with a symptomatic disc herniation undergoing lumbar discectomy. Patients were selected for an automated percutaneous lumbar discectomy only if they presented with a contained disc protrusion exhibiting a concordant (positive) pain response on provocative discography. Discography was analysed by two independent radiologists.
Lee (2017) (348)	Patients with spinal surgery (including, disk herniation, stenosis, spondylolisthesis, degenerative scoliosis, and traumatic injuries) were identified from the electronic medical records derived from two University “institutions.”
Furunes (2018) (359)	Participants had low back pain as the main symptom for at least 1 year, Oswestry Disability Index score ≥ 30, had conservative treatment for ≥ 6 months without sufficient effect, and degenerative changes in the intervertebral disc L4/L5 and/or L5/S1. Degenerative disc and chronic low back pain was treated with lumbar total disc replacement at one of five Norwegian University Hospitals.

Classification of work outcomes

In order of frequency, the most commonly reported work outcomes across the literature were categorised as work disability or disability pension,(9–13,336,338,339,344,351,357) return to work after disability,(345–348,350,351,355,356,366) sickness absence,(335,337,340,341,353,364) employment status or job

loss,(338,341,342,349,352,354,361) presenteeism or reduced productivity,(334,335,343,361,365) and work transitions.(363) The classification of these work outcomes was also not consistent, as outlined in Table 17, and summarised below.

As described in earlier chapters, work disability can be defined as having a physical or mental impairment that has a substantial or long-term negative impact on a person's ability to carry out the employee-role, and usually refers to a person who is no longer employed as a result of poor health. In this review, work disability outcomes were classified as those in which participants described themselves as unable to work due to health problems, where certified or official disability was apparent, or participants were receiving disability pension. Among the included studies, work disability was generally self-reported. In some studies, participants were asked whether they had any "official" or certified work disability, or if they were in receipt of a disability pension.(9–11,339) Other studies simply asked whether there was a health problem that prevented participants from working.(12,338,358) Some studies grouped sickness absence along with more permanent disability.(13,336,351) In one study, work disability was limited to that caused by the index disease (ankylosing spondylitis).(11)

Studies reporting return to work following a period of work disability, considered the relative time taken to return to work, or whether the participant had returned to employment at a certain point on follow up. The follow-up period varied and ranged from 1 to 2 years. Frequently, data was derived from electronic administrative databases, such as those used for insurance, (345,348,351,356,364,366) in others return to work was self-reported.(346,347,355) In addition, studies had differing criteria for what constituted a "return to work" for example, one required that participants had sustained work for at least 6 months,(345) while another older study simply asked participants if they had returned to 'any' work.(355)

Sickness absence was self-reported in included studies.(199,337,340,341,361,362,364) Participants were generally asked about recent days of sick leave taken from work. However, the length of time over which participants were asked to recall sickness absence varied from 7 days,(337,341,361) to the past month,(199) to the past year.(340,364) In analysis, some studies considered any full days of absence from work in the past week,(337) or even year,(340) as having had "sick leave," others analysed the total number of days of sickness absence,(199,364) while others calculated total hours missing from work in the past week.(341,361)

Some studies estimated productivity losses, presenteeism, or perceived work limitations as a result of health problems; these were self-reported. Presenteeism was defined using the validated Work Productivity and Activity Impairment (WPAI) questionnaire in two studies.(343,361) Two studies used other validated questionnaires to measure health-associated productivity losses combined with the amount of time absent from work due to sickness for an overall work limitations score.(199,334) Over different time scales, the remaining three studies recorded single questionnaire items about whether the participant felt they had experienced significant work restriction or limitation.(199,361,365) For one of these studies the question did not specify that the work restriction was due to a health problem,(353) for another the question specified work restriction was as a result of "arthritis or joint symptoms".(365)

Studies reporting employment status were generally more homogeneous in their measurement of this outcome, which was self-reported in all cases. Participants were asked whether they were currently employed, a question that implied paid employment. In analysis, some studies used "current employment",(338,341,359,361) others "unemployment"(342,352) for the outcome of interest.

Job loss was self-reported and comprised one study that defined job loss as being unemployed or on disability pension at 1 year follow up,(354) and another that classified it as stopping work participation after 2 years of treatment (patients who had paid work or did voluntary work were defined as working in this study).(349)

Lastly, one study also reported "work transitions" in the prior 6 months using a validated questionnaire.(363) The Work Transitions Scale summarised information about a participant's loss of work hours, and changes in work hours, and changes in type of work performed as a direct result of knee problems.

Table 17: Classifications used for each reported work outcome

Included study	Classification of work outcome used in study
	Work disability
Castillo-Ortiz (2016) (9)	Work disability- questionnaire data (self-report). Participants were asked if they were not working because of "official work disability due to disease."
Ward (2001) (10)	Work disability- questionnaire data (self-report). Patients were asked whether they received payments for work disability, their current work status, and dates of retirement or permanent work disability (if applicable). Participants were analysed for permanent work disability and for receipt of disability payments, separately.

Boonen (2001) (11)	AS-related work disability – questionnaire data (self-report). Defined as officially recognised inability to perform paid work because of ankylosing spondylitis.
Csupak (2018)(358)	Permanent work disability. Questionnaire data (self-report). Participants were asked whether they had permanent inability to work.
Abraido-Lanza (2006) (12)	Work disability- interview survey data (self-report). Participants were asked whether any health problem or condition prevents them from working in a job or a business, or limits the type or amount of work that they can perform.
Hudson (2009) (13)	Work disability- questionnaire (self-report). Those considered work disabled were of working age and stated "I am currently disabled or on sick leave."
Lowe (2004) (336)	Work disability – questionnaire (self-report) with validation by insurance statements for participants claiming to be on disability pension: Patients were classified "work-disabled" if: 1) formerly employed, currently receiving temporary or permanent disability pension, 2) employed (full-time or part-time) with a sick leave of at least 4 weeks, or 3) unemployed and unable to do their usual activities for at least 4 weeks because of medical illness.
Panopalis (2007) (338)	Unable to work – telephone interview (self-report). Participants stated their employment status as "unable to work."
Callahan (1992) (339)	Work disability- questionnaire (self-report). Participants indicated if they were receiving work disability payments.
Olofsson (2017) (351)	Time until work disability (long-term sickness absence). Data from linked health insurance databases. Among working participants, defined as time to lose 15 days of 30 with sick leave or disability pension over follow up (maximum 3 years).
Hansen (2016) (357)	Work disability (long-term sickness absence). Linked data from the Danish (public) Register of Evaluation of Marginalization (DREAM) register,(374) which provides weekly information on social transfer payments for all residents in Denmark. Long-term sickness absence was defined as ≥3 weeks of receiving sickness absence benefits more than one year after diagnosis with RA.
Return to work after disability	
Anderson (2016) (345)	Return to work – data derived from workers compensation database. Participants were classified as returning to work if they returned within 2 years after lumbar fusion and remained working for more than 6 months.
Brede (2013) (346)	Failure to retain work at 12 months – structured interview (self-report). To be classified "working" at 1 year, participants were employed full- or part-time, either at full or light-duty. Participants who returned to work after discharge but did not maintain employment at the 1-year evaluation and patients who did not return to work at any point in the year after discharge were classified as failing to retain work.
Kuijer (2016) (347)	Return to work after at least 2 years follow up following total knee arthroplasty – questionnaire (self-report). Patients responding affirmatively to the question "I didn't get back to work" at follow-up were classified as not having returned to work.
Lee (2017) (348)	Return to work – data from electronic medical records. Defined as return to full employment within 1 year of spinal surgery and still working on last follow up (follow-up for at least 2 years after surgery).

Nordin (2002) (364)	Time to return to work – data obtained from administratively maintained occupational health records. Following work disability, worker was followed up over time to determine the point at which the employee first returned to unrestricted, full duty. This period defined the duration of work disability (episode duration). First return to regular duty was the outcome of interest.
Olofsson (2017) (351)	Time to return to work. Data from linked health insurance databases. Return to work was defined as (for patients with no work ability at baseline) the time taken to achieve ≤15 net days with sick leave or disability pension out of 30, over (maximum) three year follow up.
Schade (1999) (355)	Return to work at 2 years. Questionnaire (self-report). Participants reported if they had returned to 'any' work.
Cote (2001) (356)	Time to insurance claim closure (for whiplash). Linked data derived from two insurance company administrative databases. Time-to-claim-closure was defined as the period extending from the collision date to the date of final compensation payment made by the insurer to a claimant or, for permanent benefits, the date of final agreement between the insurer and the claimant. The decision to close a claim corresponds to the end of treatment, the attainment of maximal medical improvement, or the termination of income replacement benefits.
Kausto (2017) (366)	Time to sustained return to work– data derived from sickness insurance databases. Sickness absence period was started from the initial day of work absence until the end of the compensation period. Sustained return to work was defined as the end of the sickness benefit period that was not followed by a recurrent sickness absence period for same diagnosis in 30 days.
	Sickness absence
Csupak (2018)(358)	Absenteeism in the past week. Questionnaire data (self-report). Participants were asked whether they were unable to work in the past week (which was distinct from permanently being unable to work).
Kessler (2003) (335)	Number of work loss days – questionnaire (self-report). Participants were asked "how many days out of the past 30 were you totally unable to work or carry out your normal activities" because of problems with physical or mental health.
Melkevik (2018)(360)	Any sickness-absence for four consecutive weeks or more during the 550 days following study entry.
Munce (2007) (337)	Absenteeism in the past week. Survey questionnaire data (self-report). Absenteeism was defined as a positive response to the questions "you were absent from your job or business in the last week" and the "main reason for not working last week" was due to "illness/disability."
van den Berg (2017) (340)	Sickness absence in the year prior. Online questionnaire (self-report). Employees were asked to indicate on a 5-point scale how many days of sick leave that they had during the past year. Sick leave was defined as anyone with 1–365 days of sick leave in the prior year.
Van der Zee-Neuen (2017) (341)	Absenteeism. Work Productivity and Activity Impairment questionnaire (self-report). Outcome was percentage of working hours absent during the prior 7 days.

Buist-Bouwman (2005) (364)	Number of work-loss days over the last year. Survey interview data (self-report). Participants were asked "how many days in the past year were you unable to work due to mental health problems or substance use disorders or physical health problems?"
Nikiphorou (2018)(361)	Absenteeism. Work Productivity and Activity Impairment questionnaire (self-report).(380) Percentage of working hours absent during the prior 7 days.
Webers (2018)(362)	AS-related sick leave over 6 years follow up. Questionnaire data (self-report). Study recorded sick leave without a minimum duration, since last clinic visit (every 2 months during the first 2 years of follow-up, and annually till 6 years).
	Reduced productivity, presenteeism, and work limitation
Kennedy (2014) (334)	Work limitations. Work Limitations Questionnaire (WLQ) (self-report).(381) Patients completed the 25-item self-administered WLQ as well as the WLQ 2-Question Time Loss Module; the latter asks patients to quantify the number of full and partial workdays missed during the past two weeks due to health concerns. The questions of the 25-item WLQ were grouped into four subscales that address time, physical, mental-interpersonal, and output demands, respectively. Scores ranging from 0 to 100 were calculated for each subscale, with higher scores corresponding to greater work limitation and productivity loss. An overall WLQ Productivity Score was calculated and expressed as the percentage loss in productivity associated with illness. Patients were assigned to one of four levels of work impairment based on productivity scores, where normal corresponds to <5% productivity loss, mild impairment 5–10.9%, moderate impairment 11–16.9%, and severe impairment ≥17% work productivity loss. Outcome was risk of moderate-severe work impairment.
Kessler (2001) (199)	Work impairment days – questionnaire (self-report). Participants were asked about 30-day prevalence of work-loss days and work cut-back days (i.e. how many days out of the past 30 were participants "totally unable to work or carry out your normal household work activities because of your physical health or mental health"; and how many additional days out of the past 30 were participants able to work but had to "cut back on work or how much you got done because of your physical health or mental health"). Information on work-loss and work cut-back days was combined into a summary measure of work-impairment days on a scale on which a work-cut-back day was counted as one-half of a work-loss day.
Kessler (2003) (344)	Number of work cut back days – questionnaire (self-report). Participants were asked the number of days out of the past 30 when they were able to work "but had to cut back on what (they) did or did not get as much done as usual" because of problems with their physical or mental health.
Agaliotis (2013) (343)	Presenteeism. Questionnaire data derived from the Work Productivity and Activity Impairment Questionnaire (WPAI). Participants were asked "Your knee problems may affect your ability to work or perform daily activities. Please estimate your capacity for each day from 0% (unable to do usual work/activities) to 100% (fully functioning in usual role)." This index was dichotomised as "exposed to presenteeism" (participants who scored an average of 99.99% and below) vs those not exposed (100%).

Joshi (2015) (365)	Work limitation – telephone interview data (self-report). Participants were asked "Do arthritis or joint symptoms now affect whether you work, the type of work you do, or the amount of work you do?''
Nikiphorou (2018)(361)	Presenteeism. Work Productivity and Activity Impairment (WPAI) questionnaire (self-report). (380) Outcome was percentage of impairment while at work during the prior 7 days.
Wilkie (2013) (353)	Work restriction- one item from the Keele Assessment of Participation (KAP) questionnaire(382): ''During the past 4 weeks, if you work, have you taken part in paid or voluntary work as and when you have wanted?''- Three year onset of work restriction was defined as moving from no restriction at baseline (all/most of the time) to work restriction at 3 years (some/a little or none of the time).
Employment status	
Furunes (2018) (359)	Employment at follow up (minimum 3 years). Structured interview (self-report). Work status was categorised as employed (part time or full time) or unemployed.
Panopalis (2007) (338)	Current employment. Interview survey data (self-report). Employment status: Participants were asked about their work situation for both the year of diagnosis and the current year (i.e. in the last week). Participants were employed if they reported that they had a job (whether or not they were at work in the last week) or they had done any work for pay or profit.
Van der Zee-Neuen (2017) (341)	Current employment. Work Productivity and Activity Impairment (WPAI) questionnaire (self-report).(380) Participants were asked their current employment status (employed vs. not employed).
Marengo (2008) (342)	Current unemployment. Questionnaire (self-report). Participants could respond they were employed, unemployed, retired, or pensioner.
Schofield (2014) (352)	Not being in the labour force. Survey data (self-report). Categories included labour force participation, employment restrictions, or retirement.
Nikiphorou (2018)(361)	Current employment. Work Productivity and Activity Impairment (WPAI) questionnaire (self-report).(380) Participants were asked their current employment status (employed vs. not employed).
Job loss	
de Buck (2006) (354)	Job loss. Interview or questionnaire (self-report). Job loss was defined as receiving a full work disability pension or being unemployed in a person employed at baseline after 2 year follow up.
Manders (2014) (349)	Stopping work participation after 2 years of treatment. Structured interview (self-report). At the start and after 2 years, patients indicated whether they had paid work, did voluntary work, received a retirement pension, or received a work disability allowance. Patients who had paid work or did voluntary work were defined as working.
Work transitions	
Agaliotis (2017) (363)	Work transitions in past 6 months. Work Transitions Scale (self-report). Work Transitions Scale was a 10-item scale evaluating three categories of work transitions due to knee problems, including: 1) occasional loss of work hours or work interruptions, 2) change in the type or nature of work, or 3) permanent changes of work hours. Each question required a no/yes response. A score of one

was given for each ‘‘yes’’ response. Scores were summed for a total range of 0 to 10; a higher score indicated more work changes.

Classification of comorbidity

Table 18, below, shows the criteria by which comorbidity was defined and the method of attainment. Data on comorbidities was usually drawn from self-report (interview survey or questionnaire), however some comorbidity data was drawn from electronic health records or other administrative databases,(9,348,350,357,362,366) or involved physician (e.g. rheumatologist or occupational health physician) history taking or assessment.(334,339,349,359,361) Validated comorbidity scores or indexes were used in nine studies (including the Self-Administered Comorbidity Questionnaire, the Functional Comorbidity Index, and the Rheumatoid Disease Comorbidity Index).(9,13,334,341,343,353,361–363) Other studies used pre-defined checklists of important conditions but it was unclear if these lists had been validated previously or by what criteria a co-presenting disease would be considered for inclusion.(11,12,199,349,350,352,353,357,365,366) Several studies did not give sufficient information about the comorbidities considered and the classifications used. (10,11,199,339,342,348,353,359,365) For example, one older study relied on a rheumatologist definition of number of comorbidities with no standardised checklist described;(339) another gave no details at all regarding how presence of comorbidity was assessed or classified.(359)

Study quality

The methodological quality of the included studies was rated from 3 to 8 stars, using the NOS criteria (Table 13 – 15, Appendix), with most studies moderately well reported and conducted (mean quality was 6.2). In most cases, the participants with comorbidity were selected from the same cohort as the non-exposed participants. Some studies did not adjust the final analyses for one of age, sex, or socioeconomic status and were marked down accordingly.(11,199,335–337,342,343,347,348,350–352,354–357,364) However, in most cases, analysis was adjusted, or stratified, for age and gender as a minimum. Some studies did not provide enough information about the representativeness of their populations, or the reliability of the databases from which information was drawn.(9,10,338,340,342–345,347–349,352,353,359,360,363) Another common limitation of this literature was that most work outcomes were self-reported. Similarly, in most cases,

the health exposures were self-reported with no validation or confirmation using more objective data from test results or medical records.(9–11,13,199,334–337,339–344,346–348,353–355,359,360,362–365) Studies were also frequently marked down for failing to compare characteristics of study participants and non-participants; failure to maintain at least 80% of their baseline population for follow up; or for failing to report about the quantity of missing data.(9,13,199,334,336–342,344–346,348–351,353,356,357,361,364–366)

Table 18: Classifications of comorbidity used in included studies

Included study	Population	Source of information	Validated comorbidity index used	Components or definition
ABRAI´DO-LANZA (2006)(12)	Arthritis (non-specific)	Survey questionnaire (self-report)	No	Included conditions were defined as any chronic impairment or departure from normal health with onset 1-3 months from the date of the interview, such as chronic disorders of the digestive, genitourinary, nervous, endocrine, circulatory, respiratory systems, or other chronic conditions (specific examples included glaucoma, ulcers, diseases of the prostate, multiple sclerosis, diabetes, hypertension, heart disease, asthma).
Agaliotis (2013)(343)	Knee osteoarthritis	Questionnaire (self-report)	Self-Administered Comorbidity Questionnaire	Questionnaire recorded the presence of 12 current medical conditions: high blood pressure, heart disease, lung disease, diabetes, ulcer or stomach disease, kidney disease, liver disease, anaemia or other blood problems, cancer, depression, back pain, and rheumatoid arthritis. Additional scores are given if the participant reported receiving treatment and if this condition limited activities. The scores range from 0 to 36 points, where a higher score indicates more comorbidity. The comorbidity score was further categorized into three levels: 0-1 comorbidities; 2-3 comorbidities and 4 or more comorbidities.
Agaliotis (2017)(363)	Knee Pain	Questionnaire (self-report)	Self-Administered Comorbidity Questionnaire	Classification of comorbidity was as in Agaliotis (2013), above.
Boonen (2001)(11)	Ankylosing spondylitis	Questionnaire (self-report)	No	Comorbidity was assessed using a list of 19 comorbid conditions. No further information given.

Furunes (2018)(359)	Degenerative disc and low back pain after total disc replacement	Patient history and self-report	No	Undefined
Hudson (2009)(13)	Scleroderma	Questionnaire (self-report)	Self-Administered Comorbidity Questionnaire	A questionnaire recorded the presence of 12 current medical conditions: high blood pressure, heart disease, lung disease, diabetes, ulcer or stomach disease, kidney disease, liver disease, anaemia or other blood problems, cancer, depression, back pain, and rheumatoid arthritis. Additional scores are given if the participant reported receiving treatment and if this condition limited activities.
Joshi (2015)(365)	Arthritis, rheumatoid arthritis, gout, lupus, or fibromyalgia	Survey telephonic questionnaire (self-report)	No	Number of chronic conditions was computed by adding up the chronic conditions reported as present by patients
Kausto (2017) (366)	Intervertebral disc disorders	Administrative database	No	Comorbid conditions were assessed as those with entitlement to special reimbursements (due to diabetes, rheumatoid arthritis, asthma/COPD or coronary heart disease)
Kennedy (2014)(334)	Psoriatic arthritis	Patient history and self-report at clinic	Functional Comorbidity Index	Included conditions were: arthritis (rheumatoid and osteoarthritis), osteoporosis, asthma, COPD, acute respiratory distress syndrome, or emphysema, angina, congestive heart failure (or heart disease), heart attack (myocardial infarct), neurological disease (such as multiple sclerosis or Parkinson's), stroke or TIA, peripheral arterial disease, diabetes (types I and II), upper gastrointestinal disease (ulcer, hernia, reflux), depression, anxiety or panic disorders, visual impairment (such as cataracts, glaucoma, macular degeneration), hearing Impairment (very hard of hearing, even with hearing

				aids), degenerative disc disease (back disease, spinal stenosis, or severe chronic back pain), obesity and/or BMI >30.
Kessler (2001)(199)	Arthritis (non-specific)	Survey-questionnaire (self-report)	Unclear if validated	In the a self-administered questionnaire, "In the past 12 months, have you experienced or been treated for any of the following?" was asked for: asthma, bronchitis, or emphysema; tuberculosis; other lung problems; arthritis, rheumatism, or other bone or joint diseases; sciatica, lumbago, recurring backache; persistent skin trouble (e.g. eczema); thyroid disease; hay fever; recurring stomach trouble, indigestion, or diarrhoea; urinary or bladder problems; being constipated all or most of the time; gall bladder trouble; persistent foot trouble (e.g. bunions, ingrown toenails); trouble with varicose veins requiring medical treatment; AIDs or HIV infection; lupus or other autoimmune disorders; persistent trouble with your gums or mouth; persistent trouble with teeth; high blood pressure or hypertension; anxiety, depression, or some other emotional disorder; alcohol or drug problems; migraine headaches; chronic sleeping problems; diabetes; multiple sclerosis, epilepsy, or other neurological disorders; stroke; ulcer; hernia or rupture; piles or haemorrhoids; swallowing problems.
Lee (2017) (348)	Spinal Surgery	Electronic medical records	No	A patient was positive for comorbidity status if a "significant medical comorbidity" was listed in the patient's medical history.
Manders (2014)(349)	Rheumatoid arthritis	Clinic assessments-appears to be self-report but unclear	No	The following comorbidities were included: cardiovascular disease, diabetes mellitus, COPD, and malignancy.
Marengo (2008)(342)	Ankylosing Spondylitis	Interview questionnaire (self-report)	No	Participants were asked about comorbid diseases "cardiovascular, respiratory, gastrointestinal, traumatic, neuropsychiatric, etc." but no information was given regarding checklists or questionnaires used.

Nikiphorou (2018)(361)	Spondyloarthritis	Based on patient and physician report	Rheumatic Disease Comorbidity Index	Pulmonary disease, myocardial infarction, other heart disease, stroke, hypertension, diabetes, fracture, ulcer, other gastrointestinal, and depression were used to compute the Rheumatic Disease Comorbidity Index (RDCI), a weighted index (range 0 – 9).
Nordin (2002)(350)	Non-specific low back pain (NSLBP)	Clinic records of occupational health physician (administrative database).	No	The evaluating physician defined comorbidity as any secondary diagnoses to NSLBP assigned at the index visit. To facilitate the analysis, comorbid conditions were classified on the basis of 10 different body systems according to the ICD-9 classification scheme: “neoplasms”; “endocrine, nutritional, metabolic diseases and immunity disorders”; “mental disorders”; “diseases of the nervous system and sense organs”; “diseases of the circulatory system”; “diseases of the respiratory system”; “diseases of the digestive system”; “diseases of the musculoskeletal system and connective tissue”; “symptoms, signs, and ill-defined conditions”; and “injury or poisoning.” Other categories of the ICD-9 classification were excluded because of no episodes or a lack of applicability.
Schofield (2014) (352)	Included: individual records were extracted for those aged 45–64 years (8,864 records).	Interview survey (self-report)	No	Computer assisted disease grouping by ICD codes, these were separated into the groups used by the Australian Beureau of Statistics (ABS): deformities of the joints/limbs, back problems, repetitive strain injury/occupational overuse syndrome, synovitis/tenosynovitis, other soft tissue/muscle disorders, osteoporosis, other acquired deformities of the musculoskeletal system and connective tissue, other disorders of the musculoskeletal system, and connective tissue. Due to low record numbers in the survey for conditions comorbid with arthritis, the following conditions were grouped together to form an ‘other conditions’ group: certain infectious and parasitic diseases, diseases of the blood and blood-forming organs, Alzheimer’s disease, certain conditions originating in the perinatal period, congenital malformations, deformations and chromosomal abnormalities, and a group that the ABS originally called ‘other conditions’.

Van der Zee-Neuen (2017)(341)	Rheumatoid arthritis	Questionnaire (self-report)	Rheumatic Disease Comorbidity Index	Physician-confirmed ischaemic cardiovascular disease (myocardial infarction, stroke), cancer (colon, skin, lung, breast and uterus in women, prostate in men, and lymphoma), gastrointestinal diseases (diverticulitis, ulcers), infections (hepatitis), lung disease (COPD and asthma) and psychiatric disorders (depression) were used to compute the Rheumatic Disease Comorbidity Index (RDCI). A history of fractures was not collected.
Ward (2001)(10)	Ankylosing spondylitis	Questionnaire (self-report)	No	Study asked for the presence of any comorbid medical condition, no further information given.
Webers (2018)(362)	Ankylosing spondylitis	"Clinical records"	Rheumatic Disease Comorbidity Index	Pulmonary disease, myocardial infarction, other heart disease, stroke, hypertension, diabetes, fracture, ulcer, other gastrointestinal, and depression are used to compute the Rheumatic Disease Comorbidity Index (RDCI), a weighted index (range 0 – 9).
Wilkie (2013)(353)	Osteoarthritis	Questionnaire: self-report	No	Study asked about the presence of any comorbid medical condition, no further information given.
Callahan (1992)(339)	Rheumatoid Arthritis	Physician assessment at clinic	No	Number of comorbid conditions-determined by rheumatologist. No further information, unclear if checklist used.
CASTILLO-ORTIZ (2016)(9)	Ankylosing Spondylitis	"Medical records"	Rheumatic Disease Comorbidity Index and medical records.	The presence of extra-articular manifestations (uveitis, psoriasis, and inflammatory bowel disease [IBD]) and of comorbidities was retrieved from medical records. Using this data the Rheumatic Disease Comorbidity Index (RDCI) was calculated (range 0–9), representing the weighted sum score of common comorbidities including lung disease, diabetes mellitus, hypertension, myocardial infarction, stroke, other heart disease, cancer, fracture [spine, hip, or leg], gastrointestinal ulcer, other gastrointestinal problems, and depression.

Hansen (2016)(357)	Rheumatoid arthritis	National Patient Registry and National Prescription Registry (administrative database)	No	18 groups of chronic, somatic comorbidities were considered (cancer, thyroid diseases, diabetes, other endocrine, nutritional and metabolic diseases, obesity, neurological diseases, chronic diseases of the ears, hypertension, chronic pulmonary diseases including asthma, cardiac disease, stroke, inflammatory bowel disease, diseases of the liver, diseases of the skin, kidney diseases, gynecological diseases, and transplantations) and 4 groups of psychiatric comorbidities (dementia, substance abuse, anxiety, and depression). These comorbidities were selected by an expert panel prior to data analysis.

4.3.1 Do comorbidities worsen work outcomes in MSDs?

Twenty published studies (9 cohort, 10 cross-sectional, 1 case-control), explored the association between presence of comorbidity, or number of comorbid conditions, and risk of adverse employment outcomes.(9–13,199,334,339,341–343,348–350,352,353,357,363,365,366) Results from studies where confidence intervals were reported, or could be imputed, are shown in Figure 26.

Work disability and disability pension

The association between comorbidity and various classifications of work disability was reported in seven studies amongst AS, RA, arthritis, and scleroderma populations.(9–13,339,357) For six of these studies a statistically significant increased odds or hazard of work disability was observed, see Table 19, below. One older study (Callahan 1992), in RA, showed no significant association between number of comorbidities and a participant's self-reported receipt of disability payments, although it was very unclear what definition was used for comorbidity.(339) One study among people with AS, found that presence of comorbidity strongly increased the rate of self-reported disability certification/payment (HR 4.07 95%CI 1.23 to 13.43), but was underpowered to detect an effect for permanent work disability (HR 2.62 95%CI 0.58 to 11.86).(10)

Table 19: Summary of included studies reporting the impact of comorbidity upon work disability

Study	MSD population	Exposure	Definition of work outcome	Effect size
Abrai'do-Lanza (2006) (12)	Arthritis	Number of comorbidities	Health problem preventing work in a job or limiting type or amount of work that can be performed.	OR **1.22 (1.13 to 1.33)**
Boonen (2001) (11)	Ankylosing spondylitis	Presence of comorbidity	Officially recognised inability to perform paid work due to AS	OR **3.15 (1.96 to 5.09)**
Castillo-Ortiz (2016) (9)	Ankylosing spondylitis	Rheumatic Disease Comorbidity Index (RDCI) score	Not working because of official work disability due to disease	OR **2.2 (1.2 to 4.0)**

Callahan (1992) (339)	Rheumatoid arthritis	Number of comorbidities	Receipt of work disability payments	OR 1.5 (0.85 to 2.15)*
Hansen (2016) (357)	Rheumatoid arthritis	Presence of comorbidity	Greater than 3 weeks of receiving sickness absence benefits payments first year after RA diagnosis	HR **1.2 (1.0 to 1.5)**
Hansen (2016) (357)	Rheumatoid arthritis	Presence of comorbidity	Greater than 3 weeks of receiving sickness absence benefits payments one year after diagnosis with RA	HR **1.3 (1.1 to 1.4)**
Hudson (2009) (13)	Scleroderma	Self-Administered Comorbidity Questionnaire (SCQ) score	Currently disabled or on sick leave	OR **1.14 (1.07 to 1.20)**
Ward (2001) (10)	Ankylosing spondylitis	Presence of comorbidity	Receipt of disability payments	HR **4.07 (1.23 to 13.43)**
Ward (2001) (10)	Ankylosing spondylitis	Presence of comorbidity	Permanent work disability	HR 2.62 (0.58 to 11.86)

*confidence intervals imputed using reported p-value and point estimates

Return to work

The impact of comorbidity upon return to work was reported in three studies, summarised in Table 20. (348,350,366) Two studies among spinal surgery and non-specific low back pain populations found a statistically significant impact of comorbidity upon return to work after work disability.(348,350) Presence of comorbidity was associated with a reduced likelihood of full employment one year after surgery,(OR 0.19 95%CI 0.04 to 0.85)(348) and a greater time taken to return to full work duty (HR 1.31 95%CI 1.12 to 1.52).(350) Another study amongst those with disc disorders found no significant impact of comorbidity among men or women (HR 0.93 95%CI 0.71 to 1.23),(366) although a narrow definition of comorbidity was used, as participants were only counted as having a comorbidity if they were receiving special reimbursements as a result of four selected conditions.

Table 20: Summary of included studies reporting the impact of comorbidity upon return to work

Study	MSD population	Exposure	Definition of work outcome	Effect size
Kausto (2017) (366)	Intervertebral disc disorders (men)	Presence of comorbidity	Return to sustained work (30 days) following sickness absence	HR 0.93 (0.71 to 1.23)
Kausto (2017) (366)	Intervertebral disc disorders (women)	Presence of comorbidity	Return to sustained work (30 days) following sickness absence	HR 1.00 (0.88 to 1.13)
Lee (2017) (348)	Spinal surgery	Presence of comorbidity	Return to full employment within one year of surgery and still working at 2 years follow up	OR **0.19 (0.04 to 0.85)**
Nordin (2002) (350)	Non-specific low back pain	Number of comorbidities	Time to first return to unrestricted full work duty following disability	HR **1.31 (1.12 to 1.52)**

Sickness absence

Four studies considered the impact of comorbidity upon sickness absence among participants with MSDs.(199,341,361,362) All of these studies found comorbidity was associated with increased odds, or rates, of sickness absence (OR 1.18 95%CI 1.04 to 1.34; OR 1.44 95%CI 1.25 to 1.68; OR 1.52 95%CI 1.00 to 2.29; beta coefficient: 4.0 95%CI 0.3 to 7.7) see Table 21. In one study a comorbidity disease score was not associated with AS-related sick leave among those with high educational attainment (OR 1.58 95%CI 0.34 to 7.38), however, estimated effect sizes were similar to those for people with low educational attainment and the study may have been underpowered to show a statistically significant effect for this sub-group.

Table 21: Summary of included studies reporting the impact of comorbidity upon sickness absence

Study	MSD population	Exposure	Definition of work outcome	Effect size
Kessler (2001)(199)	Arthritis	Three or more comorbidities	Days out of the past 30 unable to work or carry out	Beta coefficient **4.0 (0.28 to 7.7)***

			normal activities as a result of physical or mental health.	
Nikiphorou (2018)(361)	Spondyloarthritis	Rheumatic Disease Comorbidity Index score	Working hours absent over past 7 days	OR **1.18 (1.04 to 1.34)**
Van de Zee-Neuen (2017) (341)	Rheumatoid arthritis	Rheumatic Disease Comorbidity Index score	Working hours absent over past 7 days	OR **1.44 (1.25 to 1.68)**
Webers (2018) (362)	Ankylosing spondylitis (low educational attainment)	Rheumatic Disease Comorbidity Index score	AS-related sick leave days over 6 years	OR 1.58 (0.34 to 7.38)
Webers (2018) (362)	Ankylosing spondylitis (high educational attainment)	Rheumatic Disease Comorbidity Index score	AS-related sick leave days over 6 years	OR **1.52 (1.00 to 2.29)**

*confidence intervals calculated using reported standard error

Reduced productivity and presenteeism

Of five reporting studies,(334,343,353,361,365) two found a significant association between comorbidity and presenteeism or reduced productivity (OR: 2.31 95%CI 1.19 to 4.5; OR 1.42 95%CI 1.26 to 1.61).(334,361) Although non-significant, the effect estimates reported by Agaliotis et al., among people with knee pain, were in the range described by Kennedy et al. and Nikiphorou et al. One study among participants with arthritis found a non-significant and almost non-existent effect of number of comorbidities upon arthritis-specific impaired working, type of work, or amount of work. This study used a very broad work outcome (only partially including aspects of productivity loss) and also relied on patients to define the number of comorbidities, with no use of a checklist or validated score as in the other studies.(365) In another study, the presence of one to four comorbidities was not significantly associated with three-year onset of work restriction, as defined by not taking part in paid or voluntary work as and when desired. Once again, a very broad work outcome was used, and this study gave insufficient information about how comorbidities were assessed.(353) See Table 22, below.

Table 22: Summary of included studies reporting the impact of comorbidity upon reduced productivity and presenteeism

Study	MSD population	Exposure	Definition of work outcome	Effect size
Agaliotis (2013) (343)	Knee pain	Self-Administered Comorbidity Questionnaire (One to three comorbidities)	Work Productivity and Activity Impairment (presenteeism score)	OR 1.27 (0.64 to 2.50)
Agaliotis (2013) (343)	Knee pain	Self-Administered Comorbidity Questionnaire (four or more comorbidities)	Work Productivity and Activity Impairment (presenteeism score)	OR 2.15 (0.91 to 5.09)
Joshi (2015) (365)	Arthritis	Number of comorbidities	Arthritis/joint symptoms currently affect whether working, type of work, or the amount of work.	OR 1.01 (0.99 to 1.03)
Kennedy (2014) (334)	Psoriatic arthritis	Functional Comorbidity Index score	Work limitations questionnaire (productivity score)	OR **2.31 (1.19 to 4.50)**
Nikiphorou (2018)(361)	Spondyloarthritis	Rheumatic Disease Comorbidity Index score	Work Productivity and Activity Impairment (presenteeism score)	OR **1.42 (1.26 to 1.61)**
Wilkie (2013) (353)	Osteoarthritis	Presence of one to four comorbidities	Not taking part in paid or voluntary work as and when wanted over past 4 weeks, over 3 years follow up.	OR 1.28 (0.81 to 2.02)

Employment status and job loss

Six studies reported the impact of comorbidity upon employment status or job loss.(341,342,349,352,359,361) Five of these studies reported a statistically significant association between comorbidity and unemployment or job loss, see Table 23.(341,349,352,359,361) A non-significant finding was reported in one case-control study of people with AS, although confidence intervals were very wide (OR: 2.5 95%CI 0.23 to

26.5).(342) Interestingly, Van der Zee-neuen et al. found that the impact of comorbidity on current employment was statistically significant only across countries with high GDP, however the direction and size of effect estimates was not very different when compared to data from all countries (OR 0.89 vs OR 0.93, respectively).(341)

Table 23: Summary of included studies reporting the impact of comorbidity upon employment status or job loss

Study	MSD population	Exposure	Definition of work outcome	Effect size
Furunes (2018)(359)	Lumbar total disc replacement surgery patients	Absence of comorbidity	Employment at follow up (minimum 3 year)	OR **7.7 (2.0 to 30.5)**
Manders (2014) (349)	Rheumatoid arthritis	Presence of comorbidity	Stopping work participation after 2 years (defined as paid or voluntary work)	OR **2.67 (2.14 to 3.20)***
Marengo (2008) (342)	Ankylosing Spondylitis	Presence of comorbidity	Current unemployment	OR 2.5 (0.23 to 26.5)
Nikiphorou (2018)(361)	Spondyloarthritis	Rheumatic Disease Comorbidity Index score	Current employment	OR **0.83 (0.76 to 0.91)**
Schofield (2014)(352)	Arthritis	One comorbidity	Current unemployment	OR **1.67 (1.06 to 2.64)**
Schofield (2014)(352)	Arthritis	Two comorbidities	Current unemployment	OR **1.73 (1.06 to 2.86)**
Schofield (2014)(352)	Arthritis	Three or more comorbidities	Current unemployment	OR **3.68 (2.43 to 5.58)**
Van der Zee-Neuen (2017) (341)	Rheumatoid arthritis (all countries)	Rheumatic Disease Comorbidity Index score	Current employment	OR 0.93 (0.85 to 1.02)
Van der Zee-Neuen	Rheumatoid arthritis (high GDP countries)	Rheumatic Disease	Current employment	OR **0.89 (0.81 to 0.97)**

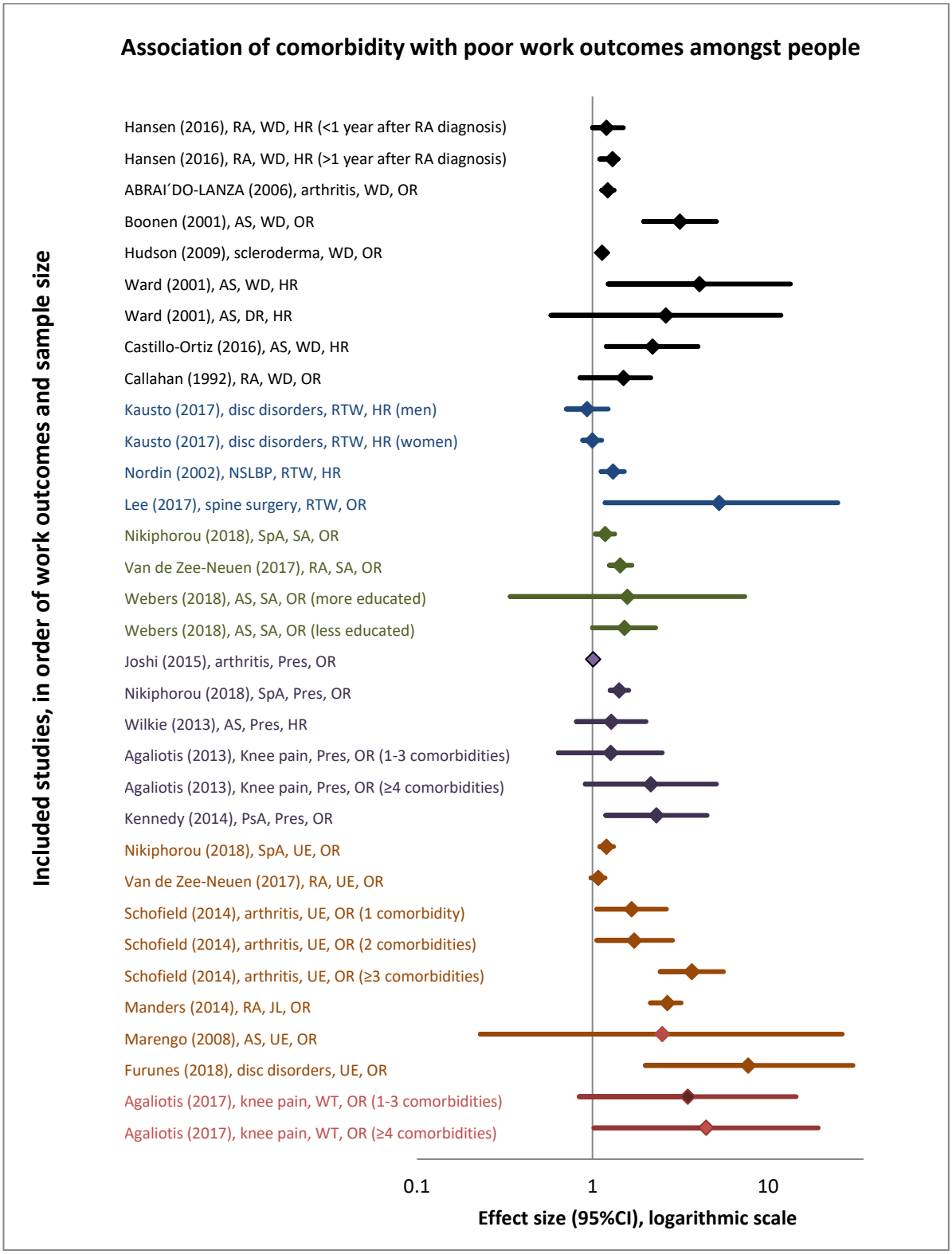
(2017) (341)		Comorbidity Index score		

*confidence intervals imputed using reported p-value and point estimates

Work transition

One study, among participants with knee pain, reported the impact of number of comorbidities (defined using the Self-administered Comorbidity Questionnaire) upon work transition.(363) This was defined using a Work Transitions Scale, which was a composite score capturing loss of work hours, interruptions to work, or changes in the type or nature of work over the previous 6 months. Compared to having no comorbidities, having one to three comorbidities had a non-significant 3.49-fold increased odds of work transition (95%CI 0.84 to 14.46). While four or more comorbidities was associated with a 4.44-fold increased odds of work transition (95%CI 1.02 to 19.32).(363)

Figure 26: Impact of comorbidity on adverse work outcomes amongst people with MSDs. Chart is colour-coded by category of work outcome: work disability or disability pension (black), return to work (blue), sickness absence (green), productivity loss or presenteeism (purple), unemployment or job loss (orange), work transition (red). See Glossary for abbreviations.



4.3.2 Psychiatric disease comorbidity

Seventeen published studies (10 cohort, 7 cross-sectional), explored the association between psychiatric comorbidity and work outcomes among people with MSDs.(336–338,345,346,351–358,360,364–366) Results from included studies that also reported confidence intervals, or where confidence intervals could be imputed, are shown in Figure 27.

Work disability and disability pension

Five included studies reported the effect of mental health comorbidity on work disability.(336,338,351,357,358) All studies reported a statistically significant effect, see Table 24. Comorbid depression, or depressive symptoms, were significantly associated with development of work disability in two studies among inflammatory rheumatic disorders and lupus populations (OR 1.6 95%CI 1.1 to 2.3 and OR 1.7 95%CI 1.15 to 2.54, respectively).(336,338) One study reported comorbid anxiety disorders were associated with work disability in back pain and arthritis cohorts (OR 4.26 95%CI 2.06 to 8.81; OR 5.38 95%CI 2.44 to 11.84, respectively).(358) Diagnosed depression or anxiety was associated with a 1.67-fold hazard (95%CI 1.15 to 2.54) of long-term sickness absence/disability benefits among participants with rheumatoid arthritis.(351) Finally, one study found comorbid psychiatric disorders increased the rate of >3 weeks sickness absence with benefits following diagnosis with rheumatoid arthritis, both after short- and long-term follow up (HR 1.9 95%CI 1.8 to 2.0 and HR 1.9 95%CI 1.8 to 2.0, respectively).

Table 24: Summary of included studies reporting the impact of psychiatric comorbidity on work disability

Study	MSD population	Exposure	Definition of work outcome	Effect size
Csupak (2018)(358)	Arthritis	Generalised anxiety disorder	Permanent inability to work	OR **5.38 (2.44 to 11.84)**
Csupak (2018)(358)	Back pain	Generalised anxiety disorder	Permanent inability to work	OR **4.26 (2.06 to 8.81)**
Hansen (2016) (357)	Rheumatoid arthritis	Diagnosed psychiatric comorbidity	Sickness absence benefits >3 weeks during year after RA diagnosis	HR **2.2 (2.0 to 2.5)**

Hansen (2016) (357)	Rheumatoid arthritis	Diagnosed psychiatric comorbidity	Sickness absence benefits >3 weeks more than one year after RA diagnosis	HR **1.9 (1.8 to 2.0)**
Lowe (2004) (336)	Inflammatory rheumatic diseases	Depression (Patient health questionnaire PHQ-9)	Receiving disability pension, or sick leave of at least 4 weeks, or unemployed for at least 4 weeks due to health problems.	OR **1.6 (1.1 to 2.3)**
Olofsson (2017) (351)	Rheumatoid arthritis	Diagnosed depression or anxiety	Loss of 15 days of 30 with sick leave or disability pension over follow up (maximum 3 years)	HR **1.67 (1.08 to 2.55)**
Panopalis (2007) (338)	Systemic Lupus Erythematosus	Depressive symptoms (Centre for Epidemiologic Studies Depression Scale)	Inability to work	OR **1.71 (1.15 to 2.54)**

Return to work

Six studies considered the impact of psychiatric comorbidity upon return to work after disability, which are summarised in Table 25, below.(345,346,351,355,356,366)

Time to return to work after disability due to whiplash and discectomy was significantly increased with comorbid depression (HR 0.63 95%CI 0.51 to 0.77; HR 0.64 95%CI 0.54 to 0.75; and beta coefficient: 0.43 95%CI 0.12 to 0.74).(355,356) One study, in which effect estimates could not be estimated, found that no participants with depression (n=29/686) returned to work following surgery for spondylolisthesis.(345) In contrast, one study did not find a significant association between depressive symptoms or major depressive disorders and time to return to work after completing rehabilitation for occupational musculoskeletal injury (OR 1.06 95%CI 0.77 to 1.45; and OR 1.21 95%CI 0.89 to 1.64, respectively).(346)

Two studies considered comorbid psychiatric disorders other than depression.(351,366) In one study, purchase of antidepressants or hospitalisation due to mental health disorders was associated with reduced rate of return to work after intervertebral disc disorder-

related work disability, both in men and women (HR: men 0.82 95%CI 0.74 to 0.91; women 0.86 95%CI 0.82 to 0.9).(366) Finally, Olofsson et al. reported participants with depression or anxiety had a lower rate of sustained return to work among those not working at baseline with rheumatoid arthritis, but this did not reach statistical significance (HR 0.62 95%CI 0.37 to 1.03).(351)

Table 25: Summary of included studies reporting the impact of psychiatric comorbidity on return to work following disability

Study	MSD population	Exposure	Definition of work outcome	Effect size
Anderson (2016) (345)	Lumber fusion treated spondylolisthesis patients	Diagnosed depression	Sustained (>6 months) return to work within 2 years	No subjects with depression returned to work following fusion (OR not estimable)
Brede (2012) (346)	Occupational musculoskeletal injury	Depressive symptoms (Beck Depression Inventory)	Failure to retain work at 12 months	OR 1.06 (0.77 to 1.45)
Brede (2012) (346)	Occupational musculoskeletal injury	Diagnosed major depressive disorder	Failure to retain work at 12 months	OR 1.21 (0.89 to 1.64)
Cote (2001) (356)	Road traffic injury (whiplash)	Depressive symptoms (Centre for Epidemiologic Studies Depression Scale)	Rate of claim closure (insurance dataset 1)	HR **0.628 (0.514 to 0.769)**
Cote (2001) (356)	Road traffic injury (whiplash)	Depressive symptoms (Centre for Epidemiologic Studies Depression Scale)	Rate of claim closure (insurance dataset 2)	HR **0.636 (0.537 to 0.753)**

Kausto (2017) (366)	Intervertebral disc disorders (men)	Purchase of antidepressants or hospitalisation due to mental disorders	Time to return to sustained work (end of sickness benefit period with no recurrent sickness absence for 30 days)	HR **0.82 (0.74 to 0.91)**
Kausto (2017) (366)	Intervertebral disc disorders (women)	Purchase of antidepressants or hospitalisation due to mental disorders	Time to return to sustained work (end of sickness benefit period with no recurrent sickness absence for 30 days)	HR **0.86 (0.82 to 0.90)**
Olofsson (2017) (351)	Rheumatoid arthritis	Diagnosed depression or anxiety	Time to regain >15 days of 30 without sick leave or disability pension over follow up (maximum 3 years)	HR 0.62 (0.37 to 1.03)
Schade (1999) (355)	Discectomy patients	Depression (psychological general wellbeing index)	Return to "any" work at 2 years follow up	Beta coefficient **0.43 (0.12 to 0.74)***

*confidence intervals calculated using reported standard error

Sickness absence

Five included studies considered the association between psychiatric comorbidities and sickness absence from work, see Table 26, below.(335,337,358,360,364) Psychiatric comorbidities were significantly associated with sickness absence in three of these studies.(335,337,364) Of these, a comorbid major depressive event was associated with increased absenteeism in the prior week for participants with chronic pain conditions (RR 2.9 95%CI 2.8 to 2.9).(337) Comorbid mental disorders among participants with arthritis was associated with a mean difference of 2.3 sick leave days extra in the past 30 (95%CI 0.7 to 3.9). Finally, Buist-Bouwman et al. found anxiety, mood disorder, or substance misuse disorder in past 12 months was associated with significantly increased number of sickness absence days over the past year among those with chronic back trouble, but not

rheumatism (beta coefficient 10.4 95%CI 4.1 to 16.7; and beta coefficient 1.7 95%CI -4.8 to 8.2, respectively).

Two studies did not find a statistically significant impact.(358,360) One study among participants with musculoskeletal pain at 1 to 3 locations (in the low back, in the neck/shoulders, or in the knees) found a medium or high depressive symptom score had no observable, or consistent, impact on rate of long-term sickness absence over follow up.(360) Csupak et al. found no statistically significant relationship between generalised anxiety disorder (diagnosed in the past 12 months) and absenteeism in the prior week for back pain and arthritis participants (OR 1.48 95%CI 0.61 to 3.64; and OR 1.90 95%CI 0.67 to 5.36, respectively).

Table 26: Summary of included studies reporting the impact of psychiatric comorbidity on sickness absence

Study	MSD population	Exposure	Definition of work outcome	Effect size
Buist-Bouwman (2005)(364)	Rheumatism	Anxiety, mood disorder, or substance misuse disorder in past 12 months (composite International Diagnostic Interview criteria)	Number of days unable to work due to mental health problems or substance use disorders or physical health problems (in past 12 months)	Beta coefficient **1.7 (-4.8 to 8.2)***
Buist-Bouwman (2005)(364)	Chronic back trouble	Anxiety, mood disorder, or substance misuse disorder in past 12 months (composite International Diagnostic Interview criteria)	Number of days unable to work due to mental health problems or substance use disorders or physical health problems (in past 12 months)	Beta coefficient **10.4 (4.1 to 16.7)***
Csupak (2018)(358)	Arthritis	Generalised anxiety disorder (composite International Diagnostic Interview criteria)	Absent from work in the past week	OR 1.90 (0.67 to 5.36)

Csupak (2018)(358)	Back pain	Generalised anxiety disorder (composite International Diagnostic Interview criteria)	Absent from work in the past week	OR 1.48 (0.61 to 3.64)
Kessler (2003)(335)	Arthritis and related conditions	Comorbid mental health disorder (Diagnostic and Statistical Manual, 3rd edition, revised)	Number of days unable to work out of past 30	Mean difference 2.3 days (0.7 to 3.9)*
Melkevik (2018)(360)	Musculoskeletal pain in 1 location	Depression (Major Depression Inventory mean score, multiplied by 10: 0 – 12.99 low, 13 – 20.99 moderate, >21 high)	Sickness absence for four consecutive weeks or more during 550 days follow up	Medium depressive symptoms: HR 0.79 (0.50 to 1.25) High depressive symptoms: HR 1.55 (0.95 to 2.55)
Melkevik (2018)(360)	Musculoskeletal pain in 2 locations	Depression (Major Depression Inventory mean score, multiplied by 10: 0 – 12.99 low, 13 – 20.99 moderate, >21 high)	Sickness absence for four consecutive weeks or more during 550 days follow up	Medium depressive symptoms: HR 1.30 (0.96 to 1.77) High depressive symptoms: HR 0.97 (0.62 to 1.50)
Melkevik (2018)(360)	Musculoskeletal pain in 3 locations	Depression (Major Depression Inventory mean score, multiplied by 10: 0 – 12.99 low, 13 – 20.99 moderate, >21 high)	Sickness absence for four consecutive weeks or more during 550 days follow up	Medium depressive symptoms: HR 0.91 (0.62 to 1.32) High depressive symptoms: HR 1.31 (0.87 to 1.98)

Munce (2007)(337)	Chronic pain condition	Major depressive event (composite International Diagnostic Interview criteria)	Absent from work in the last week, mainly due to illness or disability.	RR **2.9 (2.8 to 2.9)**

*confidence intervals calculated using reported standard error

Presenteeism and productivity loss

Three studies considered the impact of psychiatric comorbidity on work outcomes that included an assessment of productivity loss among people with MSDs; see Table 27.(335,353,365) Joshi et al. found that arthritic patients with diagnosed depressive disorders were more likely to report their arthritis/joint symptoms were currently affecting whether they worked, the type of work, or the amount of work they were producing (OR 1.51 95%CI 1.41 to 1.60).(365) Kessler et al. considered role impairment, an overall measure of the number of days lost in the last 30, or with reduced productivity as a result of health problems. This study found, on average, 2.6 more days of role impairment among people with arthritis and comorbid mental health problems (95%CI 1.0 to 4.2).(335) Finally, among participants with lower limb pain in the prior year (classified as osteoarthritis), comorbid depression, but not anxiety, was significantly associated with not taking part in paid or voluntary work as and when desired over the prior 4 weeks (OR 2.11 95%CI 1.13 to 3.95).(353)

Table 27: Summary of included studies reporting the impact of psychiatric comorbidity on presenteeism and productivity loss

Study	MSD population	Exposure	Definition of work outcome	Effect size
Joshi (2015) (365)	Arthritis	Physician diagnosed depressive disorder (self-reported)	Arthritis/joint symptoms currently affect whether working, type of work, or the amount of work.	OR **1.51 (1.41 to 1.60)**

Kessler (2003) (335)	Arthritis and related conditions	Comorbid mental health disorder (Diagnostic and Statistical Manual, 3rd edition, revised)	Role impairment score taking into account work loss days and number of days out of the past 30, when able to work but needed to cut back on what (they) did or did not get as much done as usual because of problems with physical or mental health.	Mean difference **2.6 (1.0 to 4.2)***
Wilkie (2013) (353)	Lower limb osteoarthritis	Anxiety (Hospital Anxiety and Depression Scale)	Not taking part in paid or voluntary work as and when wanted over past 4 weeks, for 3 years follow up.	OR 0.95 (0.57 to 1.56)
Wilkie (2013) (353)	Lower limb osteoarthritis	Depression (Hospital Anxiety and Depression Scale)	Not taking part in paid or voluntary work as and when wanted over past 4 weeks, for 3 years follow up.	OR **2.11 (1.13 to 3.95)**

*confidence intervals calculated using reported standard error

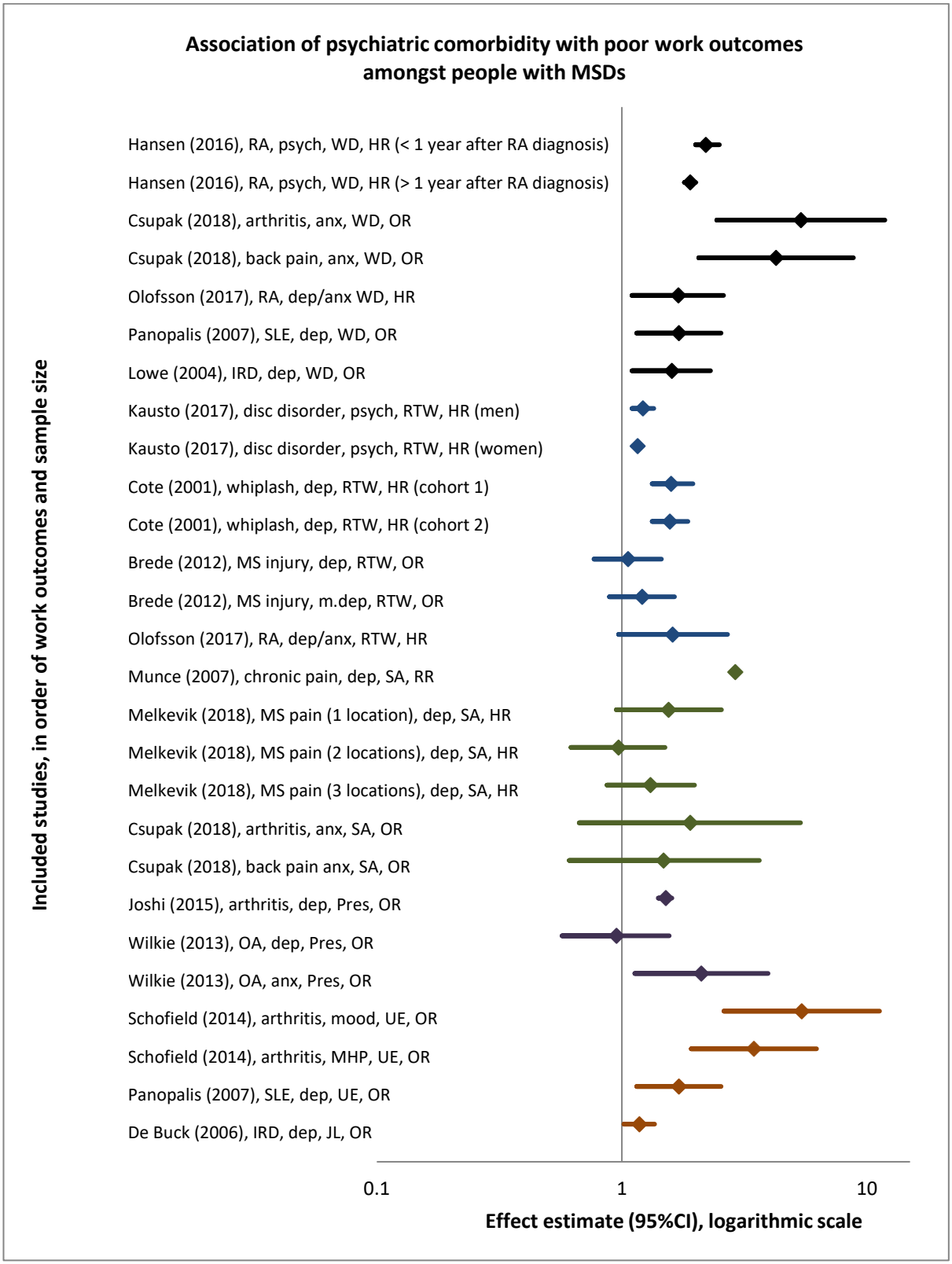
Employment status and job loss

Three studies considered the relationship between comorbid mental health problems and employment status among MSD populations; see Table 28.(338,352,354) Among an SLE cohort, comorbid depression was significantly associated with reduced odds of employment (OR 0.64 95%CI 0.44 to 0.94),(338) and comorbid mental health disorders and comorbid mood disorders were associated with unemployment amongst arthritis patients (OR: 3.46 95%CI 1.92 to 6.23 and OR 5.42 95%CI 2.61 to 11.26, respectively).(352) Finally, among participants with inflammatory rheumatic disorders, a 1.18-fold increased risk of job loss was found with comorbid depression (95%CI 1.02 to 1.36).

Table 28: Summary of included studies reporting the impact of psychiatric comorbidity on employment status and job loss

Study	MSD population	Exposure	Definition of work outcome	Effect size
De Buck (2006) (354)	Rheumatoid arthritis, ankylosing spondylitis, or lupus	Depression (HADS)	Job loss after 2 year follow up	OR **1.18 (1.02 to 1.36)**
Panopalis (2007) (338)	Systemic lupus erythematosus	Symptoms of depression (CES-D)	Current employment	OR **0.64 (0.44 to 0.94)**
Schofield (2014) (352)	Arthritis	Diagnosed depression or mood/affective disorders	Current unemployment	OR **5.42 (2.61 to 11.26)**
Schofield (2014) (352)	Arthritis	Diagnosed mental health and related disorders	Current unemployment	OR **3.46 (1.92 to 6.23)**

Figure 27: Impact of psychiatric comorbidity upon work participation in people with MSDs. Chart is colour-coded by category of work outcome: work disability or disability pension (black), return to work (blue), sickness absence (green), productivity loss or presenteeism (purple), unemployment or job loss (orange), work transition (red). See Glossary for abbreviations.



4.3.3 Cardio-metabolic comorbidity

Seven included studies (four cohort, three cross-sectional) explored the association between cardiovascular comorbidities and work outcomes in MSD populations (see Table 29 below).(340,344,347,351–353,365)

Work disability and disability pension

Among a cohort with lupus, comorbid hypertension was associated with an increased risk of being unemployed due to disability (self-reported) (OR 2.23 95%CI 1.16 to 4.32).(344) However, among working participants with rheumatoid arthritis, comorbid hypertension was not significantly associated with time to significant (>15 days) sick leave/disability pension over follow up (HR: 1.25 95%CI 0.85 to 1.85).(351)

Return to work

Among participants with rheumatoid arthritis (with 90 days of sick leave and disability pension at baseline - prior to biologic therapy) hypertension was also not associated with time to achieve >15 days without sick leave or disability pension over follow up (HR 0.9 95%CI 0.56 to 1.45).(351)

In another study, obesity (BMI ≥ 30.0) was significantly associated with failure to return to work within 2 years following knee arthroplasty (OR 2.8 95%CI 1.1 to 7.1).(347)

Sickness absence

Obesity (BMI ≥ 30.0) was also associated with any absenteeism (1–365 days of sick leave from work) in the year prior amongst those with self-reported musculoskeletal disorders in one cross sectional study (OR 1.37 95%CI 1.1 to 1.71).(340)

Presenteeism and reduced productivity

Being obese was associated with whether participants with arthritis felt arthritis/joint symptoms were currently affecting whether they worked, the type of work, or the amount of work they were performing (OR 1.07 95%CI 1.01 to 1,14).(365) In another study amongst people with lower limb “osteoarthritis” (defined as hip, knee, or foot pain for 1 day or more during the past year) obesity was not significantly associated with not taking part in paid or voluntary work as and when desired over the prior 4 weeks (OR 1.36 95%CI 0.74 to 2.52).(353)

Unemployment

Heart disease, hypertension, and other diseases of the circulatory system were all independently and significantly associated with unemployment (being out of the labour force) in one study of arthritis patients. In this study, the strength of association was relatively high for these conditions (OR 4.31 95%CI 1.94 to 9.55; OR 2.44 95%CI 1.55 to 3.83; and OR 6.95 95%CI 2.76 to 17.51, respectively).(352)

Table 29: Summary of included studies reporting the impact of cardiovascular comorbidity on various work outcomes

Study	MSD population	Exposure	Definition of work outcome	Effect size
Al Dhanhani (2009) (344)	Systemic lupus erythematosus	Hypertension	Being unemployed due to disability	OR **2.23 (1.16 to 4.32)**
Joshi (2015) (365)	Arthritis	Obesity	Arthritis/joint symptoms currently affect whether working, type of work, or the amount of work	OR **1.07 (1.01 to 1.14)**
Kuijer (2016) (347)	Total knee arthroplasty	Obesity	Return to work after at least 2 years follow up following total knee arthroplasty	OR **2.8 (1.1 to 7.1)**
Olofsson (2017) (351)	Rheumatoid arthritis	Hypertension	Time to regain >15 days of 30 without sick leave or disability pension over follow up (maximum 3 years)	HR 0.90 (0.56 to 1.45)
Olofsson (2017) (351)	Rheumatoid arthritis	Hypertension	Loss of 15 days of 30 with sick leave or disability pension over follow up (maximum 3 years)	HR 1.25 (0.85 to 1.85)
Schofield (2014) (352)	Arthritis	Heart disease	Unemployment (not being in the labour force)	OR **4.31 (1.94 to 9.55)**

Schofield (2014) (352)	Arthritis	Hypertension	Unemployment (not being in the labour force)	OR **2.44 (1.55 to 3.83)**
Schofield (2014) (352)	Arthritis	Other diseases of the circulatory system	Unemployment (not being in the labour force)	OR **6.95 (2.76 to 17.51)**
Ven den Berg (2017) (340)	Musculoskeletal disorders	Obesity	1–365 days of sick leave in the prior year.	OR **1.37 (1.10 to 1.71)**
Wilkie (2013) (353)	Osteoarthritis (lower limb pain)	Obesity	Occurrence of not taking part in paid or voluntary work as and when wanted over past 4 weeks (3 years follow up).	OR 1.36 (0.74 to 2.52)

4.3.4 Diabetes comorbidity

Only, two studies (2 cohort, 1 cross-sectional), explored the association between diabetes and risk of adverse work outcomes (see Table 30).(344,352) Diabetes was significantly associated with unemployment among people with arthritis (OR 2.55 95%CI 1.29 to 5.02),(352) but not with self-reported unemployment due to disability in another study amongst participants with SLE (OR 1.00 95%CI 0.41 to 2.44).(344)

Table 30: Summary of included studies reporting the impact of diabetes comorbidity on work outcomes

Study	MSD population	Exposure	Definition of work outcome	Effect size
Al Dhanhani (2009) (344)	Systemic lupus erythematosus	Diabetes	Being unemployed due to disability	OR 1.00 (0.41 to 2.44)
Schofield (2014) (352)	Arthritis	Diabetes	Unemployment (not being in the labour force)	OR **2.55 (1.29 to 5.02)**

4.3.5 Respiratory disease comorbidity

Only one cross-sectional study explored the association between respiratory diseases and unemployment status in arthritis patients (see Table 31). Both asthma and general respiratory diseases were significantly associated with being unemployed (OR 2.46 95%CI 1.37 to 4.42; and OR 3.16 95%CI 1.35 to 7.43, respectively).(352)

Table 31: Summary of included studies reporting the impact of respiratory comorbidity on work outcomes

Study	MSD population	Exposure	Definition of work outcome	Effect size
Schofield (2014) (352)	Arthritis	Asthma	Unemployment (not being in the labour force)	OR **2.46 (1.37 to 4.42)**
Schofield (2014) (352)	Arthritis	Diseases of the respiratory system	Unemployment (not being in the labour force)	OR **3.16 (1.35 to 7.43)**

4.3.6 Other comorbidities

Two studies reported work outcomes associated with other comorbidities among people with MSDs (see Table 32). One paper amongst those with lower limb "osteoarthritis" (defined as hip, knee, or foot pain for 1 day or more during the past year) did not find cognitive impairment was a significantly associated with not taking part in paid or voluntary work as and when desired over the prior 4 weeks (OR 1.09 95%CI 0.67 to 1.75).(353) Another cross-sectional study among people with arthritis reported unemployment was associated with comorbid diseases of the eye and adnexa (OR 3.86 95%CI 1.13 to 13.14), comorbid skin and subcutaneous tissue disease (OR 3.75 95%CI 1.31 to 10.72), comorbid digestive system disorders (OR 3.63 95%CI 1.91 to 6.89), and nervous system disorders (OR 3.30 95%CI 1.72 to 6.32).(352)

Table 32: Summary of included studies reporting the impact of "other" comorbidity on work outcomes

Study	MSD population	Exposure	Definition of work outcome	Effect size
Schofield (2014) (352)	Arthritis	Diseases of the eye and adnexa	Unemployment (not being in the labour force)	OR **3.86 (1.13 to 13.14)**
Schofield (2014) (352)	Arthritis	Diseases of the skin and subcutaneous tissue	Unemployment (not being in the labour force)	OR **3.75 (1.31 to 10.72)**
Schofield (2014) (352)	Arthritis	Diseases of the digestive system	Unemployment (not being in the labour force)	OR **3.63 (1.91 to 6.89)**
Schofield (2014) (352)	Arthritis	Diseases of the nervous system	Unemployment (not being in the labour force)	OR **3.30 (1.72 to 6.32)**
Schofield (2014) (352)	Arthritis	Other endocrine/nutritional and metabolic disorders	Unemployment (not being in the labour force)	OR 2.06 (0.92 to 4.58)
Schofield (2014) (352)	Arthritis	Neoplasms (tumours/cancers)	Unemployment (not being in the labour force)	OR 2.60 (0.84 to 7.99)
Schofield (2014) (352)	Arthritis	Diseases of the genitourinary system	Unemployment (not being in the labour force)	OR 1.65 (0.71 to 3.81)
Schofield (2014) (352)	Arthritis	"Other" comorbidity	Unemployment (not being in the labour force)	OR 2.64 (0.76 to 9.17)
Wilkie (2013) (353)	Osteoarthritis (lower limb pain)	Cognitive impairment (Score >0 on Cognitive and Alertness behaviour subscale of the Functional Limitations Profile)	Occurrence of not taking part in paid or voluntary work as and when wanted over past 4 weeks (3 years follow up).	OR 1.09 (0.67 to 1.75)

4.4 Discussion

The presence of comorbidity was found to have a detrimental effect on work among people with MSDs. The majority of included studies showed comorbid health disorders were significantly associated with adverse work outcomes across various MSD populations (populations with an existing high risk of poor work outcomes).(9–13,199,334,341,348–350,352,357,359,361–363) Of the five studies that did not observe significant findings: two used very broad and unvalidated indicators of work restriction and reduced productivity;(353,365) one was underpowered with only 15 events and wide confidence intervals;(342) another found that comorbidity was not significantly associated with work disability when disease severity factors such as joint count, radiographic score and functional status (ADL) were adjusted for.(339) It is possible that by adjusting for activities of daily living (ADL), this study was adjusting for a mediating variable, since increased comorbidity could lead to functional impairment, followed by reduced ability to remain in work.

Effect size estimates ranged from small/non-significant (e.g. OR 1.01) to large and significant (e.g. OR 3.68) for odds, or risk, of adverse work outcomes. However, the direction of effect was very consistent (see Figure 26). The possible reasons for this variability are discussed below and include the measurement of comorbidity used, the measurement of work outcomes, and the underlying musculoskeletal populations studied.

Comorbidity was commonly classified by counting the number of known comorbidities, (12,339,350,365) or, by dichotomising to the presence or absence of comorbidity. (10,11,199,342,348,349,353,357,359,366) Comorbidity may be described by an extensive array of possible disease combinations, each with varied effect on health and function. Therefore, even measuring comorbidity by number of health disorders may be over-simplistic and dilute power to detect the true impact of certain specific comorbidities on work. In addition, classification of comorbidity was heterogeneous, drawing on different selections of health disorders, often with no justification for the health disorders selected. Some studies did make use of validated comorbidity checklists, however these checklists were validated against health outcomes (including health care utilisation, medical records, all-cause mortality, and physical functioning) not work outcomes. (9,13,334,341,343,361–363) An agreed systematic approach to recording comorbidity burden should be encouraged to allow better comparison between studies, and the use of validated

checklists can facilitate this. However, I am unaware of any comorbidity/multimorbidity score or checklist which has been validated against important work outcomes.

Work outcome measures were also heterogeneous, capturing different aspects of ability to remain and thrive in work. In 2016, the OMERACT (Outcome Measures in Rheumatology) worker productivity group produced consensus-based guidance for the standardisation of work and productivity outcome measures in rheumatology research. The following absenteeism and productivity loss measures were recommended: WALS (Workplace Activity Limitations Scale), WLQ PDmod (Work Limitations Questionnaire with modified physical demands scale), WAI (Work Ability Index), WPS (Arthritis-specific Work Productivity Survey), and WPAI (Work Productivity and Activity Impairment questionnaire).(383) Of the included studies in this review, only six used the recommended questionnaires (or items from these questionnaires).(334,340,341,343,361) As described above, the use of such validated questionnaires can facilitate consistency and comparability across research. Another advantage, over the use of a single closed questions, is that responses from these questionnaires can be graded to assess severity of work impairment. However, even the use of validated questionnaires does not guarantee that the data will be analysed in a consistent manner. For example, in Agaliotis (2013), WPAI presenteeism was dichotomised to those "exposed to presenteeism" (participants who scored an average of 99.99% and below) vs those not exposed (100%).(343)

OMERACT recommended the use of questionnaires focussed on the short-term or "usual" work ability of participants who are currently employed. In this review, many studies focussed on other adverse employment events, such as being unable to work for a health reason;(9,11–13,336,338,358) return to work following a period of long-term sickness absence;(345–348,351,355,356,364,366) or the receipt of disability pension.(10,336,339,351,357) For these work outcomes, there are also challenges for consistency in reporting. For example, the follow-up period to assess return to work varied; appropriate length of follow up may depend on the cause of disability. Additionally, assessment of the presence of "official" work disability, or the receipt of disability pension, may have different legal classifications depending on the national social security system. In the UK, there are several kinds of disability benefits which may be awarded as a result of temporary or permanent inability to work, and may be paid to persons who are still working.(384)

Some studies reported work outcomes that were not health-specific. For example, employment status,(338,341,342,352,359,361) job loss,(349,354) and not taking part in paid or voluntary work as and when desired.(353) The obvious problem with these work outcomes is that it is unclear whether they have occurred specifically as a result of a health issue, or for some other reason which may be related to health (for example, lower educational attainment). However, for many important comorbid exposures such as heart disease, diabetes, and asthma these were the only work outcomes that were reported.(352)

Finally, variability in the effect sizes reported may reflect differences in the underlying musculoskeletal population studied. The reference group of interest was people with musculoskeletal disorders and no comorbidities, however, most included studies were restricted to sub-populations of specific musculoskeletal disease groups such as SLE and rheumatoid arthritis; conditions with their own specific characteristics, demographics, and risk of adverse work outcomes. Effect sizes for the impact of comorbidity may therefore vary depending on the existing level of risk in the underlying musculoskeletal population.

However, there were consistent trends. For example, as mentioned above, comorbidity was significantly associated with adverse work outcomes across various MSD populations, and effect estimates suggested a negative influence on work-health in all cases. Specifically, there was consistent evidence to suggest that psychiatric comorbidities had a detrimental impact on work. A significant effect was reported in 16 of 18 reporting studies, which included eight cross-sectional studies (NOS mean quality 6.5/10, range 5 – 8),(335–338,358,364–366) and eight cohort studies (NOS mean quality 6.1/9, range 5 – 7).(345,351–357) However, work restriction was not associated with comorbid anxiety in one study.(353) This study used a very broad definition of work restriction, which was not health specific and may have failed to discriminate those with significant work restriction (‘‘During the past 4 weeks, if you work, have you taken part in paid or voluntary work as and when you have wanted?”). Another study did not find that major depressive event, or moderate depressive symptoms, were related to ability to remain in active work 12 months after occupational MSD injury.(346) In this case, the reasoning behind the multivariable adjustments were unclear and appeared to include multiple measures of depression in the same statistical model. Finally, one study did not find depression (Major Depression Inventory- mean score) among people with self-reported musculoskeletal pain was associated with onset of prolonged sickness absence, although depression symptoms rather than clinically diagnosed depression was assessed here.(360)

A few studies reported that mental and musculoskeletal comorbidity had a multiplying, not just additive, impact upon work ability and sickness absence.(335,357,364,385) In other words, mental health problems may have a synergistic relationship with musculoskeletal disorders whereby the combined effect on work-health is greater than would be expected from the individual effects of each disease alone. The impact of comorbid mental health problems may be broad, for example, depression has been found to be detrimental for home, work, and social relationships, morbidity and even all-cause mortality in patients with chronic medical disorders.(386,387) The development of a psychiatric comorbidity may therefore initiate precipitous deterioration in the ability to remain working among people with MSDs.

There was little evidence on the impact of other comorbid health disorders for work outcomes in MSDs. Comorbid diabetes was associated with unemployment in arthritis in one study,(352) but was not associated with work disability in a lupus population.(344) One study showed comorbid heart disease, vascular disease, asthma, "other respiratory diseases," diseases of the digestive system, diseases of the eye and adnexa, diseases of the skin, injury and poisoning were associated with unemployment in arthritis.(352) But no health-specific work outcomes were reported. More research is required to understand the role of a broader range of comorbid health disorders on work outcomes, particularly for cardiometabolic disorders which are highly prevalent among people with MSDs.(388,389)

Health risk factors, such as hypertension and obesity, are frequently not included in the definition of comorbidity.(150) However, in this review, two studies linked hypertension to risk of being unemployed due to disability, or just unemployed, in MSDs (one amongst SLE and one amongst arthritic participants, respectively).(344,352) In addition, comorbid obesity was associated with sickness absence in the prior year,(340) no return to work following knee arthroplasty,(347) and whether arthritis/joint symptoms were affecting work status, type of work, or the amount of work produced,(365) amongst MSD and arthritis populations. The mechanism of effect in each of these cases is unclear. These health risk factors are associated with a range of other, possibly unmeasured, cardiovascular disorders and may be indicators of greater musculoskeletal disease severity through known inflammatory pathways.(390) Obesity can also mechanically exacerbate underlying arthritis symptoms.(391)

The limitations of this evidence base have been described in detail above. One further limitation included the fact that the MSD populations studied were not necessarily

representative of the MSDs most frequently seen in UK populations. For instance, more evidence is needed from the two most prevalent MSD populations: osteoarthritis and low back pain. Some publication bias towards diseases with more expensive and novel treatments (i.e. inflammatory rheumatic disorders) was apparent. As a result, while the methodological quality of the included studies was relatively strong the use of this review to draw conclusions about the general MSD population may be hampered by indirectness.

Weaknesses of the review methodology include the broad search strategy. Papers that did not include the words comorbidity or multimorbidity (and derivatives) in their titles, abstracts or keywords would not have been identified. Therefore, studies that focused only on the relationship between two diseases (for example, depression and rheumatoid arthritis) without using the terms co- or multi-morbid may have been missed. I hoped to mitigate this risk by performing thorough citation checks of the included studies, since running the search with multiple specific disease terms would have resulted in an unmanageable number of references.

Across studies included in this systematic review, important trends have been highlighted, showing the relationship between comorbidities, and specifically psychiatric comorbidities, and adverse work outcomes among people with MSDs. Additionally, this review has highlighted several research areas which have not been sufficiently addressed. For example, the impact of non-psychiatric comorbidities upon work outcomes among people with MSDs is still unclear. This is particularly important for cardiovascular comorbidities which are common, and therefore naturally likely to co-occur with MSDs. Secondly, this review highlighted poor consistency in the measurement of work outcomes, and in the measurement of comorbidity (or multimorbidity) itself. The development and use of validated measures for comorbidity exposures and work outcomes will be necessary for future research.

4.5 Conclusion

This review draws conclusions from a heterogeneous evidence base. Varying populations, outcome definitions, analysis and study design can make interpretation difficult but, even so, trends were identified. Compared to having a musculoskeletal disorder alone, comorbidity, and specifically comorbid mental health problems, were associated with multiple adverse work outcomes across different MSD populations. Impact is likely to depend on the type of comorbid condition and its severity. However, while psychiatric

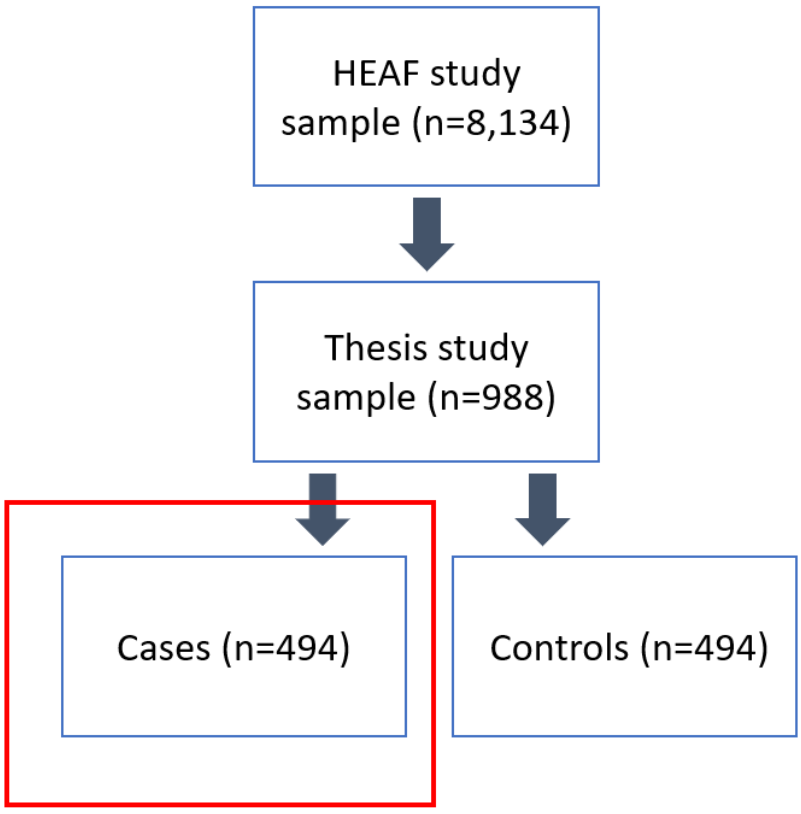
comorbidities were well reported, further research is required to study other important comorbid diseases that may be predictive of poor work ability in MSDs.

Chapter 5- describing "case" participants with HRJL

5.1 Introduction

This chapter describes the primary population of interest in this thesis: people who reported that they had stopped working mainly or partly because of a health problem (those with HRJL, the "cases") on the baseline questionnaire of the Health and Employment After Fifty (HEAF) study, see Figure 28. This population are described for the following characteristics: their socio-demographic factors; details of the last job worked prior to HRJL; age when stopped working; and the health-cause of job loss as indicated by questionnaire responses. Next, their CPRD-defined health disorders are presented, along with the more specific health disorder sub-groups that contributed to these variables (see Chapter 3). Finally, case participants are stratified by gender, their age at the time of HRJL, and whether they reported a health problem was mainly or partly responsible for the job loss, to look for any important differences between these sub-groups.

Figure 28: The cohort described in this chapter, as indicated by the red square



5.2 Methods

A descriptive analysis of participants with premature exit from work due to health was undertaken. Case participants were described for demographic factors, previous work, social class, factors relating to lifestyle, and lastly for CPRD-defined health problems. The classifications used to define these variables are outlined in Chapter 3. When describing CPRD-defined health disorders, each disease variable was considered in detail to see which constituent disease codes were prevalent. For example, among cases with a chronic MSD, the proportion due to osteoarthritis, inflammatory arthritis, or connective tissue diseases was described. This higher definition description of disease groups was conducted in order to gain a greater understanding of the common diseases contributing to the main health exposures under study in this thesis and, in turn, to aid interpretation of results going forwards.

Among case participants, there were certain sub-groups of interest. To date, few studies of the determinants of early exit from work due to health have explored the effect of gender. Therefore, male and female cases were compared for their demographic, lifestyle, and health-related factors to look for important differences. Case participants also differed for the age at which they left work. In the UK, the 50 – 60-year-old age band are of particular economic interest, since they are the most common HRJL group and still a considerable distance from state pension retirement age. Descriptive analysis was therefore stratified by those under the age of 50, those 50 to <60 years old, and those older than 60 at the time of HRJL. Finally, as outlined in chapter 3, case participants could respond that a health problem had been the “main reason” or “part of the reason” for their job loss. I looked for important differences in demographic, lifestyle, and health-related factors, between these sub-groups, in order to ascertain whether sensitivity analysis by “type” of HRJL is necessary in later chapters.

Statistical analyses were performed using Stata-13. Participants with HRJL were described using simple statistics such as percentages for categorical data, means and standard deviations for continuous data, and medians and interquartile ranges for non-gaussian continuous variables.

5.3 Results

5.3.1 Describing all participants with HRJL

5.3.1.4 Demographic factors

Case participants were vast-majority white (98.2%). 19.8% had attained a university-level education, 39.7% had vocational or professional-level qualifications, 18.4% had high school qualifications, and 22.1% had no qualifications. Most case participants were married (67.2%), 9.8% were single, 18.1% were divorced and 4.9% were widowed. See Table 33.

Table 33: Distribution of demographic factors among cases

Variable	Number of cases (%)[1]
Ethnicity (non-white)	9 (1.8)
Ethnicity (white)	485 (98.2)
University degree	98 (19.8)
Vocational	196 (39.7)
High school qualifications	91 (18.4)
No qualifications	109 (22.1)
Married/Civil partnership	330 (67.2)
Single	48 (9.8)
Divorced	89 (18.1)
Widowed	24 (4.9)

1. data on relationship status was missing for three case participants

5.3.1.5 Occupations

Cases were grouped for their previous occupations using the SOC-10 classification system (see Chapter 3). The distribution of major SOC-10 occupational groups can be found in Table 34 below. Most cases were either in professional (20.0%), administrative (15.6%), elementary (12.8%), or skilled trade (10.7%) work, which together accounted for over half of the jobs lost. This was closely followed by caring, leisure, and service occupations (9.5%), associate professional and technical occupations (8.9%), sales and customer service occupations (7.1%), process, plant and machine operatives (7.1%), and finally managers, directors, and senior officials (6.7%).

Table 34: Strata of SOC-10 major occupational groups for previous employment among cases

Variable	Number of cases (%)[1]
Managers, directors and senior officials	33 (6.7)
Professional occupations	99 (20.0)
Associate professional and technical occupations	44 (8.9)
Administrative and secretarial occupations	77 (15.6)
Skilled trades occupations	53 (10.7)
Caring, leisure, and other service occupations	47 (9.5)
Sales and customer service occupations	35 (7.1)
Process, plant and machine operatives	35 (7.1)
Elementary occupations	63 (12.8)

1. data on SOC-10 occupational class was missing for eight case participants

The SOC-10 sub-major categories provide a greater level of detail. The frequency of these occupational sub-groups among case participants are outlined in Table 35 and are visualised in Figure 29. Teaching (9.7%), administration (13.2%), and elementary administration (10.7%) accounted for approximately one third of all jobs lost due to poor health. Other common previous careers among cases included: caring personal service occupations (6.9%); sales occupations (6.1%); and health professional occupations (5.7%). By the SOC-10 classification of skill level, almost a quarter of all cases had worked in the highest skill category (23.6%), 22.6% in level 3, 39.3% in level 2, and 12.6% in the lowest skill group.

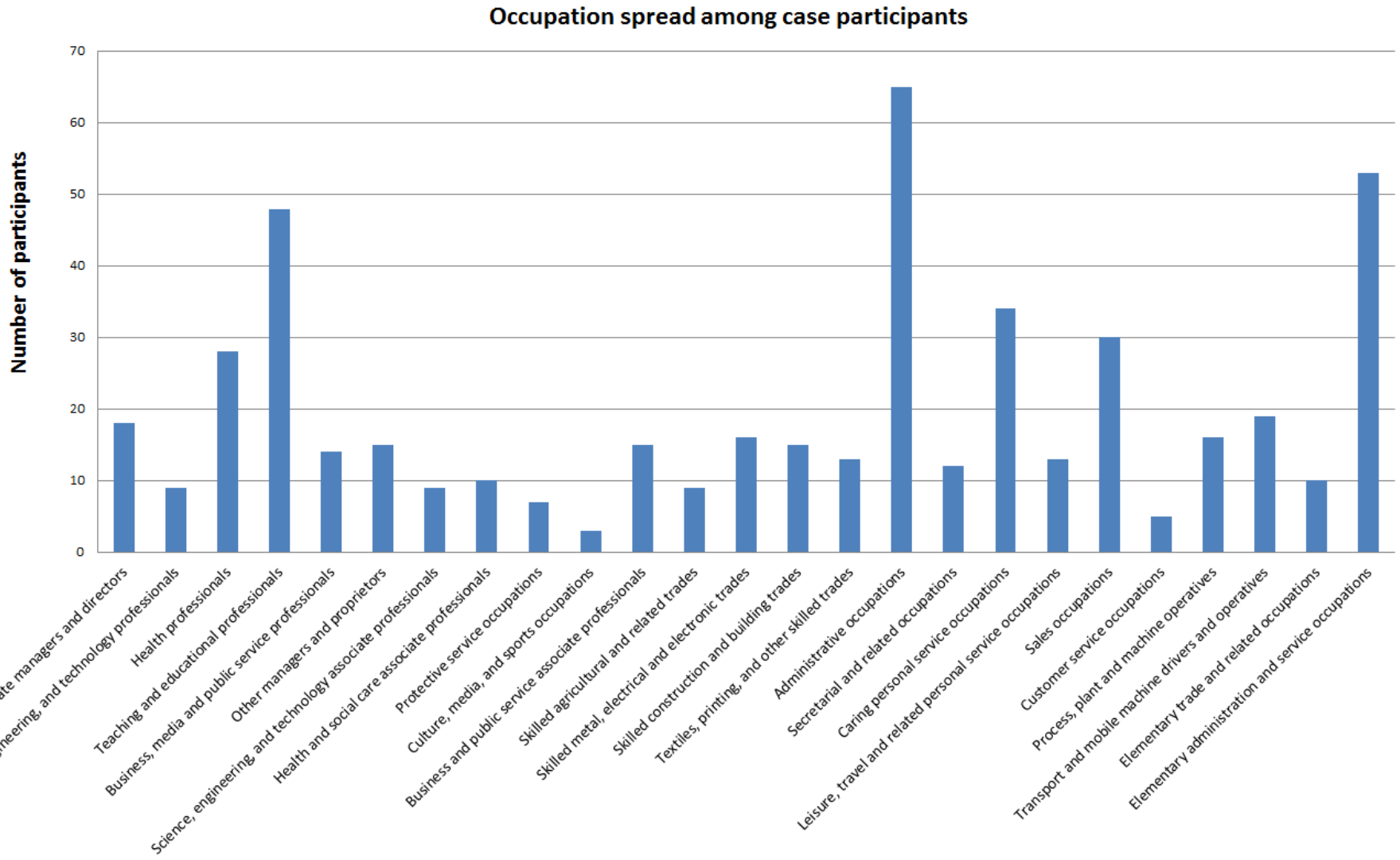
Table 35: Strata of SOC-10 sub-major occupational groups among cases

Variable	Skill level	Number of cases (%)[1]
Corporate managers and directors	Level 4	18 (3.6)
Science, research, engineering, and technology professionals		9 (1.8)
Health professionals		28 (5.7)
Teaching and educational professionals		48 (9.7)
Business, media and public service professionals		14 (2.8)
Other managers and proprietors	Level 3	15 (3.0)
Science, engineering, and technology associate professionals		9 (1.8)
Health and social care associate professionals		10 (2.0)
Protective service occupations		7 (1.4)
Culture, media, and sports occupations		3 (0.6)

Business and public service associate professionals		15 (3.0)
Skilled agricultural and related trades		9 (1.8)
Skilled metal, electrical and electronic trades		16 (3.2)
Skilled construction and building trades		15 (3.0)
Textiles, printing, and other skilled trades		13 (2.6)
Administrative occupations	Level 2	65 (13.2)
Secretarial and related occupations		12 (2.4)
Caring personal service occupations		34 (6.9)
Leisure, travel and related personal service occupations		13 (2.6)
Sales occupations		30 (6.1)
Customer service occupations		5 (1.0)
Process, plant and machine operatives		16 (3.2)
Transport and mobile machine drivers and operatives		19 (3.9)
Elementary trade and related occupations	Level 1	10 (2.0)
Elementary administration and service occupations		53 (10.7)

1. data on SOC-10 occupational class was missing for eight case participants

Figure 29: Occupation spread among case participants



5.3.1.6 Socio-economic class

The SOC-10 occupational categories could be used to classify socio-economic status according to the NS-SEC simplified criteria, see Chapter 3. Table 36 shows the distribution of three-level and eight-level NS-SEC socioeconomic class among case participants. Using the broader three-level socio-economic categories, 32.4% were in the higher managerial class, 26.7% in the intermediate class, and 39.3% in the routine and manual class.

Table 36: Strata of NS-SEC, 8-level, and 3-level criteria, among cases

Variable	NS-SEC 3-levels	Number of cases (%)	Number of cases (%)[1]
Large employers and higher managerial and administrative occupations	Higher managerial	10 (2.1)	160 (32.4)
Higher professional occupations		30 (6.2)	
Lower managerial, administrative and professional occupations		120 (24.7)	
Intermediate occupations	Intermediate	101 (20.8)	132 (26.7)
Small employers and own account workers		31 (6.4)	
Lower supervisory and technical occupations	Routine and manual	26 (5.4)	194 (39.3)
Semi-routine occupations		110 (22.3)	
Routine occupations		58 (11.7)	

1. data on NS-SEC occupational class was missing for eight case participants

5.3.1.7 Lifestyle

Among case participants, approximately half were ever-smokers, of whom 16.6% were current smokers and 33.8% were ex-smokers. A history of heavy alcohol intake was indicated in 3.6%. See Table 37, below.

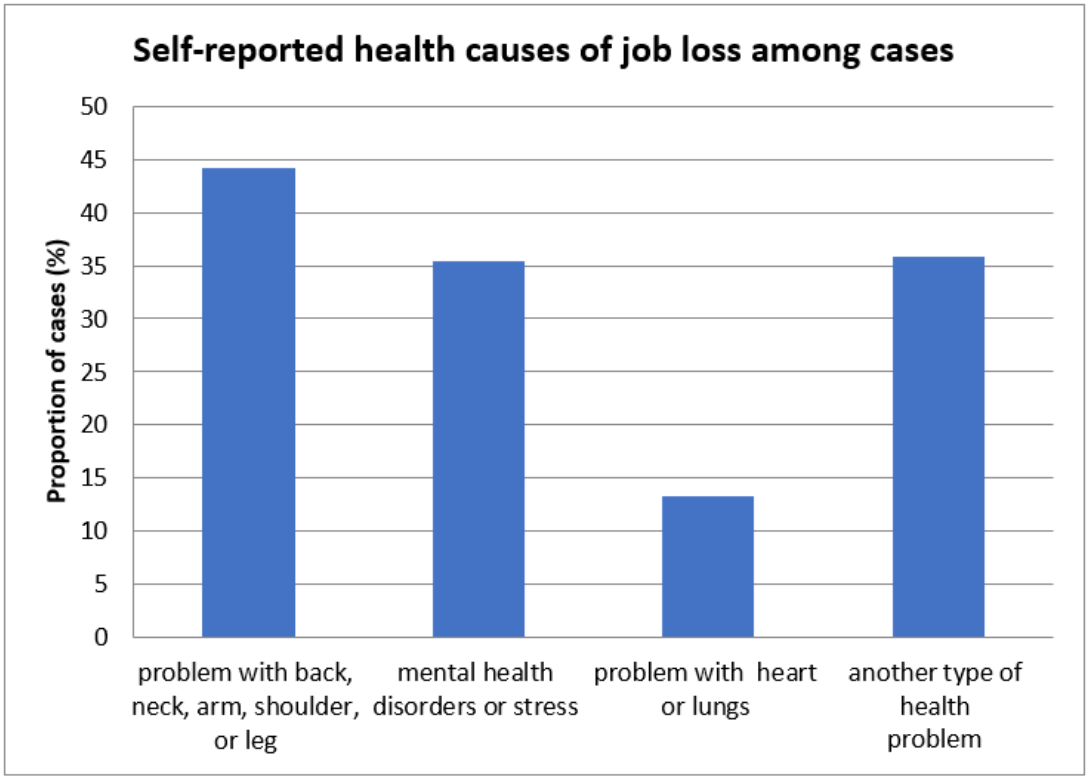
Table 37: Distribution of lifestyle factors among case participants

Variable	Number of cases (%)
Smoking	
Never smokers	245 (49.6)
Ex-smokers	167 (33.8)
Current smokers	82 (16.6)
Heavy drinking	
No history of heavy drinking	476 (96.4)
History of heavy drinking	18 (3.6)

5.3.1.8 *Patient-reported health causes of job loss*

As described in Chapter 3, in the HEAF baseline questionnaire participants with HRJL also classified the health problem that led to their job loss according to a few possible categories. Among case participants, 44.2% reported that leaving work was at least partially because of "a problem with their back, neck, arm, shoulder, or leg"; 35.4% because of "mental health disorders or stress"; 13.2% because of "a problem with the heart or lungs"; and 35.9% because of "another type of health problem". See Figure 30.

Figure 30: Self-reported health causes of job loss among case participants



5.3.1.9 *Musculoskeletal disorders*

Clinical data from study participants' CPRD records were considered. Chronic MSDs were identified in 136 (27.5%) case participants prior to their HRJL. Of these cases, 61.8% considered "a problem with their back, neck, arm, shoulder, or leg" to be a contributing factor to their job loss.

A large majority of cases with chronic MSDs had a diagnosis of osteoarthritis (OA) (n=114, 83.8%) which was largely probable OA unclear site (58.1%) or OA knee (18.4%). Other than

OA, 10.3% had rheumatoid arthritis, 17.7% had another kind of inflammatory arthritis, 7.4% had gout, and 4.4% had connective tissue disease. See Table 38, below.

Table 38: CPRD-defined health disorders contributing to the chronic MSD variable, among case participants

Variable	No. of cases with HRJL and chronic MSD (%)
Rheumatoid arthritis	14 (10.3)
Other inflammatory arthritis	24 (17.7)
Probable osteoarthritis unclear site	79 (58.1)
OA back	9 (6.6)
OA neck	19 (14.0)
OA shoulder and elbow	1 (0.7)
OA hip	7 (5.2)
OA knee	25 (18.4)
OA lower limb, not specified	3 (2.2)
OA back or neck, not specified	2 (1.5)
OA hand, wrist, digits	3 (2.2)
Gout	10 (7.4)
Connective tissue disease	6 (4.4)
Arthroplasty of the hip	10 (7.4)
Arthroplasty of the knee	8 (5.9)
Probable OA (combined OA groups)	114 (83.8)

Recent musculoskeletal pain, in the year prior to HRJL, was identified in 153 (31.0%) case participants. Among these cases, 61.8% said “a problem with their back, neck, arm, shoulder, or leg” had contributed to their job loss.

Over one third (n=65, 42.5%) of cases with recent MSD pain had presented with back pain. Other common problems included knee pain (21.6%), shoulder pain (13.1%), and widespread pain (10.5%). Of the body region-specific MSD pain codes, there were 40 participants with upper limb pain (26.1%), 84 participants with recent back and spine pain (54.9%), and 50 with recent lower limb pain (32.7%). See Table 39, below.

Table 39: CPRD-defined health disorders contributing to the recent MSD pain variable, among case participants

Variable	No. of cases with HRJL and recent MSD pain (%)
Disorder of joints, non-specific	19 (12.4)
Back pain	65 (42.5)
Discogenic/nerve root pain	10 (6.5)
Neck pain	14 (9.2)
Hip pain	13 (8.5)
Knee pain	33 (21.6)
Lower limb pain unspecified	4 (2.6)
Knee bursitis	1 (0.7)
Knee joint swelling or effusion	3 (2.0)
Widespread pain	16 (10.5)
Shoulder pain	20 (13.1)
Elbow pain	1 (0.7)
Wrist/hand or forearm pain	5 (3.3)
Specific disorders of the shoulder or shoulder girdle	6 (3.9)
Specific disorders of the elbow	12 (7.8)
Shoulder surgery and other procedures	2 (1.3)
Non-specific sprain/injury	1 (0.7)
Neck injury	1 (0.7)
Back injury	2 (1.3)
Shoulder/upper limb injury	1 (0.7)
Other lower limb injury	1 (0.7)
Other specific disorders	3 (2.0)
Other knee procedures (not arthroplasty)	4 (2.6)
Rheumatism, non-specific	12 (7.8)

5.3.1.10 Mental health problems

Among those with HRJL, 140 participants (28.3%) had a recent mental health problem (MHP). This included 129 participants with a primary-care-level MHP (26.1%), eight participants with a psychiatric-care-level MHP (1.6%), and 37 participants with a sleep disorder (7.5%). A history of severe mental health problems was also present in 37 participants (7.5%). Case participants ascribed their HRJL to "mental health problem or

stress" in 59.4% with a recent primary care level MHP, 46.0% with a recent sleep disorder, 62.5% with a psychiatric care-level MHP, and 62.2% with history of a severe MHP.

The majority of case participants with recent primary care-level MHPs had mood or depressive disorders (83.0%) or anxiety disorders (31.8%). There were few case participants with psychiatric care-level MHPs, of whom five (62.5%) had a diagnosis of schizophrenia and three (37.5%) bipolar disorder. Of case participants with a history of severe mental health problems, there were 67.6% who had been under psychiatric care, 27.0% with a history of crisis admission, section, or being on a severe mental health register, and 21.6% with a history of self-harm, suicidal actions, or ideations. See Table 40.

Table 40: CPRD-defined health disorders contributing to MHP variables, among case participants

Variable	No. of cases with HRJL and MHPs (%)
Primary care-level mental health problems	
Mood or depressive disorders	107 (83.0)
Anxiety disorders	41 (31.8)
Somatoform disorders	3 (2.3)
Adjustment disorders	14 (10.9)
Sleep disorders	
Sleep disorders	37 (100.0)
Psychiatric care-level mental health problems	
Schizophrenia and other psychotic disorders	5 (62.5)
Sexual and gender identity disorders	1 (12.5)
Bipolar disorders	3 (37.5)
Severe mental health problems	
Self-harm, suicidal actions, or ideations	8 (21.6)
Under the psychiatric team	25 (67.6)
Crisis admission, section, on a severe mental health register	10 (27.0)

5.3.1.11 Cardiovascular disease

Among case participants, there were 44 with heart failure (8.9%), 30 with ischaemic heart disease (6.1%), 133 with hypertension (26.9%), one with venous thromboembolism (0.2%), 11 with peripheral atherosclerosis (2.2%), seven with cardiac arrhythmia (1.4%), and seven with structural heart disease (1.4%). When asked, 54.6% with heart failure, 63.3% of participants with ischaemic heart disease, 17.4% of participants with hypertension, none

with venous thromboembolism (of one participant), 27.3% of participants with peripheral arterial disease, and 100.0% of seven participants with cardiac arrythmia stated that "a problem with the heart or lungs" had contributed to their job loss.

The majority of case participants with ischaemic heart disease had myocardial ischaemia, atherosclerosis, or angina (86.7%), 40.0% had myocardial infarction or unstable angina, and 36.7% had a coronary angioplasty, bypass, or stent. Case participants with structural heart disease included four participants (57.1%) with diseases of the endocardium and valves and three participants (42.9%) with cardiomyopathies. Cases with recent cardiac arrythmias included five participants (71.4%) with atrial fibrillation or supraventricular tachycardia, two participants (28.6%) with arrythmias requiring cardioversion, ablation, or a pacemaker (0.4%) and two participants (28.6%) with other arrythmias. Cases with venous thromboembolism included only one participant who had a pulmonary embolism (0.2%). Lastly, cases with peripheral atherosclerosis included seven participants (63.6%) with a diagnosis of peripheral atherosclerotic disease and five participants (45.5%) with vascular atherosclerotic events, occlusions, or vascular surgery. See Table 41, below.

Table 41: CPRD-defined health disorders contributing to cardiovascular disease variables, among case participants

Variable	No. of cases with HRJL and CV disorder (%)
Ischaemic heart disease	
Myocardial infarction and unstable angina	12 (40.0)
Myocardial ischaemia, atherosclerosis, and angina	26 (86.7)
Coronary angioplasty, bypass, and stent	11 (36.7)
Heart failure	
Heart failure	44 (100.0)
Structural heart disease	
Diseases of the endocardium and valves	4 (57.1)
Cardiomyopathies	3 (42.9)
Hypertension	
Hypertension	133 (100.0)
Cardia arrhythmias	
Arrythmia other than atrial fibrillation	2 (28.6)
Atrial fibrillation and supraventricular tachycardia	5 (71.4)
Arrythmia requiring cardioversion, ablation or a pacemaker	2 (28.6)
Venous thromboembolic disease	

Pulmonary embolism	1 (100.0)
Peripheral arterial disease	
Vascular atherosclerotic events, occlusions, and non-coronary surgery	5 (45.5)
Peripheral arterial disease	7 (63.6)

5.3.1.12 Respiratory disorders

There were 47 case participants with asthma (9.5%), and 15 with COPD (3.0%). In questionnaire responses 21.3% of the participants with asthma, and 66.7% of the participants with COPD indicated "a problem with the heart or lungs" had contributed to their job loss.

Participants with asthma included 93.6% with asthma or probable asthma codes and only three participants (6.4%) with specific indicators of severe asthma (e.g. emergency hospital admissions for asthma). Participants with COPD had all received COPD or emphysema specific diagnostic codes, two participants (13.3%) were also diagnosed with chronic bronchitis. See Table 42, below.

Table 42: CPRD-defined health disorders contributing to respiratory disorder variables, among case participants

Variable	No. of cases with HRJL and respiratory disorder (%)
Asthma	
Asthma or probable asthma	44 (93.6)
Severe asthma	3 (6.4)
COPD	
Chronic bronchitis	2 (13.3)
COPD or emphysema	15 (100.0)

5.3.1.13 Neurological disorders

There were 17 case participants (3.4%) with CVA prior to job loss, and seven participants (1.4%) with epilepsy. Of these, 64.7% with CVA, and 28.6% with epilepsy indicated "another type of health condition" had contributed to their HRJL, possibly referring to their epilepsy or CVA.

Participants with CVA were all diagnosed with stroke, of which three participants (17.6%) also had a diagnosis of recent TIA. Six participants (85.7%) with epilepsy had specific

epilepsy-related codes while five had a fit or seizure before job loss and also epilepsy-specific codes any time prior to the baseline of the HEAF study. See Table 43.

Table 43: CPRD-defined health disorders contributing to neurological disorder variables, among case participants

Variable	No. of cases with HRJL and neurological disorder (%)
Cerebrovascular accident	
TIA	3 (17.6)
Stroke	17 (100.0)
Epilepsy	
Epilepsy	6 (85.7)
Fit/seizure	5 (71.4)

5.3.1.14 Diabetes

There were 60 case participants with diabetes (12.2%). Of these, 50.0% indicated "another type of health condition" had contributed to their HRJL, possibly referring to their diabetes.

All diabetic case participants had diabetes-specific codes prior to HRJL. Additionally, 53.3% had indicators of poor diabetes control (e.g. diabetic ketoacidosis), 23.7% had diabetic eye complications, and three participants (5.0%) had another type of diabetic complication. See Table 44.

Table 44: CPRD-defined health disorders contributing to diabetes variable, among case participants

Variable	Total with HRJL and diabetes, 60 (12.15%)
Diabetes	60 (100.0)
Eye involvement	16 (26.7)
Poor control	32 (53.3)
Other complication	3 (5.0)

5.3.2 Describing cases by gender

5.3.1.15 Demographic factors

Male and female case participants were similar for the median age at which they left work, and for their ethnicity. A greater proportion of female cases than male appeared to have

left education after attaining a high school qualification (21,9% vs 14.1%) and more men than women after attaining vocational level qualifications (43.6% vs 36.5%), however similar proportions had no qualifications or were educated to university level. Finally, male cases were more frequently single than female cases (13.2% vs 7.0%, respectively). See Table 45, below.

Table 45: Distribution of demographic factors among case participants, by gender

Variable	No. of men with HRJL (%)	No. of women with HRJL (%)
Age at HRJL, y (IQR)	58.56 (53.66 – 61.23)	57.86 (53.27 – 60.39)
Ethnicity (non-white)	4 (1.8)	5 (1.8)
Ethnicity (white)	216 (98.2)	269 (98.2)
University degree	45 (20.5)	53 (19.3)
Vocational	96 (43.6)	100 (36.5)
High school qualifications	31 (14.1)	60 (21.9)
No qualifications	48 (21.8)	61 (22.3)
Married/Civil partnership	145 (66.2)	185 (68.0)
Single	29 (13.2)	19 (7.0)
Divorced	37 (16.9)	52 (19.1)
Widowed	8 (3.7)	16 (5.9)

5.3.1.16 Occupations

Across SOC-10 major occupational categories, considerably more female than male cases were working in administration (21.2% vs 8.6%); caring, leisure, and service occupations (14.2% vs 3.6%); sales and customer service occupations (10.2% vs 3.2%); and in professional occupations (23.0% vs 16.4%). While proportionally more men than women were in skilled trade occupations (21.4% vs 2.2%); working as process, plant, and machine operatives (14.1% vs 1.5%); and in professional and technical occupations (11.4% vs 6.9%). See Table 46, below.

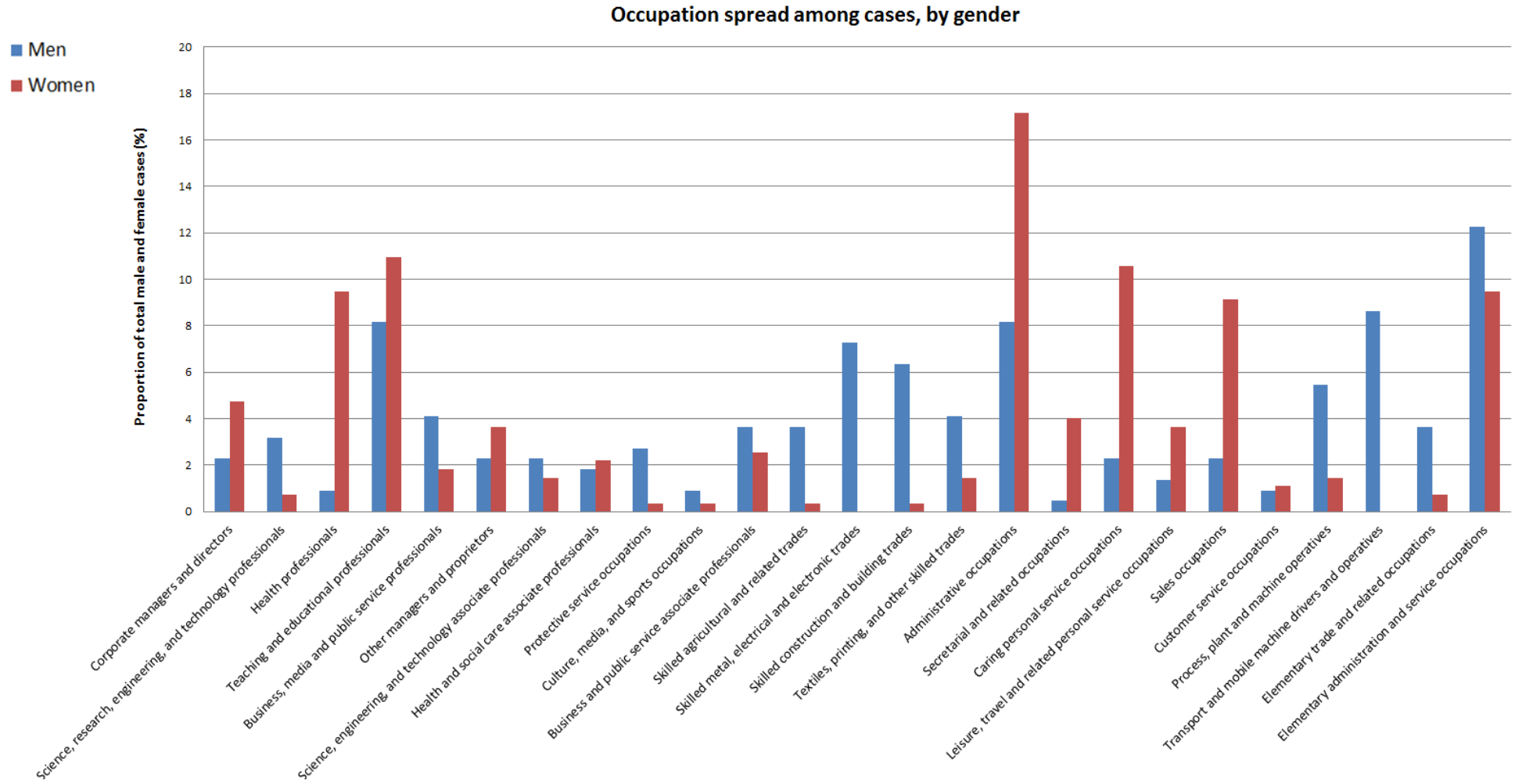
Table 46: Strata of SOC-10 major occupational groups among case participants, by gender.

Variable	No. of men with HRJL (%)	No. of women with HRJL (%)
Managers, directors and senior officials	10 (4.6)	23 (8.4)
Professional occupations	36 (16.4)	63 (23.0)
Associate professional and technical occupations	25 (11.4)	19 (6.9)
Administrative and secretarial occupations	19 (8.6)	58 (21.2)

Skilled trades occupations	47 (21.4)	6 (2.2)
Caring, leisure, and other service occupations	8 (3.6)	39 (14.2)
Sales and customer service occupations	7 (3.2)	28 (10.2)
Process, plant and machine operatives	31 (14.1)	4 (1.5)
Elementary occupations	35 (15.9)	28 (10.2)

Observing the occupations in finer detail using the SOC-10 sub-major categories, female cases, more frequently than male, had been working as health professionals (9.5% vs 0.9%), in administrative occupations (17.2% vs 8.2%), secretarial and related occupations (4.0% vs 0.5%), caring and personal service occupations (10.6% vs 2.3%), or sales occupations (9.1% vs 2.3%). Male cases, more commonly than female, previously worked in protective service occupations (2.7% vs 0.4%), skilled agricultural and related trades (3.6% vs 0.4%), skilled metal, electrical and electronic trades (7.3% vs 0.0%), skilled construction and building trades (6.4% vs 0.4%), as process, plant and machine operatives (5.5% vs 1.5%), transport and mobile machine drivers and operatives (8.6% vs 0.0%), or in elementary trade and related occupations (3.6% vs 0.7%). See Figure 31, below, and Table 16, Appendix.

Figure 31: Occupation spread among cases, by gender



5.3.1.17 Socio-economic class

Using the broad three-level NS-SEC system, 26.8% of male cases and 36.9% of female had previously worked in managerial class occupations, 29.1% and 24.8% were in intermediate class occupations, and 43.2% and 36.1% were in routine and manual class work, respectively. See Table 47, below.

Table 47: Three-level strata of NS-SEC, among case participants, by gender

Variable	No. of men with HRJL (%)	No. of women with HRJL (%)
Higher managerial class	59 (26.8)	101 (36.9)
Intermediate class	64 (29.1)	68 (24.8)
Routine and manual class	95 (43.2)	99 (36.1)

5.3.1.18 Lifestyle

Among case participants, 43.6% of men and 54.4% of women had never smoked. The proportion of current smokers was similar between men and women (15.9% vs 17.2%), although ex-smoking was more common among men (40.5% vs 28.5%). 5.5% of male cases and 2.2% of female cases had a history of heavy alcohol consumption. See Table 48, below.

Table 48: Distribution of lifestyle factors among case participants, by gender.

Variable	No. of men with HRJL (%)	No. of women with HRJL (%)
Smoking		
Never smokers	96 (43.6)	149 (54.4)
Ex-smokers	89 (40.5)	78 (28.5)
Current smokers	35 (15.9)	47 (17.2)
Heavy drinking		
History of heavy drinking	12 (5.5)	6 (2.2)

5.3.1.19 Musculoskeletal disorders

Among case participants, 25.0% of men and 29.6% of women had CPRD-defined chronic MSDs. Recent musculoskeletal pain occurred in a similar proportion of men and women (30.0% and 31.8%, respectively). See Table 49, below.

Table 49: Frequency of musculoskeletal disorder variables, among case participants, by gender

Variable	No. of men with HRJL (%)	No. of women with HRJL (%)
Chronic MSD	55 (25.0%)	81 (29.6%)
Recent MSD pain	66 (30.0%)	87 (31.8%)

5.3.1.20 Mental Health Problems

Among case participants, primary care-level MHPs (30.3% vs 20.9%) and sleep disorders (9.1% vs 5.5%) occurred more frequently among women than men. However, psychiatric care-level MHPs were similarly uncommon in men (1.8%) and women (1.5%). A history of severe MHPs was present in 8.2% of men and 6.9% of women. See Table 50, below.

Table 50: Frequency of mental health problem variables, among case participants, by gender

Variable	No. of men with HRJL (%)	No. of women with HRJL (%)
Primary care-level MHPs	46 (20.9)	83 (30.3)
Sleep disorders	12 (5.5)	25 (9.1)
Psychiatric care-level MHPs	4 (1.8)	4 (1.5)
Severe MHPS	18 (8.2)	19 (6.9)

5.3.1.21 Cardiovascular disease

Most of the cardiovascular disorders were found in male, rather than female, cases. Specifically, 10.5% of men and 2.6% of women had ischaemic heart disease; 13.2% of men and 5.5% of women had heart failure, 3.2% of men and 0.0% of women had structural heart disease; 31.4% of men and 23.4% of women had hypertension; 2.7% of men and 0.4% of women had cardiac arrythmias, 0.0% of men and 0.4% of women had venous thromboembolic disease; and 4.1% of men and 0.7% of women had thromboembolic disease. See Table 51, below.

Table 51: Frequency of cardiovascular problem variables, among case participants, by gender

Variable	No. of men with HRJL (%)	No. of women with HRJL (%)
Ischaemic heart disease	23 (10.5)	7 (2.6)
Severe ischaemic heart disease	8 (3.6)	4 (1.5)
Heart failure	29 (13.2)	15 (5.5)
Structural heart disease	7 (3.2)	0 (0.0)
Hypertension	69 (31.4)	64 (23.4)
Cardiac arrythmias	6 (2.7)	1 (0.4)
Venous thromboembolic disease	0 (0.0)	1 (0.4)
Peripheral atherosclerosis	9 (4.1)	2 (0.7)

5.3.1.22 Respiratory disorders

Among case participants, a similar proportion of men and women were diagnosed with asthma (8.2% and 10.6%, respectively). Indicators of severe asthma were relatively rare (0.5% and 0.7%, respectively). COPD was slightly more common among men than women (4.6% vs 1.8%). See Table 52, below.

Table 52: Frequency of respiratory disorder variables, among case participants, by gender

Variable	No. of men with HRJL (%)	No. of women with HRJL (%)
Asthma	18 (8.2)	29 (10.6)
Severe asthma	1 (0.5)	2 (0.7)
COPD	10 (4.6)	5 (1.8)

5.3.1.23 Neurological disorders

Among case participants, CVA was found in 4.6% of men and 2.6% of women. Epilepsy was rare, reported in 1.8% of men and 1.1% of women. See Table 53, below.

Table 53: Frequency of neurological disorder variables, among case participants, by gender

Variable	No. of men with HRJL (%)	No. of women with HRJL (%)
CVA	10 (4.6)	7 (2.6)

Epilepsy	4 (1.8)	3 (1.1)

5.3.1.24 Diabetes

Among case participants, a greater proportion of men than women had diabetes (17.7% vs 7.7%). Indicators of poor diabetes control also occurred more commonly among the men (11.8% and 4.0%, respectively). See Table 54, below.

Table 54: Frequency of diabetes variables, among case participants, by gender

Variable	No. of men with HRJL (%)	No. of women with HRJL (%)
Diabetes	39 (17.7)	21 (7.7)
Diabetes with poor control	26 (11.8)	11 (4.0)

5.3.3 Describing cases by age at HRJL

The time that elapsed between when a case experienced HRJL and their eventual entry into the HEAF study varied. Figure 32 shows a density plot of case participants and time, in years, between their job loss and later recruitment into the HEAF study.

Figure 32: Density plot of the time from HRJL to enrolling in HEAF.

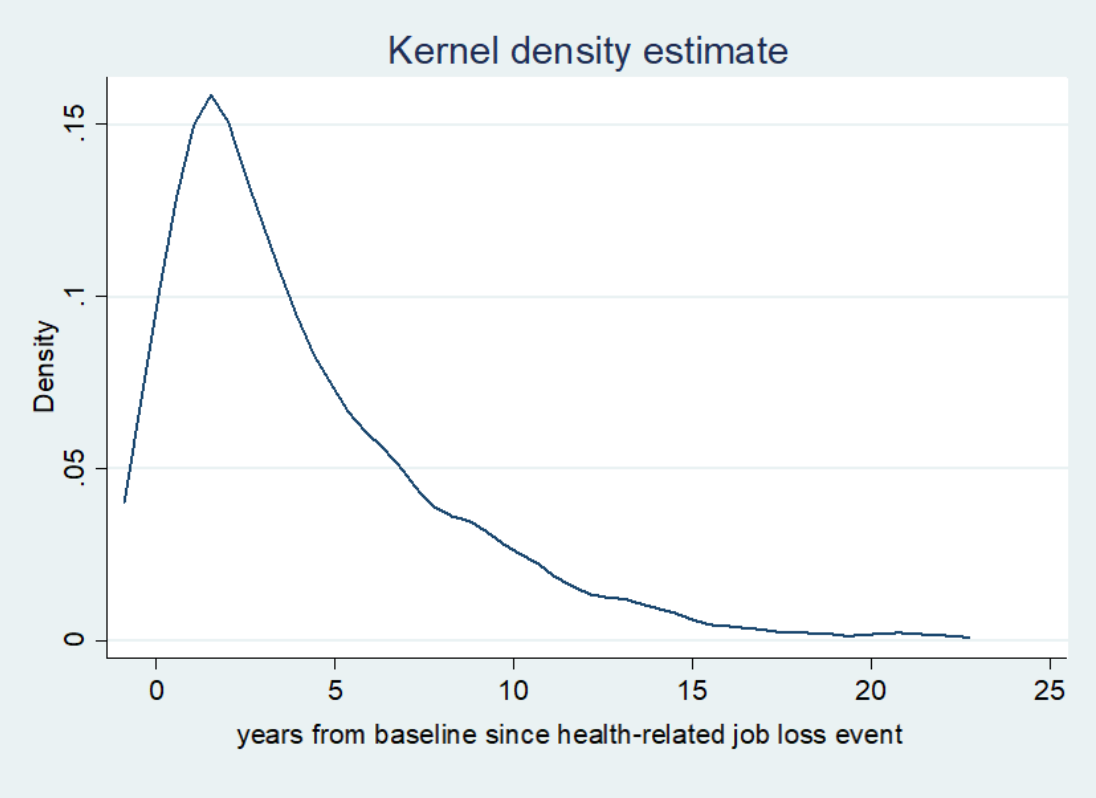
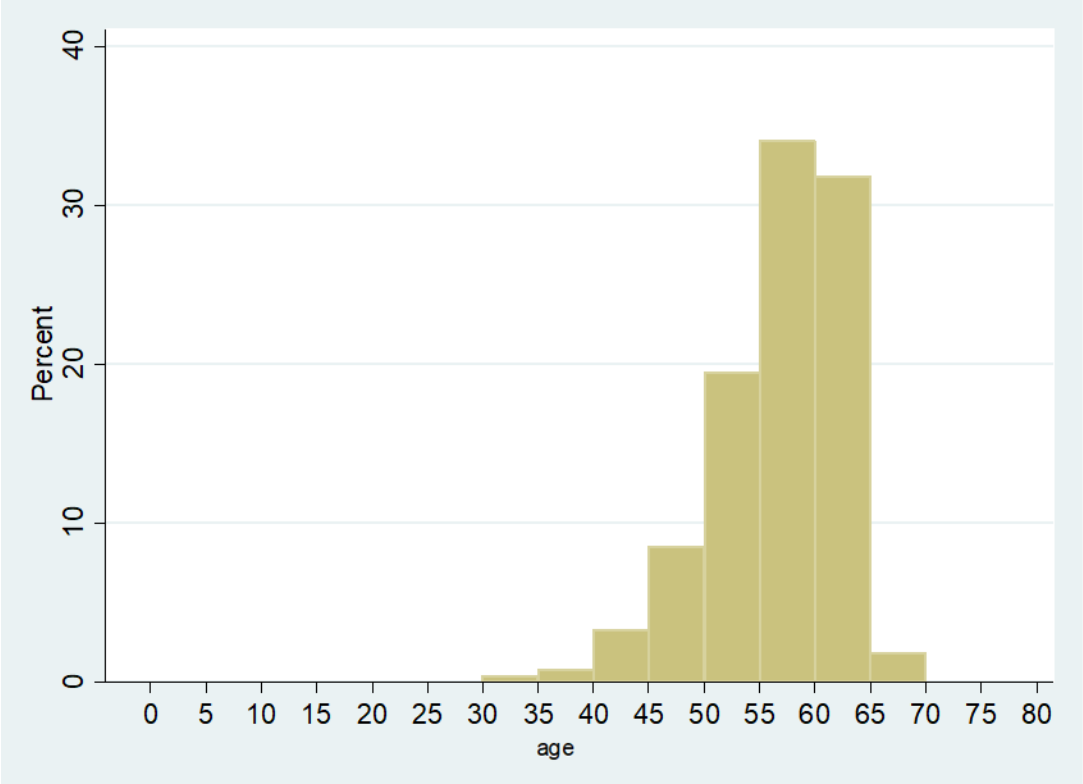


Figure 32 shows a skewed distribution, with median time since HRJL of 2.98 years and mean of 4.18 years. The interquartile range was 1.26 – 5.87 years, showing that most case participants had experienced job loss within the past 6 years.

Age at HRJL varied correspondingly, Figure 33 is a histogram plot displaying the ages of participants at the point of HRJL. Once again there was a skewed distribution, with the median age at HRJL 58.21 years (IQR 53.36 – 60.89 years), and the mean 56.65 years. The youngest participant was 34.46 years old at the time of job loss and the oldest 65.58 years old.

Figure 33: Histogram of participant ages, in years, at the time of HRJL



Case participants were stratified into the following age bands: those who exited work earlier than age 50 (13.0%), those who exited work over the age of 50 but prior to 60 years old (53.4%), and those who were older than 60 (33.6%). See Table 55, below.

Table 55: Distribution of age at HRJL among cases

Age at HRJL	Number of cases (%)
<50 years old	64 (13.0)
50 to <60 years old	264 (53.4)
>60 years old	166 (33.6)

5.3.1.25 Demographic factors

The three age-groups of HRJL were similar for distribution of gender and ethnicity. Compared to the other age-bands, single relationship status was more common among cases that left work between 50 – 60 years of age (13.0%) and being married was less common in this group (64.5%). A higher proportion of participants with university-level education were in the age 50 – 60 age band (25.8%). Vocational-level education was more prevalent among those who left work >60 years of age and having attained no qualifications was most prevalent in the group with HRJL earlier than 50. See Table 56, below.

Table 56: Distribution of demographic factors among case participants, by age at HRJL

Variable	HRJL <50 years old (%)	HRJL 50 to <60 years (%)	HRJL 60+ years old (%)
Male	29 (45.3)	111 (42.1)	80 (48.2)
Female	35 (54.7)	153 (58.0)	86 (51.8)
Ethnicity (non-white)	3 (4.7)	2 (0.8)	4 (2.4)
Ethnicity (white)	61 (95.3)	262 (99.2)	162 (97.6)
University degree	9 (14.1)	68 (25.8)	21 (12.7)
Vocational	20 (31.3)	93 (35.2)	83 (50.0)
High school qualifications	16 (25.0)	47 (17.8)	28 (16.9)
No qualifications	19 (29.7)	56 (21.2)	34 (20.5)
Married/Civil partnership	45 (71.4)	169 (64.5)	116 (69.9)
Single	4 (6.4)	34 (13.0)	10 (6.0)
Divorced	10 (15.9)	46 (17.6)	33 (19.9)
Widowed	4 (6.4)	13 (5.00)	7 (4.2)

5.3.1.26 Occupations

Across SOC-10 major occupational categories, there were few obvious patterns (see Table 57, below). However, a larger proportion of participants who left work prior to age 50 were working sales and customer service jobs (10.9%) and elementary occupations (25.0%) compared to the other two age groups. Cases who worked administrative and secretarial occupations featured more commonly among those who fell out of work at older ages (7.8%, 16.3%, and 17.5%, respectively). Again, few obvious patterns were observed using the SOC-10 sub-major categories. However, administrative occupations were increasingly prevalent at the older age bands (7.8%, 12.9%, and 15.7%, respectively); while sales

occupations (10.9%, 5.7%, and 4.8%, respectively) and elementary administration and service occupations (20.3%, 9.5%, and 9.0%, respectively) were more prevalent among those who fell out of work at earlier ages. See Table 17, Appendix.

Table 57: Strata of SOC-10 major occupational groups among case participants, by age at HRJL

SOC-10 major occupational group	HRJL <50 years old (%)	HRJL 50 to <60 years (%)	HRJL 60+ years old (%)
Managers, directors and senior officials	5 (7.8)	20 (7.6)	8 (4.8)
Professional occupations	10 (15.6)	58 (22.0)	31 (18.7)
Associate professional and technical occupations	3 (4.7)	28 (10.6)	13 (7.8)
Administrative and secretarial occupations	5 (7.8)	43 (16.3)	29 (17.5)
Skilled trades occupations	7 (10.9)	24 (9.1)	22 (13.3)
Caring, leisure, and other service occupations	5 (7.8)	26 (9.9)	16 (9.6)
Sales and customer service occupations	7 (10.9)	18 (6.8)	10 (6.0)
Process, plant and machine operatives	4 (6.3)	15 (5.7)	16 (9.6)
Elementary occupations	16 (25.0)	29 (11.0)	18 (10.8)

5.3.1.27 Socio-economic class

Using the broad three-level NS-SEC system, for those who left work earlier than age 50, 25.8% had previously worked in managerial class occupations, 21.0% in intermediate class occupations, and 53.2% in routine and manual class work. Of those who left work aged 50 - <60 years old, 36.4% previously worked in managerial class occupations, 25.3% in intermediate class, and 37.3% in routine class occupations. Of those who left work later than 60 years old, 30.1% previously worked in managerial class occupations, 32.5% in intermediate class, and 37.4% in routine class occupations. Socio-economic class defined using the three-level NS-SEC system, by age-band at HRJL, can be found in Table 58, below.

Table 58: Strata of NS-SEC, 8-levels and 3-levels, among case participants, by age at HRJL

NS-SEC, three-level	HRJL <50 years old (%)	HRJL 50 to <60 years (%)	HRJL 60+ years old (%)
Higher managerial class	16 (25.8)	95 (36.4)	49 (30.1)
Intermediate class	13 (21.0)	66 (25.3)	53 (32.5)
Routine and manual class	33 (53.2)	100 (37.3)	61 (37.4)

5.3.1.28 Lifestyle

Among case participants, the proportion of ever-smokers was similar across all three age-bands. However, ex-smokers were more common among those who left work at a later age (18.8%, 31.4%, and 43.4%, respectively) and current smokers were more common among those who left work at an earlier age (34.4%, 16.7%, and 9.6%, respectively). The proportion of participants with a known history of heavy alcohol consumption was similar across all age bands. See Table 59, below.

Table 59: Distribution of lifestyle factors among case participants, by age at HRJL

Variable	HRJL <50 years old (%)	HRJL 50 to <60 years (%)	HRJL 60+ years old (%)
Smoking			
Never smokers	30 (46.9)	137 (51.9)	78 (47.0)
Ex-smokers	12 (18.8)	83 (31.4)	72 (43.4)
Current smokers	22 (34.4)	44 (16.7)	16 (9.6)
Heavy drinking			
History of heavy drinking	2 (3.1)	10 (3.8)	6 (3.6)

5.3.1.29 Musculoskeletal disorders

Chronic MSDs were increasingly prevalent among cases who left work at a later age (14.1%, 26.1%, and 34.9%, respectively). In contrast, the proportion of participants with recent musculoskeletal pain became decreasingly prevalent as age-at-HRJL increased (35.9%, 31.1%, and 28.9%, respectively). See Table 60, below.

Table 60: Frequency of musculoskeletal disorder variables, among case participants, by age at HRJL

Variable	HRJL <50 years old (%)	HRJL 50 to <60 years (%)	HRJL 60+ years old (%)
Chronic MSD	9 (14.1)	69 (26.1)	58 (34.9)
Recent MSD pain	23 (35.9)	82 (31.1)	48 (28.9)

5.3.1.30 Mental Health Problems

Among case participants, there was a trend for MHPs to be more prevalent among those who left work at an earlier age, for example, the prevalence of primary care-level MHPs (31.3%, 31.1%, and 16.3, respectively), sleep disorders (9.4%, 6.8% and 7.8%, respectively)

and history of severe MHP (10.9%, 9.1%, 3.6%, respectively), was higher in the younger age-bands. See Table 61, below.

Table 61: Frequency of mental health problem variables, among case participants, by age at HRJL

Variable	HRJL <50 years old (%)	HRJL 50 to <60 years (%)	HRJL 60+ years old (%)
Primary care-level MHPs	20 (31.3)	82 (31.1)	27 (16.3)
Sleep disorders	6 (9.4)	18 (6.8)	13 (7.8)
Psychiatric care-level MHPs	1 (1.6)	6 (2.3)	1 (0.6)
Severe MHP	7 (10.9)	24 (9.1)	6 (3.6)

5.3.1.31 Cardiovascular disease

Cardiovascular disorders tended to occur with greater frequency among case participants who left work at an older age. Specifically, ischaemic heart disease (1.6%, 5.3% and 9.0%, respectively), severe ischaemic heart disease (1.6%, 1.1% and 4.8%, respectively), heart failure (1.6%, 4.9% and 18.1%, respectively), structural heart disease (0.0%, 1.1% and 2.4%, respectively), and hypertension (14.1%, 26.5% and 32.5%, respectively) occurred with greater frequency at older age-bands. No obvious patterns were clear for cardiac arrythmias, venous thromboembolic disease, and peripheral atherosclerosis, for which total prevalence was very low. See Table 62, below.

Table 62: Frequency of cardiovascular problem variables, among case participants, by age at HRJL

Variable	HRJL <50 years old (%)	HRJL 50 to <60 years (%)	HRJL 60+ years old (%)
Ischaemic heart disease	1 (1.6)	14 (5.3)	15 (9.0)
Severe ischaemic heart disease	1 (1.6)	3 (1.1)	8 (4.8)
Heart failure	1 (1.6)	13 (4.9)	30 (18.1)
Structural heart disease	0 (0.0)	3 (1.1)	4 (2.4)
Hypertension	9 (14.1)	70 (26.5)	54 (32.5)
Cardiac arrythmias	0 (0.0)	5 (1.9)	2 (1.2)
Venous thromboembolic disease	0 (0.0)	1 (0.4)	0 (0.0)
Peripheral atherosclerosis	1 (1.6)	7 (2.7)	3 (1.8)

5.3.1.32 Respiratory disorders

Among case participants, asthma occurred with greatest prevalence among those who fell out of work aged 50 to <60 years (11.4%) although there were no clear patterns by age-band. COPD occurred more commonly among case participants who left work at an older age (0.0%, 2.7%, and 4.8%, respectively). See Table 63, below.

Table 63: Frequency of respiratory disorder variables, among case participants, by age at HRJL

Variable	HRJL <50 years old (%)	HRJL 50 to <60 years (%)	HRJL 60+ years old (%)
Asthma	4 (6.3)	30 (11.4)	13 (7.8)
Severe asthma	0 (0.0)	3 (1.1)	0 (0.0)
COPD	0 (0.0)	7 (2.7)	8 (4.8)

5.3.1.33 Neurological disorders

Cerebrovascular accident occurred with increasing prevalence among case participants who left work at older ages (0.0%, 2.7%, and 4.8%, respectively). Epilepsy was rare and no clear patterns emerged by age at HRJL. See Table 64, below.

Table 64: Frequency of neurological disorder variables, among case participants, by age at HRJL

Variable	HRJL <50 years old (%)	HRJL 50 to <60 years (%)	HRJL 60+ years old (%)
CVA	0 (0.0)	10 (3.8)	7 (4.2)
Epilepsy	2 (3.1)	4 (1.5)	1 (0.6)

5.3.1.34 Diabetes

Among case participants, the prevalence of diabetes increased by age at HRJL (7.8%, 11.7%, and 14.5%, respectively). However, the prevalence of poorly controlled diabetes was highest in the 50 to <60 years age-band (9.1%). See Table 65, below.

Table 65: Frequency of diabetes variables, among case participants, by age at HRJL

Variable	HRJL <50 years old (%)	HRJL 50 to <60 years (%)	HRJL 60+ years old (%)
Diabetes	5 (7.8)	31 (11.7)	24 (14.5)

Diabetes with poor control	4 (6.3)	24 (9.1)	9 (5.4)

5.3.4 Describing cases by "type" of HRJL

5.3.1.35 Demographic factors

Among case participants, 220 (46.6%) stated that job loss was mainly due to a health problem, and 274 (53.4%) reported job loss was partly due to a health problem. Compared to "partly" cases, "mainly" cases were more often male (50.9% vs 39.0%) and a younger age when their HRJL occurred (median 55.19 years, IQR 50.50 to 59.73 vs median 59.57 years, IQR 56.03 to 61.32). "Mainly" cases also less frequently had a university-level education (14.4% vs 24.6%) and more frequently left school with no qualifications (26.5% vs 18.2%). "Mainly" cases were less frequently married (64.5% vs 69.6%) and more frequently widowed (21.1% vs 15.6%). Otherwise, these sub-groups were similar for ethnicity. See Table 66, below.

Table 66: Distribution of demographic factors among case participants, by type of HRJL.

Variable	Health main reason (%)	Health part reason (%)
Gender (male)	117 (50.9)	103 (39.0)
Age at HRJL	55.19 (50.50 – 59.73)	59.57 (56.03 – 61.32)
Ethnicity (non-white)	4 (1.7)	5 (1.9)
Ethnicity (white)	226 (98.3)	259 (98.1)
University degree	33 (14.4)	65 (24.6)
Vocational	91 (39.6)	105 (39.8)
High school qualifications	45 (19.6)	46 (17.4)
No qualifications	61 (26.5)	48 (18.2)
Married/Civil partnership	147 (64.5)	183 (69.6)
Single	24 (10.5)	24 (9.1)
Divorced	9 (4.0)	15 (5.7)
Widowed	48 (21.1)	41 (15.6)

5.3.1.36 Occupations

Using the SOC-10 major occupational groups, the largest differences between "mainly" and "partly" cases were for having previously worked in elementary (16.5% vs 9.5%) and skilled trade occupations (13.5% vs 8.3%), which were more frequently worked among "mainly" cases. While administrative/secretarial occupations (11.3% vs 19.3%) and professional

occupations (15.2% vs 24.2%) were less frequently worked among “mainly” cases. See Table 67, below. Using the SOC-10 sub-major groupings, occupations mostly occurred with similar frequency across “mainly” and “partly” cases. However, more “mainly” cases were previously working in skilled construction and building trades (6.1% vs 0.4%) and elementary administration and service occupations (13.9% vs 8.0%); while more “partly” cases were previously working as teaching and educational professionals (14.0% vs 4.8%) or in administrative occupations (16.3% vs 9.6%). See Table 18, Appendix.

Table 67: Strata of SOC-10 major occupational groups among case participants, by type of HRJL.

Variable	Health main reason (%)	Health part reason (%)
Managers, directors and senior officials	16 (7.0)	17 (6.4)
Professional occupations	35 (15.2)	64 (24.2)
Associate professional and technical occupations	18 (7.8)	26 (9.9)
Administrative and secretarial occupations	26 (11.3)	51 (19.3)
Skilled trades occupations	31 (13.5)	22 (8.3)
Caring, leisure, and other service occupations	23 (10.0)	24 (9.1)
Sales and customer service occupations	18 (7.8)	17 (6.4)
Process, plant and machine operatives	20 (8.7)	15 (5.7)
Elementary occupations	38 (16.5)	25 (9.5)

5.3.1.37 Socio-economic class

Using the three-tier NS-SEC, 46.1% of “mainly” cases and 33.3% of “partly” cases were previously working routine and manual jobs, 24.8% and 28.4% of cases were previously working in intermediate class occupations, and 27.0% and 37.1% were working in higher managerial or professional class occupations, respectively. See Table 68, below.

Table 68: Three-level strata of NS-SEC, among case participants, by type of HRJL.

Variable	Health main reason (%)	Health part reason (%)
Higher managerial class	62 (27.0)	98 (37.1)
Intermediate class	57 (24.8)	75 (28.4)
Routine and manual class	106 (46.1)	88 (33.3)

5.3.1.38 Lifestyle

Compared to "partly" cases, "mainly" cases were more frequently current smokers (22.2% vs 11.7%) and ex-smokers (36.5% vs 31.4%) at the time of HRJL. However, history of heavy drinking was similar between the two groups. See Table 69, below.

Table 69: Distribution of lifestyle factors among case participants, by type of HRJL

Variable	Health main reason (%)	Health part reason (%)
Smoking		
Never smokers	95 (41.3)	150 (56.8)
Ex-smokers	84 (36.5)	83 (31.4)
Current smokers	51 (22.2)	31 (11.7)
Drinking		
No history of heavy drinking	221 (96.1)	255 (96.6)
History of heavy drinking	9 (3.9)	9 (3.4)

5.3.1.39 Musculoskeletal disorders

Chronic MSDs occurred with a similar frequency among "mainly" and "partly" cases. A slightly higher proportion of "mainly" cases were diagnosed with recent musculoskeletal pain (34.4% vs 28.0). See Table 70, below.

Table 70: Frequency of musculoskeletal disorder variables, among case participants, by type of HRJL

Variable	Health main reason (%)	Health part reason (%)
Chronic MSD	62 (27.0)	74 (28.0)
Recent MSD pain	79 (34.4)	74 (28.0)

5.3.1.40 Mental Health Problems

Psychiatric-care-level MHPs were similarly uncommon in "mainly" and "partly" case participants. However, recent primary-care-level MHPs occurred more frequently in "mainly" cases (30.0% vs 22.7%). Similarly, sleep disorders (8.3% vs 6.8%) and history of severe MHP (8.7% vs 6.4%) was slightly more common among "mainly" cases. See Table 71, below.

Table 71: Frequency of mental health problem variables, among case participants, by type of HRJL

Variable	Health main reason (%)	Health part reason (%)
Primary-care-level MHPs	69 (30.0)	60 (22.7)
Sleep disorders	19 (8.3)	18 (6.8)
Psychiatric-care-level MHPs	3 (1.3)	5 (1.9)
Severe MHPS	20 (8.7)	17 (6.4)

5.3.1.41 Cardiovascular disease

Cardiovascular disorders occurred with a similar prevalence in "mainly" and "partly" cases, except for hypertension which occurred more frequently in "partly" cases (30.3% vs 23.0%), and arrythmias which mostly occurred among "mainly" cases (2.6% vs 0.4%). See Table 72, below.

Table 72: Frequency of cardiovascular disorder variables, among case participants, by type of HRJL

Variable	Health main reason (%)	Health part reason (%)
Ischaemic heart disease	14 (6.1)	16 (6.1)
Severe ischaemic heart disease	5 (3.9)	7 (2.7)
Heart failure	22 (9.6)	22 (8.3)
Structural heart disease	4 (1.7)	3 (1.1)
Hypertension	53 (23.0)	80 (30.3)
Cardiac arrythmias	6 (2.6)	1 (0.4)
Venous thromboembolic disease	1 (0.4)	0 (0.0)
Peripheral atherosclerosis	4 (1.7)	7 (2.7)

5.3.1.42 Respiratory disorders

A similar proportion of "mainly" and "partly" cases were diagnosed with asthma (9.6% and 9.5%, respectively) and indicators of severe asthma (0.9% and 0.4%, respectively). COPD occurred slightly more commonly among "mainly" cases (4.4% vs 1.9%). See Table 73, below.

Table 73: Frequency of respiratory disorder variables, among case participants, by type of HRJL

Variable	Health main reason (%)	Health part reason (%)
Asthma	22 (9.6)	25 (9.5)
Severe asthma	2 (0.9)	1 (0.4)
COPD	10 (4.4)	5 (1.9)

5.3.1.43 Neurological disorders

Cerebrovascular accident was reported more commonly among "mainly" cases (5.2% vs 1.9%). Epilepsy was similarly uncommon among "mainly" and "partly" cases. See Table 74, below.

Table 74: Frequency of neurological disorder variables, among case participants, by type of HRJL

Variable	Health main reason (%)	Health part reason (%)
CVA	12 (5.2)	5 (1.9)
Epilepsy	4 (1.7)	3 (1.1)

5.3.1.44 Diabetes

Diabetes occurred with a similar prevalence between "mainly" and "partly" cases, although the proportion of participants with indicators of poor diabetic control was slightly higher among "mainly" cases (9.1% vs 6.1%). See Table 75, below.

Table 75: Frequency of diabetes variables, among case participants, by type of HRJL

Variable	Health main reason (%)	Health part reason (%)
Diabetes	26 (11.3)	34 (12.9)
Diabetes with poor control	21 (9.1)	16 (6.1)

5.4 Discussion

This chapter has described a contemporary cohort of older-workers with HRJL (cases) for their demographic, occupational, lifestyle, and health-related factors. Results were stratified by gender, age at time of HRJL, and whether a health problem was reported to be

mainly or partly the cause of the job loss. Important differences between these strata were considered in order to decide whether sub-group analysis might be appropriate in future chapters (see discussions below). However, no statistical analysis of the differences between these strata was performed as the current cohort was highly selected to answer only the research questions outlined in the objectives (Chapter 2). Therefore, statistical analysis would not have been meaningful.

Case participants were most frequently white, married, and qualified at a vocational level (more advanced than high-school but lower than university level). Prior to job loss, cases had commonly worked as teachers, in administration, and in elementary service occupations, which together comprised approximately one third of the jobs lost. Regarding socioeconomic class, there was a relatively equal split between higher managerial, intermediate, and routine/manual class participants with most cases last working routine-level jobs (39.9%). However, it should be noted that this classification was based on job title alone and did not consider size of company or whether the participant was self-employed. For lifestyle factors, a slim majority of case participants were ever smokers, with 16.6% current smokers, 33.8% ex-smokers, and just less than half never smokers (49.6%).

Next, cases were considered for their CPRD-defined health disorders. The most prevalent conditions included musculoskeletal disorders, primary-care level mental health problems, hypertension, ischaemic heart disease, heart failure, asthma, and diabetes. Chronic musculoskeletal disorders were mostly comprised of participants with osteoarthritis, while participants with recent musculoskeletal pain most commonly had low back pain and knee pain. Recent primary care-level mental health problems were the most common mental health problem group and were mostly comprised of people with mood disorders, depressive disorders, or anxiety. The most common cardio-metabolic problems among cases were hypertension, ischaemic heart disease, heart failure, and diabetes. A participant's self-reported cause of job loss did not always correspond to their CPRD-defined health disorder, for example, 66.7% of those with COPD ascribed their job loss to a health problem of the heart or lungs, while only 28.6% of those with epilepsy indicated that "another type of health condition" had contributed to their job loss. The perceived severity of the underlying health disorder could account for this difference, as well as a participant's own recall bias (since job loss had occurred some time ago, in many cases). Additionally, some confusion about the questionnaire categories may be apparent, for example, is hypertension a condition of the "heart and lungs"? Finally, respondents may be thinking

about the totality of factors contributing to their decision to leave work, for example, their finances, job quality and support, not only the symptomatic impact of the health condition.

Considerably more male than female cases were single and previously worked manual careers such as protective services, agricultural work, metal, electrical and electronic trades, construction and building trades, process, plant and machine operating, and driving and machine operating. Meanwhile, female cases were more likely to have been working as health professionals, in administrative and secretarial occupations, in caring services, and in sales occupations. If this difference reflects a true difference in the work context of men and women, this could be important as some health conditions may be more incompatible with certain types of work. For example, musculoskeletal disorders are known to be caused by, and predictors of, work disability in occupations requiring heavy physical lifting.(392–394) More male than female cases were ever smokers, mostly due to the greater proportion of ex-smokers. Male cases were also more frequently diagnosed with cardio-metabolic disorders such as hypertension, heart failure, ischaemic heart disease, and diabetes. Also, the greater prevalence of ever-smokers among men may have been responsible for the higher prevalence of COPD. Conversely, women with HRJL more frequently experienced recent primary-care level mental health problems, the majority of which were mood or anxiety disorders. These differences likely reflect the underlying distributions of such disorders in the general population, in which, the greater prevalence of cardio-metabolic disorders among men(395) and mental health disorders among women is already known.(235) In this sample, the observed differences between male and female cases, both for their common work environments and health exposures, provides evidence to support the use of sub-group evaluation by gender in future chapters.

Most case participants lost their jobs in the 50 – 60 year-old age band (53.4%). Vocational or professional level qualifications were most prevalent among those over 60 at HRJL, university-level education was most prevalent among those aged 50 – 60 at HRJL, and participants with no qualifications or high school level education were most prevalent among those with HRJL earlier than age 50. Correspondingly, intermediate socioeconomic class was most common among cases who left work in the oldest age band, professional and managerial class was most common in the 50 – 60 age band, and routine and manual class was most common among those with HRJL earlier than age 50. All these participants were experiencing poor health, however, those with more advanced education may be better equipped to survive later in the workforce, even with poor health (e.g. because of the greater availability of non-manual work options). For those who earn enough, there

may also be the financial option to leave work at an earlier age with less necessity to "struggle on"- which could explain the U-shaped distribution of university level qualifications across the age bands. Finally, for people working routine and manual occupations, with poor health, few qualifications, and often more physical work, the options may be fewer and exit from work may occur earlier, on average.

The prevalence of certain health problems also varied depending on age of HRJL. Among cases, chronic musculoskeletal problems became significantly more common as age of HRJL increased; this is likely to represent the growing prevalence of osteoarthritis at older ages.(396) Similarly, age-related cardio-metabolic diseases (such as heart failure, hypertension, atherosclerotic disease, and diabetes) were also more prevalent among those who lost work at an older age.(397) Interestingly, the prevalence of primary-care-level MHDs appeared to be considerably lower among those aged over 60 with HRJL. This has been outlined in the literature already, with most mental health problems dipping in prevalence as they approach age 65.(398) Older patients may be more reluctant to present with a mental health problem at an older age, or additionally mental health problems may be missed more frequently in the older patient due to the coexistence of other health problems. Alternatively, mental health problems may simply be more strongly linked to premature exit from work at earlier ages.(398) The differences between these populations once again supports the use of sub-group analysis by age of HRJL, going forwards.

Cases who answered that job loss was mainly due to a health problem were different from cases who answered that job loss was partly due to a health problem e.g. they were more often male. A participant's perception that their health problem was the main cause of job loss also appeared to be related to the severity of their underlying health disorder(s). "Mainly" cases had a greater prevalence of more disabling conditions, such as CVA, COPD, and diabetes with indicators of poor control. "Mainly" cases were also younger on average when their job loss occurred. Finally, there was a slightly higher prevalence of recent musculoskeletal pain, primary-care level mental health problems, and current smoking, among "mainly" cases. These indicators of worse overall health also coincided with indicators of lower socioeconomic class. For example, "mainly" cases were less often university educated, and more often left school with no qualifications, compared to "partly" cases. Correspondingly, fewer "mainly" cases were working in professional and managerial jobs, while more were working routine and manual jobs. This accords with the socioeconomic gradient in health described in the literature, whereby being of a lower socioeconomic class is associated with a greater disease burden.(399) While these groups

will still be analysed together going forwards, sensitivity analysis will also be used to unpick any important differences between “mainly” and “partly” cases for the impact of health upon work.

This chapter has some limitations. Strong inferences about the cause of HRJL can’t be made since cases have been described without reference to a control group. In addition, while the HEAF study population was found to be broadly representative of the general UK population, this study sample did not include all HEAF participants who had left work because of a health problem (there were 907 such participants in total). Excluded participants either did not have sufficient coverage for their CPRD data (extending back to at least a year prior to their job loss) or had refused consent for its linkage in the first place. Furthermore, all participants who agreed to take part in the HEAF study were well enough to fill in a lengthy questionnaire: this survivor bias means that people with particularly poor health, or those who had died, would not have been represented in the study. Some data was also potentially subject to recall bias, including the reported date of job loss, whether the loss was mainly or partly due to a health problem, and the health factors that a participant felt had contributed to their leaving work.

While the entirety of participant’s CPRD health records were not requested, it was a strength of this study that the selected health problems for which information was available were those recognised as being responsible for two-thirds of sickness absence and long-term incapacity in the UK: mental health problems, musculoskeletal disorders, and cardio-respiratory conditions.(48) The use of objective data here was also a strength, with CPRD records representing a validated source of health information that did not rely on the memory of study participants. The size of the study sample from which these cases were drawn, provided the opportunity to select working controls from the same study population who could be matched on multiple important confounding factors. An examination of the association between CPRD-defined health disorders and HRJL, including important subgroup analysis, is detailed in the next chapter.

5.5 Summary

- Case participants commonly lost work as teachers, in administration, and in elementary service occupations. Overall, cases had most frequently worked routine-level jobs.

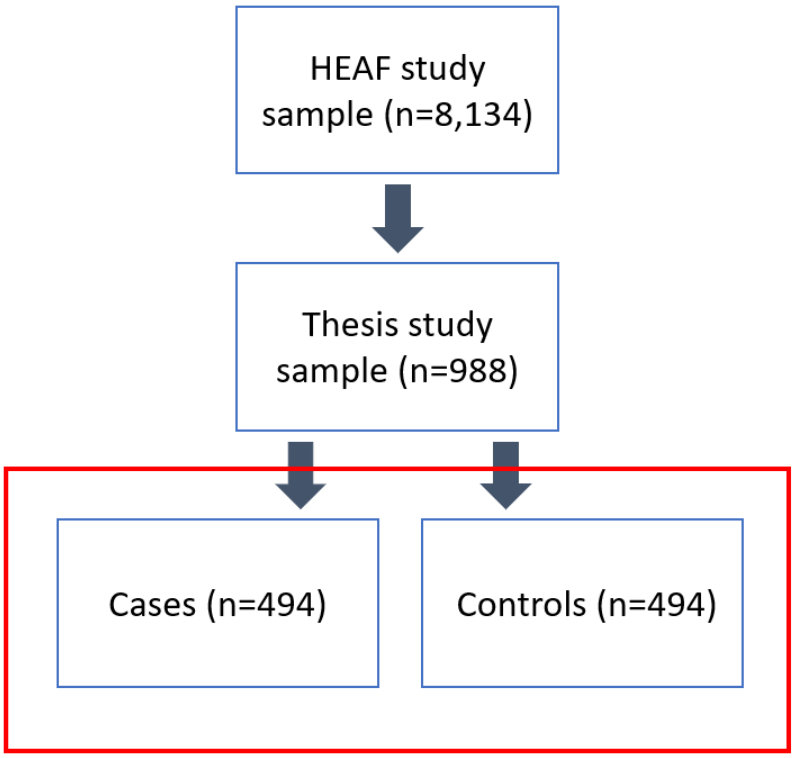
- Musculoskeletal disorders, mental health problems, and cardio-metabolic disorders were common among cases.
- Male cases more commonly fell out of work in routine and manual-type jobs, and were more commonly diagnosed with cardiovascular diseases, COPD, and diabetes, while female cases were more commonly diagnosed with primary-care level mental health disorders.
- Cases who experienced HRJL at an earlier age were broadly less well educated and were of lower socioeconomic class. However, cases with university level education commonly exited work aged 50 – 60 years old.
- Cases who experienced HRJL at an earlier age were less likely to have chronic musculoskeletal disorders and cardiovascular disorders, but more likely to have mental health problems.
- Cases who stated that a health problem was the main cause of their job loss, compared to part of the cause, were more commonly male, less well educated, and more likely to be working in routine and manual occupations. Disabling conditions such as CVA, COPD, and poorly controlled diabetes were more common in this group.

Chapter 6- the associations between CPRD-defined health disorders and health-related job loss

6.1 Introduction

In order to address the third research objective of this thesis (see Chapter 2), this chapter explores the association of demographic factors, lifestyle factors, and CPRD-defined health disorders with health-related job loss (HRJL). In the last chapter, participants with HRJL, the "cases", were described and important subgroups were established. In this chapter, a nested-case control analysis is performed: cases are compared to matched control participants (see Figure 34) who were similar for key confounding factors and were working at the time of the case participant's job loss. Given the important differences described between: male and female cases; cases who left work at different ages; and cases who described a health problem as being "mainly" or "partly" the cause of their job loss (see Chapter 5); stratified analysis is performed according to these subgroups.

Figure 34: the cohort studied in this chapter, as indicated by the red square



6.2 Methods

As outlined previously, cases were participants of the HEAF study who were unemployed at baseline and reported that a health problem was "part of the reason" or "the main reason" reason for their dropping out of work. Cases were included in the current study if they had CPRD coverage for a minimum of a year prior to their job loss. Control participants were participants of HEAF who did not report HRJL at baseline. Controls were working at the time their matched case participant experienced HRJL. All control participants were within 1 year of age of their matched cases, were of the same sex, and from the same GP practice. Control participants were included if they had CPRD coverage for a minimum of a year prior to the date of health-related job loss of their matched case.

Cases and controls were compared using simple descriptive statistics. Conditional logistic regression was used to assess the association between the occurrence of HRJL and individual demographic, lifestyle, and CPRD-defined health disorder exposures. Available CPRD information included date-stamped Read codes for the following disorders: musculoskeletal disorders, mental health problems, cardiovascular disorders, asthma, COPD, CVA, epilepsy, and diabetes. Using these data, CPRD-derived health disorder variables were defined according to the classification criteria, outlined in Chapter 3.

Conditional logistic regression takes case and control matched pairs into account, meaning all associations found were independent of age, gender, and GP practice, since cases and controls were matched on these factors. Other factors may confound the observed relationship between HRJL and health exposures of interest, such as: ethnicity; education; socioeconomic class; factors representing familial support, such as marital status; and lifestyle-related variables such as heavy alcohol intake and smoking. The number of available control participants was not sufficient to match for all these factors; therefore, where appropriate, important confounding factors were adjusted for statistically in multivariable conditional logistic regression models.

Demographic and lifestyle variables were considered in turn to elicit their possible roles as confounders. As discussed earlier in this thesis (Section 3.6.5), to adjust for confounders appropriately in multivariable analysis (i.e. to avoid unnecessary adjustment or over-adjustment) there needed to be strong reason to believe a factor was associated both with the health exposure of interest and outcome of interest, without being an intermediate variable on the causal pathway between the exposure of interest and the outcome of interest.(319) Some factors measured in this study, such as lower education

attainment,(400) single relationship status,(401) and lifestyle factors such as smoking(402,403) and heavy alcohol intake(404) are already known to be associated with greater morbidity in the literature. In this chapter, the relationship between HRJL and these demographic and lifestyle variables was also assessed using matched logistic regression analysis. Factors that were significantly associated with HRJL were considered confounders and were included in adjusted multivariable models, going forwards.

CPRD-defined health exposures were initially assessed for their relationship to HRJL in univariable analysis, then with statistical adjustment for confounding lifestyle and demographic variables in multivariable conditional logistic regression models. Statistical analysis was performed using Stata-13.

Analysis was then stratified for important sub-groups, which included gender (stratified for men and women), age (stratified for <50 years of age, between 50 – <60 years of age, and greater than age 60), and type of HRJL (stratified by whether a health problem was reported “mainly” or “partly” the cause of job loss). Stratifications were considered for how they modulated the association between HRJL and CPRD-defined health exposures.

Throughout this chapter, qualitative descriptors were used to distinguish strength of association using Cohen’s classification scheme and Rosenthal’s later extension for odds ratios(405) which is as follows: about 1.5 to 1 is a small effect, about 2.5 to 1 is a moderate effect, about 4 to 1 is a strong effect, and about 10 to 1 is a very strong effect. Although these are arbitrary parameters, they help to facilitate consistent data interpretation and communication.

Where effect estimates suggested an important relationship, but analysis was underpowered to show a statistically significant result, it was important not to interpret this as evidence of no association. Therefore, post-hoc power calculations were also performed to aid interpretation. To calculate statistical power, a method for matched case-control studies using 1:1 matching was applied (Schlesselman 1982).(327,328) Statistical power was affected by: the number of case participants available (maximum 498 for this thesis, with fewer available for subgroup analyses); the number of controls per case (1:1 for all analyses); the alpha significance level (set by convention at 5%); and the prevalence of the exposure of interest among control participants. I considered the minimum (most subtle) strength of association that could be detected at a statistical power of 80% and an alpha significance level of 5%, for common, moderately prevalent, and rare exposures of interest.

6.3 Results

6.3.1 Statistical power calculations

Across the total sample (n=988), in most cases, sample size and prevalence of exposures meant that analyses were well powered. For example, for health exposures that were common, it was possible to detect a weak strength of association with HRJL at a sufficient statistical power e.g. for musculoskeletal pain disorders (prevalence 29.4% in this sample) it was possible to detect a minimum odds ratio of 1.55 at 80% power and 5% alpha significance level. For moderately common health exposures it was also possible to detect a weak strength association with HRJL at sufficient statistical power. For example, for diabetes (prevalence 9.2% in this sample) it was possible to detect a minimum odds ratio of 1.90 at 80% power. However, for rarer conditions, it must be noted that was only possible to detect a strong association with HRJL at sufficient statistical power. For example, for COPD (prevalence 2.0% in this sample) odds ratios of 3.6 and upwards were detectable at 80% power. Some analyses became particularly underpowered after stratification for gender, age, and "type" of HRJL. Using the male only subgroup as an example (n=440), for common health exposures, it was still possible to detect a weak strength association with HRJL e.g. for musculoskeletal pain (prevalence 24.6% among men) it was possible to detect a minimum odds ratio of 1.87 at 80% power. For moderately common health exposures it was only possible to detect a moderate strength association HRJL at sufficient statistical power. For example, for diabetes (prevalence 13.4% among men) it was possible to detect a minimum odds ratio of 2.20 at 80% power. However, for rarer conditions such as COPD (prevalence 2.7% among men), at sufficient statistical power, it was only possible to detect very strong associations at odds ratios of 5.87 and upwards.

6.3.2 Assessment of confounding factors, with stratification by gender

In the following section, lifestyle, demographic, and occupational class variables are assessed for their relationship to HRJL and considered for their possible role as confounding factors. Results are also stratified by gender.

6.3.2.1 Demographic factors

Ethnicity

The difference between cases and controls for ethnicity was minor since both groups were vast-majority white (98.2% vs. 98.0%, respectively), this reflected the characteristics of the whole HEAF study population; of which participants were also mostly white Caucasian. In conditional logistic regression, no significant association was found between white ethnicity and the likelihood of being out of work for health reasons, see Table 76. Point estimates were in the direction of white ethnicity being predictive of HRJL, however, confidence intervals were wide (OR 1.11 95%CI 0.45 to 2.73). Similarly, confidence intervals were too wide to draw reasonable conclusions after considering men and women separately. Given its apparent weak association with the main outcome of interest, ethnicity was not adjusted for as a confounder in multivariable analysis, going forwards.

Table 76: Association between ethnicity and health-related job loss, across total study population and by gender

Variable	Prevalence among controls, n (%)	Prevalence among cases, n (%)	Association with HRJL, unadjusted. OR (95% CI)
Total study sample			
Ethnicity (non-white)	10 (2.0)	9 (1.8)	1.00
Ethnicity (white)	484 (98.0)	485 (98.2)	1.11 (0.45 to 2.73)
Men			
Ethnicity (non-white)	3 (1.4)	4 (1.8)	1.00
Ethnicity (white)	217 (98.6)	216 (98.2)	0.75 (0.17 to 3.35)
Women			
Ethnicity (non-white)	7 (2.6)	5 (1.8)	1.00
Ethnicity (white)	267 (97.5)	269 (98.2)	1.40 (0.44 to 4.41)

Educational attainment

There were a slightly higher proportion of cases with no qualifications (22.1% vs 17.2%) and a slightly lower proportion of cases with university degrees (19.8% vs 25.3%) compared to controls. Proportions were otherwise similar for school level and vocational or professional level degrees between groups. Using university-level qualifications as the reference group, high school-level qualifications, and vocational or higher-professional qualifications trended towards association with HRJL, although this did not reach statistical significance (OR 1.23 95%CI 0.84 to 1.81; and OR 1.30 95%CI 0.94 to 1.79, respectively). Having no qualifications

was significantly associated with HRJL compared to university-level qualifications (OR 1.66 95%CI 1.12 to 2.48), see Table 77. Overall, a lower level of educational attainment had a statistically significant association with HRJL (OR 1.15 95%CI 1.02 to 1.30). Therefore, this variable was adjusted for in multivariable analysis, going forwards.

Lower level of educational attainment was similarly predictive of HRJL amongst men and women, however, was only statistically significant among men (OR 1.21 95%CI 1.00 to 1.46; and OR 1.11 95%CI 0.94 to 1.30, respectively). Similarly, having no qualifications was significantly associated with HRJL among men but not women, compared to having university-level qualifications (OR 2.01 95%CI 1.08 to 3.74; and OR 1.45 95%CI 0.86 to 2.44, respectively).

Table 77: Association between level of education and health-related job loss, across total study population and by gender

Variable	Prevalence among controls, n (%)	Prevalence among cases, n (%)	Association with HRJL, unadjusted. OR (95% CI)
Total study sample			
University degree	125 (25.3)	98 (19.8)	1.00
Vocational/professional	191 (38.7)	196 (39.7)	1.30 (0.94 to 1.79)
High school qualifications	93 (18.8)	91 (18.4)	1.23 (0.84 to 1.81)
No qualifications	85 (17.2)	109 (22.1)	**1.66 (1.12 to 2.48)**
Men			
University degree	59 (26.8)	45 (20.5)	1.00
Vocational/professional	96 (43.6)	96 (43.6)	1.35 (0.84 to 2.17)
High school qualifications	32 (14.6)	31 (14.1)	1.26 (0.68 to 2.33)
No qualifications	33 (15.0)	48 (21.8)	**2.01 (1.08 to 3.74)**
Women			
University degree	66 (24.1)	53 (19.3)	1.00
Vocational/professional	95 (34.7)	100 (36.5)	1.28 (0.82 to 1.99)
High school qualifications	61 (22.3)	60 (21.9)	1.20 (0.73 to 1.98)
No qualifications	52 (19.0)	61 (22.3)	1.45 (0.86 to 2.44)

Marital status

Relatively few participants reported themselves as single among cases or controls (n= 76). However, single relationship status was significantly associated with HRJL (OR 1.82 95%CI 1.11-3.01), compared to being married or in a civil partnership, see Table 78. In contrast, being widowed or divorced was not associated with HRJL (being widowed may even be protective) (OR 0.77 95%CI 0.43 to 1.35; and OR 1.07 95%CI 0.76 to 1.50, respectively).

After adjusting for educational attainment, singleness remained associated with HRJL (aOR 1.79 95%CI 1.08 to 2.96). Therefore, single status appeared to be independently associated with HRJL and was adjusted for in multivariable analysis, going forwards.

In both men and women, single relationship status was positively associated with HRJL, although this was not statistically significant among women (OR 2.01 95%CI 1.05 to 3.83; and OR 1.76 95%CI 0.78 to 3.97, respectively). Being divorced or widowed was associated with HRJL among men (OR: 1.55 95%CI 0.89 to 2.71; and OR 2.36 95%CI 0.70 to 7.97, respectively), but had a protective effect among women (OR: 0.84 95%CI 0.54 to 1.29; and OR 0.51 95%CI 0.26 to 1.01, respectively), compared to being married or in a civil partnership. However, these effects were not statistically significant.

Table 78: Association between marital status and health-related job loss, across total study population and by gender

Variable	Prevalence among controls, n (%)[1]	Prevalence among cases, n (%)[2]	Association with HRJL, unadjusted. OR (95% CI)	Association with HRJL, adjusted for education level. aOR (95%CI)[3]
Total study sample				
Married/Civil partnership	334 (70.5)	330 (67.2)	1.00	1.00
Single	28 (5.7)	48 (9.8)	**1.82 (1.11 to 3.01)**	**1.79 (1.08 to 2.96)**
Divorced	86 (17.6)	89 (18.1)	1.07 (0.76 to 1.50)	1.07 (0.76 to 1.50)
Widowed	30 (6.2)	24 (4.9)	0.77 (0.43 to 1.35)	0.76 (0.43 to 1.34)
Men				
Married/Civil partnership	171 (77.7)	145 (66.2)	1.00	1.00
Single	17 (7.7)	29 (13.2)	**2.01 (1.05 to 3.83)**	1.83 (0.95 to 3.52)
Divorced	28 (12.7)	37 (16.9)	1.55 (0.89 to 2.71)	1.62 (0.92 to 2.84)
Widowed	4 (1.8)	8 (3.7)	2.36 (0.70 to 7.97)	2.31 (0.68 to 7.84)
Women				
Married/Civil partnership	173 (64.6)	185 (68.0)	1.00	1.00
Single	11 (4.1)	19 (7.0)	1.76 (0.78 to 3.97)	1.89 (0.83 to 4.30)
Divorced	58 (21.6)	52 (19.1)	0.84 (0.54 to 1.29)	0.82 (0.53 to 1.27)
Widowed	26 (9.7)	16 (5.9)	0.51 (0.26 to 1.01)	0.51 (0.26 to 1.01)

1. Data on relationship status was missing for three case participants
2. Data on relationship status was missing for six control participants
3. Missing data on relationship status meant that data from nine pairs (18 participants) were not included in adjusted analysis. Adjusted analysis included data from 970 participants.

6.3.2.2 *Lifestyle prior to HRJL*

History of heavy alcohol intake

CPRD-defined history of heavy alcohol intake was classified using Read codes referring to heavy alcohol intake that occurred any time prior to the point of analysis (for example, "chronic alcoholism" or "ex-heavy drinker", see Table 6, Appendix). This was more prevalent amongst cases than controls (3.6% vs 1.2%) and had a strong association with HRJL (OR 3.00 95%CI 1.19 to 7.56), see Table 79. In multivariable analysis, after adjusting for educational attainment and single relationship status, history of heavy drinking remained associated with HRJL (aOR 2.84 95%CI 1.11 to 7.23). Only a small number of study participants had CPRD-defined history of heavy alcohol consumption (n=24) but it was clearly associated with HRJL, and therefore was adjusted for in multivariable analysis, going forwards.

More men than women had a history of heavy alcohol intake (3.6% vs 1.5%), which was similarly associated with HRJL in men and women. However, analysis was underpowered to show statistical significance.

Table 79: Association between heavy alcohol intake and health-related job loss, across total study population and by gender

Variable	Prevalence among controls, n (%)	Prevalence among cases, n (%)	Association with HRJL, unadjusted. OR (95% CI)	Association with HRJL, adjusted for education and single status. aOR (95% CI)
Total study sample				
No heavy drinking	488 (98.8)	476 (96.4)	1.00	1.00
Heavy alcohol intake	6 (1.2)	18 (3.6)	**3.00 (1.19 to 7.56)**	**2.84 (1.11 to 7.23)**
Men				
No heavy drinking	216 (98.2)	208 (94.6)	1.00	1.00
Heavy alcohol intake	4 (1.8)	12 (5.5)	3.00 (0.97 to 9.30)	3.01 (0.95 to 9.51)
Women				
No heavy drinking	272 (99.3)	268 (97.8)	1.00	1.00
Heavy alcohol intake	2 (0.7)	6 (2.2)	3.00 (0.61 to 14.86)	2.61 (0.52 to 13.22)

Smoking

Ex-smokers were more prevalent among cases than controls (33.8% vs 29.6%) although the proportion of current smokers was similar (16.6% vs 17.4%). In matched analysis, ex-smoking and current smoking were not associated with HRJL (OR 1.24 95%CI 0.92 to 1.66;

and OR 1.03 95%CI 0.72 to 1.47, respectively), see Table 80. Smoking status remained unassociated after adjusting for low educational attainment, single status, and history of heavy alcohol consumption (aOR 1.02 95%CI 0.82 to 1.22). Given its apparent weak association with the main outcome of interest, smoking was not adjusted for as a confounder in multivariable analysis, going forwards.

Table 80: Association between smoking and health-related job loss, across total study population and by gender

Variable	Prevalence among controls, n (%)	Prevalence among cases, n (%)	Association with HRJL, unadjusted. OR (95% CI)	Association with HRJL, adjusted for education level, single status, history of heavy alcohol use. OR (95% CI)
Total study sample				
Non-smoker	262 (53.0)	245 (49.6)	1.00	1.00
Ex-smoker	146 (29.6)	167 (33.8)	1.24 (0.92 to 1.66)	1.23 (0.91 to 1.65)
Current smoker	86 (17.4)	82 (16.6)	1.03 (0.72 to 1.47)	0.96 (0.67 to 1.39)
Men				
Non-smoker	106 (48.2)	96 (43.6)	1.00	1.00
Ex-smoker	70 (31.8)	89 (40.5)	1.41 (0.93 to 2.16)	1.42 (0.92 to 2.19)
Current smoker	44 (20.0)	35 (15.9)	0.89 (0.53 to 1.48)	0.84 (0.50 to 1.42)
Women				
Non-smoker	156 (56.9)	149 (54.4)	1.00	1.00
Ex-smoker	76 (27.7)	78 (28.5)	1.09 (0.72 to 1.64)	1.06 (0.70 to 1.62)
Current smoker	42 (15.3)	47 (17.2)	1.21 (0.72 to 2.02)	1.09 (0.64 to 1.86)

6.3.2.3 Socioeconomic status

Participant's occupations were grouped using the Standard Occupational Classification (SOC-10) based on reported job title and industry alone. These occupational groups were then arranged by socioeconomic status using the National Statistics Socioeconomic Classification, NS-SEC. Refer to Chapter 3, Section 3.4.6 for a full discussion of these classification systems.

Case participants were mostly similar to controls for SOC-10 major occupational categories (see Tables 19 and 20, Appendix). However, more cases were working in elementary occupations (12.8% vs 8.5%) and as teaching or educational professionals (9.7% vs 6.5%), see Figure 35, below. Using SOC-10 occupational categories, participants were organised

into the three-tier NS-SEC categories: higher managerial class, intermediate class, and routine and manual class.(205)

More case participants were in the routine and manual class (39.9% vs 33.5%) and more controls were in the higher managerial class (38.6% vs 32.9%), with almost identical proportions in the intermediate class (27.9% vs 27.2%). Compared to being in the higher managerial and professional class, routine and manual class was associated with HRJL (OR 1.43 95%CI 1.05 to 1.94). However, this effect was non-significant after adjusting for education level, single status, and history of heavy alcohol intake (aOR 1.28 95%CI 0.91 to 1.80), see Table 81.

Educational attainment is known as a key indicator of socioeconomic status, along with income, and occupational status.(406) NS-SEC has also been validated by its ability to measure and predict education.(407) Therefore, in the adjusted model, it is likely that educational attainment is acting as a mediator between NS-SEC socioeconomic class and HRJL, resulting in a non-significant finding. The inclusion of both NS-SEC and education in multivariable analysis amounts to statistical over-adjustment so, given the established use of education as an indicator of socioeconomic status, and the fact that NS-SEC was calculated on the basis of job title alone (an 88% accuracy compared to the gold-standard full method of deriving NS-SEC from SOC-10), multivariable models were adjusted for education, not NS-SEC, going forwards.

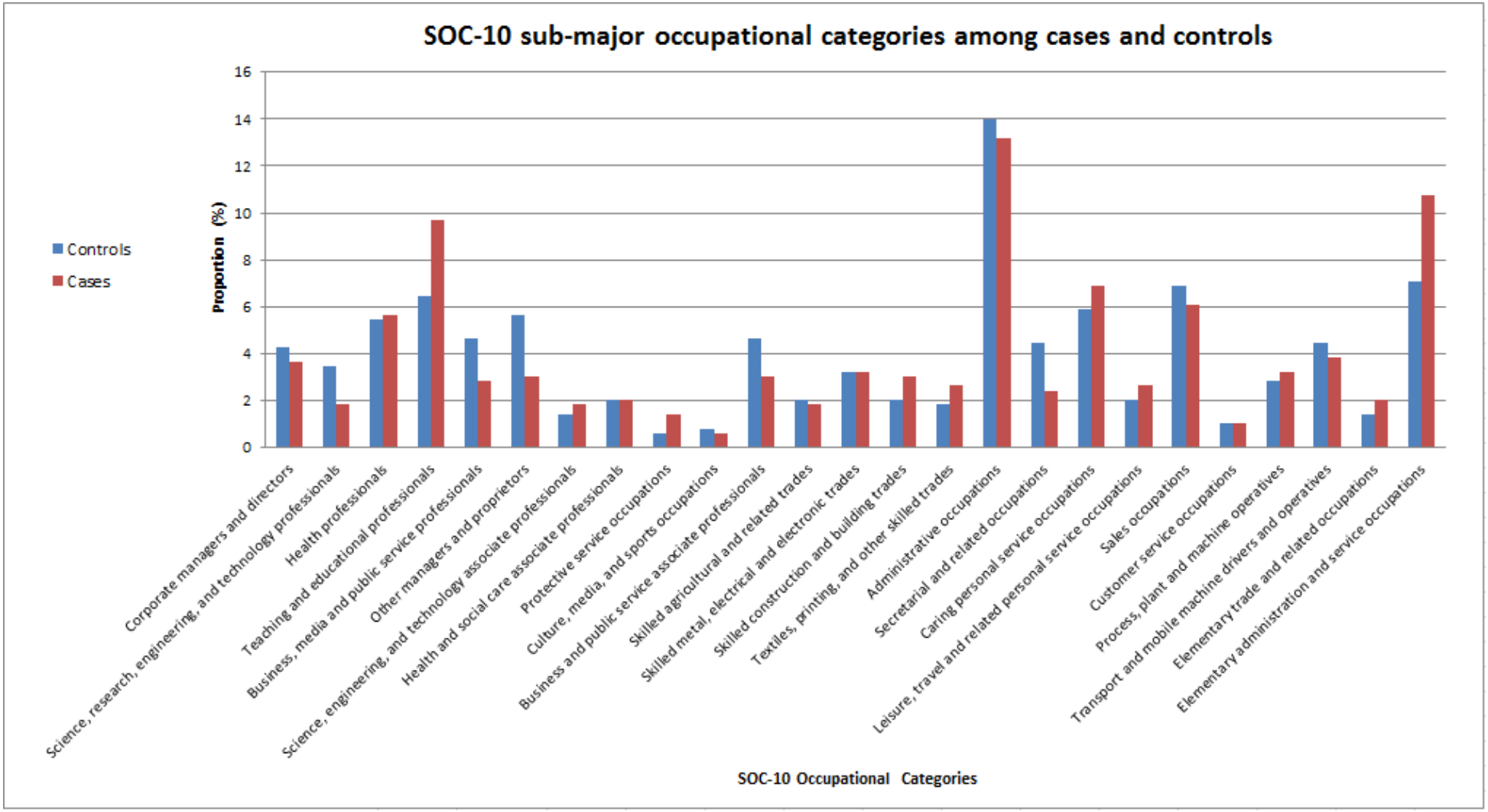
By gender, there was a statistically significant overall association between NS-SEC socioeconomic class and HRJL, among men (OR 1.33 95%CI 1.05 to 1.68) but not women (OR 1.10 95%CI 0.90 to 1.35). As above, no statistically significant effect was observed among men or women after adjustment for education, single status, and history of heavy alcohol use (aOR 1.28 95%CI 0.98 to 1.66; and aOR 1.04 95%CI 0.83 to 1.30, respectively).

Table 81: Association between social class and health-related job loss, across total study population and by gender

Variable	Prevalence among controls, n (%)[1]	Prevalence among cases, n (%)[2]	Association with HRJL, unadjusted. OR (95% CI)	Association with HRJL, adjusted for education level, single status, history of heavy alcohol use. OR (95% CI)[3]
Total study sample				
Higher managerial and professional	188 (38.6)	160 (32.9)	1.00	1.00
Intermediate	136 (27.9)	132 (27.2)	1.19 (0.86 to 1.63)	1.09 (0.78 to 1.53)
Routine and manual	163 (33.5)	194 (39.9)	**1.43 (1.05 to 1.94)**	1.28 (0.91 to 1.80)
Men				
Higher managerial and professional	88 (40.6)	59 (27.1)	1.00	1.00
Intermediate	50 (23.0)	64 (29.4)	**1.81 (1.11 to 2.96)**	**1.82 (1.08 to 3.05)**
Routine and manual	79 (36.4)	95 (43.6)	**1.75 (1.09 to 2.79)**	1.62 (0.95 to 2.76)
Women				
Higher managerial and professional	100 (37.0)	101 (37.7)	1.00	1.00
Intermediate	86 (31.9)	68 (25.4)	0.85 (0.55 to 1.30)	0.73 (0.47 to 1.16)
Routine and manual	84 (31.1)	99 (36.9)	1.21 (0.81 to 1.81)	1.07 (0.68 to 1.68)

1. Data on SOC-10/NS-SEC was missing for eight case participants
2. Data on SOC-10/NS-SEC was missing for seven control participants
3. Missing data on SOC-10/NS-SEC meant that data from 15 pairs (30 participants) were not included in adjusted analysis. Adjusted analysis included data from 958 participants.

Figure 35: SOC-10 sub-major occupational categories among cases and controls



6.3.3 Assessment of CPRD-defined health disorders, with stratification by gender

In the following sections, cases and controls are compared for the presence of CPRD-defined health disorders, and I present the association of these health exposures with HRJL. Health disorders for which CPRD-information was available included chronic MSDs, recent MSD pain, primary care-level MHPs, sleep disorders, psychiatric care-level MHPs, history of severe MHPs, hypertension, heart failure, ischaemic heart disease, PAD, venous thromboembolism, cardiac arrythmias, structural heart disease, asthma, COPD, CVA, epilepsy, and diabetes. A full discussion of these CPRD-defined disorders and their classifications is presented in Chapter 3, Section 3.5.8 and Section 3.7. Most study participants had at least one of these health problems (n=653, 66.1%), including 77.7% of cases and 54.5% of controls.

6.3.3.1 Musculoskeletal disorders

Almost half of all case participants (46.8%) were diagnosed with an MSD (chronic MSD or recent MSD pain) and prevalence was lower among control participants (30.8%). The presence of an MSD was moderately associated with HRJL (OR: 2.10 95%CI 1.58 to 2.78). After adjustment for known confounders, MSDs remained associated with HRJL (aOR 2.08 95%CI 1.55 to 2.78). Gender did not appear to be an important modifier of this effect, as effect estimates remained similar strength among men and women, and after adjustment.

Chronic musculoskeletal disorders

Chronic MSDs included participants with diagnostic codes for osteoarthritis, inflammatory rheumatic disease, connective tissue disease, or who had arthroplasty of the hip or knee prior to the point of analysis. In total, 218 participants fulfilled classification criteria for having “chronic MSDs.” These were more common among cases (27.5% vs 16.6%). A significant association was observed between chronic MSDs and HRJL (OR 1.9 95%CI 1.38 to 2.60), which remained significant after adjustment for known confounders, see Table 82.

Among men, the strength of association was slightly higher (aOR 2.30 95%CI 1.36 to 3.89) than among women (aOR 1.72 95%CI 1.15 to 2.54).

Table 82: Association between chronic MSD and health-related job loss, across total study population and by gender

Variable	Prevalence among controls, n (%)	Prevalence among cases, n (%)	Association with HRJL, unadjusted. OR (95% CI)	Association with HRJL, adjusted for education level, single status, history of heavy alcohol use. OR (95% CI)
Total study sample				
No chronic MSD	412 (83.4)	358 (72.5)	1.00	1.00
Chronic MSD	82 (16.6)	136 (27.5)	**1.90 (1.39 to 2.60)**	**1.89 (1.36 to 2.57)**
Men				
No chronic MSD	191 (86.8)	165 (75.0)	1.00	1.00
Chronic MSD	29 (13.2)	55 (25.0)	**2.30 (1.36 to 3.89)**	**2.19 (1.29 to 3.74)**
Women				
No chronic MSD	221 (80.7)	193 (70.4)	1.00	1.00
Chronic MSD	53 (19.3)	81 (29.6)	**1.70 (1.15 to 2.51)**	**1.72 (1.15 to 2.56)**

Recent musculoskeletal pain

Recent MSD pain included participants who were diagnosed with any musculoskeletal pain, widespread pain, discogenic or nerve root pain, or musculoskeletal injury in the year prior to the point of analysis. There were 241 participants who met the criteria for recent MSD pain. There were more cases than controls with these symptoms (31.0% vs 17.8%), which occurred in nearly a third of all people with HRJL. Recent MSD pain was moderately-strongly associated with HRJL (OR 2.23 95%CI 1.65 to 3.00) and this remained a significant and similar strength association in adjusted analysis, see Table 83.

Table 83: Association between musculoskeletal pain and health-related job loss, across total study population and by gender

Variable	Prevalence among controls, n (%)	Prevalence among cases, n (%)	Association with HRJL, unadjusted. OR (95% CI)	Association with HRJL, adjusted for education level, single status, history of heavy alcohol use. OR (95% CI)
Total study sample				
No MSD pain	406 (82.2)	341 (69.0)	1.00	1.00
MSD pain	88 (17.8)	153 (31.0)	**2.23 (1.61 to 3.08)**	**2.17 (1.56 to 3.03)**
Men				

No MSD pain	178 (80.9)	154 (70.0)	1.00	1.00
MSD pain	42 (19.1)	66 (30.0)	**1.83 (1.16 to 2.87)**	**1.79 (1.12 to 2.85)**
Women				
No MSD pain	228 (83.2)	187 (68.3)	1.00	1.00
MSD pain	46 (16.8)	87 (31.8)	**2.71 (1.70 to 4.33)**	**2.69 (1.66 to 4.38)**

6.3.3.2 Mental Health Problems

Mental health problems were sub-classified as primary care-level MHPs (such as depression, anxiety and other mood disorders), sleep disorders, or psychiatric care-level MHPs (including schizophrenia, bipolar disorders). I also considered participants who had a history of severe MHPs (such as those requiring crisis admission or involving self-harm). Overall, MHPs had a moderate-strong association with HRJL (OR 3.36 95%CI 2.32 to 4.88) and remained similarly associated after adjustment for known confounders. The association was strong among men, and moderate among women (OR 4.08 95%CI 2.17 to 7.68; and OR 3.00 95%CI 1.89 to 4.76, respectively).

Primary-care-level mental health problems

Recent primary-care-level MHPs included participants with evidence of mood disorders, anxiety disorders, somatoform disorders, or adjustment disorders in the year prior to the point of analysis. These were the most prevalent mental health problems (n=177) affecting approximately a quarter of cases and one in 10 controls (26.1% vs 9.7%). Primary care-level MHPs were significantly and strongly associated with HRJL (OR 3.53 95%CI 2.38 to 5.23), see Table 84.

Around a fifth of men with HRJL, and a third of women with HRJL, had a recent primary-care-level MHP, which was strongly associated with HRJL in both subgroups (OR: 4.20 95%CI 2.11 to 8.37 and 3.23 95%CI 2.00 to 5.21, respectively). After adjustment for known confounders, strength of associations remained similar.

Table 84: Association between primary-care-level mental health problems and health-related job loss, across total study population and by gender

Variable	Prevalence among controls, n (%)	Prevalence among cases, n (%)	Association with HRJL, unadjusted. OR (95% CI)	Association with HRJL, adjusted for education level, single status, history of heavy alcohol use. OR (95% CI)
Total study sample				
No primary care-level MHPS	446 (90.3)	365 (73.9)	1.00	1.00
Primary care-level MHPs	48 (9.7)	129 (26.1)	**3.53 (2.38 to 5.23)**	**3.53 (2.38 to 5.23)**
Men				
No primary care-level MHPS	206 (93.6)	174 (79.1)	1.00	1.00
Primary care-level MHPs	14 (6.4)	46 (20.9)	**4.20 (2.11 to 8.37)**	**4.20 (2.11 to 8.37)**
Women				
No primary care-level MHPS	240 (87.6)	191 (69.7)	1.00	1.00
Primary care-level MHPs	34 (12.4)	83 (30.3)	**3.23 (2.00 to 5.21)**	**3.23 (2.00 to 5.21)**

Recent sleep disorders

Recent sleep disorders included participants who had evidence of sleep problems such as insomnia or somnolence in the year prior. Fifty-one participants met the criteria for having a recent sleep disorder. This was more prevalent among cases than controls (7.5% vs 2.8%). Recent sleep disorders were significantly and moderately associated with HRJL (OR: 2.92 95%CI 1.51 to 5.62). The strength of association was similar for male and female sub-groups (OR: 3.00 95%CI 0.97 to 9.30 and 2.87 95%CI 1.29 to 6.43, respectively). After adjustment for known confounders, associations remained a similar strength, see Table 85.

Table 85: Association between sleep disturbance and health-related job loss, across total study population and by gender

Variable	Prevalence among controls, n (%)	Prevalence among cases, n (%)	Association with HRJL, unadjusted. OR (95% CI)	Association with HRJL, adjusted for education level, single status, history of heavy alcohol use. OR (95% CI)
Total study sample				
No sleep disorder	480 (97.2)	457 (92.5)	1.00	1.00
Sleep disorder	14 (2.8)	37 (7.5)	**2.92 (1.51 to 5.62)**	**2.74 (1.40 to 5.38)**
Men				
No sleep disorder	216 (98.2)	208 (94.6)	1.00	1.00
Sleep disorder	4 (1.8)	12 (5.5)	3.00 (0.97 to 9.30)	**3.40 (1.04 to 11.08)**
Women				
No sleep disorder	264 (96.4)	249 (90.9)	1.00	1.00
Sleep disorder	10 (3.7)	25 (9.1)	**2.87 (1.29 to 6.43)**	**2.58 (1.12 to 5.90)**

Psychiatric-care-level mental health problems

Psychiatric-care-level MHPs included participants with schizophrenia, psychotic disorders, bipolar disorders or sexual and gender identity disorders. In total, there were only 15 participants who met the criteria for psychiatric care-level MHPs. However, these mental health problems were more common among cases (1.6% vs 0.4%). There was an estimated strong association between psychiatric care-level MHPs and HRJL but this was not statistically significant (OR 4.00 95%CI 0.85 to 18.84), nor after adjustment for known confounders (see Table 86). Analysis was also underpowered to confidently assess for differences between male and female subgroups.

Table 86: Association between psychiatric-level mental health problems and health-related job loss, across total study population and by gender

Variable	Prevalence among controls, n (%)	Prevalence among cases, n (%)	Association with HRJL, unadjusted. OR (95% CI)	Association with HRJL, adjusted for education level, single status, history of heavy alcohol use. OR (95% CI)
Total study sample				
No psychiatric-level MHPs	492 (99.6)	486 (98.4)	1.00	1.00
Psychiatric-level MHPs	2 (0.4)	8 (1.6)	4.00 (0.85 to 18.84)	3.77 (0.77 to 18.46)
Men				

No psychiatric-level MHPs	218 (99.1)	216 (98.2)	1.00	1.00
Psychiatric-level MHPs	2 (0.9)	4 (1.8)	2.00 (0.37 to 10.92)	2.23 (0.39 to 12.68)
Women				
No psychiatric-level MHPs	274 (100.0)	270 (98.5)	1.00	1.00
Psychiatric-level MHPs	0 (0.0)	4 (1.5)	NE	NE

History of severe mental health problems

Participants with CPRD codes relating to self-harm or suicidal ideation, who were under psychiatric care, had been on a severe mental health register, or had experienced crisis admission or section any time prior to HRJL, were classified as having a history of severe mental health problems. There were 47 such participants, who were more common among cases (7.5% vs 2.0%). History of severe mental-health disorders was significantly and strongly associated with HRJL (OR 4.38 95%CI 2.03 to 9.43), see Table 87. This association appeared to be stronger among women compared to men, however confidence intervals were wide (OR 6.00 95%CI 1.77 to 20.37 and OR 3.40 95%CI 1.25 to 9.22, respectively).

Estimated strength of association remained similar after adjusting for known confounders (aOR 4.36 95%CI 1.91 to 9.98), while the difference between women and men widened (aOR 3.22 95%CI 1.16 to 8.95 and aOR 8.53 95%CI 1.82 to 40.00, respectively). However, confidence intervals were very wide.

Table 87: Association between severe mental health disorders and health-related job loss, across total study population and by gender

Variable	Prevalence among controls, n (%)	Prevalence among cases, n (%)	Association with HRJL, unadjusted. OR (95% CI)	Association with HRJL, adjusted for education level, single status, history of heavy alcohol use. OR (95% CI)
Total study sample				
No severe MHPs	484 (98.0)	457 (92.5)	1.00	1.00
Severe MHPs	10 (2.0)	37 (7.5)	**4.38 (2.03 to 9.43)**	**4.36 (1.91 to 9.98)**
Men				
No severe MHPs	214 (97.3)	202 (91.8)	1.00	1.00
Severe MHPs	6 (2.7)	18 (8.2)	**3.40 (1.25 to 9.22)**	**3.22 (1.16 to 8.95)**
Women				

No severe MHPs	270 (98.5)	255 (93.1)	1.00	1.00
Severe MHPs	4 (1.5)	19 (6.9)	**6.00 (1.77 to 20.37)**	**8.53 (1.82 to 40.00)**

6.3.3.3 Cardiovascular disease

Cardiovascular disorders were sub-classified as: hypertension, heart failure, ischaemic heart disease, peripheral atherosclerotic disease, venous thromboembolic disease, cardiac arrythmia, and structural heart disease. Hypertension is a key risk factor for many of these conditions and therefore is considered separately. Excluding hypertension, a higher proportion of cases had cardiovascular disorders than controls (14.4% vs 5.7%). Having a cardiovascular disorder had a significant moderate-strong association with HRJL (OR 3.05 95%CI 1.86 to 4.99). This association appeared stronger, and was statistically significant, among men, in whom cardiovascular disorders were also more common compared to women (OR 3.54 95%CI 1.91 to 6.55 and OR 2.25 95%CI 0.98 to 5.17, respectively). Strength of association remained broadly similar after adjusting for confounding factors.

Hypertension

Participants with codes relating to hypertension (e.g. “high blood pressure”, “essential hypertension”) prior to the time of analysis were classified as having hypertension. In total, 217 participants had CPRD-defined hypertension. Hypertension was more common among cases compared to controls (26.9% vs 17.0%) and was weakly, but significantly, associated with HRJL (OR 1.89 95%CI 1.36 to 2.62), see Table 88. Hypertension appeared to have a stronger association with HRJL among women, in whom there was a moderate-strength association (OR 2.90 95%CI 1.74 to 4.82), than among men, in whom there was no significant association (OR 1.31 95%CI 0.85 to 2.04). After adjustment for known confounders, associations remained similar strength.

Table 88: Association between hypertension and health-related job loss, across total study population and by gender

Variable	Prevalence among controls, n (%)	Prevalence among cases, n (%)	Association with HRJL, unadjusted. OR (95% CI)	Association with HRJL, adjusted for education level, single status, history of heavy alcohol use. OR (95% CI)
Total study sample				
No hypertension	410 (83.0)	361 (73.1)	1.00	1.00
Hypertension	84 (17.0)	133 (26.9)	**1.89 (1.36 to 2.62)**	**1.79 (1.28 to 2.50)**

Men				
No hypertension	162 (73.6)	151 (68.6)	1.00	1.00
Hypertension	58 (26.4)	69 (31.4)	1.31 (0.85 to 2.04)	1.27 (0.81 to 2.00)
Women				
No hypertension	248 (90.5)	210 (76.6)	1.00	1.00
Hypertension	26 (9.5)	64 (23.4)	**2.90 (1.74 to 4.82)**	**2.74 (1.63 to 4.61)**

Heart failure

Heart failure was defined as having codes relating to heart failure, or a heart transplant, any time prior to the point of analysis. In total, 61 participants were classified as having heart failure which was more common among cases (8.9% vs 2.8%). There was a strong association between heart failure and HRJL (OR 3.73 95%CI 1.92 to 7.25), see Table 89. Heart failure was strongly associated regardless of sex (OR 3.37 95%CI 1.53 to 7.43 in men, and OR 4.67 95%CI 1.34 to 16.24 in women), although there were fewer female participants with heart failure. After adjustment for known confounders, associations remained a similar strength.

The last known occupations of the fourteen participants who managed to remain in work despite heart failure were varied and included non-manual occupations such as managing, shop assistant, salesman, supervisor, computer operator, customer advisor, and journalist, and manual occupations such as, courier, machine operator, van driver, production engineer, engineer, sub assembler, and cleaner/gardener.

Table 89: Association between heart failure and health-related job loss, across total study population and by gender

Variable	Prevalence among controls, n (%)	Prevalence among cases, n (%)	Association with HRJL, unadjusted. OR (95% CI)	Association with HRJL, adjusted for education level, single status, history of heavy alcohol use. OR (95% CI)
Total study sample				
No heart failure	480 (97.2)	450 (91.1)	1.00	1.00
Heart failure	14 (2.8)	44 (8.9)	**3.73 (1.92 to 7.25)**	**3.56 (1.80 to 7.03)**
Men				
No heart failure	210 (95.5)	191 (86.8)	1.00	1.00
Heart failure	10 (4.6)	29 (13.2)	**3.37 (1.53 to 7.43)**	**3.35 (1.49 to 7.54)**
Women				
No heart failure	270 (98.5)	259 (94.5)	1.00	1.00
Heart failure	4 (1.5)	15 (5.5)	**4.67 (1.34 to 16.24)**	**4.14 (1.17 to 14.66)**

Ischaemic heart disease

Ischaemic heart disease included all participants with diagnostic codes relating to angina, myocardial infarction or ischaemia, or who had a coronary angioplasty, bypass, or stent. In total, 51 participants had CPRD-defined ischaemic heart disease, which was more common among cases (6.1% vs 4.3%). The presence of ischaemic heart disease was not significantly associated with HRJL (OR 1.45 95%CI 0.82 to 2.56), see Table 90. This was also true for more severe indicators of ischaemic heart disease (n=19) which, despite a larger (but still weak) estimate of effect, remained non-significantly associated with HRJL (OR 1.74 95%CI 0.68 to 4.42). Strength of associations remained similar after adjustment for known confounders.

Table 90: Association between ischaemic heart disease (IHD) and health-related job loss, across total study population and by gender

Variable	Prevalence among controls, n (%)	Prevalence among cases, n (%)	Association with HRJL, unadjusted. OR (95% CI)	Association with HRJL, adjusted for education level, single status, history of heavy alcohol use. OR (95% CI)
Total study sample				
No IHD	473 (95.8)	464 (93.9)	1.00	1.00
Non-severe IHD	14 (2.8)	18 (3.6)	1.31 (0.65 to 2.63)	1.32 (0.65 to 2.70)
Severe IHD	7 (1.4)	12 (2.4)	1.74 (0.68 to 4.42)	1.33 (0.51 to 3.45)
Men				
No IHD	205 (93.2)	197 (89.6)	1.00	1.00
Non-severe IHD	9 (4.1)	15 (6.8)	1.69 (0.74 to 3.87)	1.73 (0.74 to 4.09)
Severe IHD	6 (2.7)	8 (3.6)	1.39 (0.48 to 4.01)	1.03 (0.34 to 3.11)
Women				
No IHD	268 (97.8)	267 (97.5)	1.00	1.00
Non-severe IHD	5 (1.8)	3 (1.1)	0.60 (0.14 to 2.51)	0.59 (0.14 to 2.47)
Severe IHD	1 (0.4)	4 (1.5)	4.00 (0.45 to 35.79)	3.47 (0.38 to 31.41)

Peripheral atherosclerotic disease

PAD was classified as having CPRD diagnostic codes relating specifically to PAD, or evidence of non-coronary vascular atherosclerotic events, occlusions, or surgery any time prior to the point of analysis. Few participants met the criteria for PAD (n=12) but prevalence was greater among cases (2.2% vs 0.2%). PAD was significantly and very strongly associated with HRJL (OR 11.00 95%CI 1.42 to 85.2), although confidence intervals were wide. Prevalence of

PAD was too low to consider men and women separately. The association between PAD and HRJL remained significant and very strong after adjustment for confounding factors.

Table 91: Association between peripheral atherosclerotic disease and health-related job loss, across total study population and by gender

Variable	Prevalence among controls, n (%)	Prevalence among cases, n (%)	Association with HRJL, unadjusted. OR (95% CI)	Association with HRJL, adjusted for education level, single status, history of heavy alcohol use. OR (95% CI)
Total study sample				
No PAD	493 (99.8)	483 (97.8)	1.00	1.00
PAD	1 (0.2)	11 (2.2)	**11.00 (1.42 to 85.20)**	**8.19 (1.04 to 64.65)**
Men				
No PAD	219 (99.6)	211 (95.9)	1.00	1.00
PAD	1 (0.5)	9 (4.1)	**9.00 (1.14 to 71.04)**	6.48 (0.80 to 52.69)
Women				
No PAD	274 (100.0)	272 (99.3)	1.00	1.00
PAD	0 (0.0)	2 (0.7)	NE	NE

Venous thromboembolism, cardiac arrhythmias, and structural heart disease

Venous thromboembolism included participants with CPRD-evidence of pulmonary embolism or DVT, in the year prior. Cardiac arrhythmias included participants with CPRD-evidence of atrial fibrillation, supraventricular tachycardia, other arrhythmias, or treatment for cardiac arrhythmias, in the year prior. Structural heart disease included participants with CPRD-evidence of cardiomyopathies or diseases of the endocardium or valves, any time prior to the point of analysis.

There were few participants with CPRD-evidence of venous thromboembolism (n=1), cardiac arrhythmias (n= 8), and structural heart disease (n=7). With only a single participant, venous thromboembolism was dropped from further individual analysis. A greater proportion of cases were classified as having structural heart disease or recent cardiac arrhythmias, compared to controls (1.4% vs 0.2% and 0.0% vs 7.0%, respectively) however the number of exposed participants was too small to determine statistical association, see Table 21, and Table 22, Appendix.

6.3.3.4 Respiratory disorders

The association between obstructive lung disease and HRJL was assessed by combining COPD and asthma categories (n=86). Obstructive lung disease was significantly, but weakly, associated with HRJL in matched analysis (OR 1.92 95%CI 1.20 to 3.09). The association appeared to be slightly stronger in women compared to men (OR 2.25 95%CI 1.14 to 4.44 and 1.64 95%CI 0.85 to 3.19, respectively). All effect estimates remained similar after adjustment for known confounders.

Asthma

Asthma was defined as having CPRD-evidence of asthma, or severe asthma, that was still being treated, any time prior to the point of analysis. In total, 109 participants met the criteria for asthma, which was more prevalent among cases (13.0% vs 9.1%). Amongst these, only three people fulfilled the case definition for severe asthma and all three of these reported having HRJL. Asthma was weakly associated with HRJL (OR 1.66 95%CI 1.04 to 2.65) and appeared to be more strongly associated with HRJL in women than men, in whom there was no significant association (OR 2.00 95%CI 1.00 to 4.00; and OR 1.29 95%CI 0.64 to 2.59, respectively). Strength of association remained similar after adjustment for known confounders, see Table 92.

Table 92: Association between asthma and health-related job loss, across total study population and by gender

Variable	Prevalence among controls, n (%)	Prevalence among cases, n (%)	Association with HRJL, unadjusted. OR (95% CI)	Association with HRJL, adjusted for education level, single status, history of heavy alcohol use. OR (95% CI)
Total study sample				
No asthma	463 (93.7)	447 (90.5)	1.00	1.00
Asthma	45 (9.1)	64 (13.0)	**1.66 (1.04 to 2.65)**	**1.77 (1.10 to 2.87)**
Men				
No asthma	206 (93.6)	202 (91.8)	1.00	1.00
Asthma	14 (6.4)	18 (8.2)	1.33 (0.68 to 2.61)	1.43 (0.72 to 2.84)
Women				
No asthma	257 (93.8)	245 (89.4)	1.00	1.00
Asthma	17 (6.2)	29 (10.6)	**2.03 (1.05 to 3.94)**	**2.16 (1.09 to 4.28)**

Chronic Obstructive Pulmonary Disease

COPD was defined as having CPRD-evidence of COPD, emphysema, or chronic bronchitis any time prior to the point of analysis. In total, 20 participants were classified as having COPD, although this condition was more common among cases (3.0% vs 1.0%) and had a significant strong association with HRJL in matched analysis (OR 3.00 95%CI 1.09 to 8.25), see Table 93. While the association appeared to be much stronger among men than women (OR 5.00 95%CI 1.10 to 22.82 vs OR 1.67 95%CI 0.40 to 6.97), confidence intervals were wide. Associations with HRJL remained similar after adjustment for known confounders.

Five control participants, classified as having COPD, were apparently still working. These participants had quite varied occupations including archivist, benefit fraud investigator, club stewardess, head teacher, and computer aided design operator. Notably, none of these roles seem to require physically demanding activities.

Table 93: Association between COPD and health-related job loss, across total study population and by gender

Variable	Prevalence among controls, n (%)	Prevalence among cases, n (%)	Association with HRJL, unadjusted. OR (95% CI)	Association with HRJL, adjusted for education level, single status, history of heavy alcohol use. OR (95% CI)
Total study sample				
No COPD	489 (99.0)	479 (97.0)	1.00	1.00
COPD	5 (1.0)	15 (3.0)	**3.00 (1.09 to 8.25)**	**3.76 (1.22 to 11.60)**
Men				
No COPD	218 (99.1)	210 (95.5)	1.00	1.00
COPD	2 (0.9)	10 (4.6)	**5.00 (1.10 to 22.82)**	**5.50 (1.15 to 26.20)**
Women				
No COPD	271 (98.9)	269 (98.2)	1.00	1.00
COPD	3 (1.1)	5 (1.8)	1.67 (0.40 to 6.97)	2.25 (0.42 to 11.91)

6.3.3.5 Neurological disorders

Cerebrovascular accident

CVA was defined as having evidence of TIA, in the year prior, or stroke any time prior to the point of analysis. In total, 21 participants were classified as having CVA which was more common among cases (3.4% vs 0.8%). A strong significant association was observed between CVA and HRJL (OR 4.25 95%CI 1.43 to 12.63), see Table 94. Strength of association

remained similar after adjustment for known confounders, although the number of participants with CVA was too low to confidently compare men and women.

The four participants that remained in work despite CVA had likely had strokes and their last known occupations included payroll administrator, chief technician, HGV driver, and carer. As well as the fact that, by law, HGV drivers would have been out of work for a year following CVA,(408) it is also likely that these participants must have made significant recovery following stroke/TIA to allow them to continue working. Additionally, TIA/stroke misdiagnosis is also possible, as this is a common error in CPRD, as described in Chapter 3.

Table 94: Association between cerebrovascular accident and health-related job loss, across total study population and by gender

Variable	Prevalence among controls, n (%)	Prevalence among cases, n (%)	Association with HRJL, unadjusted. OR (95% CI)	Association with HRJL, adjusted for education level, single status, history of heavy alcohol use. OR (95% CI)
Total study sample				
No CVA	490 (99.2)	477 (96.6)	1.00	1.00
CVA	4 (0.8)	17 (3.4)	**4.25 (1.43 to 12.63)**	**4.82 (1.57 to 14.76)**
Men				
No CVA	217 (98.6)	210 (95.5)	1.00	1.00
CVA	3 (1.4)	10 (4.6)	3.33 (0.92 to 12.11)	**3.84 (1.01 to 14.59)**
Women				
No CVA	273 (99.6)	267 (97.5)	1.00	1.00
CVA	1 (0.4)	7 (2.6)	7.00 (0.86 to 56.89)	7.54 (0.90 to 63.43)

Epilepsy

CPRD-defined epilepsy included participants diagnosed with epilepsy specific codes (e.g. “epileptic seizures”, “epilepsy medication review”) or participants with evidence of fits or seizures who were later diagnosed with epilepsy. Few participants were classed as having epilepsy (n=10) and these were more common among cases (1.4% vs 0.6%). Epilepsy was not significantly associated with HRJL, however, confidence intervals were wide (OR 3.00 95%CI 0.81 to 11.08), see Table 95. Although analysis was underpowered, point estimates suggested a moderate-strong association between epilepsy and HRJL, as well as after adjustment for known confounders. The number of participants with epilepsy was also too low for conclusive findings among men and women.

Table 95: Association between epilepsy and health-related job loss, across total study population and by gender

Variable	Prevalence among controls, n (%)	Prevalence among cases, n (%)	Association with HRJL, unadjusted. OR (95% CI)	Association with HRJL, adjusted for education level, single status, history of heavy alcohol use. OR (95% CI)
Total study sample				
No epilepsy	491 (99.4)	487 (98.6)	1.00	1.00
Epilepsy	3 (0.6)	7 (1.4)	3.00 (0.61 to 14.86)	3.74 (0.73 to 19.20)
Men				
No epilepsy	219 (99.6)	216 (98.2)	1.00	1.00
Epilepsy	1 (0.5)	4 (1.8)	4.00 (0.45 to 35.79)	6.11 (0.65 to 57.75)
Women				
No epilepsy	272 (99.3)	271 (98.9)	1.00	1.00
Epilepsy	2 (0.7)	3 (1.1)	2.00 (0.18 to 22.06)	1.73 (0.15 to 19.80)

6.3.3.6 Diabetes

Diabetes included participants with CPRD diagnostic codes for diabetes mellitus (e.g. “type 2 diabetes mellitus”, “follow-up diabetic assessment”) prior to the point of analysis. Poorly controlled diabetes included participants with additional codes suggesting more “severe” diabetes (e.g. “diabetic neuropathy”, “unstable diabetes”). In total, there were 91 participants with CPRD-defined diabetes and 55 with signs of poorly controlled diabetes. Both diabetes without complications and poorly controlled diabetes were more common amongst cases (4.7% vs 2.6% and 7.5% vs 3.6%, respectively). Diabetes was moderately associated with HRJL (OR 2.32 95%CI 1.41 to 3.82); the association was only slightly stronger among those with indicators of poor diabetic control (OR 2.38 95%CI 1.31 to 4.35), see Table 96. Effect estimates were similar after adjustment for known confounders.

In male participants, poorly controlled diabetes had a stronger association with HRJL (OR 3.14 95%CI 1.40 to 7.05 vs OR 1.57 95%CI 0.65 to 3.82). Notably, this seemed to reverse in women, among whom diabetes without indicators of poor control was more strongly associated with HRJL (aOR 4.97 95%CI 1.05 to 23.45 vs aOR 1.62 95%CI 0.63 to 4.17). However, there were fewer female participants coded as having diabetes and confidence intervals were wide.

Table 96: Association between diabetes and health-related job loss, across total study population and by gender

Variable	Prevalence among controls, n (%)	Prevalence among cases, n (%)	Association with HRJL, unadjusted. OR (95% CI)	Association with HRJL, adjusted for education level, single status, history of heavy alcohol use. OR (95% CI)
Total study sample				
No diabetes	463 (93.7)	434 (87.9)	1.00	1.00
Diabetes no complications	13 (2.6)	23 (4.7)	**2.21 (1.05 to 4.67)**	**2.09 (0.98 to 4.47)**
Diabetes poorly controlled	18 (3.6)	37 (7.5)	**2.38 (1.31 to 4.35)**	**1.98 (1.07 to 3.67)**
Men				
No diabetes	200 (90.9)	181 (82.3)	1.00	1.00
Diabetes no complications	10 (4.6)	13 (5.9)	1.57 (0.65 to 3.82)	1.51 (0.60 to 3.76)
Diabetes poorly controlled	10 (4.6)	26 (11.8)	**3.14 (1.40 to 7.05)**	**2.74 (1.20 to 6.28)**
Women				
No diabetes	263 (96.0)	253 (92.3)	1.00	1.00
Diabetes no complications	3 (1.1)	10 (3.7)	**4.97 (1.05 to 23.45)**	4.49 (0.94 to 21.39)
Diabetes poorly controlled	8 (2.9)	11 (4.0)	1.62 (0.63 to 4.17)	1.31 (0.49 to 3.47)

6.3.4 Summary of the associations between CPRD-defined health disorders and HRJL

For ease of reference, the information presented above was assimilated into a summary table showing the association between CPRD-defined health disorders and HRJL, across the total study sample, and split by gender, see Table 97. Relative effect sizes were adjusted for educational attainment, single relationship status, and history of heavy alcohol use, and can be visualised in Figure 36.

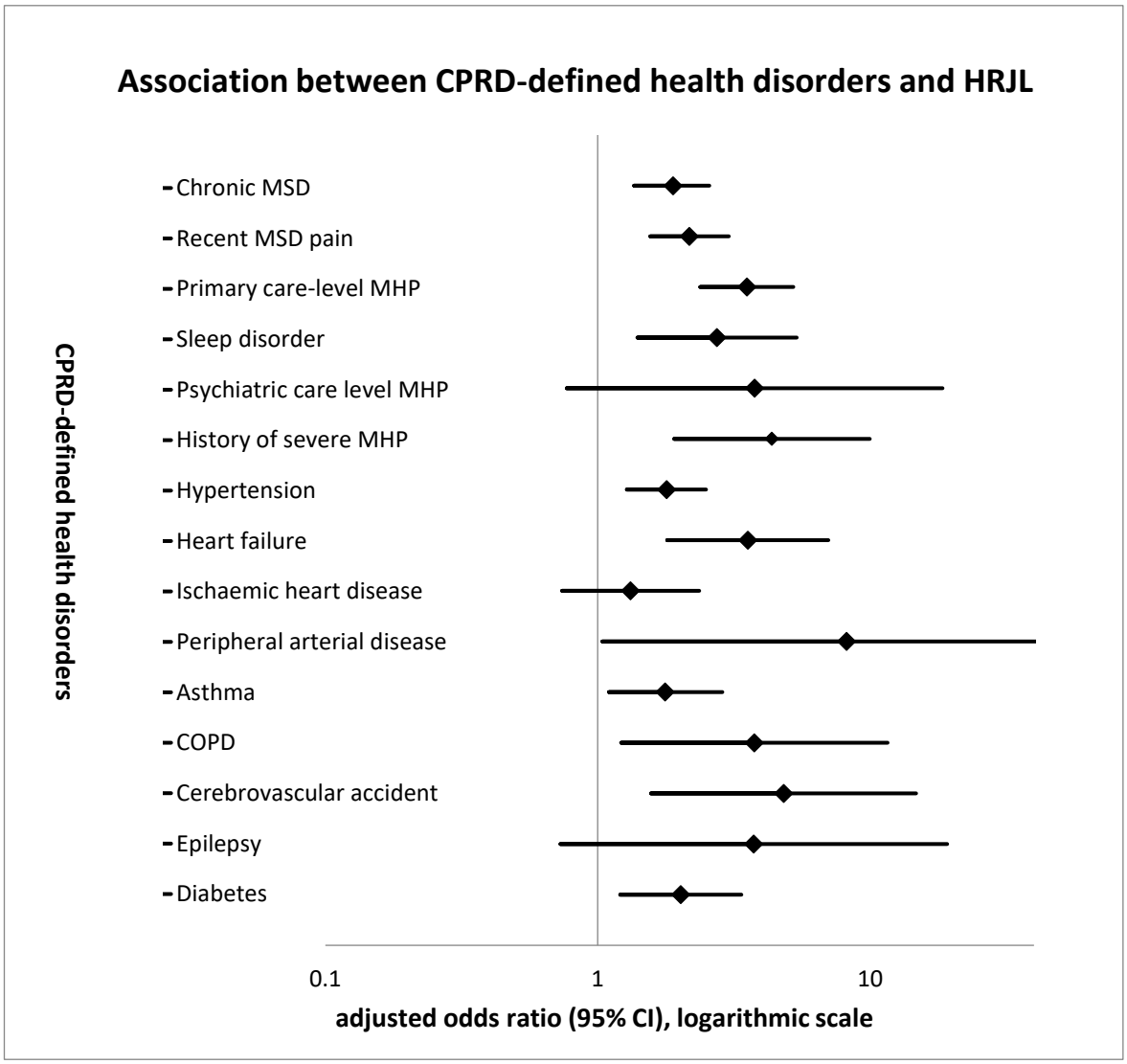
Table 97: Summary table –adjusted association between CPRD-defined health disorders and HRJL, with stratification by gender

CPRD-defined health disorder	Total study sample (n=988) aOR* (95% CI)	Male participants (n=440) aOR* (95% CI)	Female Participants (n=548) aOR* (95% CI)
Chronic MSD	**1.89 (1.36 to 2.57)**	**2.19 (1.29 to 3.74)**	**1.72 (1.15 to 2.56)**

Recent MSD pain	**2.17 (1.56 to 3.03)**	**1.79 (1.12 to 2.85)**	**2.69 (1.66 to 4.38)**
Recent primary care-level MHP	**3.53 (2.38 to 5.23)**	**4.20 (2.11 to 8.37)**	**3.23 (2.00 to 5.21)**
Recent sleep disorder	**2.74 (1.40 to 5.38)**	**3.40 (1.04 to 11.08)**	**2.58 (1.12 to 5.90)**
Psychiatric care-level MHP	3.77 (0.77 to 18.46)	2.23 (0.39 to 12.68)	NE
History of severe MHP	**4.36 (1.91 to 9.98)**	**3.22 (1.16 to 8.95)**	**8.53 (1.82 to 40.00)**
Hypertension	**1.79 (1.28 to 2.50)**	1.27 (0.81 to 2.00)	**2.74 (1.63 to 4.61)**
Heart failure	**3.56 (1.80 to 7.03)**	**3.35 (1.49 to 7.54)**	**4.14 (1.17 to 14.66)**
Ischaemic heart disease	1.32 (0.74 to 2.36)	1.44 (0.72 to 2.86)	1.09 (0.36 to 3.26)
PAD	**8.19 (1.04 to 64.65)**	6.48 (0.80 to 52.69)	NE
Asthma	**1.77 (1.10 to 2.87)**	1.43 (0.72 to 2.84)	**2.16 (1.09 to 4.28)**
COPD	**3.76 (1.22 to 11.60)**	**5.50 (1.15 to 26.20)**	2.25 (0.42 to 11.91)
CVA	**4.82 (1.57 to 14.76)**	**3.84 (1.01 to 14.59)**	7.54 (0.90 to 63.43)
Epilepsy	3.74 (0.73 to 19.20)	6.11 (0.65 to 57.75)	1.73 (0.15 to 19.80)
Diabetes	**2.02 (1.21 to 3.37)**	**2.13 (1.12 to 4.04)**	1.91 (0.81 to 4.48)

*Adjusted odds ratio (aOR): adjusted for educational attainment, single relationship status, and history of heavy alcohol intake

Figure 36: Forest plot showing association between CPRD-defined health disorders and HRJL



6.3.5 Subgroup analysis by age at time of analysis

Subgroup analysis was performed comparing the association between CPRD-defined health disorders and HRJL, stratified by the age at which the case had experienced HRJL. Control participants were working at the time their matched cases had fallen out of work, and a control's CPRD-defined health information was taken from this point in time. Participants were grouped in the following age bands accordingly: aged <50 years old; aged 50 to <60 years old; age 60 and older.

The prevalence of musculoskeletal disorders together (chronic and recent pain conditions), was 29.7% in the age <50 subgroup, 38.3% in the age 50 - <60 subgroup, and 43.1% in the age >60 subgroup. Musculoskeletal disorders were strongly associated with HRJL in the age <50 subgroup (OR 3.29 95%CI 1.41 to 7.66), weakly associated with HRJL in the age 50 – 60

subgroup (OR 1.90 95%CI 1.31 to 2.77), and moderately associated with HRJL in the age >60 subgroup (OR 2.09 95%CI 1.27 to 3.43). Effect estimates were similar after adjustment for known confounders.

The prevalence of MHPs together (primary care-level, psychiatric care-level, and sleep disorders) was 22.7% of the age <50 subgroup, 23.1% in the age 50 - <60 subgroup, and 13.3% in the age >60 subgroup. MHPs were very strongly associated with HRJL in the age <50 subgroup (OR 18.00 95%CI 2.40 to 134.83), although confidence intervals were very wide. MHPs were also strongly associated with HRJL in the age 50 – 60 subgroup (OR 3.36 95%CI 2.09 to 5.41), and moderately associated with HRJL in the age >60 subgroup (OR 2.23 95%CI 1.16 to 4.29). Effect estimates were similar after adjustment for known confounders, except in the age <50 subgroup, in which association remained significant but confidence intervals became extremely wide (aOR 85.40 95%CI 5.85 to 1246.83), suggesting a very uncertain effect estimate in this group.

Excluding hypertension, cardiovascular disease were present in 2.3% of the age <50 subgroup, 8.3% of the age 50 - <60 subgroup, and 15.7% of the age >60 subgroup. Association with HRJL was non estimable in the <50 subgroup, however cardiovascular disease had a significant moderate association with HRJL in the age 50 – 60 subgroup (OR 2.23 95%CI 1.16 to 4.29) and a significant strong association in the age >60 subgroup (OR 4.00 95%CI 1.84 to 8.68). Estimates of effect remained similar after adjusting for known confounders.

Obstructive lung disease (asthma and COPD, together) was present in 6.3% of the age <50 subgroup, 10.0% of the age 50 - <60 subgroup, and 7.5% of the age >60 subgroup. Obstructive lung disease had a non-significant association with HRJL in the <50 group (OR: 1.00 95%CI 0.25 to 4.00), a weak significant association in the 50 – 60 age group (OR: 1.87 95%CI 1.00 to 3.49) and a moderate significant association in the >60 age group (OR 2.57 95%CI 1.07 to 6.16). Estimates of association became slightly stronger after adjustment for known confounding factors (aOR: 1.12 95%CI 0.24 to 5.17; 2.09 95%CI 1.08 to 4.05; and 3.19 95%CI 1.27 to 8.04, respectively).

Psychiatric care-level MHPs, PAD, cardiac arrhythmias, structural heart disease, and epilepsy were present in 1.6%, 0.8%, 0.0%, 0.0%, and 1.6% of the age <50 subgroup, respectively; 1.3%, 1.5%, 1.0%, 0.6%, and 1.3% of the age 50 - <60 subgroup, respectively; and 0.3%, 0.9%, 0.9%, 1.2%, and 0.3% of the age >60 subgroup, respectively. The total

number of participants with these conditions was too small to meaningfully assess association with HRJL across different age subgroups, which was either non-significant with wide confidence intervals, or not estimable, see Tables 23 – 27, Appendix.

For the remaining CPRD-defined health disorders, the associations between CPRD-defined health disorders and HRJL, split by age sub-group, are presented below (Table 98). Relative effect sizes are adjusted for educational attainment, single relationship status, and history of heavy alcohol use. For a full presentation of these data, including unadjusted effect sizes and the prevalence of CPRD-defined health disorders within each sub-group, see Tables 28 – 39, Appendix.

Table 98: Summary table –adjusted association between CPRD-defined health disorders and HRJL, with stratification by age at point of analysis

CPRD-defined health disorder	Age <50 (n=128) aOR* (95% CI)	Age 50 - <60 years old (n=528) aOR* (95% CI)	Age >60 (n=332) aOR* (95% CI)
Chronic MSD	2.55 (0.63 to 10.33)	**1.58 (1.04 to 2.41)**	**2.25 (1.31 to 3.88)**
Recent MSD pain	**4.40 (1.48 to 13.08)**	**2.33 (1.46 to 3.71)**	1.51 (0.85 to 2.67)
Recent primary care-level MHP	**29.70 (2.78 to 317.56)**	**3.61 (2.14 to 6.09)**	2.04 (0.98 to 4.25)
Recent sleep disorder	**2.71 (0.46 to 16.05)**	**2.45 (0.94 to 6.42)**	**4.34 (1.18 to 15.97)**
History of severe MHP	NE	**4.00 (1.49 to 10.76)**	3.09 (0.57 to 16.80)
Hypertension	3.52 (0.77 to 16.01)	**1.90 (1.19 to 3.04)**	**1.64 (0.97 to 2.76)**
Heart failure	NE	1.83 (0.71 to 4.72)	**7.63 (2.52 to 23.11)**
Ischaemic heart disease	NE	1.25 (0.55 to 2.88)	1.23 (0.52 to 2.93)
Asthma	1.12 (0.24 to 5.17)	1.94 (0.99 to 3.81)	2.19 (0.84 to 5.72)
COPD	NE	2.67 (0.54 to 13.30)	6.12 (1.14 to 32.74)
CVA	NE	**5.76 (1.19 to 27.79)**	3.33 (0.67 to 16.48)
Diabetes	NE	**2.07 (1.03 to 4.19)**	1.77 (0.81 to 3.87)

*Adjusted odds ratio (aOR): adjusted for educational attainment, single relationship status, and history of heavy alcohol intake

6.3.6 Sub-group analysis by "type" of HRJL

In the HEAF study, cases indicated whether they had left work mainly because of a health problem or partly because of a health problem. Sub-group analysis was performed comparing the association between CPRD-defined health disorders and HRJL, stratified by

"mainly" or "partly" HRJL. The modifying influence of "type" of HRJL on the association between CPRD-defined health disorders and HRJL was considered.

Musculoskeletal disorders (chronic and recent pain conditions together), were present in 37.4% of the "mainly" subgroup and 40.0% of the "partly" subgroup. Musculoskeletal disorders were moderately associated with HRJL in the "mainly" subgroup (OR: 2.56 95%CI 1.70 to 3.86) and weakly associated with HRJL in the "partly" subgroup (OR: 1.73 95%CI 1.17 to 2.55). Effect estimates were similar after adjustment for known confounders.

The prevalence of any MHP (primary care-level, psychiatric care-level, and sleep disorders) was 20.9% in the "mainly" subgroup and 18.8% in the "partly" subgroup. MHPs were strongly associated with HRJL in the "mainly" subgroup (OR 6.09 95%CI 3.22 to 11.52) and moderately associated with HRJL in the "partly" subgroup (OR 2.16 95%CI 1.34 to 3.47). Effect estimates were similar after adjustment for known confounders.

Excluding hypertension, cardiovascular disease was present in 10.4% of the "mainly" subgroup and 9.7% of the "partly" subgroup. Cardiovascular disease had a significant strong association with HRJL in the "mainly" group (OR 4.00 95%CI 1.84 to 8.68), and a significant moderate strength association in the "partly" group (OR 2.46 95%CI 1.29 to 4.69). Effect estimates remained similar after adjustment for known confounding factors.

Obstructive lung disease (asthma and COPD) was present in 8.5% of the "mainly" subgroup and 8.9% of the "partly" subgroup. Obstructive pulmonary disease had a significant moderate-strength association with HRJL in the "mainly" group (OR 2.50 95%CI 1.20 to 5.21) and a non-significant weak association in the "partly" group (OR 1.56 95%CI 0.83 to 2.93). Estimates of association remained similar after adjustment for known confounding factors.

Psychiatric-care-level MHPs, PAD, cardiac arrhythmias, structural heart disease, COPD, and epilepsy were present in 1.1%, 1.1%, 1.3%, 0.9%, 2.2%, and 1.1% of the "mainly" sub-group, respectively; and 1.0%, 1.3%, 0.4%, 0.6%, 1.9% and 1.0% of the "partly" sub-group, respectively. The total number of participants with these conditions was too small to assess for differences in strength of association between these sub-groups. Estimates were either non-significant with wide confidence intervals, or not estimable, see Tables 40 – 45, Appendix.

For the remaining CPRD-defined health disorders, the associations between CPRD-defined health disorders and HRJL, split by "type" of HRJL, are presented below (Table 99). Relative effect sizes are adjusted for educational attainment, single relationship status, and history of heavy alcohol use. For a full presentation of these data, including unadjusted effect sizes, and the prevalence of these health disorders within "mainly" and "partly" sub-groups, see Tables 46 – 56, Appendix.

Table 99: Summary table –adjusted association between CPRD-defined health disorders and HRJL, with stratification by "type" of HRJL

CPRD-defined health disorder	"Mainly" HRJL (n=460) aOR* (95% CI)	"Partly" HRJL (n=528) aOR* (95% CI)
Chronic MSD	**2.71 (1.60 to 4.57)**	1.47 (0.98 to 2.22)
Recent MSD pain	**2.01 (1.30 to 3.12)**	**2.42 (1.44 to 4.07)**
Recent primary care-level MHP	**6.93 (3.37 to 14.25)**	**2.08 (1.24 to 3.46)**
Recent sleep disorder	**3.57 (1.27 to 10.04)**	2.18 (0.89 to 5.33)
History of severe MHP	**4.29 (1.42 to 12.92)**	**4.46 (1.27 to 15.72)**
Hypertension	**1.34 (0.80 to 2.22)**	**2.26 (1.44 to 3.55)**
Heart failure	**4.34 (1.46 to 12.95)**	**3.42 (1.38 to 8.44)**
Ischaemic heart disease	1.32 (0.56 to 3.12)	1.34 (0.61 to 2.97)
Asthma	**2.18 (1.05 to 4.55)**	1.51 (0.79 to 2.87)
CVA	**13.49 (1.71 to 106.34)**	2.09 (0.46 to 9.60)
Diabetes	**2.48 (1.08 to 5.70)**	**1.79 (0.93 to 3.44)**

*Adjusted odds ratio (aOR): adjusted for educational attainment, single relationship status, and history of heavy alcohol intake

6.4 Discussion

In this chapter, I conducted an analysis of the relationship between CPRD-defined health disorders and health-related job loss. Case and control participants, selected from the HEAF study, were compared in a nested, matched, case-control design. Lower level of educational qualification, single relationship status, and CPRD-defined history of heavy alcohol intake were found to be significantly associated with HRJL, and these confounding factors were adjusted for in multivariable analysis. Of the health disorders explored in this study, it was found that chronic MSDs, recent MSD pain, primary-care-level MHPs, sleep disorders, history of severe MHPs, hypertension, heart failure, PAD, asthma, COPD, CVA,

and diabetes are significantly associated with HRJL. Although underpowered to show statistical significance, effect estimates suggest that psychiatric-level MHPs, cardiac arrhythmias, structural heart disease, and epilepsy may also impact an older worker's ability to stay in work.

Demographic factors were initially assessed for their role in HRJL. Low qualification level and NS-SEC occupational class reflect facets of a participant's socioeconomic status, which is well described for its associated gradient in health,(399) and is also an important predictor of sickness absence and work disability.(21–23,32,40,222,225–230) As a result, the weak strength of association found between these factors and HRJL in this analysis was surprising, but may be accounted for by the fact that cases and controls had already been matched for GP practice, which adjusts for regional levels of deprivation. Single relationship status was significantly associated with HRJL. One meta-review of modifiable and non-modifiable risk factors for work outcomes found that, in general, marriage was a consistent protective factor for work disability.(21) Being married or in a committed relationship has also been associated with current employment and increased return to work across multiple conditions.(23,24) Interestingly, in this study, being divorced or widowed appeared of less importance as a predictor of HRJL than self-reported singleness; being divorced may even be protective of work loss in women. I am not aware that the sex-stratified impact of divorce and widowhood on work outcomes has been reported in the literature previously, and this may be worth follow up in future research, with better statistical power to detect an effect.

Lifestyle factors were considered next. In the literature, smoking is an established risk factor for innumerable adverse health outcomes, leading to increased mortality, cancer, and chronic disease (particularly respiratory and cardiovascular disorders).(409) it has also been linked to work disability and long-term sickness absence in certain studies,(410) although found to be of little significance to work in others.(411,412) While no important association between smoking and HRJL was observed in this study, smoking status was self-reported and a smoker's status as a current or ex-smoker was based on their self-reported dates of quitting smoking. These may be strongly subject to recall bias. To derive information about a participant's drinking habits, it was necessary to rely on CPRD coding. However, in CPRD, alcohol intake was not recorded for the majority of study participants. Instead, I considered evidence of heavy alcohol intake, or alcohol abuse, which is more likely to be consistently identified and recorded by a general practitioner. The evidence for heavy alcohol intake as an explanatory factor for poor work outcomes is understudied and

inconsistent,(413,414) however, in this study, a moderate-strong association between history of heavy alcohol intake and HRJL was observed.

Chronic MSDs and recent MSD pain were both associated with HRJL. The mild-moderate strength associations observed and the very large prevalence of these disorders across the total study sample establishes these conditions as having a very important role in work disability, at the population level. Similar effect sizes have previously been reported for MSDs and risk of disability pension (RR 2.23 95%CI 1.93 to 2.59).(115) Recent MSD pain disorders and chronic MSDs appeared to define different sets of diseases (e.g. mostly osteoarthritis in chronic MSDs and largely back pain in recent MSD pain, see Chapter 3 and 5). However, there was considerable overlap between these conditions. Of participants with a chronic MSD, 34.9% had presented to their GP with MSD pain in the prior year. This suggests that some of the musculoskeletal pain may have stemmed from an underlying chronic MSD condition.

Mental health problems were also highly prevalent in the study sample, and a strong relationship with HRJL was observed. Specifically, primary-care-level MHPs and having a history of severe MHPs, were strongly associated with HRJL; sleep disorders were moderately associated with HRJL; and point estimates suggest that psychiatric disorders may also be strongly associated, although this did not reach statistical significance. These findings correspond with those reported previously: a systematic review and meta-analysis using data from 282,459 patients found mental health problems (together) were associated with an increased risk of disability pension (RR 1.80 95%CI 1.41 to 2.31).(115) Specifically, mood disorders have been linked to work disability and long-term sickness absence in several studies(415–417) including a Finnish epidemiological study of over 3000 participants, aged 30 – 58 years old, which found depression (OR 2.67 95%CI 1.58 to 4.52) and anxiety (OR: 3.34 95%CI 1.65 to 6.77) were significantly associated with disability pension.(413) Psychotic disorders, such as schizophrenia, are less well reported but in a Finnish twin study were strongly associated with disability pension (OR: 6.3 95%CI 2.0 to 20.1 across all twins, 8.7 95%CI 2.1 to 36.8 among dizygotic twins, and 2.5 95%CI 0.2 to 30.8 among monozygotic twins). In this study, as with the twin study, confidence intervals were wide and results were limited by the number of participants with psychiatric care-level MHPs, however point estimates suggested a strong positive relationship with HRJL among older workers.

As a whole, cardiovascular disorders were moderately associated with HRJL (OR: 2.72 95%CI 1.65 to 4.49) and moderately-strongly if hypertension was excluded (OR: 3.05 95%CI 1.86 to 4.99). Individually, heart failure and peripheral atherosclerotic disease were particularly strongly associated with HRJL. Seven participants had structural heart disease, and eight had cardiac arrhythmias; all but one of these participants had HRJL. Ischaemic heart disease is likely to be weakly associated with HRJL, however this study was underpowered to find statistical significance (OR 1.45 95%CI 0.82 to 2.56). Even after restricting to those participants who had a history of myocardial infarction or unstable angina (severe ischaemic heart disease) impact was non-significant (OR 1.45 95%CI 0.82 to 2.56). Coronary heart disease has previously been associated with higher rate of labour market withdrawal (HR 1.32 95%CI 1.11 to 1.57)(418) and higher rate of absenteeism (IRR 1.17 95%CI 1.03 to 1.32).(419) However, comparisons with the literature are difficult since, despite the prevalence of cardiovascular disorders in the workforce, the evidence for their impact on work disability is scarce.(420) While findings may suggest a relatively encouraging outlook for remaining in work after acute coronary event, a survivor bias may impact findings here since people with fatal myocardial infarction (and possibly near-fatal myocardial infarction) would not have been captured in the HEAF study sample. Nonetheless, the findings of this study provide much needed evidence for the importance of cardiovascular disorders on ability to stay in work in the older working-age population.

Hypertension was also statistically associated with work disability, but only weakly. In prospective studies, hypertension has been linked to increased risk of disability pension (RR 1.50 95%CI 1.31-1.72)(421) as well as longer sickness absence duration.(422) The association between hypertension and HRJL is curious since it is usually symptomless, but this may reflect its role as a risk factor for other unmeasured adverse health problems. For example, hypertension is associated with obesity(423) and with microvascular complications in diabetes, such as nephropathy.(424) The high prevalence of hypertension in this older-age population also allows for the identification of small effect sizes. Finally, a bias (conceptually similar to Berkson's bias) may arise, since people with more severe kinds of disease, or requesting sickness absence from work, may be seen more frequently in GP clinic and therefore have a greater opportunity to have their blood pressure measured and hypertension diagnosed. Interestingly, the association between hypertension and HRJL did become non-significant after adjusting for the number of GP consultations in the prior year (aOR 1.17 95%CI 0.80 to 1.70).

Diabetes had a moderate-strength association with HRJL in this study. Previous studies have also identified a relationship between diabetes and absenteeism (OR: 2.29 95%CI 1.17 to 4.47),(425) and work disability (HR 1.7 95%CI 1.0 to 2.9).(420,426) Surprisingly, effect sizes were similar for participants with general diabetes codes and those with indicators of worse diabetic control. Codes indicating more severe diabetes may have been inconsistently recorded in CPRD, and as a result, these groups may be more similar than is apparent. Additionally, the fact that 60.44% of those with diabetes were defined as "diabetes with poor control" suggests that the Read codes used to define diabetic control were overly inclusive. Therefore, going forwards, diabetes was analysed without stratification for severity.

A mild significant relationship between asthma and HRJL was observed in this older working-age population, and a moderate-strong association between COPD and HRJL. Similarly, in the literature, COPD and, to a lesser extent, asthma have been associated with a substantially shortened working life.(427) The evidence for the impact of asthma on health-related job loss is scarce, although asthma was associated with all-cause long-term work disability in one study (HR 1.8 95%CI 1.62 to 2.09).(428) Likewise, COPD is rarely reported for occupational outcomes but has been associated with absenteeism (IRR 1.57 95%CI 1.33 to 1.86)(419,420) and prolonged labour force non-participation (OR: 2.92 95%CI 1.35 to 6.29).(429)

CPRD diagnostic information was available for two neurological conditions: epilepsy and cerebrovascular accident. Cerebrovascular accident was strongly associated with HRJL and epilepsy may have a moderate-strong association with HRJL, although this analysis was underpowered to show a significant effect. Evidence linking stroke to health-related work loss is scarce, however, several studies outlined the low rates of return to work a year or more following stroke which ranged from 21% – 75%.(420) Very few papers were found that considered the association between epilepsy and work status. In an old study (1991) in an area of high unemployment, people with epilepsy were found to have 59% unemployment, with 79% unemployment in those with associated neurological or psychiatric disability.(430) A dedicated study, with sufficient statistical power, is needed to assess the rate and predictors of adverse work outcomes in epilepsy.

Generally, adjustment for confounders did not impact the estimates of association between these CPRD-defined health disorders and HRJL. This is unsurprising since qualification level

and single relationship status was only weakly associated with the main outcome (HRJL), and history of heavy alcohol intake was not common in the study sample.

A unique strength of this study was the stratification of results by gender. The rationale for doing so was clear since, as described in Chapter 5, occupational environment differed in a gender-dependent manner and, surprisingly, gender differences have not yet been sufficiently explored in the literature. However, analysis was underpowered, and confidence intervals too wide, to confidently assess gender differences for psychiatric-level MHPs, history of severe MHPs, heart failure, ischaemic heart disease, peripheral atherosclerotic disease, cardiac arrhythmias, structural heart disease, COPD, CVA, and epilepsy. For chronic MSDs, sleep disorders, and asthma there was no strong evidence of effect-modification by gender. Recent MSD pain appeared to have a slightly stronger association with HRJL among women than men (OR: 2.71 vs 1.83), differences may result from the different kinds of pain conditions experienced by men and women in this sample, for example, there were 17 female participants with widespread pain and only three male. Hypertension was also more significantly associated with HRJL among women, compared to men (OR: 2.90 vs 1.31). There is some evidence to suggest post-menopausal women present with more advanced cardiovascular disease than men, and that hypertension acts as a stronger risk factor for heart disease among women.(431) Unfortunately, this study was underpowered to explore these differences for other cardiovascular disorders. Primary care-level MHPs may be more strongly associated with HRJL among men than women (OR: 4.20 vs 3.23). Although these conditions are more prevalent among women, men appear broadly more reluctant to present with MHPs (432) and are less often detected as having MHPs by their general practitioners.(433) The men presenting with mental health problems in this study may therefore have had more severe MHPs (that are more easily detectable) resulting in the observed stronger impact on work. Overall, it should be noted that these differences were small, and indeed may not exist, since confidence intervals were overlapping.

After stratification by age at HRJL, chronic MSDs, recent MSD pain, primary-care-level MHP, sleep disorders, history of severe MHPs, hypertension, CVA, and diabetes remained significantly associated with HRJL in the age 50 to <60 subgroup. As described in Chapter 5, the 50 – 60 year old age band are of particular economic interest in the UK, since they are the most common group to drop out of work while still being some distance from state pension retirement age.(46) For certain, progressive age-related conditions, such as chronic MSDs, heart failure, and COPD, strength of association increased towards the older age

groups, in whom the disease is more prevalent and likely more severe. Interestingly, primary-care-level MHPs and recent musculoskeletal pain, seemed more strongly associated with HRJL in the younger age groups. However, in all cases, confidence intervals were wide and overlapping between subgroups and observed differences in size of association may not be meaningful.

Finally, I stratified analysis by whether a case had stated that a health problem was the main reason or part of the reason for their leaving employment. Since this response indicates the extent that a person recalled poor health had affected their job loss, it is also likely to be related to the overall health burden among cases. Unsurprisingly then, for the majority of CPRD-defined health disorders (apart from recent musculoskeletal pain and hypertension) the estimated strength of association with HRJL was greater when analysis was restricted to "mainly" cases. However, recent MSD pain, primary care-level MHPs, sleep disorders, history of severe MHPs, hypertension, and diabetes also remained significantly associated with HRJL among "partly" cases. Both "mainly" and "partly" HRJL appeared to be related to CPRD-indicators of poor health and, for the purposes of this thesis, I was interested in either of these outcomes. So for the remainder of the thesis, cases were recombined to assess relative odds of HRJL.

The main weaknesses of this study have already been highlighted, particularly the fact that in several cases analysis was underpowered to detect a statistically significant effect. In the total sample (n=988), as described in Section 6.3.1, for certain rarer health exposures, analysis would not have been powered to detect a weak or even moderate-strength association. This was true for psychiatric care-level mental health problems, epilepsy, venous thromboembolic disease, cardiac arrhythmias, and structural heart disease, for which non-statistically significant associations were observed but an important relationship with HRJL could not be ruled out. For other rarer exposures such as peripheral arterial disease, COPD, and CVA the large strength of association observed meant that analysis was sufficiently powered (power ≥ 80%) to detect a statistically significant effect. However, for all other health exposures, analysis was sufficiently powered to detect weak, moderate, or strong associations with HRJL.

Statistical power dropped further after stratification for gender, age, and "type" of HRJL. For example, analysis in the male subgroup (n=440), as well as being underpowered to assess the rare exposures described above, was only sufficiently powered to detect moderate or strong associations with HRJL for chronic MSDs, heart failure, ischaemic heart

disease, and asthma, and strong associations only for sleep disorders and history of severe mental health problems. Nonetheless, due to the large strength of association observed with HRJL, analyses were sufficiently powered (power ≥ 80%) to detect a statistically significant relationship for chronic MSDs, heart failure, and history of severe mental health problems even after stratification by male participants. In addition, analysis remained sufficiently powered to detect a weak, moderate, or strong association with HRJL for musculoskeletal pain, primary care-level mental health problems, and hypertension.

In addition, while this work describes multiple health disorders that have not yet been studied for their association with work disability in the literature, there were many health problems for which no CPRD information was available, for example, cancers and gastrointestinal disorders. Other weaknesses mentioned in the previous chapter remain a problem, including the fact that case definitions were subject to recall bias. Extent of measurement error is also likely to vary between CPRD-defined health disorders, which makes comparing the effects of these conditions difficult. This study is overly reliant on face validity to define health exposures; the CPRD-defined health disorders used here ideally require their own validation study, however, time resources were limited to accomplish this. Finally, there were weaknesses related to unmeasured confounders. It is particularly difficult to adequately adjust for a complicated concept such as socioeconomic status. For example, in this study, no information was available for a participant's income at the point of HRJL. Instead, qualification level was used to define educational attainment, which is frequently used as an indicator of socioeconomic status in the literature.(19–24,28,32,36,132,221–224) Certain factors related to the workplace have also been found to be associated with the risk of work disability. For example, heavy manual work,(19,21,24,25,136,222,232) absence of workplace accommodations,(25) high job strain,(231,232) and poor colleague support.(25,232) Available data limited the ability to adjust for all of these factors. However, case and control participants were found to be broadly similar for SOC-10 categories of occupation, with some exceptions (for example, teaching and elementary administrative jobs were more common among cases, business professionals and managers were more common among control participants, see Figure 35).

Otherwise, the adjusted analysis is a strength of this study. The major (non-health) predictors of work disability reported in the literature were accounted for. These included: age (19–41); female gender (19,21–24,28,30,31,33,39,132); socioeconomic status (21–23,32,40,222,225–230); education (19–24,28,32,36,132,221–224); geography or regional

differences (21,23,221,223,233,434,435); ethnicity (20,21,23,30,32); maritial status (21,23,24); and the beliefs and practices of treating healthcare professionals.(436,437) In matched analysis, age, gender, and GP practice were accounted for. By matching for GP practice, it was also possible to adjust for regional differences in work, the ethos and practices of any particular general practice and, to some extent, local levels of deprivation. I also adjusted statistically for educational attainment and marital status and adjustment for ethnicity was not necessary in this majority-white study population. The use of stratification in this chapter provides some preliminary data to show how the impact of health disorders upon ability to stay in work is modified across important age-bands and gender. Other strengths of this study have been touched on previously. In brief, CPRD records provided an objective source of health information that did not rely on the memory of study participants. Selected health problems for which information was available covered those recognised as being responsible for two-thirds of sickness absence and long-term incapacity in the UK.(48) Finally, working controls were drawn from the same study population as the case participants.

6.5 Summary

- Chronic musculoskeletal disorders, recent musculoskeletal pain, primary-care-level mental health problems, sleep disorders, hypertension, heart failure, peripheral arterial disease, COPD, cerebrovascular accident, and diabetes were significantly associated with the development of HRJL, after statistical adjustment for other known confounders.
- The effect estimates for psychiatric-level mental health disorders, ischaemic heart disease, cardiac arrythmias, and epilepsy suggested that they may also be associated with HRJL, however analysis was underpowered to show a statistically significant effect. Structural heart disease is also likely to be important at the individual level since all seven participants with this condition were cases, however for this reason it was also not possible to estimate strength of association.
- Studied health disorders appeared to have a broadly consistent association with HRJL after stratification by gender.
- Generally, studied health disorders appeared to have a stronger association with HRJL in the sub-group of cases for whom a health problem was the main reason, rather than partly the reason for job loss. However, many health disorders appeared to have a positive association with both classifications of HRJL.

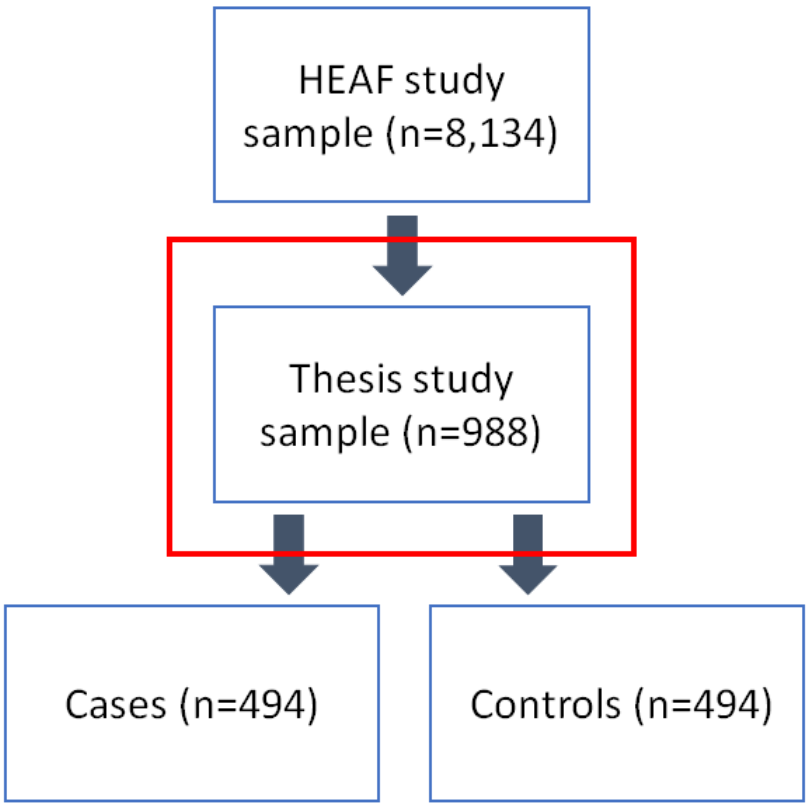
- For certain progressive age-related conditions, such as chronic MSDs, heart failure, and COPD, the strength of association was greater in the sub-group of cases with HRJL at older ages, in whom these diseases were more prevalent and possibly more severe. Conversely, the association between primary-care-level MHPs or recent musculoskeletal pain and HRJL seemed more marked in the younger age groups. However, in all cases following stratification, confidence intervals were wide.

Chapter 7- the patterns of CPRD-defined multimorbidity

7.1 Introduction

In the previous chapter, the association between individual health disorders and health-related job loss (HRJL) was explored. However, these disorders often do not occur in isolation, a large proportion of the older working-age population, particularly, have to manage multiple health problems (multimorbidity).(438) The co-presentation of health disorders may inhibit a person's ability to stay in work for reasons that go beyond the physical manifestations of these conditions and includes aspects of treatment burden and the necessity of attending multiple healthcare appointments.(190) In this chapter, participants under study are described for the presence and patterns of CPRD-defined multimorbidity. All participants are analysed together (unmatched) rather than by their case/control status, see Figure 37.

Figure 37: the cohort described in this chapter, as indicated by the red square



7.2 Methods

7.2.1 Description of multimorbidity and common disease pairs

Study participants were described for the presence of multimorbidity, which was defined as two or more co-occurring CPRD-defined health problems. As outlined previously, CPRD-defined health disorders included: chronic or recent musculoskeletal disorders, structural heart disease, hypertension, heart failure, ischaemic heart disease, venous thromboembolism, peripheral atherosclerotic disease, arrhythmias, primary-care-level mental health problems, psychiatric-care-level mental health problems, sleep disorders, COPD, asthma, cerebrovascular accident, epilepsy, and diabetes. With each health problem weighted equally as 1, participants were described for "number of morbidities" (in this case, participants were not scored twice for having both a chronic MSD and recent MSD pain). All CPRD-defined health disorders were also cross-tabulated and the most frequently co-occurring comorbidity pairs were described. Proportional statistics (i.e. percentages) were used to describe these categorical outcomes.

Additionally, participants were described for the total number of drug prescriptions they had been issued in the prior year, and the number of GP consultations they had attended. While these metrics are not true measures of multimorbidity, they are related to the overall health burden experienced. These continuous outcomes had a skewed distribution, therefore medians and inter-quartile ranges were used to report central tendency and spread.

7.2.2 Cluster analysis

Cluster analysis is a set of techniques used to separate participants into groups or "clusters" based on specific characteristics. Cluster analysis uses geometric distance (if plotted graphically) to find participants who are similar for a set of predefined variables, and is distinct from factor analysis, which defines a construct or "factor" which is a condensed statement of the relationships between a set of variables, and is based on correlations.(439) In the literature, cluster analysis has been used in many different clinical areas, including for finding groups of genes that have similar functions,(440) and in taxonomy, for example, when trying to characterise the clinical features of a certain subset of people with a disease.(441)

In this chapter, cluster analysis was used to describe common groups, or patterns, of multimorbidity. Many different methods are available for performing cluster analysis; the

rationales behind selecting the methods used in this chapter are outlined in Chapter 3, Section 3.8.3. The specific methods used in this chapter are outlined again, in brief, below.

In the first stage, the variables on which to perform cluster analysis were selected. Participants were clustered based on the presence or absence of disease codes alone, which included the list of CPRD-defined health disorders described above.

Cluster analysis grouped individuals based on their mathematical "similarity" for these selected variables. To mathematically describe the degree of similarity, the Jaccard coefficient was used.(321) This coefficient defines similarity between two individuals using a count-based algorithm which considers the proportion of binary variables that are present in two individuals over those that are present in both or only in one person, $J = M_{11} / M_{01} + M_{10} + M_{11}$, see Figure 38.

Figure 38: binary variables used in calculating the Jaccard similarity coefficient

	Disease absent (0)	**Disease present (1)**
Disease absent (0)	M_{00}	M_{10}
Disease present (1)	M_{01}	M_{11}

Cluster analyses can take hierarchical or non-hierarchical approaches. In order to take an explorative approach to cluster analysis and to visualise how groups merged at different levels of similarity, I undertook a hierarchical cluster analysis, making use of the generated dendrograms to visualise the clustering solution. For the current chapter, analysis was performed in STATA v13, which uses agglomerative, rather than divisive, hierarchical cluster analysis.(322)

Similarity measures, such as the Jaccard coefficient, may be employed in different clustering algorithms. These choose which groups of individuals (clusters) should be grouped together at each step in the clustering solution. In this chapter, an average-linkage algorithm was used which considered the average dissimilarity between participants of two clusters, and combines groups accordingly. Average-linkage algorithms are commonly used, reasonably robust, and produce more stable dendrograms.(324,325)

During hierarchical cluster analysis, the researcher must consider at what point clusters are most meaningful i.e. when individuals within each cluster are similar enough for their selected characteristics but the total number of clusters is also small enough to allow for intelligible comparison. This process is facilitated by the production of a tree-like dendrogram which allows the researcher to observe the overall similarity measure (the average within-cluster distance) at each point in the stepwise process. As part of this process, I observed points at which there were large leaps in the within-cluster dissimilarity between cluster steps, reflecting the algorithm's "reluctance" to join two clusters together, as occurs when there appear to be substantial inter-cluster differences. This was visualised by longer drawn out vertical lines on the dendrogram. When such leaps were visible, the process was stopped, and the comparative disease and demographic profiles of the generated clusters were examined. To compliment this process, the variance ratio criterion, or pseudo F-statistic, was calculated to suggest the optimum number of clusters.(326) When the F-statistic was similar at different stop points, the dendrogram was observed to make a final decision regarding number of clusters.

As part of this process, outlying clusters were identified and described. Such clusters are usually composed of few or single individuals with marked differences to the majority (e.g. rarer disorders). Outlying clusters were defined as those composed of less than 10 participants and were discarded from further analysis.

I have previously described how the relative prevalence of CPRD-defined health disorders varied between men and women in the study population (see Chapter 5). As a result, I was interested in whether the major patterns of multimorbidity also varied by gender. Cluster analysis was performed with stratification for men and women, accordingly.

Participants with chronic MSDs and participants with recent MSD pain tended to cluster together since approximately one third (34.9%) of participants with chronic MSDs also had recent MSD pain. As I could not rule out that recent MSD pain was a direct result of the underlying chronic MSD, and in order to avoid the formation of a meaningless musculoskeletal cluster, cluster analysis was run twice for each section of this chapter: first using chronic MSDs, then recent MSD pain. The generated clusters were compared.

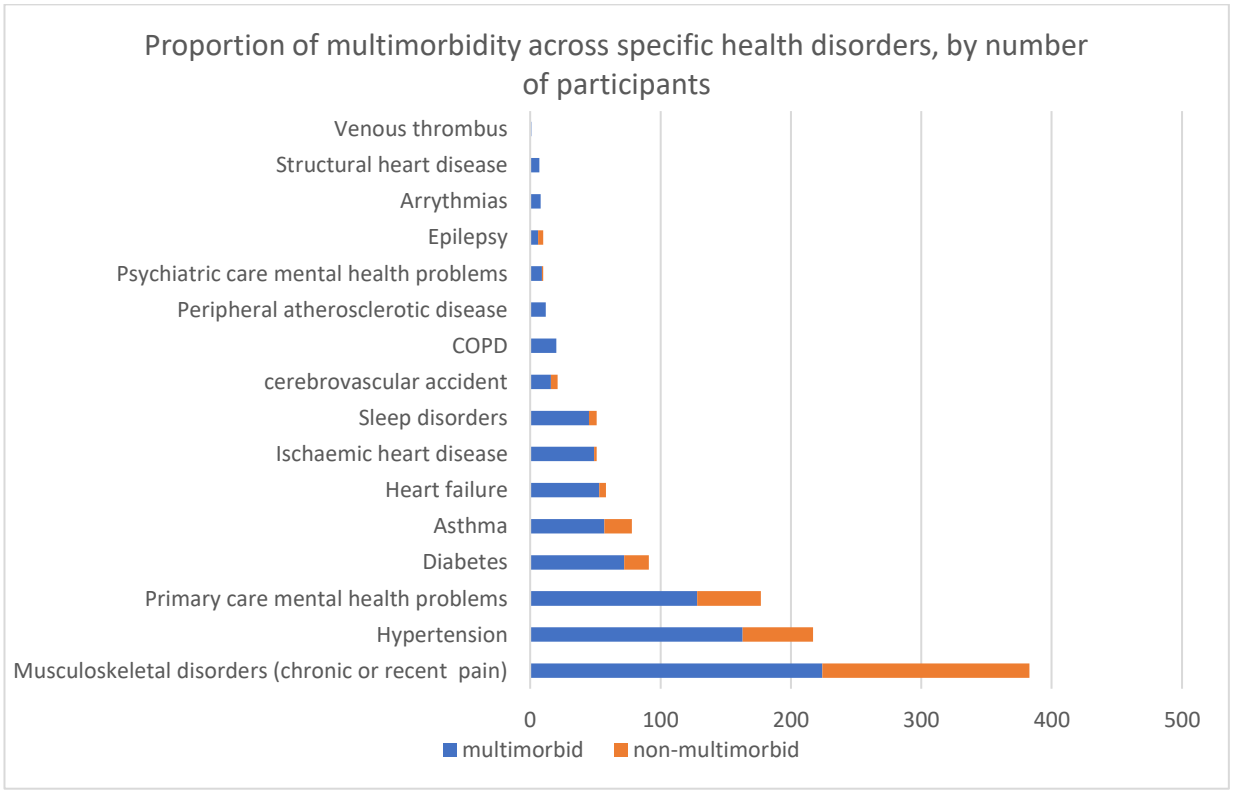
7.3 Results

7.3.1 Description

Including all cases and controls, there were 988 participants, half of whom had experienced HRJL and half who were matched controls. The median age was 58.21 years (IQR 53.36 to 60.89 years), at the point of analysis. Of these, 44.5% were men, 98.1% were white, 68.9% were married, and 7.8% were single. A university-level qualification had been attained by 22.6% and 19.6% reported having no qualifications. Finally, 35.8% were working in higher managerial or professional class occupations, 27.5% in intermediate occupations, and 36.7% in routine or manual occupations.

In total, 33.2% had multimorbidity, according to the definition of two or more co-occurring CPRD-defined health disorders (or morbidities); this was 38.0% among men and 29.4% among women. In total, there were 335 participants with no known health disorders (33.9%), 325 participants with one health problem (32.9%), 179 participants with two morbidities (18.1%), 103 participants with three morbidities (10.4%), 31 participants with four morbidities (3.1%), 12 participants with five morbidities (1.2%), two participants with six morbidities (0.2%), and one participant with seven morbidities (0.1%).

Figure 39: Prevalence of multimorbidity among participants with specific health disorders



The proportion of participants with multimorbidity by the number with specific health disorders was assessed (see Figure 39). Multimorbidity was present in 58.5% of participants with musculoskeletal disorders, 75.1% of participants with hypertension, 72.3% of participants with primary-care-level mental health problems, 79.1% of participants with diabetes, 73.1% of participants with asthma, 91.4% of participants with heart failure, 88.2% of participants with sleep disorders, 76.2% of participants with cerebrovascular accident, all participants with COPD, all participants with peripheral atherosclerotic disease, 90.0% of participants with psychiatric-level mental health disorders, 60.0% of participants with epilepsy, and all participants with arrhythmias, structural heart disease, or venous thromboembolism.

CPRD-defined health disorders were then cross tabulated to find the proportion of participants with specific comorbidity pairs (see Appendix, Table 57 and 58). In order of frequency, the most common comorbid disease pairs were: musculoskeletal disorders with hypertension (n=111, 11.2%); musculoskeletal disorders with primary-care-level mental health problems (n=89, 9.0%); diabetes with hypertension (n=46, 4.7%); musculoskeletal disorders with diabetes (n=39, 4.0%); primary-care-level mental health problems with sleep disorders (n=37, 3.7%); musculoskeletal disorders with asthma (n=34, 3.4%); primary-care-level mental health problems with hypertension (n=34, 3.4%); musculoskeletal disorders with sleep disorders (n=31, 3.1%); hypertension with ischaemic heart disease (n=27, 2.7%); musculoskeletal disorders with heart failure (n=24, 2.4%); heart failure with ischaemic heart disease (n=26, 2.6%); hypertension with heart failure (n=23, n=2.3%); musculoskeletal disorders with ischaemic heart disease (n=22, 2.2%); and hypertension with asthma (n=21, 2.1%).

CPRD data on the number of GP consultations attended by all study participants in the year prior to the point of analysis was considered. The median number of GP consultations in the prior year was four (IQR 1 to 9) ranging from 0 to 35 consultations. Information on the number of drug prescriptions issued in the prior year was also available (it is important to note that this is not the same as the total number of drugs taken by a patient in the prior year and would include repeat prescriptions). Across the total sample, the median number of prescriptions issued in the prior year was five (IQR 0 to 18) ranging from 0 to 86 prescriptions.

7.3.2 Cluster analysis of health problems across the total sample

Performing a cluster analysis of the total population (n=988) resulted in clusters that were primarily characterised by the presence of one condition, in addition to one large cluster of people with no known health disorders, see Appendix, Tables 59 and 60. This result was unsurprising since a sizable proportion of participants had only one known health disorder (n=325). However, these generated clusters were uninformative for characterising patterns of multimorbidity (overlapping health problems). Multimorbidity, as defined by the presence of two or more CPRD-defined health disorders, was common in the study population, but it was still unclear what combinations of diseases most frequently contributed to this condition. I therefore excluded participants with one or fewer known health problems from analysis and performed cluster analysis again, restricted to participants with multimorbidity.

7.3.3 Cluster analysis of health problems among people with multimorbidity

7.3.3.1 Using chronic MSDs as a measure of musculoskeletal disorders

An agglomerative hierarchical cluster analysis was performed using average-linkage methods and including participants with multimorbidity only.

Figure 40: Dendrogram of the clustering solution, for participants with multimorbidity

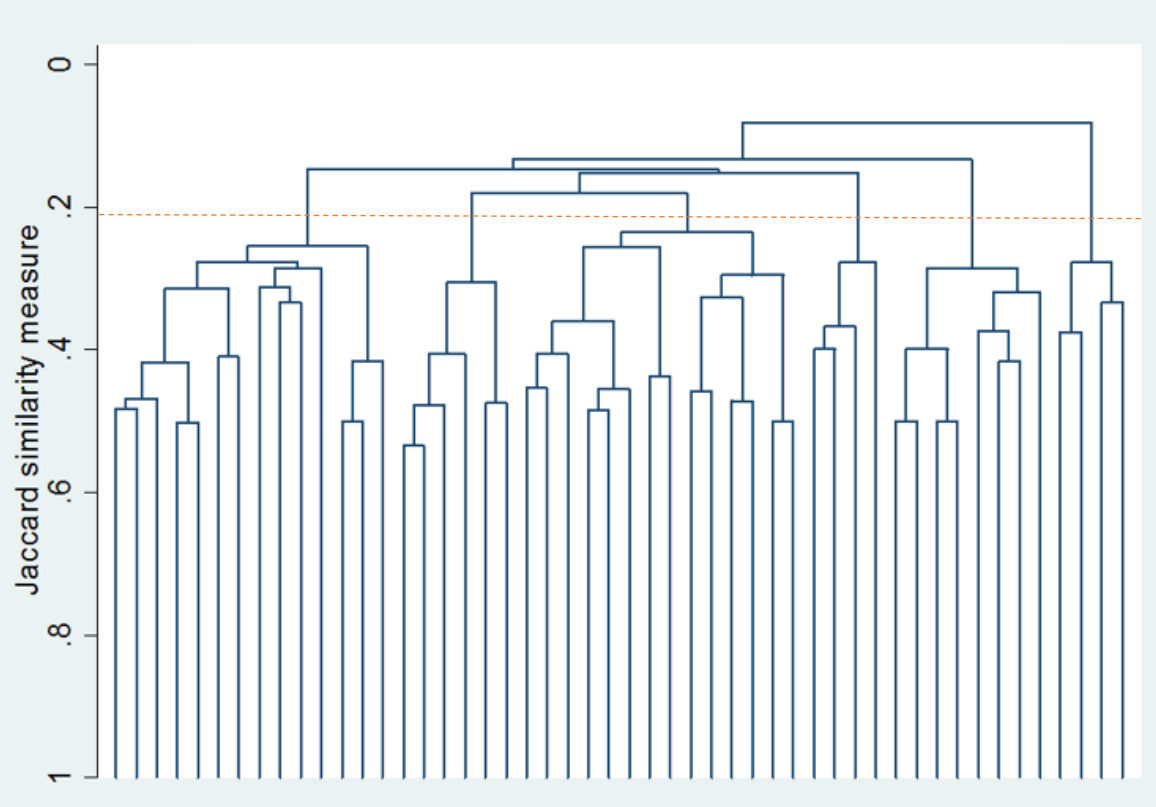


Figure 40 shows the resultant dendrogram. On the dendrogram, each vertical line represents a cluster at any point in the analysis, each horizontal line represents the merging of two clusters to become one. The graph has been simplified by hiding any clustering that occurred prior to around 0.5 Jaccard similarity. By observing which clusters are geometrically near to one another it was possible to consider which clusters would have merged had the clustering solution been permitted to continue for more steps.

Following the cluster solution, the pseudo F-statistics for each stop point were examined (see Table 100). For this analysis, the pseudo F-statistic suggested three possible stop points at a similar optimum stop-level with no clear peak. After reviewing the dendrogram, the analysis was stopped at six clusters (see orange dashed line, Figure 40). These clusters were characterised for their health disorder composition below.

Table 100: pseudo-F statistic across different stop points in the cluster solution for participants with multimorbidity

Number of clusters	Calinski-Harabasz pseudo-F statistic
2	4.47
3	12.87
4	28.91
5	23.08
6	28.74
7	29.06
8	26.29
9	24.10
10	22.61
11	18.88
12	18.55
13	17.33
14	16.49

Two small outlier groups were observed in the cluster solution. These included one cluster comprising four people with epilepsy (66.7% of the total number with epilepsy) and another made up of five participants with arrythmias (62.5% of the total number with arrhythmias). Excluding these, there were four main clusters which are summarised below, see Table 101 and Table 102. For a full description of these clusters for their demographics and CPRD-defined health disorders, see Tables 63 and 64, Appendix.

Cluster A was moderately large (n=88, 32.2% of multimorbid participants). All participants in this group had mental health problems, 96.6% of which were primary-care-level MHPs, with a 39.8% prevalence of sleep disorders. Additionally, this group contained five participants with psychiatric-care-level MHPs, 55.6% of the total number with these disorders. 50.0% also had chronic musculoskeletal disorders and 23.9% had hypertension. This group was characterised as the MHP-chronic MSD group. The majority in this group were case participants (77.3%).

Cluster B was smaller (n=35, 12.8%). Participants in this cluster all had cardiovascular disease, with a 94.3% prevalence of ischaemic heart disease, 74.3% prevalence of heart failure, and 62.9% prevalence of hypertension. In addition, 31.4% of participants had diabetes (accounting for 15.9% of the total number of multimorbid participants with diabetes). This group was characterised as the cardio-metabolic cluster. Most were cases (60.0%).

Cluster C was large (n=109, 39.9%). This cluster was comprised of a majority with chronic musculoskeletal disorders (73.4%) and hypertension (77.1%). The prevalence of participants with diabetes was also high in this group at 43.12% (68.1% of the total number of participants with diabetes). This group was characterised as the chronic MSD-hypertension cluster. Most in this cluster were cases (71.6%).

Lastly, Cluster D was small (n=32, 11.7%). The contributors to this cluster all had respiratory disorders. The majority had asthma (93.8%) and 40.6% had COPD, which represents 56.6% and 68.4% of the total multimorbid participants with asthma and COPD, respectively. Within this cluster, 40.6% had hypertension and 37.5% had primary-care-level mental health problems. This group was characterised as the respiratory cluster. Once again, the majority were cases (71.9%).

Table 101: major disease constituents of clusters among people with multimorbidity, using chronic MSDs to measure musculoskeletal disorders

Cluster name (abbreviation)	Number of participants (%)	Median number of health disorders (IQR)	Major disease constituents (prevalence >30%)
Cluster A (MHP-cMSD)	88 (32.2)	2 (2 – 3)	Primary care MHPs (96.6%) Chronic musculoskeletal disorders (50.0%) Sleep disorders (39.8%)

Cluster B (Cardio-metabolic)	35 (12.8)	3 (2 – 4)	Ischaemic heart disease (94.3%) Hypertension (62.9%) Heart failure (74.3%) Diabetes (31.4%)
Cluster C (HTN-cMSD-diab)	109 (39.9)	2 (2 – 3)	Hypertension (77.1%) Chronic musculoskeletal disorders (73.4%) Diabetes (43.1%)
Cluster D (OPD-HTN-MHP)	32 (11.7)	2 (2 – 3)	Asthma (93.8%) COPD (40.6%) Hypertension (40.6%) Primary care MHPs (37.5%)

Table 102: major demographics in clusters among people with multimorbidity, using chronic MSDs to measure musculoskeletal disorders

Cluster name (abbreviation)	Number of participants (%)	Median age, y (IQR)	Proportion of males, n (%)	Proportion with HRJL, n (%)	Qualification level, n (%)
Cluster A (MHP-cMSD)	88 (32.2)	57.30 (54.12 to 60.17)	29 (33.0)	68 (77.3)	University: 18 (20.5) Vocational: 29 (33.0) High school: 21 (23.9) No qualifications: 20 (22.7)
Cluster B (Cardio-metabolic)	35 (12.8)	61.13 (58.50 to 62.44)	29 (82.9)	21 (60.0)	University: 5 (14.3) Vocational: 13 (37.1) High school: 5 (14.3) No qualifications: 12 (34.3)
Cluster C (HTN-cMSD-diab)	109 (39.9)	59.63 (56.42 to 61.27)	61 (56.0)	78 (71.6)	University: 17 (15.6) Vocational: 44 (40.4) High school: 19 (17.4) No qualifications: 29 (26.6)
Cluster D (OPD-HTN-MHP)	32 (11.7)	57.43 (53.96 to 61.37)	14 (43.8)	23 (71.9)	University: 6 (18.8) Vocational: 13 (40.6) High school: 5 (15.6) No qualifications: 8 (25.0)

7.3.3.2 Using recent MSD pain as a measure of musculoskeletal disorders

Cluster analysis was run again for participants with multimorbidity, this time using recent MSD pain but not chronic MSDs in the analysis, any differences in the results were

considered. Excluding outliers, there were five main clusters, which are briefly summarised below, see Table 103 and Table 104. For a full description of these clusters for their demographics and CPRD-defined health disorders, see Table 65 and 66, Appendix.

Cluster E was large (n=95, 32.5% of multimorbid participants) and corresponded to Cluster C, above, as it was largely composed of participants with hypertension (76.8%) and recent MSD pain (77.9%). However, the proportion of participants with diabetes was not as high (16.8%) as an extra cluster (Cluster F) formed, which was comprised of diabetes and hypertension without recent MSD pain, see below. These two clusters merged in the next step of the clustering solution.

Cluster F was smaller (n=36, 12.3%). This cluster was comprised of participants with diabetes, the majority of whom had hypertension (72.2%). In addition, 30.6% of these participants had been diagnosed with a recent primary-care level MHP.

Cluster G was also small (n=35, 12.0%) and corresponded to Cluster B, above. This cluster was comprised of participants with majority cardiometabolic disorders, such as ischaemic heart disease (97.1%), heart failure (68.6%), hypertension (57.1%), and diabetes (34.3%).

Cluster H was large (n=110, 37.7%) and corresponded to Cluster A, above. The majority of participants in this cluster had primary-care-level MHPs (93.6%) and recent MSD pain (53.6%). A large proportion of this cluster also had recent sleep disorders (39.1%).

Lastly, Cluster I was small (n=12, 4.1%) and corresponded to Cluster D, above. Like Cluster D, the majority had asthma (83.3%) and COPD (97.7%). However, unlike Cluster D, Cluster I did not have a high prevalence of any other CPRD-defined health disorders.

Table 103: major disease constituents of clusters among people with multimorbidity, using recent MSD pain to measure musculoskeletal disorders

Cluster name (abbreviation)	**Number of participants (%)**	**Median number of health disorders (IQR)**	**Major disease constituents (prevalence >30%)**
Cluster E (MSpain- HTN)	95 (32.5)	2 (2 – 3)	Musculoskeletal pain (77.9%) Hypertension (76.8%)
Cluster F (Diab-HTN-pcMHP)	36 (12.3)	2 (2 – 3)	Diabetes (100.0%) Hypertension (72.2%) Primary care mental health problems (30.6%)

Cluster G (Cardio-metabolic)	35 (12.0)	3 (2 – 3)	Ischaemic heart disease (97.1%) Heart failure (68.6%) Hypertension (57.1%) Diabetes (34.3%)
Cluster H (MHP-MSpain)	110 (37.7)	2 (2 – 3)	Primary care mental health problems (93.6%) Musculoskeletal pain (53.6%) Sleep disorders (39.1%)
Cluster I (OPD)	12 (4.1)	2 (2 – 2.5)	COPD (97.7%) Asthma (83.3%)

Table 104: major demographics in clusters among people with multimorbidity, using recent MSD pain to measure musculoskeletal disorders

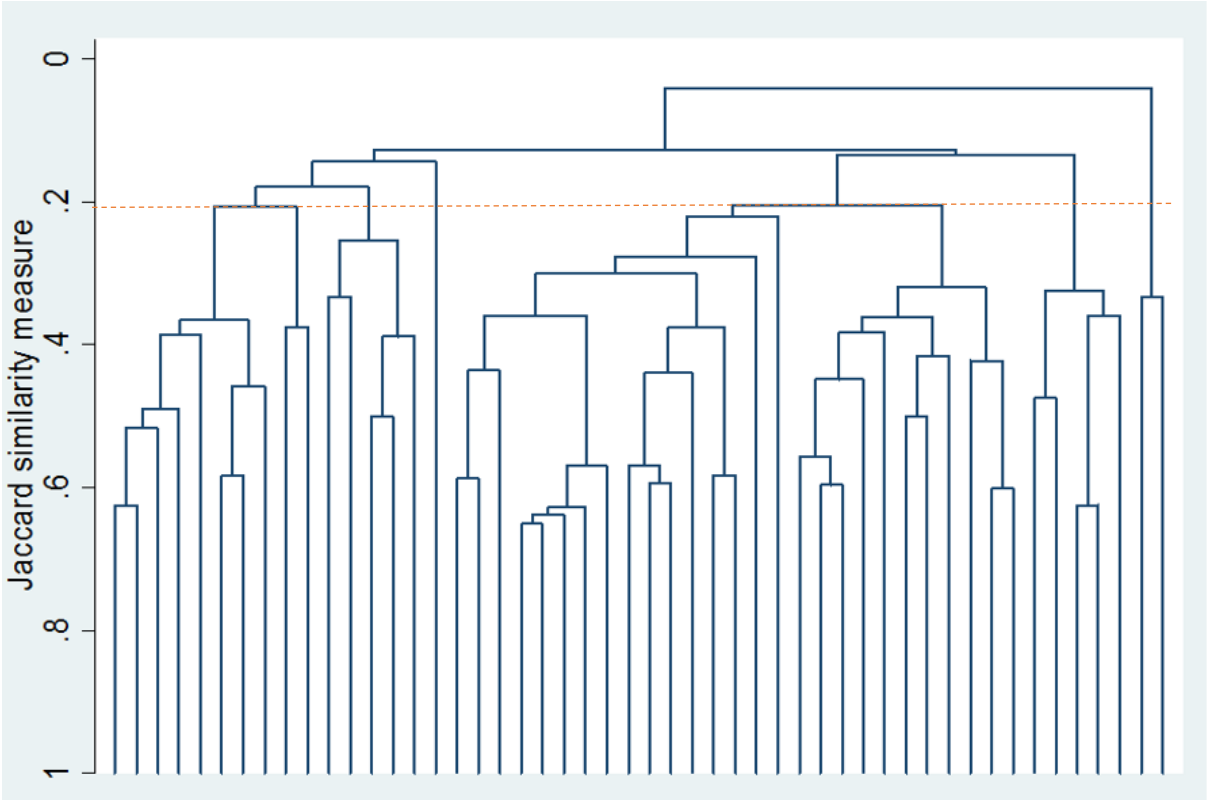
Cluster name (abbreviation)	Number of participants (%)	Median age, y (IQR)	Proportion of males, n (%)	Proportion with HRJL, n (%)	Qualification level, n (%)
Cluster E (MSpain-HTN)	95 (32.5)	59.10 (55.37 – 61.72)	56 (59.0)	64 (67.4)	University: 12 (12.6) Vocational: 44 (46.3) High school: 20 (21.1) No qualifications: 19 (20.0)
Cluster F (Diab-HTN-pcMHP)	36 (12.3)	59.18 (54.88 – 61.01)	23 (63.9)	26 (72.2)	University: 4 (11.1) Vocational: 12 (33.3) High school: 9 (25.0) No qualifications: 11 (30.6)
Cluster G (Cardio-metabolic)	35 (12.0)	60.09 (58.39 – 62.36)	30 (85.7)	24 (68.6)	University: 6 (17.1) Vocational: 14 (40.0) High school: 5 (14.3) No qualifications: 10 (28.6)
Cluster H (MHP-MSpain)	110 (37.7)	56.04 (51.99 – 60.00)	35 (85.7)	90 (81.8)	University: 27 (24.6) Vocational: 34 (30.9) High school: 25 (22.7) No qualifications: 24 (21.8)
Cluster I (OPD)	12 (4.1)	61.23 (58.21 – 63.99)	75 (68.2)	6 (50.0)	University: 2 (16.7) Vocational: 5 (41.7) High school: 3 (25.0) No qualifications: 2 (16.7)

7.3.4 Cluster analysis of health disorders among multimorbid men

7.3.4.1 Using chronic MSDs as a measure of musculoskeletal disorders

To determine whether multimorbidity patterns manifest in the same way among men and women, analysis was stratified by sex and cluster analysis was repeated, starting with multimorbid men.

Figure 41: Dendrogram of the clustering solution, for male participants with multimorbidity



Following the cluster solution, the pseudo F-statistic suggested five possible optimal cut points, but with a clearer peak around 7 (see Table 105). After consideration of the dendrogram the analysis was stopped at seven clusters (see orange dashed line, Figure 41). These clusters were characterised for their health disorder composition.

Table 105: pseudo-F statistic across different stop points in the cluster solution for multimorbid men

Number of clusters	Calinski-Harabasz pseudo-F statistic
2	2.25
3	9.58
4	12.07
5	9.44

6	9.09
7	13.47
8	12.50
9	11.30
10	10.46
11	9.58
12	11.37
13	12.26
14	12.22

There were three outlying clusters. These included: a cluster of seven participants with chronic MSDs, of whom four also had heart failure; a "cluster" comprised of one participant with heart failure and a recent sleep disorder; and a cluster of two participants with psychiatric-care level MHPs. Excluding these, there were four main clusters which are summarised below, see Table 106 and Table 107. For a full description of these clusters for their demographics and CPRD-defined health disorders, see Table 67 and 68, Appendix.

Cluster J among multimorbid men (n=21, 15.1%) was composed of participants with mental health disorders, including primary-care-level MHPs (90.5%) and sleep disorders (52.4%). Most also had chronic MSDs (66.7%). The large majority of participants in this group were cases (85.7%).

Cluster K (n=54, 38.9%) contained participants with a high prevalence of hypertension (96.30%), chronic MSDs (48.2%), and diabetes (44.4%). Most were cases (72.2%).

Cluster L (n=37, 26.6%) represented participants with cardio-metabolic conditions including 83.8% with ischaemic heart disease, 70.3% with heart failure, 62.2% with hypertension, and 35.1% with diabetes. The majority were cases (62.2%).

Finally, Cluster M contained people with respiratory disorders and was the smallest cluster (n=17, 12.2%). Most participants in this group had asthma (94.1%) however a large proportion also had COPD (41.2%), chronic MSDs (41.2%), and hypertension (41.2%). The majority were cases (70.6%).

Table 106: major disease constituents of clusters among multimorbid men, using chronic MSDs to measure musculoskeletal disorders

Cluster name (abbreviation)	Number of participants (%)	Median number of health disorders (IQR)	Major disease constituents (prevalence >30%)
Cluster J (MHP-cMSD)	21 (15.1)	3 (2 – 3)	Primary care mental health disorders (90.5%) Chronic musculoskeletal disorders (66.7%) Sleep disorders (52.4%)
Cluster K (HTN-cMSD-diab)	54 (38.9)	2 (2 – 3)	Hypertension (96.3%) Chronic musculoskeletal disorders (48.2%) Diabetes (44.4%)
Cluster L (Cardio-metabolic)	37 (26.6)	3 (2 – 3)	Ischaemic heart disease (83.8%) Heart failure (70.3%) Hypertension (62.2%) Diabetes (35.1%)
Cluster M (OPD-HTN-cMSD)	17 (12.2)	2 (2 – 3)	Asthma (94.1%) COPD (41.2%) Chronic musculoskeletal disorders (41.2%) Hypertension (41.2%)

Table 107: major demographics of clusters among multimorbid men, using chronic MSDs to measure musculoskeletal disorders

Cluster name (abbreviation)	Number of participants (%)	Median age, y (IQR)	Proportion with HRJL, n (%)	Qualification level, n (%)
Cluster J (MHP-cMSD)	21 (15.1)	56.07 (51.71 to 62.03)	18 (85.7)	University: 4 (19.1) Vocational: 7 (33.3) High school: 4 (19.1) No qualifications: 4 (19.1)
Cluster K (HTN-cMSD-diab)	54 (38.9)	58.84 (56.05 to 60.72)	39 (72.2)	University: 11 (20.4) Vocational: 22 (40.7) High school: 8 (14.8) No qualifications: 11 (20.4)
Cluster L (Cardio-metabolic)	37 (26.6)	61.13 (58.67 to 63.47)	23 (62.2)	University: 11 (29.7) Vocational: 13 (35.1) High school: 6 (16.2) No qualifications: 11 (29.7)

Cluster M (OPD-HTN-cMSD)	17 (12.2)	59.10 (55.82 to 63.47)	12 (70.6)	University: 4 (23.5) Vocational: 12 (70.6) High school: 0 (0.0) No qualifications: 4 (23.5)

7.3.4.2 Using recent MSD pain as a measure of musculoskeletal disorders

Cluster analysis was run again for male participants with multimorbidity, this time using recent MSD pain but not chronic MSDs in the analysis, any differences in the results were considered. Excluding outliers, this also resulted in four main clusters, which are briefly described below, see Table 108 and Table 109. For a full description of these clusters for their demographics and CPRD-defined health disorders, see Table 69 and 70, Appendix.

Cluster N was moderate sized (n=64, 41.6% of male multimorbid participants) and corresponded to Cluster K, above, as it was largely composed of participants with hypertension (73.4%) and recent MSD pain (62.5%), with a high prevalence of diabetes (43.8%).

Cluster O was smaller (n=31, 20.1%). This cluster corresponded to Cluster L, above, and was comprised of participants with cardio-metabolic conditions. These included ischemic heart disease (96.8%), heart failure (67.7%), hypertension (54.8%), diabetes (35.5%), and structural heart disease (12.9%).

Cluster P was also small (n=36, 12.0%) and corresponded to Cluster J, above. This cluster contained a high proportion of participants with primary care-level MHPs, many of whom also had musculoskeletal pain (44.4%), and sleep disorders (25.0%). However, unlike Cluster J, Cluster P also had a high prevalence of hypertension (38.9%).

Cluster Q was small (n=19, 12.3%) and corresponded well to Cluster M, above. Like Cluster M, the majority of participants in this cluster had asthma (94.7%) or COPD (36.8%), with a high prevalence of recent MSD pain (47.4%) and hypertension (42.1%).

Table 108: major disease constituents of clusters among multimorbid men, using recent MS pain to measure musculoskeletal disorders

Cluster name (abbreviation)	Number of participants (%)	Median number of health disorders (IQR)	Major disease constituents (prevalence >30%)
Cluster N (MSpain-HTN-Diab)	64 (41.6)	2 (2 – 3)	Musculoskeletal pain (62.5%) Hypertension (73.4%) Diabetes (43.8%)
Cluster O (Cardio-metabolic)	31 (20.1)	3 (2 – 4)	Ischaemic heart disease (96.8%) Heart failure (67.7%) Hypertension (54.8%) Diabetes (35.5%)
Cluster P (pcMHP-MSpain-HTN)	36 (23.4)	2 (2 – 3)	Primary care mental health problems (100.0%) Musculoskeletal pain (44.4%) Hypertension (38.9%)
Cluster Q (OPD-MSpain-HTN)	19 (12.3)	2 (2 – 3)	Asthma (94.7%) Musculoskeletal pain (47.4%) Hypertension (42.1%) COPD (36.8%)

Table 109: major demographics of clusters among multimorbid men, using recent MSD pain **to measure musculoskeletal disorders**

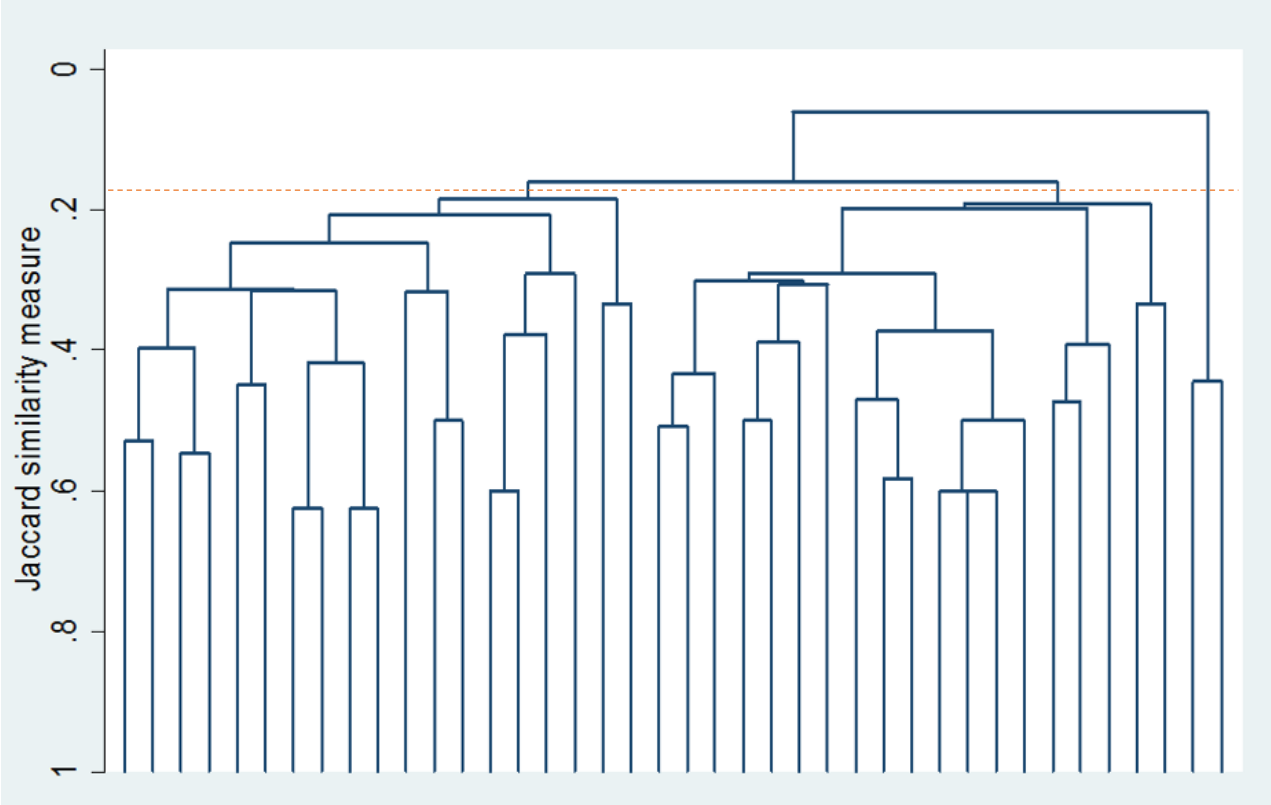
Cluster name (abbreviation)	Number of participants (%)	Median age, y (IQR)	Proportion with HRJL, n (%)	Qualification level, n (%)
Cluster N (MSpain-HTN-Diab)	64 (41.6)	59.29 (55.98 – 61.29)	44 (68.8)	University: 11 (17.2) Vocational: 28 (43.8) High school: 15 (23.4) No qualifications: 10 (15.6)
Cluster O (Cardio-metabolic)	31 (20.1)	60.09 (58.39 – 62.36)	21 (67.7)	University: 6 (19.4) Vocational: 12 (38.7) High school: 5 (16.1) No qualifications: 8 (25.8)
Cluster P (pcMHP-MSpain-HTN)	36 (23.4)	55.90 (50.44 – 60.05)	29 (80.6)	University: 9 (25.0) Vocational: 11 (30.6) High school: 7 (19.4) No qualifications: 9 (25.0)
Cluster Q (OPD-MSpain-HTN)	19 (12.3)	59.45 (54.19 – 63.70)	12 (63.2)	University: 2 (10.5) Vocational: 13 (68.4) High school: 1 (5.3) No qualifications: 3 (15.8)

7.3.5 Cluster analysis of health disorders among multimorbid women

7.3.5.1 Using chronic MSDs as a measure of musculoskeletal disorders

As with the multimorbid men, cluster analysis was restricted to multimorbid women and run again to assess common patterns of co-occurring health disorders among women.

Figure 42: Dendrogram of the clustering solution, for female participants with multimorbidity



The cluster solution for multimorbid women produced the dendrogram seen in Figure 42. Following this analysis, the pseudo F-statistic clearly suggested that three clusters was the optimal cut point (see Table 110). These clusters are characterised below. Given the small overall number of clusters I also looked for any important sub-clusters, using the dendrogram as guide.

Table 110: Pseudo-F statistic across different stop points in the cluster solution for multimorbid women

Number of clusters	Calinski-Harabasz pseudo-F statistic
2	5.67
3	19.91
4	14.17

5	11.78
6	11.66
7	12.29
8	11.62
9	12.25
10	11.14
11	11.10
12	10.28
13	11.87
14	11.72
15	11.36

There was one outlying group which did not merge with other groups until late in the clustering solution. This group comprised four participants with COPD, three of whom had asthma and two who had heart failure. Since it was difficult to derive useful information from this small cluster it was excluded from further analysis. This left two main clusters which are summarised below, see Table 111 and Table 112. For a full description of these clusters for their demographics and CPRD-defined health disorders, see Table 71 and 72, Appendix.

Cluster R (n=71, 53.0%) could be characterised by its high prevalence of hypertension (77.5%) and chronic MSDs (64.8%). A significant proportion also had diabetes (32.4%), primary care-level MHPs (25.4%), and asthma (23.9%). Four major sub-clusters were observed, three of which were small and comprised of four, nine, and two participants, respectively. The first sub-cluster was the largest and composed of participants who mostly had hypertension (n=91.1%) and chronic musculoskeletal disease (67.9%). This group also contained a significant proportion of participants with asthma (26.8%), diabetes (21.4%), and primary care level MHPs (25.0%). As a consequence of its size, it was the major driver of the characteristics of the larger cluster it contributed to. The second sub-cluster comprised four participants, all with hypertension, three with heart failure, two with cerebrovascular accident, and two with diabetes. The next sub-cluster was composed of nine participants with diabetes, six of whom also had a chronic MSD, and four with a primary-care-level MHPs. The last sub-cluster had two participants with chronic MSDs, one with comorbid cerebrovascular accident and another with comorbid epilepsy. Most participants in Cluster R were cases (71.8%).

Cluster S (n=59, 44.0%) was characterised by a high prevalence of mental health disorders (94.9%) including primary-care-level MHPs (94.9%) and sleep disorders (47.5%), primarily.

Once again, the prevalence of chronic MSDs was relatively high (42.4%). Three sub-clusters, contributing to this broad cluster group, were observable. The larger sub-cluster (n=51) was similar to the broad group; all members had mental health disorders, including 98.0% with primary care-level MHPs, and 51.0% with sleep disorders, also 45.1% in this sub-cluster had chronic MSDs. The second sub-cluster was small (n=5) and contained participants with ischaemic heart disease and heart failure, three participants in this sub-cluster had mental health disorders and two had chronic MSDs. Lastly, the third sub-cluster contained three participants with epilepsy (75% of all multimorbid women with epilepsy). Once again, the majority in Cluster S were cases (74.6%).

Table 111: Major disease constituents of clusters among multimorbid women, using chronic MSDs to measure musculoskeletal disorders

Cluster name (abbreviation)	Number of participants (%)	Median number of health disorders (IQR)	Major disease constituents (prevalence >30%)
Cluster R (HTN-cMSD-diab)	71 (53.0)	2 (2 – 3)	Hypertension (77.5%) Chronic musculoskeletal disorder (64.8%) Diabetes (32.4%)
Cluster S (MHP-cMSD)	59 (44.0)	2 (2 – 3)	Primary care mental health problems (93.2%) Sleep disorders (47.5%) Chronic musculoskeletal disorders (42.4%)

***Table 112: Major demographics of clusters among multimorbid women, using chronic MSDs* to measure musculoskeletal disorders**

Cluster name (abbreviation)	Number of participants (%)	Median age, y (IQR)	Proportion with HRJL, n (%)	Qualification level, n (%)
Cluster R (HTN-cMSD-diab)	71 (53.0)	59.86 (56.42 – 61.48)	51 (71.8)	University: 11 (15.5) Vocational: 27 (38.0) High school: 13 (18.3) No qualifications: 20 (28.2)
Cluster S (MHP-cMSD)	59 (44.0)	56.80 (52.65 – 60.00)	44 (74.6)	University: 7 (11.9) Vocational: 19 (32.2) High school: 15 (25.4) No qualifications: 18 (30.5)

7.3.5.2 Using recent MSD pain as a measure of musculoskeletal disorders

Cluster analysis was run again for female participants with multimorbidity, this time using recent MSD pain but not chronic MSDs in the analysis. Excluding outliers, this also resulted in two main clusters, which are briefly described below, see Table 113 and Table 114. For a full description of these clusters for their demographics and CPRD-defined health disorders, see Table 73 and 74, Appendix.

Cluster T was moderate sized (n=67, 48.6% of female multimorbid participants) and corresponded to Cluster R, above. It was largely composed of participants with hypertension (80.6%) and recent MSD pain (56.7%), with a high prevalence of diabetes (28.4%), primary care level MHPs (29.9%), and asthma (29.9%).

Cluster U was also moderate sized (n=62, 44.9%) and corresponded to Cluster S, above. The majority of participants in this cluster had primary care-level MHPs (98.4%) and recent MSD pain (54.8%). The prevalence of recent sleep disorders was also high (45.2%).

Table 113: Major disease constituents of clusters among multimorbid women, using recent MSD pain to measure musculoskeletal disorders

Cluster name (abbreviation)	Number of participants (%)	Median number of health disorders (IQR)	Major disease constituents (prevalence >30%)
Cluster T (HTN-MSpain)	67 (48.6)	2 (2 – 3)	Hypertension (80.6%) Musculoskeletal pain (56.7%)
Cluster U (MHP-MSpain)	62 (44.9)	2 (2 – 3)	Primary care mental health problems (98.4%) Musculoskeletal pain (54.8%) Sleep disorders (45.2%)

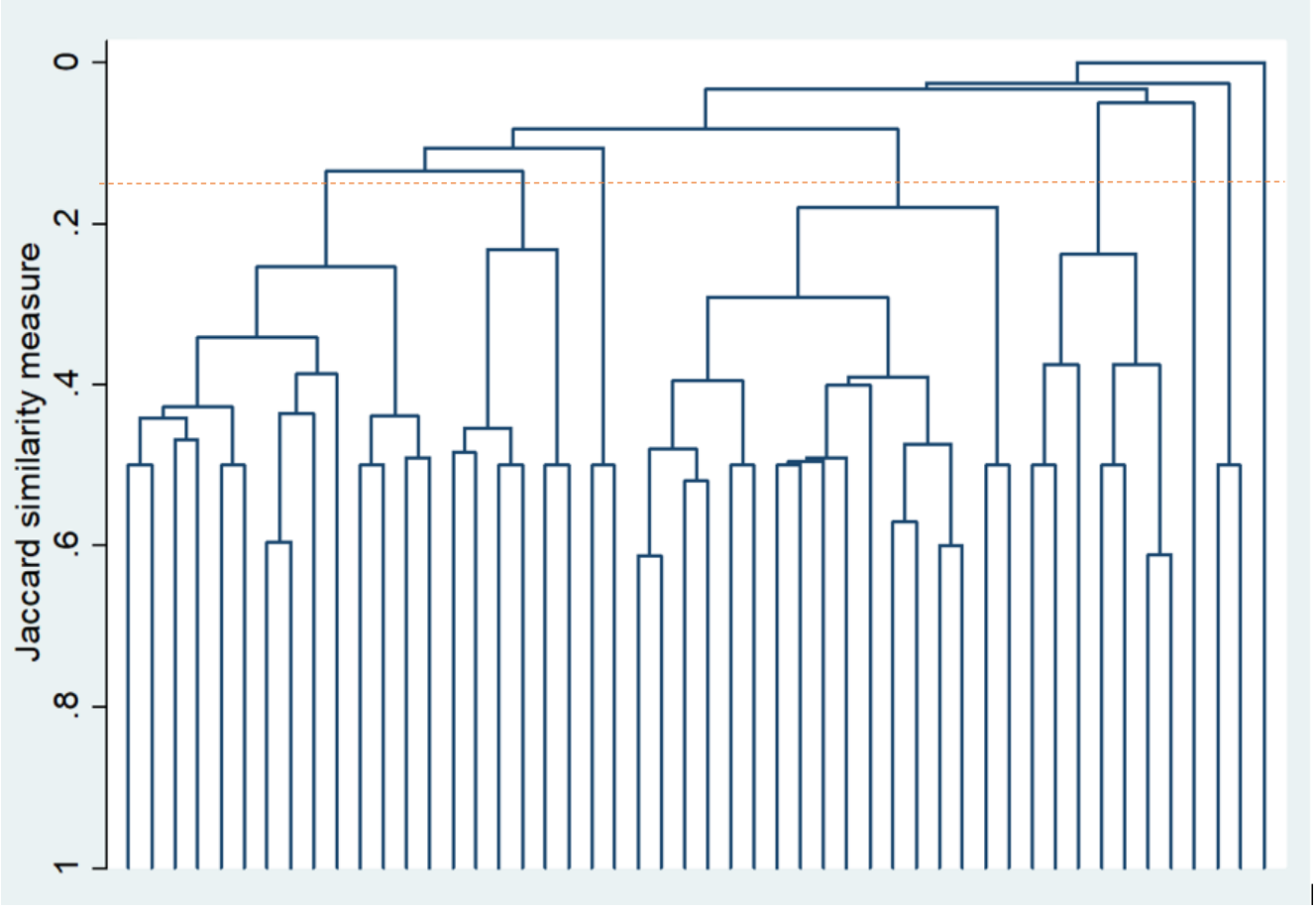
***Table 114: Major demographics of clusters among multimorbid women, using recent MSD pain* to measure musculoskeletal disorders**

Cluster name (abbreviation)	Number of participants (%)	Median age, y (IQR)	Proportion with HRJL, n (%)	Qualification level, n (%)
Cluster T (HTN-MSpain)	67 (48.6)	59.06 (55.24 – 61.21)	49 (73.1)	University: 6 (9.0) Vocational: 25 (37.3) High school: 16 (23.9) No qualifications: 20 (29.9)
Cluster U (MHP-MSpain)	62 (44.9)	56.28 (52.35 – 60.00)	50 (80.7)	University: 15 (24.2) Vocational: 19 (30.7) High school: 16 (25.8) No qualifications: 12 (19.4)

7.3.6 Cluster analysis of health disorders among people with musculoskeletal disorders (recent pain or chronic)

Because of sample size limitations, and since the observed clustering behaviours of chronic MSDs and recent MSD pain were similar, I combined chronic MSD and recent MSD pain groups to look for multimorbidity (or comorbidity) patterns among participants with musculoskeletal disorders. Cluster analysis was restricted to people with chronic MSDs or recent MSD pain and run again.

Figure 43: Dendrogram of the clustering solution, for participants with musculoskeletal disorders



The cluster solution for participants with musculoskeletal disorders produced the dendrogram seen above (Figure 43). Following this analysis, the pseudo F-statistic promoted the stopping point of 2 clusters (Table 115), however, stopping analysis here would have resulted in two groups: people with musculoskeletal disorders with comorbidities and without comorbidities. A stopping point of 13 or 14 was also suggested, however, as observed in Section 7.3.2, this would have resulted in many smaller clusters characterised by the presence of one other health problem, a result that could be achieved

with the use of simple cross tabulations and would have been uninformative for deciphering common patterns of comorbidity. I therefore stopped the analysis at a smaller number of clusters to look for common groups of co-occurring disorders. The pseudo F-statistic suggested eight clusters as offering the next best variance ratio criteria, therefore, I chose this as the stop point (see orange dashed line, Figure 43). The generated clusters are characterised below.

Table 115: Pseudo-F statistic across different stop points in the cluster solution for people with musculoskeletal disorders

Number of clusters	Calinski-Harabasz pseudo-F statistic
2	64.29
3	35.60
4	31.55
5	24.43
6	49.35
7	43.11
8	50.50
9	45.53
10	42.72
11	39.70
12	47.61
13	55.98
14	60.57

Three small outlier groups were observed in the cluster solution. One cluster contained three participants with COPD, another "cluster" contained one person with a cardiac arrythmia, and another was comprised of three participants with cerebrovascular accident. Excluding these, there were five main clusters which are summarised below, see Table 116 and Table 117. For a full description of these clusters for their demographics and CPRD-defined health disorders, see Table 75 and 76, Appendix.

Cluster V was the cluster on the far right-hand side on the dendrogram (Figure 43). This cluster comprised participants with musculoskeletal disorders, and no other known comorbid health problems (n=159, 41.5%). 56.6% of these participants had a chronic MSD and 61.6% had recent MSD pain. Since all participants in this group were identical from the perspective of known health disorders, this group was resistant to merge with the other clusters and merged last. Most participants in this cluster (56.6%) did not report HRJL (were controls).

Cluster W was large (n=96, 25.1%) and contained participants with a high prevalence of comorbid hypertension (87.5%). 61.5% of these participants had a chronic MSD and 60.4% had recent MSD pain. The prevalence of other cardiometabolic conditions was also high in this group. For example, 33.3% had comorbid diabetes, 10.4% had comorbid heart failure, 12.5% had comorbid ischaemic heart disease, and 4.2% had comorbid peripheral atherosclerotic disease. Most participants in Cluster W were cases (62.5%).

Cluster X was small (n=25, 6.5%) and the majority had comorbid asthma (96.0%). Chronic MSDs were present in 64.0% and recent MSD pain in 56.0%. In addition, 36.0% of this group had comorbid hypertension and 12.0% had comorbid ischaemic heart disease. Most participants were cases (68.0%).

Cluster Y was large (n=86, 22.5%) and most of these participants had comorbid primary care-level MHPs (91.9%). Recent MSD pain was present in 69.8% and chronic MSDs in 50.0%. A large proportion of this cluster also had comorbid sleep disorders (34.9%) and comorbid hypertension (19.8%). The large majority were cases (83.7%).

Cluster Z was very small (n=10, 2.6%) and contained nine participants with comorbid heart failure, and five participants with comorbid ischemic heart disease, although no participants with hypertension. Five of these participants had a chronic MSD and seven had recent MSD pain. Seven participants in this group were cases.

Table 116: Major disease constituents of clusters among people with MSDs (chronic or recent pain)

Cluster name (abbreviation)	Number of participants (%)	Median number of health disorders (IQR)	Major disease constituents (prevalence >30%)
Cluster V (MSD alone)	159 (41.5)	1 (1 – 1)	Musculoskeletal disorders alone (100.0%)
Cluster W (HTN-Diab)	96 (25.1)	2 (2 – 3)	Hypertension (87.5%) Diabetes (33.3%)
Cluster X (Asthma-HTN)	25 (6.5)	3 (2 – 3)	Asthma (96.0%) Hypertension (36.0%)
Cluster Y (MHP)	86 (22.5)	3 (2 – 3)	Primary care-level MHP (91.9%) Sleep disorders (34.9%)
Cluster Z (Cardio-metabolic)	10 (2.6)	3 (2 – 4)	Heart failure (90.0%) Ischaemic heart disease (50.0%)

Table 117: Major demographics of clusters among people with MSDs (chronic or recent pain)

Cluster name (abbreviation)	Number of participants (%)	Median age, y (IQR)	Proportion with HRJL, n (%)	Qualification level, n (%)
Cluster V (MSD alone)	159 (41.5)	58.10 (53.36 – 60.99)	69 (43.4)	University: 35 (22.0) Vocational: 70 (44.0) High school: 23 (14.5) No qualifications: 31 (19.5)
Cluster W (HTN-Diab)	96 (25.1)	59.72 (55.98 – 61.39)	60 (62.5)	University: 14 (14.6) Vocational: 42 (43.8) High school: 18 (18.8) No qualifications: 22 (22.9)
Cluster X (Asthma-HTN)	25 (6.5)	59.45 (56.07 – 61.85)	17 (68.0)	University: 4 (16.0) Vocational: 12 (48.0) High school: 3 (12.0) No qualifications: 6 (24.0)
Cluster Y (MHP)	86 (22.5)	55.99 (52.36 – 60.07)	72 (83.7)	University: 17 (19.8) Vocational: 29 (33.7) High school: 21 (24.4) No qualifications: 19 (22.1)
Cluster Z (Cardio-metabolic)	10 (2.6)	60.59 (57.26 – 62.13)	7 (70.0)	University: 0 (0.0) Vocational: 4 (40.0) High school: 3 (30.0) No qualifications: 3 (30.0)

7.4 Summary of results

- Among participants with multimorbidity, there were four main clusters, including: a large cluster of participants with mental health disorders and MSDs, primarily; a small cluster of participants with ischaemic heart disease, heart failure, and hypertension primarily; a large cluster of participants with hypertension and MSDs, primarily; and a small cluster of participants with asthma and COPD, primarily. Formed clusters were similar regardless of whether chronic MSDs or recent MSD pain was used in analysis.

- Among male multimorbid participants, there were four main clusters, including: a cluster of participants with mental health disorders and MSDs, primarily; a cluster of participants with hypertension, diabetes, and MSDs, primarily; a cluster of participants with cardio-metabolic disorders, primarily; and a cluster of participants

with asthma, COPD, MSDs, and hypertension, primarily. Formed clusters were similar regardless of whether chronic MSDs or recent MSD pain was used in analysis.

- Among female multimorbid participants, there were two main clusters, including: a cluster of participants with hypertension and MSDs, primarily; and a cluster of participants with mental health disorders and chronic MSDs, primarily. Formed clusters were similar regardless of whether chronic MSDs or recent MSD pain was used in analysis.

- Among participants with musculoskeletal disorders (chronic or recent pain), there were five main clusters of comorbid disorders, the largest of which was formed by participants with musculoskeletal disorders without known comorbidities. Otherwise, the following clusters were identified: a large cluster of participants with comorbid hypertension, primarily; a small cluster of participants with comorbid asthma, primarily; a large cluster of participants with comorbid mental health problems, primarily; and a very small cluster of participants with other comorbid cardiometabolic disorders, primarily.

7.5 Discussion

The most frequently occurring pairs of health disorders in the study sample were musculoskeletal disorders (chronic or pain) with hypertension, followed by musculoskeletal disorders (chronic or pain) with primary-care level MHPs, then diabetes with hypertension. In cluster analysis, among participants with two or more health problems, the most commonly occurring disease clusters were hypertension-musculoskeletal and mental health disorder-musculoskeletal groups, which together included over two thirds of all multimorbid participants. The musculoskeletal-mental health cluster was more prominent among women than men, while among men a cardio-metabolic cluster was also apparent, reflecting the relative prevalence of these conditions in these sub-populations.

A quick description of participants by number of health conditions revealed that approximately a third had no known health disorders, and of those with known health disorders, approximately half had only one. This was reflected in the cluster analysis of the total sample in which prominent clusters tended to form around the presence or absence of single conditions. Multimorbidity, by the definition used in this chapter, was present in approximately a third of all participants (33.2%). It is difficult to compare this prevalence

figure to those reported in the literature, which are often based on very different classifications of multimorbidity (using different constituent diseases, for instance), and therefore have highly variable estimates (12.9% to 95.1%).(164)

In cluster analysis of participants with multimorbidity, prominent groups formed more clearly into "body systems." For example, sleep disorders and primary-care level MHPs tended to cluster together, as did cardio-metabolic disorders, and respiratory disorders (asthma and COPD). Chronic musculoskeletal disorders, and recent musculoskeletal pain, were found to commonly cluster with mental health disorders and also with hypertension. These clusters were only generated among people with two or more conditions; there was also a significant proportion of participants with chronic musculoskeletal disorders, hypertension, and primary-care-level mental health problems who did not have other known health disorders.

Comparisons between these findings and those of existing population-based research, examining common patterns of multimorbidity, are hampered by the considerable heterogeneity in the literature. Studies differ for number, demographics, and selectivity of recruited participants; the data sources and classifications used to define health disorders; the number of health disorders considered; and the statistical techniques used (cluster and factor analysis are common approaches used). Nevertheless, a well-cited systematic review of 14 such studies (Prados-Torres, 2014) found three broad patterns, or clusters, of diseases were commonly reported: 1) cardiovascular and metabolic disease clusters 2) disorders related to mental health and 3) disorders related to musculoskeletal problems.(442) Importantly, little of the reviewed work was age- or sex-stratified, and no studies had a focus on the older-working-age population.

The results reported in this chapter show some similarities. For instance, mental health disorders were observed to naturally cluster together, as did cardiovascular-metabolic disorders. By design, the formation of a musculoskeletal disease cluster was prohibited since only one MSD variable was entered into cluster analysis at a time (see Section 7.2.2). However, this made it possible to observe how musculoskeletal disorders (the focus of this thesis) commonly overlap with other prominent disease clusters. Results showed that when musculoskeletal disorders form clusters with non-musculoskeletal conditions, they form them commonly with mental health disorders and with cardio-metabolic disorders, particularly hypertension.

Another systematic review, including primary care populations only, considered other aspects of multimorbidity including its overall prevalence and the frequency of specific comorbidity pairs.(164) This review found that osteoarthritis with hypertension constituted the most common comorbidity in primary care, a relationship largely driven by the high individual prevalence of these two conditions. The common clustering of pain conditions (such as chronic musculoskeletal disorders) with mental health disorders was also highlighted in some studies.(443–445) In this chapter, hypertension with musculoskeletal disorders (many of whom had osteoarthritis - see Chapter 5) was also the most frequently occurring comorbidity pair, followed by musculoskeletal disorders with primary-care-level mental health disorders. In cluster analysis of multimorbid participants, the hypertension-musculoskeletal clusters and mental health-musculoskeletal clusters were also the largest clusters.

In cluster analysis, large clusters formed by common health disorders may obscure the existence of smaller naturally occurring clusters. However, two smaller clusters were observed among multimorbid participants, including an asthma-COPD cluster and a cluster composed of cardio-metabolic disorders alone. The cardio-metabolic cluster was driven primarily by ischaemic heart disease, heart failure, and hypertension. This likely reflects the particularly strong pathogenetic relationship shared by these conditions, since hypertension is a major risk factor for coronary heart disease(446) and ischaemic heart disease is the most common underlying cause of heart failure.(447) The relationship between asthma and COPD is more surprising, since these are etiologically distinct conditions, but could be explained by misdiagnosis, common among older patients,(448) or the so called “overlap syndrome” between the two disorders.(449)

Sub-group analysis of multimorbid participants by sex found mental health disorder-musculoskeletal clusters, and hypertension-musculoskeletal clusters in both men and women, as in the broader sample. However, a cluster of cardio-metabolic disorders was observed among men, but not women. Additionally, the proportion of women in the mental health disorder-musculoskeletal clusters was also considerably larger than the corresponding clusters among men. These differences are likely driven by the significantly greater prevalence of structural cardiovascular disorders among men in this age group,(236) and the greater prevalence of diagnosed anxiety and depression among women across most age groups.(235)

Surprisingly few differences were observed between chronic MSDs or recent MSD pain in cluster analysis. Generated clusters were similar in size and composition regardless of which musculoskeletal variable was used, both in cluster analysis of multimorbid participants and after stratification by gender. It was reasonable, therefore, to combine these groups and look for clusters of comorbidities that commonly occur in the MSD population as a whole. The generated clusters mirrored those which occurred in the wider study sample: There was a large cluster of participants with comorbid hypertension, primarily; a small cluster of participants with comorbid asthma, primarily; a large cluster of participants with comorbid mental health problems, primarily; and a very small cluster of participants with other comorbid cardiometabolic disorders, primarily.

It was beyond the scope of this piece of work to study why certain conditions co-occur; rather the purpose of this chapter was to show how health disorders group together in the older working-age population, and which specific disorders are most commonly observed together. The use of cluster analysis, to achieve this, has strengths. These techniques use mathematical relationships that are data driven, rather than reliant upon biological or clinical assumptions, to provide new insight into relationships which are not fully understood. They also allow the exploration of complex data in a new way. For example, the prevalence of specific disease pairs in a population could be described using simple cross-tabulations; however, this task becomes precipitously more complex the more overlapping diseases are considered. Statistical techniques such as cluster analysis and factor analysis can help cut through this complexity to identify common comorbidity groups of varying size and composition.

However, a weakness of both cluster analysis and factor analysis is that the selection of defining variables, or clustering analysis options (e.g. similarity measures and clustering algorithms), can strongly influence the resultant clusters or factors. Additionally, a cluster analysis will always create clusters, even regardless of the existence of any actual patterns in the data. Therefore, there is an inherent assumption in the interpretation of such clusters that the observed patterns are based on some underlying structure. Strong conceptual support and validation is required to evidence the existence of such patterns. I performed a manner of internal validity of the cluster analysis by running Calinski-Harabasz criterion to suggest the most distinct clusters possible.(326) In addition, there was strong conceptual support, and some external validity, since the groups identified in this chapter had similarities to those found in existing systematic reviews.(164,442) Finally, generated clusters remained stable regardless of whether a recent musculoskeletal pain or chronic

MSD classification of MSDs was used. It would have also been desirable to re-run results in a randomly split or comparable dataset,(325) however, sample-size constraints meant such cross-validation methods were unfeasible.

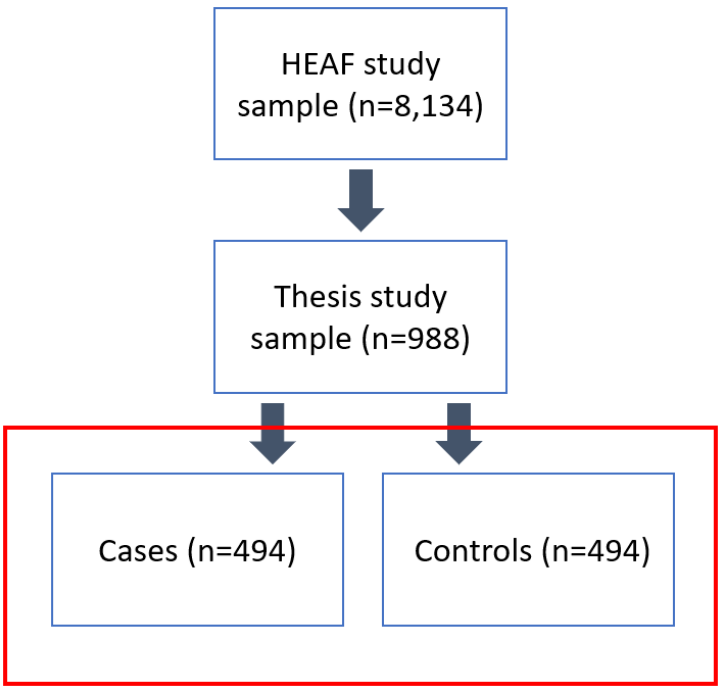
In conclusion, the descriptive analyses outlined in this chapter reveals a high degree of multimorbidity in this older working age sample. Results suggest that the studied health disorders should not be viewed in isolation when assessing their role as catalysts of adverse work outcomes in older workers. Specifically, researchers and policymakers considering work outcomes and musculoskeletal disorders should be aware that these conditions frequently overlap with mental health problems and hypertensive disorders. An increased focus on multimorbidity will promote holistic work solutions for older working-age patients in a system that too often targets single illnesses alone. The findings of this chapter also lend themselves to a study of the relationship between common multimorbidity clusters and health-related job loss.

Chapter 8- the impact of multimorbidity upon HRJL

8.1 Introduction

In the previous chapter, participants were described for patterns of multimorbidity. The work of this chapter moves beyond the study of individual diseases and their association with HRJL (as studied in Chapter 6) and focusses on the relationship between multimorbidity and HRJL. This topic is especially important in the older working-age population, in whom up to a half have been found to be multimorbid.(153) However, the relationship between multimorbidity and premature exit from work for health reasons remains understudied. In this chapter, cases and controls will be compared for four specific indicators of multimorbidity, including: the number of known CPRD-defined health disorders, the number of drug prescriptions in the prior year, the number of GP consultations attended in the prior year, and lastly the presence of disease clusters, as defined in the prior chapter. The role of gender as a mediator of this relationship is considered. Additionally, the impact of comorbidity on the relationship between MSDs and HRJL is also explored. This work will address Research Objectives 5 and 6 of this thesis (see Chapter 2).

Figure 44: the cohort studied in this chapter, as indicated by the red square



8.2 Methods

Descriptive analysis

To begin, the total study population were described for their demographic, lifestyle and occupational factors and for the overall prevalence of CPRD-defined health disorders. In addition, participants with MSDs (chronic or pain) specifically were described, since they form a focus of this chapter. I used proportions to describe categorical data and medians and inter-quartile ranges to describe continuous data with non-Gaussian distributions.

Cases and controls were then compared for the proportion with multimorbidity. Multimorbidity was defined as the presence of two or more of the following CPRD-defined health disorders: structural heart disease, hypertension, heart failure, ischaemic heart disease, venous thromboembolism peripheral atherosclerosis, cardiac arrhythmias, primary care mental health problem, psychiatric mental health problem, sleep disorder, COPD, asthma, CVA, epilepsy, diabetes, or a musculoskeletal disorder (chronic or pain). Additionally, with each health disorder weighted equally as 1, cases and controls were described and analysed for "number of health disorders." Participants with MSDs were described for the number of known comorbid health problems. These included the non-musculoskeletal CPRD-defined health disorders, as listed above. Each of these was weighted equally as 1, and case and control participants with MSDs were described for "number of comorbidities."

The number of GP consultations in the prior year and number of drug prescriptions in the prior year were described using medians and interquartile ranges (IQR). These were then categorised by quartiles and cases and controls were compared for their exposure to these variables. It was unknown for what reason a participant had attended their GP practice, or the specific indication of the drug prescribed, however, these measures gave some indication of overall disease burden: number of GP consultations is a crude measure of disease burden as it relates to the attendance of multiple appointments to manage health; and number of drugs prescribed in the prior year also reflects treatment burden and is related to polypharmacy. Available drug prescription information was limited to health disorders of interest. For example, drug prescriptions relating to musculoskeletal and pain disorders, cardiovascular disorders, mental health disorders, diabetes, asthma, COPD, and epilepsy were known but there was no information relating to prescriptions for gastrointestinal problems, cancer or other health disorders for which there was no CPRD-information available in the current study.

Lastly, cases and controls were described for their disease cluster categories, as defined in the previous chapter. This included clusters that were generated from all participants with multimorbidity; from men with multimorbidity; from women with multimorbidity; and from participants with musculoskeletal disorders.

Conditional logistic regression

I used conditional logistic regression analyses to assess the association between multimorbidity and the occurrence of HRJL. The analysis took case and control matched pairs into account; all associations found were therefore independent of age, gender, and GP practice (see Chapter 3).

Exposures of interest were first assessed in univariable analysis, then with statistical adjustment for important confounders. Known demographic and lifestyle factors which might confound the relationship between multimorbidity and HRJL included educational attainment, single relationship status, and history of heavy alcohol intake (see Chapter 6). Therefore, these factors were adjusted for in multivariable analysis. As previously, sub-group analysis was undertaken for men and women to assess whether the impact of multimorbidity on HRJL was modified by gender.

For conditional logistic regression of disease clusters, dummy variables were generated for each cluster and for participants with no known health disorders. Each generated cluster was then assessed for its relationship to HRJL, with no known health disorders as the reference group. Disease clusters generated among multimorbid men and multimorbid women were also assessed for their relationship to HRJL. In this case, the reference populations were men with no known health disorders and women with no known health disorders, respectively.

Analysis of musculoskeletal disorders, comorbidity, and HRJL

Conditional logistic regression was used to assess the association between musculoskeletal disorders and HRJL, stratified by number of comorbidities. Participants with no known health disorders were the reference group. Subgroup analysis using participants with chronic musculoskeletal disorders and recent musculoskeletal pain was also performed here.

Finally, I considered the prominent comorbidity clusters generated among participants with musculoskeletal disorders (see Chapter 7, Section 7.3.6.). Conditional logistic regression

was used to assess the association between musculoskeletal disorders and HRJL, stratified by these comorbidity clusters. Once again, participants with no known health disorders were the reference group.

Throughout , qualitative descriptors were used to distinguish the strength of association using Cohen's classification scheme and Rosenthal's later extension for odds ratios(405) as follows: about 1.5 to 1 defined as a small effect, about 2.5 to 1 as a moderate effect, about 4 to 1 as a strong effect, and about 10 to 1 as a very strong effect.

8.3 Results

8.3.1 Describing total study participants, and participants with MSDs

8.3.1.1 Demographics

The 988 study participants have been described previously. In brief, half were cases with HRJL and half were matched controls. The median age was 58.21 years (IQR 53.36 to 60.89 years), at the point of analysis. 44.5% were men, 98.1% were white, 68.9% were married, and 7.8% were single. 22.6% had a university-level qualification and 19.6% had no qualifications. Finally, 35.8% were working in higher managerial or professional class occupations, 27.5% in intermediate occupations, and 36.7% in routine or manual occupations.

Of these, 383 (38.8%) had CPRD-defined musculoskeletal disorders. These participants had a median age of 58.53 years (IQR 54.08 to 61.08) at the point of HRJL and were majority female (55.3%). Most were married (69.5%), 17.6% divorced, 6.1% widowed, and only 6.8% single. Most had vocational/higher professional qualifications (42.6%), while 21.2% had no qualifications, 18.5% had a university level degree, and 17.8% had high-school level qualifications. These participants most commonly worked, or had worked, routine occupations (41.7%), with 32.2% in managerial roles, and 26.1% in intermediate occupations.

Chronic musculoskeletal disorders and recent musculoskeletal pain sub-groups were broadly similar for demographic factors, although there were a slightly greater proportion of women and widowed among participants with chronic MSDs. People with chronic MSDs were also slightly older, on average, than those with recent MSD pain, see Table 118, below. Participants with chronic MSDs and recent MSD pain were also similar for occupational SOC-10 sub-major categories, although due to the limited number of

participants, clear differences were hard to observe. There appeared to be a slightly greater proportion of people in sales occupations (11.5% vs 7.9%) among participants with chronic MSDs, which could be as a result of the slightly higher proportion of women in this group. A full description of participants with MSDs for SOC-10 sub-major occupational categories, stratified by type of MSD, can be found in Table 77, Appendix.

Table 118: Demographic factors of study participants and participants with MSDs (stratified by type of MSD)

Demographic variable	Prevalence in total study sample, n (%)	Prevalence among participants with any MSDs, n (%)	Prevalence among participants with chronic MSDs, n (%)	Prevalence among participants with MSD pain, n (%)
Total	998 (100.0)	383 (38.8)	218 (22.1)	241 (24.4)
HRJL age, y, median (IQR)	58.21 (53.36 to 60.89)	58.53 (54.08 to 61.08)	59.45 (55.86 to 61.19)	57.83 (52.65 to 61.03)
Sex (m)	440 (44.5)	158 (41.3)	84 (38.5)	108 (44.8)
Ethnicity (white)	969 (98.1)	375 (97.9)	215 (98.6)	234 (97.1)
Married/Civil partnership	674 (68.9)	264 (69.5)	153 (70.2)	169 (71.0)
Single	76 (7.8)	26 (6.8)	9 (4.1)	19 (8.0)
Divorced	54 (5.5)	67 (17.6)	38 (17.4)	42 (17.7)
Widowed	175 (17.9)	23 (6.1)	18 (8.3)	8 (3.4)
University degree	223 (22.6)	71 (18.5)	40 (18.4)	43 (17.8)
Vocational/higher professional	387 (39.2)	163 (42.6)	93 (42.7)	103 (42.7)
High school qualifications	184 (18.6)	68 (17.8)	34 (15.6)	45 (18.7)
No qualifications	194 (19.6)	81 (21.2)	51 (23.4)	50 (20.8)
Managerial Occupation	348 (35.8)	122 (32.2)	69 (31.9)	77 (32.2)
Intermediate Occupation	268 (27.5)	99 (26.1)	54 (25.0)	65 (27.2)
Routine Occupation	257 (36.7)	158 (41.7)	93 (43.1)	97 (40.6)

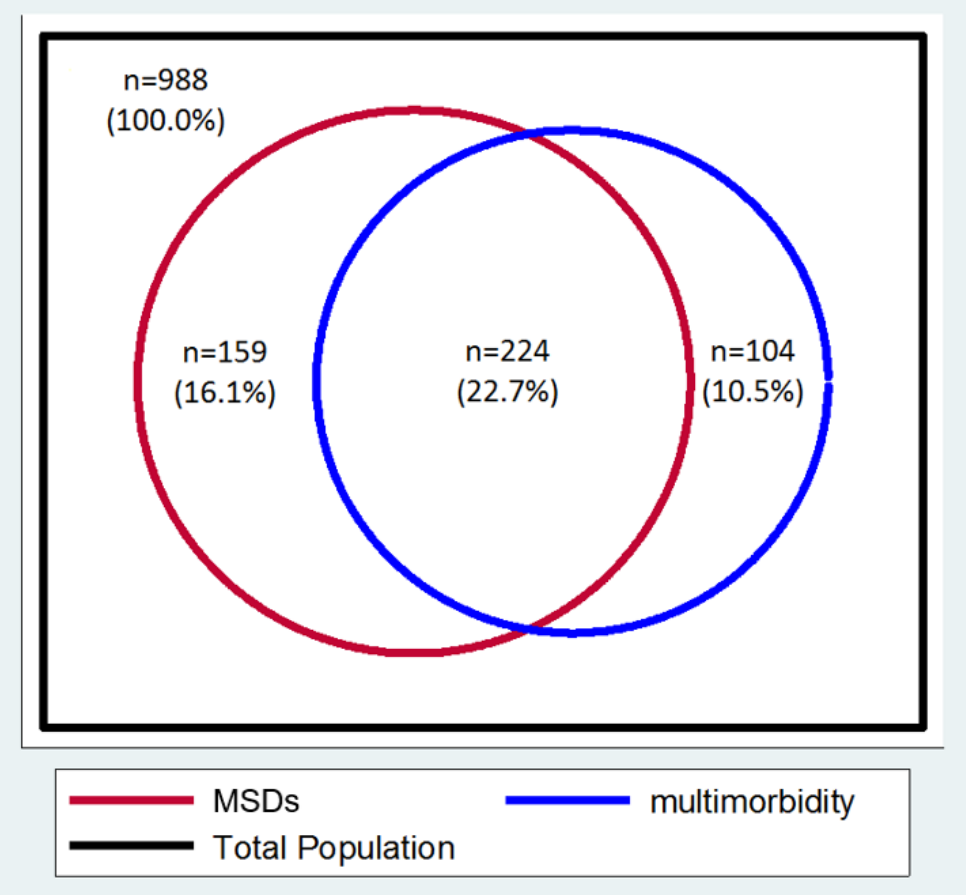
8.3.1.2 The prevalence of health disorders and comorbidities

The prevalence of CPRD-defined health disorders in the total study sample has been described previously. In brief, 22.1% had chronic MSDs, 24.4% had recent MSD pain, 17.9% had primary care level MHPs, 1.0% had psychiatric care level MHPs, 5.2% had recent sleep disorders, 22.0% had hypertension, 5.2% had ischaemic heart disease, 5.9% had heart failure, 0.7% had structural heart disease, 1.2% had peripheral atherosclerotic disease, 0.1%

had venous thromboembolic disease, 0.8% had cardiac arrhythmias, 7.9% had asthma, 2.0% had COPD, 2.1% had cerebrovascular accident, 1.0% had epilepsy, and 9.2% had diabetes. The prevalence of multimorbidity (two or more CPRD-defined health disorders) was 33.2%.

In general, participants with MSDs had a high prevalence of comorbidity (defined as the presence of another CPRD-defined health disorder) which was 58.7% among people with chronic MSDs and 59.3% among people with recent MSD pain. Among participants with chronic MSDs, 41.3% had no comorbidities, 26.2% had one comorbidity, 24.3% had two comorbidities, and 8.3% had three or more comorbidities. Among people with recent MSD pain, 40.7% had no comorbidities, 31.5% had one comorbidity, 17.0% had two comorbidities, and 10.8% had three or more comorbidities. Musculoskeletal disorders commonly presented among participants with an existing CPRD-defined health disorder (45.3%) and in the majority of those with multimorbidity (68.3%). See Figure 45.

Figure 45: proportional Venn diagram showing the proportion of participants with MSDs, the proportion with two or more conditions (multimorbidity) and the proportion with MSDs and multimorbidity, in the total sample. Area on the chart corresponds to proportion of participants.



Among people with musculoskeletal disorders, hypertension was the most prevalent comorbidity (29.0%), followed by primary-care-level mental health problems (23.2%), diabetes (10.2%), asthma (8.9%), sleep disorders (8.1%), heart failure (6.3%), and ischaemic heart disease (5.7%). Comparing participants with chronic musculoskeletal disorders and those with recent musculoskeletal pain, the prevalence of specific comorbidities was similar, although there appeared to be a slightly higher prevalence of participants with diabetes among the chronic musculoskeletal disease group (12.4% vs 8.3%). See Table 119, below.

Table 119: A description of the prevalence of CPRD-define health disorders (other than MSDs) in the total sample, and among participants with MSDs (stratified by type of MSD)

Variable	Prevalence in total study sample, n (%)	Prevalence among participants with any MSDs, n (%)	Prevalence among participants with chronic MSDs, n (%)	Prevalence among participants with MSD pain, n (%)
Primary care level MHPs	117 (17.9)	89 (23.2)	48 (22.0)	59 (24.5)
Psychiatric care level MHPs	10 (1.0)	6 (1.6)	4 (1.8)	5 (2.1)
Sleep disorders	51 (5.2)	31 (8.1)	21 (9.6)	17 (7.1)
Hypertension	217 (22.0)	111 (29.0)	63 (28.9)	72 (29.9)
Ischaemic heart disease	51 (5.2)	22 (5.7)	11 (5.1)	16 (6.6)
Heart failure	58 (5.9)	24 (6.3)	12 (5.5)	17 (7.1)
Structural heart disease	7 (0.7)	2 (0.5)	1 (0.5)	1 (0.4)
Peripheral atherosclerotic disease	12 (1.2)	7 (1.8)	5 (2.3)	3 (1.2)
Venous thromboembolism	1 (0.1)	1 (0.3)	0 (0.0)	1 (0.4)
Arrhythmias	8 (0.8)	3 (0.8)	2 (0.9)	2 (0.8)
Asthma	78 (7.9)	34 (8.9)	19 (8.7)	21 (8.7)
COPD	20 (2.0)	8 (2.1)	5 (2.3)	5 (2.1)
CVA	21 (2.1)	8 (2.1)	3 (1.4)	7 (2.9)
Epilepsy	10 (1.0)	4 (1.0)	2 (0.9)	3 (1.2)
Diabetes	91 (9.2)	39 (10.2)	27 (12.4)	20 (8.3)

8.3.2 Number of health problems

In total, 328 participants (33.2% of the total sample) were classified as having multimorbidity (two or more CPRD-defined health disorders). Participants with

multimorbidity had a median age of 58.68 years (IQR 54.58 – 61.22). 50.9% were male, 10.5% were single, 22.9% had no qualifications and 18.3% had attained university-degree level qualifications. Most participants with multimorbidity had health-related job loss (71.3%). 29.9% were working in higher managerial or professional class occupations, 29.9% in intermediate occupations, and 40.2% in routine or manual occupations.

Participants with "severe" multimorbidity (four or more health disorders) were also majority cases (78.3%) and had a median age of 59.03 years at the point of analysis (IQR 55.82 – 61.22). 56.5% were male, 6.5% were single, 32.6% had no qualifications and 8.7% had university-degree level qualifications. 23.9% were working in higher managerial or professional class occupations, 32.6% in intermediate occupations, and 43.5% in routine or manual occupations. Of the 10 control participants who managed to remain in work despite such morbidity burden, job titles included: Salesman, Supervisor, Personal Assistant, Club Stewardess, Advisor, Journalist, Payroll Manager, Van Driver, Printing Business Proprietor, and Engineer.

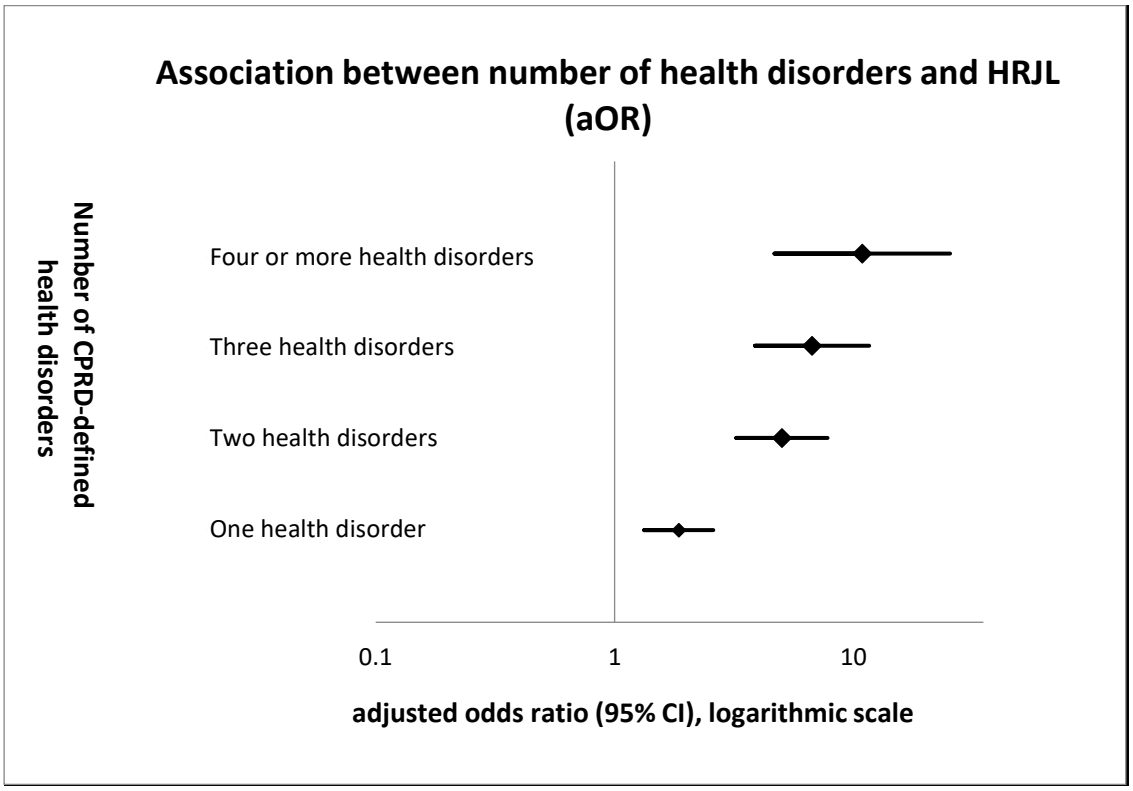
Multimorbidity was more prevalent amongst cases than controls (47.4% vs 19.0%) and was associated with 5.95-fold increased odds of HRJL (95%CI 1.32 to 2.58) compared to participants with no known health disorders. Given the small number of participants with four CPRD-defined health disorders (n=31), five health disorders (n=12), six health disorders (n=2), or seven health disorders (n=1) these groups were merged into a category of four or more health disorders. In matched analysis, as number of health disorders increased, association with HRJL increased (one morbidity: OR 1.86 95%CI 1.33 to 2.59; two morbidities: OR 5.02 95%CI 3.23 to 7.79; three morbidities: OR 6.71 95%CI 3.87 to 11.64; four or more morbidities: OR 10.89 95%CI 4.67 to 25.39). The strength of association remained similar after adjustment for educational attainment, single status, and history of heavy alcohol intake, see Table 120 and Figure 46. In sub-group analysis, multimorbidity was similarly associated with HRJL among men and women (OR 5.86 95%CI 3.27 to 10.49 in men; OR 6.04 95%CI 3.57 to 10.21 in women).

Table 120: number of known health disorders and HRJL

Variable	Prevalence among controls, n (%)	Prevalence among cases, n (%)	Association with HRJL, unadjusted. OR (95% CI)	Association with HRJL, adjusted for education level, single status, history of heavy alcohol use. aOR (95% CI)
No health disorders	225 (45.6)	110 (22.3)	1.00	1.00
One health disorder	175 (35.4)	150 (30.4)	**1.86 (1.33 to 2.59)**	**1.91 (1.35 to 2.68)**
Two health disorders	58 (11.7)	121 (24.5)	**5.02 (3.23 to 7.79)**	**5.02 (3.21 to 7.84)**
Three health disorder	26 (5.3)	77 (15.6)	**6.71 (3.87 to 11.64)**	**6.04 (3.43 to 10.62)**
Four or more health disorders	10 (2.0)	36 (7.3)	**10.89 (4.67 to 25.39)**	**11.04 (4.60 to 26.47)**
Any multimorbidity (two or more health disorders)	94 (19.0)	234 (47.4)	**5.95 (4.04 to 8.78)**	**5.71 (3.84 to 8.50)**
Men				
No health disorders	90 (40.9)	42 (19.1)	1.00	1.00
One health disorder	79 (35.9)	62 (28.2)	**1.83 (1.08 to 3.08)**	**1.76 (1.03 to 2.99)**
Two health disorder	33 (15.0)	54 (24.6)	**4.28 (2.23 to 8.22)**	**4.32 (2.22 to 8.40)**
Three health disorder	12 (5.5)	42 (19.1)	**8.25 (3.63 to 18.72)**	**7.27 (3.15 to 16.77)**
Four or more health disorders	6 (2.7)	20 (9.1)	**11.48 (3.72 to 35.45)**	**12.03 (3.73 to 38.83)**
Any multimorbidity (two or more health disorders)	51 (23.2)	116 (52.7)	**5.86 (3.27 to 10.49)**	**5.62 (3.11 to 10.16)**
Women				
No health disorders	135 (49.3)	68 (24.8)	1.00	1.00
One health disorder	96 (35.0)	88 (32.1)	**1.85 (1.20 to 2.85)**	**2.03 (1.29 to 3.19)**
Two health disorder	25 (9.1)	67 (24.5)	**5.83 (3.17 to 10.74)**	**5.84 (3.15 to 10.85)**

Three health disorder	14 (5.1)	35 (12.8)	**5.47 (2.57 to 11.64)**	**5.35 (2.42 to 11.81)**
Four or more health disorders	4 (1.5)	16 (5.8)	**9.68 (2.59 to 36.19)**	**9.10 (2.38 to 34.76)**
Any multimorbidity (two or more health disorders)	43 (15.7)	118 (43.1)	**6.04 (3.57 to 10.21)**	**5.96 (3.46 to 10.26)**

Figure 46: Forest plot showing association between number of CPRD-defined health disorders and HRJL



8.3.3 Number of GP consultations in the prior year

The relationship between number of GP consultations in the prior year and HRJL was considered; number of consultations was divided into quartiles for analysis. Quartile 1 was the reference group, containing the lowest 25% centile of numbers of consultations and included participants who had attended their GP practice once, or less than once, in the prior year (n=256, 25.9%). Quartile two, three, and four contained participants who had attended the GP two to four times (n=273, 27.6%), five to nine times (n=231, 23.4%), and 10 to 52 times (n=228, 23.1%) in the prior year, respectively.

Participants in the highest quartile of GP attendance were most commonly cases (72.8%) and had a median age of 59.12 years at the point of analysis (IQR 55.31 – 61.54). 54.0% were male, 9.7% were single, 26.8% had no qualifications, and 16.2% had attained university-degree level qualifications. 31.1% were working in higher managerial or professional class occupations, 28.4% in intermediate occupations, and 40.4% in routine or manual occupations.

The median number of GP consultations was higher among cases than controls (median: 6 IQR 3 to 12 and median 2.5 IQR 0 to 6, respectively). In matched analysis, the overall number of consultations attended in the prior year was significantly associated with HRJL (OR 1.12 95%CI 1.09 to 1.15). Compared to the lowest quartile of GP attendance, the second quartile had a 2.01-fold increased odds of HRJL (95%CI 1.37 to 2.94), the third quartile had a 4.00-fold increased odds of HRJL (95%CI 2.60 to 6.17), and the fourth quartile had a 9.33-fold increased odds of HRJL (95%CI 5.72 to 15.21). The strength of these relationships remained similar after adjusting for possible confounders, see Table 121.

The overall number of GP consultations in the prior year was similarly associated with HRJL among men and women (OR 1.09 95%CI 1.05 to 1.13 vs OR 1.15 95%CI 1.10 to 1.20). Women in the third quartile for number of consultations appeared to have a stronger relationship with HRJL than men in the third quartile (OR 4.93 95%CI 2.77 to 8.79 vs OR 3.21 95%CI 1.67 to 6.17, respectively) and in the fourth quartile (OR 9.27 95%CI 4.85 to 17.74 vs OR 6.88 95%CI 3.39 to 13.98, respectively), however confidence intervals were wide and overlapping.

Table 121: number of GP consultations in the prior year and HRJL

Variable	Prevalence among controls, n (%)	Prevalence among cases, n (%)	Association with HRJL, unadjusted. OR (95% CI)	Association with HRJL, adjusted for education level, single status, history of heavy alcohol use. aOR (95% CI)
Number of GP consultations	NA	NA	**1.12 (1.09 to 1.15)**	**1.11 (1.08 to 1.14)**
0 - 1 GP consultations (1st quartile)	179 (36.2)	77 (15.6)	1.00	1.00
2 - 4 GP consultations (2nd quartile)	154 (31.2)	119 (24.1)	**2.01 (1.37 to 2.94)**	**1.98 (1.35 to 2.91)**

5 - 9 GP consultations (3rd quartile)	99 (20.0)	132 (26.7)	**4.00 (2.60 to 6.17)**	**3.86 (2.47 to 6.02)**
10 - 52 GP consultations (4th quartile)	62 (12.6)	166 (33.6)	**9.33 (5.72 to 15.21)**	**8.74 (5.32 to 14.38)**
Men				
Number of GP consultations	NA	NA	**1.09 (1.05 to 1.13)**	**1.09 (1.05 to 1.13)**
0 - 1 GP consultations (1st quartile)	75 (34.1)	36 (16.4)	1.00	1.00
2 - 5 GP consultations (2nd quartile)	67 (30.5)	58 (26.4)	**2.17 (1.22 to 3.83)**	**2.20 (1.23 to 3.94)**
6 - 11 GP consultations (3rd quartile)	49 (22.3)	58 (26.4)	**3.21 (1.67 to 6.17)**	**3.08 (1.58 to 5.99)**
12 - 40 GP consultations (4th quartile)	29 (13.12)	68 (30.9)	**6.88 (3.39 to 13.98)**	**6.41 (3.11 to 13.18)**
Women				
Number of GP consultations	NA	NA	**1.15 (1.10 to 1.20)**	**1.15 (1.10 to 1.20)**
0 - 1 GP consultations (1st quartile)	104 (38.0)	41 (15.0)	1.00	1.00
2 - 3 GP consultations (2nd quartile)	80 (29.2)	53 (19.3)	**1.75 (1.05 to 2.92)**	**1.84 (1.09 to 3.11)**
4 - 8 GP consultations (3rd quartile)	56 (20.4)	88 (32.1)	**4.93 (2.77 to 8.79)**	**4.75 (2.60 to 8.66)**
9 - 52 GP consultations (4th quartile)	34 (12.4)	92 (33.6)	**9.27 (4.85 to 17.74)**	**10.11 (5.09 to 20.08)**

8.3.4 Number of drugs prescribed in the prior year

The relationship between number of drug prescriptions in the prior year and HRJL was considered and number of prescriptions was divided into quartiles for analysis. Quartile 1 contained participants who had no known drug prescriptions in the prior year (n=321, 32.5%) and was the main comparison group. Quartile two, three, and four contained participants who had two to five prescriptions (n=187, 18.9%), six to 18 prescriptions (n=238, 24.1%), and 19 to 131 prescriptions (n=242, 24.5%) in the prior year, respectively.

Participants in the highest quartile of drug prescriptions were most commonly cases (68.6%) and had a median age of 58.95 years at the point of analysis (IQR 54.98 to 61.22). 56.2% were male, 10.5% were single, 26.0% had no qualifications, and 17.8% had attained

university-degree level qualifications. 35.6% were working in higher managerial or professional class occupations, 24.7% in intermediate occupations, and 39.8% in routine or manual occupations.

The median number of drug prescriptions was much higher among cases, compared to controls (median 10 IQR 1 to 25 vs median 1 IQR 0 to 12, respectively). In matched analysis, the number of drugs prescribed in the prior year was significantly associated with development of HRJL (OR: 1.03 95%CI 1.02 to 1.04). Compared to the lowest quartile of drug prescription, the second quartile had 3.93-fold increased odds of HRJL (95%CI 2.55 to 6.07), the third quartile had a 4.33-fold increased odds of HRJL (95%CI 2.55 to 6.07), and the fourth quartile had a 7.61-fold increased odds of HRJL (95%CI 4.86 to 11.91). The strength of these relationships remained similar after adjusting for possible confounders, see Table 122.

The number of drug prescriptions in the prior year was similarly associated with HRJL among men and women (OR 1.03 95%CI 1.02 to 1.04 vs OR 1.04 95%CI 1.02 to 1.05). Once again, the strength of association appeared to be stronger among women in the third quartile compared to men in the third quartile (OR 5.94 95%CI 3.33 to 10.59 vs OR 3.92 95%CI 2.04 to 7.54, respectively) and in the fourth quartile (OR 8.43 95%CI 4.52 to 15.71 vs OR 5.94 95%CI 3.33 to 10.59, respectively). However, confidence intervals were wide and overlapping.

Table 122: number of drug prescriptions in the prior year and HRJL

Variable	Prevalence among controls, n (%)	Prevalence among cases, n (%)	Association with HRJL, unadjusted. OR (95% CI)	Association with HRJL, adjusted for education level, single status, history of heavy alcohol use. aOR (95% CI)
Number of drug prescriptions	NA	NA	**1.03 (1.02 to 1.04)**	**1.03 (1.02 to 1.04)**
0 prescriptions (1st quartile)	233 (47.2)	88 (17.8)	1.00	1.00
1 - 5 prescriptions (2nd quartile)	81 (16.4)	106 (21.5)	**3.93 (2.55 to 6.07)**	**4.19 (2.68 to 6.57)**
6 - 18 prescriptions (3rd quartile)	104 (21.1)	134 (27.1)	**4.33 (2.55 to 6.07)**	**4.60 (2.97 to 7.14)**

19 - 131 prescriptions (4th quartile)	76 (15.4)	166 (33.6)	**7.61 (4.86 to 11.91)**	**7.52 (4.72 to 11.98)**
Men				
Number of drug prescriptions	NA	NA	**1.03 (1.02 to 1.04)**	**1.03 (1.02 to 1.05)**
0 prescriptions (1st quartile)	92 (41.8)	36 (16.4)	1.00	1.00
1 - 5 prescriptions (2nd quartile)	42 (19.1)	53 (24.1)	**3.13 (1.71 to 5.72)**	**3.35 (1.79 to 6.25)**
6 - 18 prescriptions (3rd quartile)	50 (22.7)	58 (26.4)	**3.92 (2.04 to 7.54)**	**3.99 (2.02 to 7.85)**
19 - 131 prescriptions (4th quartile)	36 (16.4)	73 (33.2)	**5.78 (3.07 to 10.90)**	**5.97 (3.07 to 11.60)**
Women				
Number of drug prescriptions	NA	NA	**1.04 (1.02 to 1.05)**	**1.04 (1.02 to 1.05)**
0 prescriptions (1st quartile)	141 (51.5)	52 (19.0)	1.00	1.00
1 - 5 prescriptions (2nd quartile)	45 (16.4)	42 (15.3)	**3.62 (1.95 to 6.73)**	**4.08 (2.13 to 7.81)**
6 - 18 prescriptions (3rd quartile)	50 (18.3)	90 (32.9)	**5.94 (3.33 to 10.59)**	**6.67 (3.63 to 12.26)**
19 - 131 prescriptions (4th quartile)	38 (13.9)	90 (32.9)	**8.43 (4.52 to 15.71)**	**8.74 (4.51 to 16.96)**

8.3.5 Cluster analysis

8.3.5.1 Association of major multimorbidity clusters with HRJL

As described in Chapter 7, participants with multimorbidity were clustered for the following CPRD-defined health disorders: structural heart disease, hypertension, heart failure, ischaemic heart disease, venous thromboembolism, peripheral atherosclerosis, cardiac arrhythmias, primary care mental health problem, psychiatric mental health problem, sleep disorder, COPD, asthma, CVA, epilepsy, diabetes, and musculoskeletal disorders (chronic or pain, separately) using agglomerative hierarchical cluster analysis. A full description of the participants within each of these clusters can be found in Chapter 7, however the major disease constituents are summarised in Table 123 and 125, below. I explored the relationships between these multimorbidity clusters and HRJL. Results are reported separately according to whether chronic MSDs or recent MSD pain was used to define musculoskeletal disorders in the clustering solution. For these analyses, outlying clusters were not considered i.e. a cluster with fewer than 10 participants.

Chronic musculoskeletal disorders used to define MSDs

Participants without known CPRD-defined health disorders were the reference group in all analyses. For ease of reference, Cluster A was referred to as the MHP-cMSD cluster, Cluster B was the cardio-metabolic cluster, Cluster C was the HTN-cMSD-diab cluster, and Cluster D was the OPD-HTN-MHP cluster.

Compared with participants with no known health disorders, having one known health disorder was associated with HRJL (OR 2.20 95%CI 1.59 to 3.05) the MHP-cMSD cluster was strongly associated with HRJL (OR 7.56 95%CI 4.17 to 13.71), the cardio-metabolic cluster was moderately associated with HRJL (OR 2.82 95%CI 1.29 to 6.17), the HTN-cMSD-diab cluster was strongly associated with HRJL (OR 5.52 95%CI 3.27 to 9.30), and the OPD-HTN-MHP cluster was very strongly associated with HRJL (OR 8.25 95%CI 3.01 to 22.61), although confidence intervals were wide. After adjustment for educational attainment, single status, and history of heavy alcohol intake, effect estimates remained similar strength, see Table 124 and Figure 47.

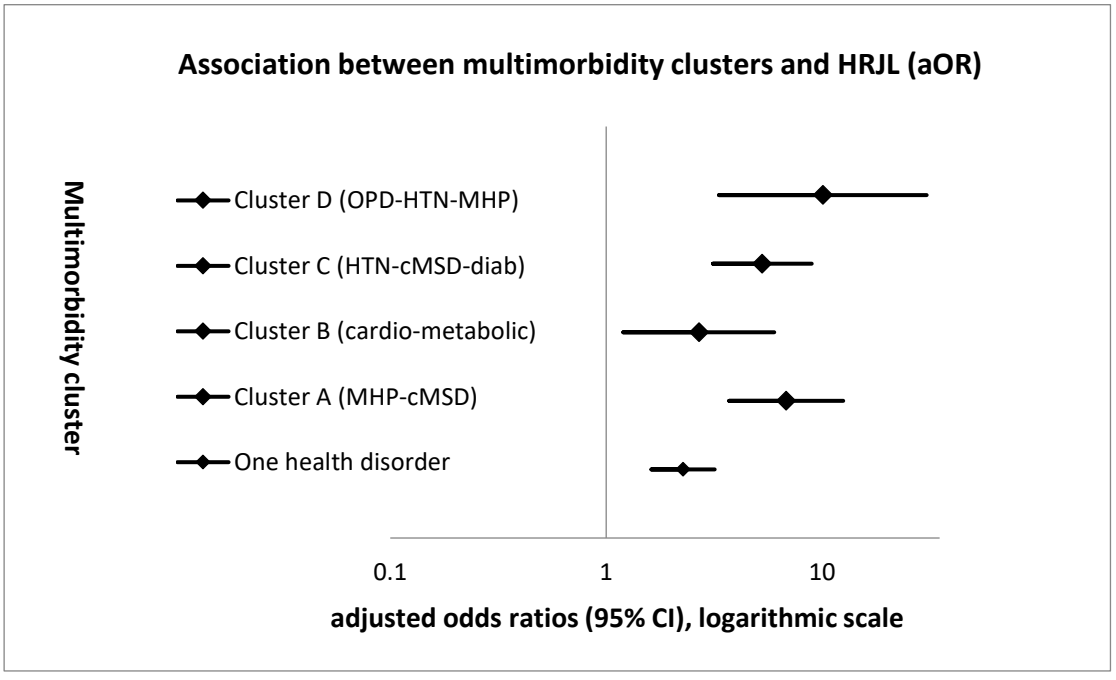
Table 123: Major disease constituents of clusters among people with multimorbidity, using chronic MSDs to measure musculoskeletal disorders

Cluster name (abbreviation)	Number of participants (%)	Major disease constituents (prevalence >30%)
Cluster A (MHP-cMSD)	88 (32.2)	Primary care MHP (96.6%) Chronic MSD (50.0%) Sleep disorders (39.8%)
Cluster B (Cardio-metabolic)	35 (12.8)	Ischaemic heart disease (94.3%) Hypertension (62.9%) Heart failure (74.3%) Diabetes (31.4%)
Cluster C (HTN-cMSD-diab)	109 (39.9)	Hypertension (77.1%) Chronic MSD (73.4%) Diabetes (43.1%)
Cluster D (OPD-HTN-MHP)	32 (11.7)	Asthma (93.8%) COPD (40.6%) Hypertension (40.6%) Primary care MHP (37.5%)

Table 124: Multimorbidity disease clusters and HRJL, using chronic MSDs to measure musculoskeletal disorders

Variable	Prevalence among controls, n (%)	Prevalence among cases, n (%)	Association with HRJL, unadjusted. OR (95% CI)	Association with HRJL, adjusted for education level, single status, history of heavy alcohol use. aOR (95% CI)
Participants with no known health disorders	270 (54.7)	134 (27.1)	1.00	1.00
One known health disorder	148 (30.0)	163 (33.0)	**2.20 (1.59 to 3.05)**	**2.27 (1.62 to 3.18)**
Cluster A (MHP-cMSD)	20 (4.1)	68 (13.8)	**7.56 (4.17 to 13.71)**	**6.81 (3.71 to 12.52)**
Cluster B (cardio-metabolic)	14 (2.8)	21 (4.3)	**2.82 (1.29 to 6.17)**	**2.69 (1.20 to 6.00)**
Cluster C (HTN-cMSD-diab)	31 (6.3)	78 (15.8)	**5.52 (3.27 to 9.30)**	**5.28 (3.12 to 8.95)**
Cluster D (OPD-HTN-MHP)	9 (1.8)	23 (4.7)	**8.25 (3.01 to 22.61)**	**10.08 (3.33 to 30.48)**

Figure 47: Association between multimorbidity clusters and HRJL (using chronic MSDs to define musculoskeletal disorders)



Recent musculoskeletal pain used to define MSDs

For ease of reference, Cluster E was referred to as the MSpain-HTN cluster, Cluster F was the Diab-HTN-pcMHP cluster, Cluster G was the cardio-metabolic cluster, Cluster H was the MHP-MSpain cluster, and Cluster I was the OPD cluster. Participants without known CPRD-defined health disorders were the reference group.

Compared with participants with no known health disorders, having one known health disorder was moderately associated with HRJL (OR 2.14 95%CI 1.52 to 2.99) the MSpain-HTN cluster was strongly associated with HRJL (OR 5.33 95%CI 3.03 to 9.39), the Diab-HTN-pcMHP cluster was strongly associated with HRJL (OR 5.57 95%CI 2.41 to 12.87), the cardio-metabolic cluster was strongly associated with HRJL (OR 5.41 95%CI 2.37 to 12.32), the MHP-MSpain cluster was very strongly associated with HRJL (OR 10.68 95%CI 5.82 to 19.57), and the OPD cluster was moderately associated with HRJL (OR 2.26 95%CI 0.63 to 8.08), although this didn't reach statistical significance. After adjustment for possible confounders, effect estimates remained at a similar strength, see Table 126 and Figure 48.

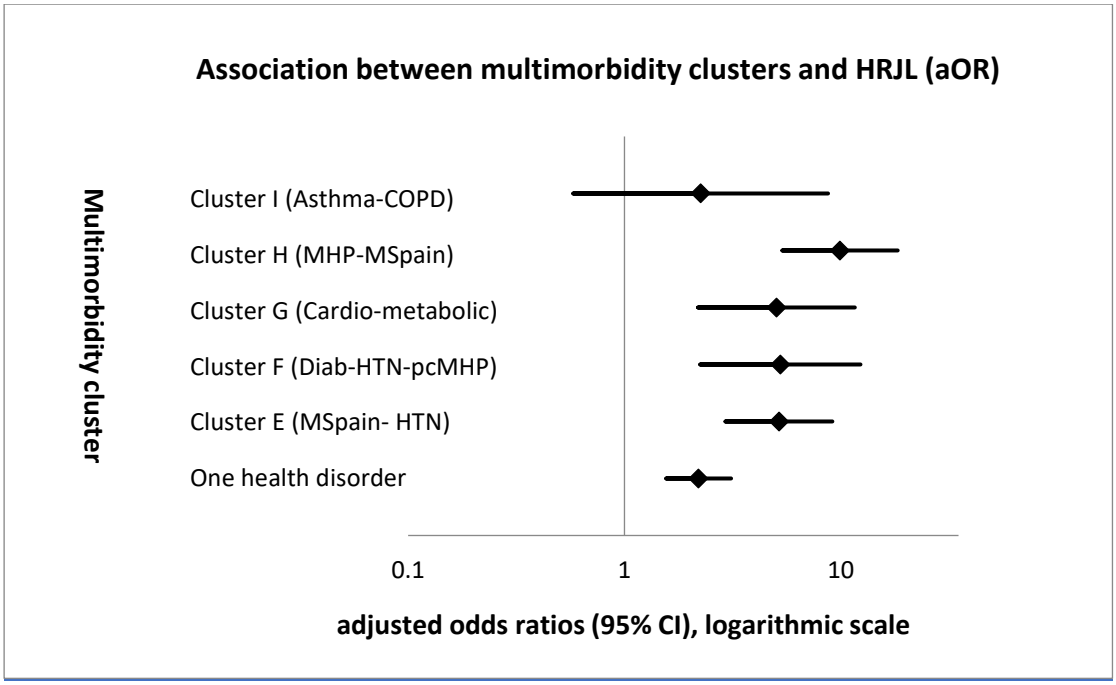
Table 125: major disease constituents of clusters among people with multimorbidity, using recent MSD pain to measure musculoskeletal disorders

Cluster name (abbreviation)	Number of participants (%)	Major disease constituents (prevalence >30%)
Cluster E (MSpain- HTN)	95 (32.5)	MSD pain (77.9%) Hypertension (76.8%)
Cluster F (Diab-HTN-pcMHP)	36 (12.3)	Diabetes (100.0%) Hypertension (72.2%) Primary care MHP (30.6%)
Cluster G (Cardio-metabolic)	35 (12.0)	Ischaemic heart disease (97.1%) Heart failure (68.6%) Hypertension (57.1%) Diabetes (34.3%)
Cluster H (MHP-MSpain)	110 (38.0)	Primary care MHP (93.6%) MSD pain (53.6%) Sleep disorders (39.1%)
Cluster I (OPD)	12 (4.1)	COPD (97.7%) Asthma (83.3%)

Table 126: Multimorbidity disease clusters and HRJL, using recent MSD pain to measure musculoskeletal disorders

Variable	Prevalence among controls, n (%)	Prevalence among cases, n (%)	Association with HRJL, unadjusted. OR (95% CI)	Association with HRJL, adjusted for education level, single status, history of heavy alcohol use. aOR (95% CI)
Participants with no known health disorders	262 (53.0)	134 (27.1)	1.00	1.00
Participants with one known health disorder	153 (31.0)	147 (29.8)	**2.14 (1.52 to 2.99)**	**2.20 (1.56 to 3.11)**
Cluster E (MSpain- HTN)	31 (6.3)	64 (13.0)	**5.33 (3.03 to 9.39)**	**5.18 (2.93 to 9.14)**
Cluster F (Diab-HTN-pcMHP)	10 (2.0)	26 (5.3)	**5.57 (2.41 to 12.87)**	**5.25 (2.24 to 12.33)**
Cluster G (Cardio-metabolic)	11 (2.2)	24 (4.9)	**5.41 (2.37 to 12.32)**	**5.04 (2.19 to 11.61)**
Cluster H (MHP-MSpain)	20 (4.0)	90 (18.2)	**10.68 (5.82 to 19.57)**	**9.92 (5.37 to 18.32)**
Cluster I (OPD)	6 (1.2)	6 (1.2)	2.26 (0.63 to 8.08)	2.25 (0.58 to 8.73)

Figure 48: Association between multimorbidity clusters and HRJL (using recent MSD pain to define musculoskeletal disorders)



8.3.5.2 Association of major multimorbidity clusters with HRJL among men

As described in Chapter 7, male participants with multimorbidity were clustered for CPRD-defined health disorders. Clusters of less than ten participants were excluded as outliers. The relationship between these multimorbidity clusters and HRJL was explored in analysis restricted to male participants.

A full description of participants within each of these clusters can be found in Chapter 7 and the major disease constituents of each cluster are summarised in Tables 127 and 129, below.

Chronic musculoskeletal disorders used to define MSDs

Male participants with no known health disorders were the comparison group. For ease of reference, Cluster J was referred to as the MHP-cMSD cluster, Cluster K was the HTN-cMSD-diab cluster, Cluster L was the cardio-metabolic cluster, and Cluster M was the OPD-HTN-cMSD cluster.

Compared to male participants with no known health disorders, having one known health disorder was weakly associated with HRJL among men (OR 1.82 95%CI 1.11 to 2.98), the MHP-cMSD cluster was very strongly associated with HRJL, although confidence intervals were wide (OR 15.00 95%CI 3.28 to 68.62), the HTN-cMSD-diab cluster was strongly associated with HRJL (OR 6.03 95%CI 2.72 to 13.39), the cardio-metabolic cluster was moderately associated with HRJL (OR 3.40 95%CI 1.50 to 7.70), and the OPD-cMSD-HTN cluster was strongly associated with HRJL (OR 4.65 95%CI 1.46 to 14.84). After adjustment for educational attainment, single status, and history of heavy alcohol intake, a similar strength of relationship was observed, see Table 128.

Table 127: Major disease constituents of clusters among multimorbid men, using chronic MSDs to measure musculoskeletal disorders

Cluster name (abbreviation)	Number of participants (%)	Major disease constituents (prevalence >30%)
Cluster J (MHP-cMSD)	21 (15.1)	Primary care MHP (90.5%) Chronic MSD (66.7%) Sleep disorders (52.4%)
Cluster K (HTN-cMSD-diab)	54 (38.9)	Hypertension (96.3%) Chronic MSD (48.2%) Diabetes (44.4%)

Cluster L (Cardio-metabolic)	37 (26.6)	Ischaemic heart disease (83.8%) Heart failure (70.3%) Hypertension (62.2%) Diabetes (35.1%)
Cluster M (OPD-HTN-cMSD)	17 (12.2)	Asthma (94.1%) COPD (41.2%) Chronic MSD (41.2%) Hypertension (41.2%)

Table 128: Multimorbidity clusters among men and HRJL, using chronic MSDs to measure musculoskeletal disorders

Variable	Prevalence among controls, n (%)	Prevalence among cases, n (%)	Association with HRJL, unadjusted. OR (95% CI)	Association with HRJL, adjusted for education level, single status, history of heavy alcohol use. aOR (95% CI)
Male participants with no known health conditions	108 (49.1)	53 (24.1)	1.00	1.00
Male participants with one known health disorder	73 (33.2)	67 (30.5)	**1.82 (1.11 to 2.98)**	**1.84 (1.11 to 3.04)**
Cluster J (MHP-cMSD)	3 (1.4)	18 (8.2)	**15.00 (3.28 to 68.62)**	**14.24 (3.05 to 66.45)**
Cluster K (HTN-cMSD-diab)	15 (6.8)	39 (17.7)	**6.03 (2.72 to 13.39)**	**5.83 (2.58 to 13.14)**
Cluster L (cardio-metabolic)	14 (6.4)	23 (10.5)	**3.40 (1.50 to 7.70)**	**3.13 (1.35 to 7.27)**
Cluster M (OPD-HTN-cMSD)	5 (2.3)	12 (5.5)	**4.65 (1.46 to 14.84)**	**5.56 (1.60 to 19.34)**

Recent musculoskeletal pain used to define MSDs

As above, male participants with no known health disorders were the comparison group. For ease of reference, Cluster N was referred to as the MSpain-HTN-diab cluster, Cluster O was the cardio-metabolic cluster, Cluster P was the pcMHP-MSpain-HTN cluster, and Cluster Q was the OPD-MSpain-HTN cluster.

Compared to male participants with no known health disorders, having one known health disorder was weakly associated with HRJL among men (OR 1.89 95%CI 1.13 to 3.14), the MSpain-HTN-diab cluster was strongly associated with HRJL (OR 5.60 95%CI 2.75 to 11.44),

the cardio-metabolic cluster was strongly associated with HRJL (OR 5.41 95%CI 2.14 to 13.67), the pcMHP-MSpain-HTN cluster was very strongly associated with HRJL, although confidence intervals were wide (OR 10.90 95%CI 4.02 to 29.55) and the OPD-MSpain-HTN cluster was strongly associated with HRJL (OR 3.85 95%CI 1.33 to 11.15). After adjustment for possible confounders, a similar strength relationship was observed across all clusters, see Table 130.

Table 129: Major disease constituents of clusters among multimorbid men, using recent MSD pain to measure musculoskeletal disorders

Cluster name (abbreviation)	Number of participants (%)	Major disease constituents (prevalence >30%)
Cluster N (MSpain-HTN-diab)	64 (41.6)	MSD pain (62.5%) Hypertension (73.4%) Diabetes (43.8%)
Cluster O (Cardio-metabolic)	31 (20.1)	Ischaemic heart disease (96.8%) Heart failure (67.7%) Hypertension (54.8%) Diabetes (35.5%)
Cluster P (pcMHP-MSpain-HTN)	36 (23.4)	Primary care MHP (100.0%) Musculoskeletal pain (44.4%) Hypertension (38.9%)
Cluster Q (OPD-MSpain-HTN)	19 (12.3)	Asthma (94.7%) MSD pain (47.4%) Hypertension (42.1%) COPD (36.8%)

Table 130: Multimorbidity clusters among men and HRJL, using recent MSD pain to measure musculoskeletal disorders

Variable	Prevalence among controls, n (%)	Prevalence among cases, n (%)	Association with HRJL, unadjusted. OR (95% CI)	Association with HRJL, adjusted for education level, single status, history of heavy alcohol use. aOR (95% CI)
Male participants with no known health conditions	100 (45.5)	49 (22.3)	1.00	1.00
Male participants with one known health condition	75 (34.1)	62 (28.2)	**1.89 (1.13 to 3.14)**	**1.87 (1.11 to 3.15)**
Cluster N (MSpain-HTN-diab)	20 (9.1)	44 (20.0)	**5.60 (2.75 to 11.44)**	**5.33 (2.59 to 10.95)**

Cluster O (Cardio-metabolic)	10 (4.6)	21 (9.6)	**5.41 (2.14 to 13.67)**	**4.87 (1.91 to 12.40)**
Cluster P (pcMHP-MSpain-HTN)	7 (3.2)	29 (13.2)	**10.90 (4.02 to 29.55)**	**10.52 (3.79 to 29.22)**
Cluster Q (OPD-MSpain-HTN)	7 (3.2)	12 (5.5)	**3.85 (1.33 to 11.15)**	**4.07 (1.34 to 12.29)**

8.3.5.3 Association of major multimorbidity clusters with HRJL among women

As described in Chapter 7, female participants with multimorbidity were clustered for the CPRD-defined health disorders listed above and clusters of less than ten participants were excluded as outliers. The relationship between these multimorbidity clusters and HRJL was explored in analysis restricted to female participants.

A full description of the participants within each of these clusters can be found in Chapter 7 however the major disease constituents of each cluster are summarised in Table 131 and 133, below.

Chronic disorders used to define MSDs

Women without known health disorders were the comparison group. For ease of reference, Cluster R was referred to as the HTN-cMSD-diab cluster, and Cluster S was the MHP-cMSD cluster.

Compared with female participants with no known health disorders, the HTN-cMSD-diab cluster was strongly associated with HRJL (OR 5.52 95%CI 2.84 to 10.74), and the MHP-cMSD cluster was strongly associated with HRJL (OR 6.62 95%CI 3.05 to 14.37). After adjustment for educational attainment, single status, and history of heavy alcohol intake, the strength of association remained similar, see Table 132.

Table 131: Major disease constituents of clusters among multimorbid women, using chronic MSDs to measure musculoskeletal disorders

Cluster name (abbreviation)	Number of participants (%)	Major disease constituents (prevalence >30%)
Cluster R (HTN-cMSD-diab)	71 (53.0)	Hypertension (77.5%) Chronic MSD (64.8%) Diabetes (32.4%)
Cluster S (MHP-cMSD)	59 (44.0)	Primary care MHP (93.2%) Sleep disorders (47.5%) Chronic MSD (42.4%)

Table 132: Multimorbidity clusters among women and HRJL, using chronic MSDs to measure musculoskeletal disorders

Variable	Number of exposed controls, n (%)	Number of exposed cases, n (%)	Association with HRJL in matched analysis, unadjusted. OR (95% CI)	Association with HRJL, adjusted for education, single status, and history of heavy alcohol intake aOR (95% CI)
Female participants with no known health conditions	162 (59.1)	81 (29.6)	1.00	1.00
Female participants with one known health disorder	75 (27.4)	96 (35.0)	**2.46 (1.59 to 3.81)**	**2.63 (1.67 to 4.16)**
Cluster R (HTN-cMSD-diab)	20 (7.3)	51 (18.6)	**5.52 (2.84 to 10.74)**	**5.33 (2.71 to 10.48)**
Cluster S (MHP-cMSD)	15 (5.5)	44 (16.1)	**6.62 (3.05 to 14.37)**	**6.34 (2.85 to 14.12)**

Recent musculoskeletal pain used to define MSDs

Women without known health disorders were the comparison group. For ease of reference, Cluster T was referred to as the HTN-MSpain cluster, and Cluster U was the MHP-MSpain cluster.

Compared to female participants with no known health disorders, the HTN-MSpain cluster was strongly associated with HRJL (OR 6.15 95%CI 3.05 to 12.41), and the MHP-MSpain cluster was very strongly associated with HRJL, although confidence intervals were wide (OR 9.07 95%CI 4.17 to 19.75). After adjustment for possible confounders the strength of these relationships remained similar, see Table 134.

Table 133: Major disease constituents of clusters among multimorbid women, using recent MSD pain to measure musculoskeletal disorders

Cluster name (abbreviation)	Number of participants (%)	Major disease constituents (prevalence >30%)
Cluster T (HTN-MSpain)	67 (48.6)	Hypertension (80.6%) Musculoskeletal pain (56.7%)
Cluster U (MHP-MSpain)	62 (44.9)	Primary care mental health problems (98.4%) Musculoskeletal pain (54.8%) Sleep disorders (45.2%)

Table 134: Multimorbidity clusters among women and HRJL, using recent MSD pain to measure musculoskeletal disorders

Variable	Prevalence among controls, n (%)	Prevalence among cases, n (%)	Association with HRJL, unadjusted. OR (95% CI)	Association with HRJL, adjusted for education level, single status, history of heavy alcohol use. aOR (95% CI)
Female participants with no known health conditions	162 (59.1)	85 (31.0)	1.00	1.00
Female participants with one known disorder	78 (28.5)	85 (31.0)	**2.32 (1.48 to 3.64)**	**2.57 (1.60 to 4.12)**
Cluster T (HTN-MSpain)	18 (6.6)	49 (17.9)	**6.15 (3.05 to 12.41)**	**6.07 (2.96 to 12.45)**
Cluster U (MHP-MSpain)	12 (4.4)	50 (18.3)	**9.07 (4.17 to 19.75)**	**8.82 (3.96 to 19.66)**

8.3.6 The impact of comorbidity on HRJL, among people with musculoskeletal disorders

Musculoskeletal disorders, number of comorbidities, and HRJL

Compared to participants with no known health disorders, having any MSD was increasingly associated with HRJL as number of comorbid conditions increased (aOR 2.07 95%CI 1.68 to 2.56). Participants with MSDs but no known comorbidities had 2.13-fold increased odds of HRJL (95%CI 1.31 to 3.46). However, association with HRJL increased as number of comorbidities increased (OR: one comorbidity 5.32 95%CI 2.88 to 9.83; two comorbidities 7.93 95%CI 3.61 to 17.45; three or more comorbidities 19.49 95%CI 5.42 to 70.10). The size of these effect estimates remained similar after adjustment for confounding factors, see Table 135.

This pattern was replicated among participants with chronic MSDs and recent MSD pain, specifically. Having chronic MSDs or recent MSD pain, without comorbid health disorders remained moderately associated with HRJL, compared to those with no known health disorders (OR 2.09 95%CI 1.16 to 3.77; and OR 2.22 95%CI 1.17 to 4.20, respectively). For both these conditions, strength of association increased considerably as number of

comorbidities increased. Effect estimates remained similar after adjustment for confounding factors, see Table 135.

Table 135: Impact of musculoskeletal disorders on HRJL, stratified by number of comorbidities and type of musculoskeletal disorder.

Demographic variable	Prevalence among controls, n (%)	Prevalence among cases, n (%)	Association with HRJL, unadjusted. OR (95% CI)	Association with HRJL, adjusted for education, history of heavy alcohol intake, and single status. aOR (95% CI)
All musculoskeletal disorders[1]				
No known health disorders	225 (45.6)	110 (22.3)	1.00	1.00
MSD alone	90 (18.2)	69 (14.0)	**2.13 (1.31 to 3.46)**	**2.18 (1.33 to 3.59)**
MSD and one comorbidity	39 (7.9)	73 (14.8)	**5.32 (2.88 to 9.83)**	**5.38 (2.88 to 10.05)**
MSD and two comorbidities	19 (3.9)	57 (11.5)	**7.93 (3.61 to 17.45)**	**7.37 (3.28 to 16.58)**
MSD and three or more comorbidities	4 (0.8)	32 (6.5)	**19.49 (5.42 to 70.10)**	**17.74 (4.84 to 65.06)**
Chronic musculoskeletal disorders[2]				
No known health disorders	270 (76.7)	134 (49.6)	1.00	1.00
MSD alone	45 (12.8)	45 (16.7)	**2.09 (1.16 to 3.77)**	**2.10 (1.15 to 3.83)**
MSD and one comorbidity	21 (6.0)	36 (13.3)	**5.08 (2.19 to 11.79)**	**5.24 (2.24 to 12.27)**
MSD and two or more comorbidities	16 (4.6)	55 (20.4)	**6.35 (2.82 to 14.32)**	**5.96 (2.57 to 13.80)**
Recent musculoskeletal pain[3]				
No known health disorders	262 (74.9)	134 (46.7)	1.00	1.00
MSD alone	53 (15.1)	45 (15.7)	**2.22 (1.17 to 4.20)**	**2.25 (1.15 to 4.37)**
MSD and one comorbidity	24 (6.9)	52 (18.1)	**7.17 (3.14 to 16.33)**	**7.40 (3.20 to 17.07)**
MSD and two or more comorbidities	11 (3.1)	56 (19.5)	**11.70 (4.23 to 32.32)**	**11.45 (3.99 to 32.89)**

1. 536 and 524 participants contributed to the unadjusted and adjusted logistic models, respectively
2. 400 and 394 participants contributed to the unadjusted and adjusted logistic models, respectively
3. 420 and 408 participants contributed to the unadjusted and adjusted logistic models, respectively

Musculoskeletal disorders, comorbidity clusters, and HRJL

The association between patterns of comorbidity among MSDs and HRJL was considered. Once again, participants without known CPRD-defined health disorders were the comparison group. For reference, Cluster V contained participants with MSDs and no comorbidities and was the MSD-alone cluster, Cluster W was the HTN-diab comorbidity cluster, Cluster X was the Asthma-HTN comorbidity cluster, Cluster Y was the MHP comorbidity cluster, and Cluster Z was the cardio-metabolic comorbidity cluster. A summary of the constituents of these clusters can be found in Table 136 below.

Compared with participants with no known health disorders, having an MSD with no known comorbidity was moderately associated with HRJL (OR 2.20 95%CI 1.35 to 3.60). The HTN-Diab cluster was strongly associated with HRJL (OR 4.25 95%CI 2.27 to 7.95), the Asthma-HTN cluster was strongly associated with HRJL (OR 7.42 95%CI 2.12 to 25.92), the MHP cluster was very strongly associated with HRJL (OR 16.18 95%CI 6.51 to 40.25), and the cardio-metabolic cluster was strongly associated with HRJL (OR 5.79 95%CI 1.23 to 27.17), although confidence intervals were wide for all comorbidity clusters. After adjustment for educational attainment, single status, and history of heavy alcohol intake, effect estimates remained similar strength, see Table 137.

Table 136: Major disease constituents of clusters among people with MSDs (chronic or recent pain)

Cluster name (abbreviation)	**Number of participants (%)**	**Major disease constituents (prevalence >30%)**
Cluster V (MSD-alone)	159 (41.5)	Musculoskeletal disorders alone (100.0%)
Cluster W (HTN-Diab)	96 (25.1)	Hypertension (87.5%) Diabetes (33.3%)
Cluster X (Asthma-HTN)	25 (6.5)	Asthma (96.0%) Hypertension (36.0%)
Cluster Y (MHP)	86 (22.5)	Primary care-level MHP (91.9%) Sleep disorders (34.9%)
Cluster Z (Cardio-metabolic)	10 (2.6)	Heart failure (90.0%) Ischaemic heart disease (50.0%)

Table 137: Impact of musculoskeletal disorders on HRJL, stratified by comorbidity clusters.

Demographic variable	Control, n (%)	With HRJL, n (%)	Association with HRJL, unadjusted. OR (95% CI)[1]	Association with HRJL, adjusted for education, history of heavy alcohol intake, and single status.[2] aOR (95% CI)
No known health disorders	225 (59.7)	110 (32.3)	1.00	1.00
Cluster V (MSD alone)	90 (23.9)	69 (20.2)	**2.20 (1.35 to 3.60)**	**2.26 (1.36 to 3.74)**
Cluster W (HTN-Diab)	36 (9.6)	60 (17.6)	**4.25 (2.27 to 7.95)**	**4.09 (2.15 to 7.77)**
Cluster X (Asthma-HTN)	8 (2.1)	17 (5.0)	**7.42 (2.12 to 25.92)**	**7.34 (2.09 to 25.77)**
Cluster Y (MHP)	14 (3.7)	72 (21.1)	**16.18 (6.51 to 40.25)**	**15.04 (5.99 to 37.77)**
Cluster Z (Cardio-metabolic)	3 (0.8)	7 (2.1)	**5.79 (1.23 to 27.17)**	**5.80 (1.20 to 28.08)**

1. 536 participants contributed to the conditional logistic model
2. 524 participants contributed to the adjusted conditional logistic model

8.4 Summary

- Multiple indicators of multimorbidity were significantly associated with health-related job loss, including number of known health disorders, number of drug prescriptions in the prior year, and number of GP consultations in the prior year.

- Among those with multimorbidity, compared to participants with no known health disorders, clusters formed by majority hypertension-musculoskeletal disorders and mental health problem-musculoskeletal clusters were common and strongly associated with health-related job loss. Particularly, clusters formed by mental health problem-musculoskeletal disorders were most strongly associated with HRJL. In addition, a small OPD-HTN-MHP cluster formed and was very strongly associated with health-related job loss, although confidence intervals were wide.

- Clusters formed primarily by hypertension-musculoskeletal disorders and mental health problems-musculoskeletal disorders remained strongly associated with HRJL in both multimorbid men and multimorbid women. Once again, clusters primarily formed by musculoskeletal disorders-mental health problems were mostly strongly

associated with health-related job loss in all cases, and these were more prevalent among multimorbid women.

- Clusters of cardio-metabolic disorders, and of obstructive pulmonary disease-hypertension-musculoskeletal disorders, which formed prominently among multimorbid men but not women, were found to be strongly associated with HRJL, compared to participants with no known health disorders.

- The strength of association between musculoskeletal disorders and HRJL increased as number of known comorbidities increased. Considering patterns of comorbidity among participants with musculoskeletal disorders, the HTN-Diab, Asthma-HTN, and cardio-metabolic comorbidity clusters were strongly associated with HRJL. The MHP comorbidity cluster had the strongest association with HRJL.

8.5 Discussion

In this chapter, in order to study the impact of multimorbidity upon HRJL, several indicators of multimorbidity and their association with HRJL were explored. Cases and controls were compared for the number of known health disorders, number of GP consultations in the prior year, number of drugs prescribed in the prior year, and cluster-analysis-defined multimorbidity groups in a nested matched case-control study. Adjusted analyses have been presented. It was observed that as the number of health disorders, number of GP consultations in the prior year, and number of drug prescriptions in the prior year increased, association with HRJL significantly increased. Compared to having no known health disorders, being in any multimorbidity cluster was also significantly, and usually strongly, associated with HRJL. In general, clusters dominated by mental health problems and musculoskeletal disorders (chronic or pain) were both common and very strongly associated with HRJL.

Multimorbid participants (two or more known health disorders) were prevalent in the study sample (33.2%) and multimorbidity was strongly associated with HRJL. The strength of this association also increased as number of known disorders increased. Although this is the first study of the impact of multimorbidity upon health-related job loss in the literature, the direction of effect broadly correlates with other reported work outcomes. Several other cross-sectional studies among western (non-UK) working populations observed that number of health disorders was correlated with sickness absence,(450,451) increased work impairment scores,(199) or presenteeism.(450) In one study among the wider population,

number of health disorders was also associated with self-reported unemployment, work disability, and receipt of living allowance.(200) The impact of multimorbidity on these work outcomes was also shown to substantially worsen with each additional condition.(200)

Number of GP consultations in the prior year was associated with HRJL. Compared to the lowest quartile of GP consultations, being in the third or fourth quartile for consultations was strongly associated with HRJL. Frequent GP attendance is a biopsychosocial phenomenon(452–454) that has been shown to carry a strong relationship with multimorbidity.(455) It shares many risk factors with premature work loss, including increasing age,(454) low socioeconomic status,(456) low educational attainment,(457) severity of existing health disorders,(453) and particularly, the presence of chronic disease,(454) arthritis,(458) back pain,(459) and mental health disorders.(454,459,460) In one study, 41% of frequent GP attendance was attributable to chronic physical illness and 30.9% to mental health disorders.(454) Evidence linking GP consultations to work outcomes is scarce and the findings of this chapter will help to establish the relationship between rate of GP consultation and premature exit from work. However, it remains unclear how much this relationship is independent of the effects of disease burden, since frequency of GP consultation also represents significant work-time cost that could be deleterious to maintaining employment. In one population-based cross sectional study, after adjustment for physical, psychological health, and tendency towards somatisation, frequent GP attendance remained associated with unemployment among men and women, and with disability pension among men.(457)

Similarly, number of drugs prescribed in the prior year was found to be associated with HRJL. Compared to the lowest quartile of drug prescription, being in the third or fourth quartile for number of drugs prescribed was strongly associated with HRJL. However, only prescription data related to the selected CPRD conditions was available for this analysis. In addition, participants taking certain drugs that are prescribed more frequently throughout the year would have had an inflated prescription count. This is appropriate if the overall number of drugs taken was higher, however, it could also be for arbitrary reasons such as the GP supplying fewer drugs per prescription. As such, this measure can only be interpreted as a crude indicator of treatment burden and multimorbidity. The concurrent use of multiple medications is referred to as polypharmacy, which is itself strongly related to multimorbidity, although different conditions are associated with different degrees of polypharmacy.(461) Polypharmacy is associated with several factors related to a person's likelihood of premature work loss, such as lower socioeconomic status,(462) increasing

age,(462,463) and chronic health disorders,(462) diabetes,(463–465) asthma,(464) and cardiovascular disease,(463–465) specifically. However, available evidence is mostly derived from elderly populations (>65 years old) and different definitions of polypharmacy exist,(466) the most common definition being five or more daily medications.(467) While preliminary, the relationship described between drug prescriptions and HRJL in this chapter is novel; no other literature exploring polypharmacy and work outcomes was identified.

Next, I considered the association between generated clusters (see Chapter 7) and the development of HRJL. In all models, compared to participants with no known health disorders, having one known health disorder did not reach higher than 2.46-fold increased odds of HRJL (a moderate strength association). Whereas being part of any multimorbidity cluster had an estimated 2.26- to 15.00-fold increased odds of HRJL. Nineteen of 21 generated multimorbidity clusters were at least strongly associated with HRJL (3.40- to 15.00-fold increased odds of HRJL) and six were very strongly associated with HRJL (7.56- to 15.00-fold increased odds of HRJL). For the individual, certain health problems may have an important impact on the ability to stay in work, regardless of the presence of comorbidity. However, these results suggest that those who are dealing with multiple health problems may represent the most common high-risk group among the older working age population.

I considered the impact of specific clusters generated in the total multimorbid population. Compared to participants with no known health disorders, clusters formed primarily by MSDs and mental health problems (Cluster A [MHP-cMSD]/Cluster H [MHP-MSpain]) were very strongly associated with HRJL; and clusters formed primarily by MSDs and hypertension (Cluster C [HTN-cMSD-diab]/Cluster E [HTN-MSpain]) were strongly associated with HRJL. These clusters were also large and together contained over two-thirds of those with multimorbidity (32.2%/37.7% and 39.9%/32.5%, respectively). At the population level, these findings represent supportive evidence that the co-occurrence of mental health disorders and musculoskeletal disorders, particularly, is of key importance to HRJL among older workers. Cluster F (Diab-HTN-pcMHP) and Cluster G (Cardio-metabolic) were also strongly associated with HRJL, although these groups accounted for a much smaller proportion of overall multimorbidity. Cluster D (OPD-HTN-MHP) was also small but very strongly associated with HRJL, although confidence intervals were especially wide. In this cluster, COPD and mental health disorders likely drove the strength of association since asthma was found to have only a weak association with HRJL in adjusted analysis (see Chapter 6).

Cluster B/Cluster G comprised cardio-metabolic clusters which were large majority male (82.9%/85.7%). Naturally, similar clusters formed again when analysis was restricted to male multimorbid participants: Cardio-metabolic clusters (Clusters L and O) accounted for 26.6%/20.1% of multimorbid men and were strongly associated with HRJL (OR 3.40 95%CI 1.50 to 7.70; and OR 5.41 95%CI 2.14 to 13.67, respectively), compared to male participants with no known health disorders. A cardio-metabolic cluster did not form prominently among women.

Among women with multimorbidity, clusters formed primarily by MSDs and hypertension (Cluster R [HTN-cMSD]/Cluster T [HTN-MSpain]) and clusters formed primarily by MSDs and mental health problems (Cluster S [MHP-cMSD]/Cluster U [MHP-MSpain]) were strongly associated with HRJL, compared with female participants with no known health disorders. Together, these clusters contained almost all women with multimorbidity in the study sample (53.0%/48.6% and 44.0%/44.9%, respectively). Chronic musculoskeletal disorders featured prominently in both clusters, establishing these conditions as a key source of multimorbidity associated with HRJL in women. The MHP-cMSD cluster was more prevalent among multimorbid women (44.0%) than among multimorbid men (15.1%). However, among both men and women musculoskeletal-mental health disorder clusters showed the strongest association with HRJL.

This chapter described the characteristics of the 383 HEAF participants with musculoskeletal disorders. Their known demographic, lifestyle, and occupational factors have been described. Musculoskeletal disorders are known to have a strong positive relationship with age, and occurred more frequently in older participants.(396) Proportionally fewer participants with any kind of musculoskeletal disorder appeared to be university educated and proportionally more had no qualifications. Routine occupations were the most common kind of work among participants with MSDs. Routine work is frequently worked by those of lower educational attainment and, more importantly, is often manual work, which has a known association with the development of musculoskeletal disorders.(392–394)

It must be emphasised that the majority (58.5%) of older working-age participants with MSDs were dealing with multiple health problems. The manner in which these musculoskeletal disorders form clusters with other disease groups was described in Chapter 7. As the number of comorbid conditions increased among people with musculoskeletal disorders, it was observed that the association with HRJL increased dramatically; this was

true for chronic MSD and recent MSD pain conditions. The literature broadly agrees that comorbidity is an important associate of work disability amongst different musculoskeletal populations,(9–13,339) although few studies have stratified exposure by number of comorbidities to show a dose-response relationship, as has been done here. Comorbidities may play a mediating role between MSDs and job loss; for example, chronic MSD pain may lead to mental health problems leading to subsequent difficulty maintaining work. Therefore, non-comorbid participants may represent those with generally less severe musculoskeletal problems, as severe MSDs are both more likely to lead to job loss (468,469) and have been associated with the co-development of mental health problems(470–472) and cardiovascular disease.(473–475) The lack of CPRD-information on underlying musculoskeletal disease severity meant I was unable to explore this, which was a limitation of this research.

Finally, an assessment of the relationship between musculoskeletal disorders and HRJL was split by the observed patterns of comorbidity among participants with MSDs. Results corresponded to those observed for analysis of multimorbidity patterns in the total study sample. Of the generated MSD comorbidity clusters, the cluster with mental health problems was both common and most strongly associated with HRJL.

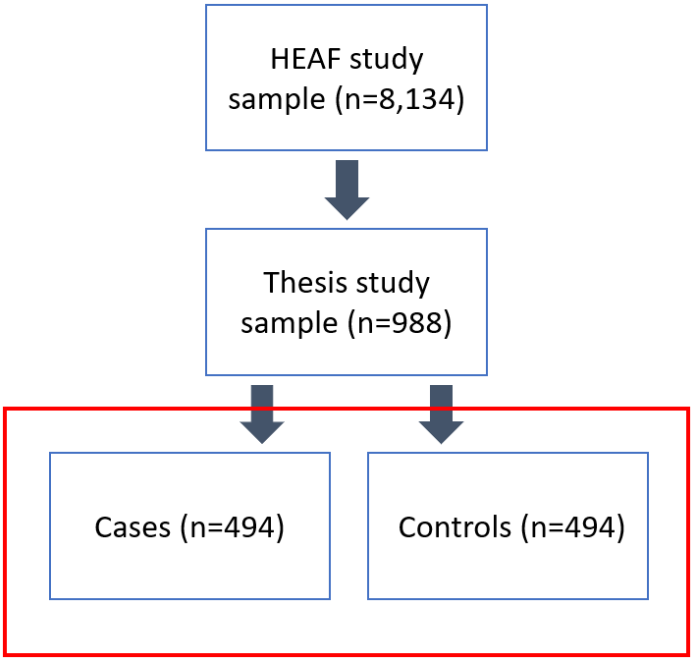
As mentioned previously, some caution is required when interpreting these results since information used to comprise multimorbidity measures was only available for selected health disorders and did not include certain prevalent health disorders such as gastrointestinal problems. In addition, confidence intervals were frequently wide and overlapping, which makes it difficult to compare effect estimates across clusters. However, multiple indicators of multimorbidity were analysed, lending greater convergent validity to the observed results, which establish multimorbidity as an important exposure in HRJL that should not be overlooked in health and work research among the older working-age population. There is currently little published about the impact of multimorbidity on work outcomes and where present, this is often restricted to the study of two specific types of diseases in combination.(476,477) I was unable to find any other study that considered the impact of multimorbidity upon health-related job loss in the older working age population. In addition, this is the first study to consider common disease clusters among the multimorbid, and their relative occupational health impact.

Chapter 9 – The population attributable fraction of HRJL for CPRD-defined health disorders

9.1 Introduction

As has been described, MSDs occur frequently among the older working-age population and are a common associate and cause of HRJL. It has also been observed that they commonly co-present alongside other health conditions, forming clusters at the population level, and that these clusters have a strong association with HRJL, when compared with participants with no known health disorders. This final results chapter considers the independent association between musculoskeletal disease exposures and HRJL, after adjusting for the presence of other CPRD-defined health disorders. Then I consider how these specific health disorders can modify the relationship between MSDs and HRJL, thereby addressing research objective 6 (see Chapter 2). Lastly, to conclude this work, I estimate the proportion of HRJL that can be attributed to MSDs (and other CPRD-defined health disorders) among the UK older working population, thereby addressing research objective 7 (see Chapter 2). Throughout the chapter, cases (with HRJL) are compared to matched working control participants to attain relative estimates of association (see Figure 49).

Figure 49: the cohort used in this chapter, as indicated by the red square



9.2 Methods

9.2.1 Description

In brief, the total study population were described again for their demographic, lifestyle and occupational factors and for the overall prevalence of CPRD-defined health disorders. I used proportions to describe categorical data and medians and inter-quartile ranges to describe continuous data with non-Gaussian distributions.

9.2.2 Preliminary main-effects model

To determine the independent association of musculoskeletal disorders with HRJL, I ran a multivariable conditional logistic regression analysis, adjusting for the presence of other known health disorders, as well as possible confounders (e.g. educational attainment, single relationship status, and history of heavy alcohol intake). Using this "independent" estimate of effect, it was possible to derive the Population Attributable Fraction (PAF) of HRJL for musculoskeletal disorders in the UK older working population (see below for a description of PAF).

Therefore, a parsimonious model of all known explanatory and confounding variables was built using the "purposeful selection" process first described by Hosmer and Lemeshow.(478) Over several stages, a small set of important (predictive) variables were included in the model from a larger initial set of possible variables. This process is described below. From the final model I derived an estimate of the relative association of MSDs with HRJL, taking into account the presence of other important health conditions and confounders.

Health and demographic factors were examined in turn for their association to HRJL at a univariable level. Chapter 6 has already outlined the resulting effect sizes. The Wald test output (z-value) from these logistic regression models, was used to select factors into a large multivariable model based on an arbitrary cut-off value (p=0.25).(479) A cut-off value of 0.20 – 0.25 is recommended since the traditional p-value of 0.05 has been found to miss important variables.(480,481)

Next, an iterative backward selection process was applied, whereby non-significant variables were removed from the large model one by one. Covariables considered non-significant at the 0.1 alpha-level, were removed from the model in order of least significance. Non-significant variables were permitted to remain in the model if they were

considered important confounding factors, defined by a 15 – 20% or more change in the effect estimate of any remaining parameter after removal of the confounder from the model.(479) After this stage, the remaining multivariable model consisted only of known important confounders and explanatory variables.

Following this, variables found to be non-significant at the univariable level were entered into the multivariable model one at a time to assess their contribution after adjustment for other important covariables and confounders. In this phase, any introduced variables significant at the 0.15 level were entered into the model, followed by backward selection of these variables to iteratively reduce the model down to a "preliminary main effects" model.(478,479)

In the total study sample, of those with chronic MSDs, 34.9% had recent MSD pain. Of those with recent MSD pain, 31.5% had a chronic MSD. The considerable overlap between these two groups and the possible role of recent MSD pain as a mediator between chronic MSDs and HRJL led to the decision to model these musculoskeletal groups separately.

The assumptions of logistic regression are fewer than for linear regression models, however, for each preliminary main effects model an assessment of goodness-of-fit, specification errors, and multicollinearity was performed.(482) Goodness-of-fit was assessed using the pseudo-R^2 value produced in the STATA output for each model. Specification error was assessed using the "linktest" command in STATA and by observing the linear predicted value and the squared linear predicted value for statistical significance. Finally, I assessed the degree of multicollinearity among independent variables using the Variance Inflation Factor (VIF). VIF is a measure of how much the variance of the estimated regression coefficient is "inflated" by the existence of correlation among included explanatory variables in the model.(483)

9.2.3 Interaction analysis

The presence of specific comorbidities may modify the influence of MSDs upon HRJL occurrence. For example, the presence of certain mental health problems may worsen pain perception and multiply the impact of musculoskeletal pain upon work, such that the effect of the diseases combined is more than their individual effects added together. If this is true, evidence of statistical interaction may be apparent. I looked for the statistical interaction between musculoskeletal disorders and other CPRD-defined health disorders in their association with HRJL, as below.

As is recommended in the literature, interaction effects were assessed on two "scales": the additive scale or the multiplicative scale.(484) Calculating additive interaction is used to describe whether the association of two exposures together is greater than *the sum* of the effects of two exposures individually. If so, this is known as additive interaction. Where risk ratios can be calculated, additive interaction can be formulated as $(RR_{11} – RR_{00}) – ((RR_{10} – RR_{00}) + (RR_{01} – RR_{00}))$ or $RR_{11} – RR_{10} – RR_{01} + RR_{00}$ (see Figure 50).

Figure 50: Relative effect statistics used in calculating additive and multiplicative interaction

		Exposure A	
		Exposure absent (0)	**Exposure present (1)**
Exposure B	**Exposure absent (0)**	RR_{00}	RR_{10}
	Exposure present (1)	RR_{01}	RR_{11}

Where the outcome is rare enough that OR approximates RR (as in this case), this formula can be rewritten as: $OR_{11} – OR_{10} – OR_{01} + 1$. This calculates the Relative Excess Risk due to Interaction (known as RERI) which approximates the additive interaction. If the result of applying the RERI formula is greater than 0 there is a positive or "super-additive" interaction, if the interaction is less than 0 the interaction is negative or "sub-additive."(484)

Multiplicative interaction describes whether the effect of both exposures together exceeds *the product* of the effects of the two exposures considered separately. Interactions on the multiplicative scale can be calculated with the following formula: $RR_{11}/(RR_{10} \times RR_{01})$ (see Figure 50). Once again, where the outcome is rare, ORs approximate RR and the same formula can be applied for ORs to approximate multiplicative interaction: $OR_{11}/(OR_{10} \times OR_{01})$. Multiplicative interactions can be calculated easily by adding an interaction term to the multivariable logistic model. The interaction term is calculated by multiplying two exposure variables together. In this case, if the resulting interaction is significantly greater than 1 there is a positive multiplicative interaction, and if less than 1 this is a negative multiplicative interaction.(484)

An interaction between two exposures may be additive or multiplicative and therefore more apparent on one scale or the other. This depends on the underlying natural mechanism. For example, smoking has been found to be strongly associated with lung cancer but not other diseases on the relative risk scale, but similarly associated with lung cancer and other diseases on the absolute risk scale. In this case, the specificity on the multiplicative scale helped to provide evidence of causality between smoking and lung cancer.(485) On which scale to appropriately report interaction effects has been the topic of debate for some time, however, it is broadly agreed that assessments of interaction should be reported on both scales.

9.2.4 Population Attributable Fraction

Until this point in the thesis, I have considered, separately, the prevalence of CPRD-defined health disorders in the study population and the association of these disorders with HRJL. However, from a public health perspective, neither of these measures provides a sufficient estimate of the total burden of HRJL that would be prevented by modification of a given health exposure. The population attributable fraction (PAF) is a useful metric that can inform efforts to reduce population HRJL, by identifying exposures that are responsible for the greatest proportion of this adverse work outcome i.e. higher risk/higher prevalence exposures. The units of PAF are percentages, which express the estimated proportion of an outcome (in this case, HRJL) that is attributable to an exposure, and indeed estimates the proportion that would disappear if that exposure were removed from the population (assuming causality).

For the use and interpretation of PAF, the examples provided by Mary Northridge are instructive.(486) One of the first uses of PAF was by Levin et al, who showed that smoking was associated with a high risk of lung cancer, and was also highly prevalent among men. He found a PAF of between 56 – 92%, meaning that the elimination of smoking could possibly reduce population lung cancer levels by more than 90% among men.(487) Another example involves the link between the BRCA1 gene and breast cancer; the risk of breast cancer is high among individuals with this allele although the prevalence in the general population is only 0.0007. Despite the low prevalence, the high individual risk associated with BRCA1 means PAF can be as high as 8.2%, depending on age.(486) Finally, certain exposures have a low associated risk but are highly prevalent in the population, and therefore warrant continued public health attention. This includes ultraviolet light

exposure, which affects virtually everyone, but has a relatively low individual risk. In this case, the PAF remains considerable (13 – 33%) due to the large population prevalence.(486)

I considered the results of the preliminary main effects model(s), and used the independent effect estimates to calculate PAF of HRJL for CPRD-defined health disorders. PAF can be calculated from effect estimates observed in matched case-control studies, so long as a reliable estimate of the population prevalence can also be derived.(488) I used the prevalence of these CPRD-defined health disorders in the total HEAF baseline study sample (n=8109): a representative UK-based sample of the older working-age (aged 50 – 65 years).(6) The formula for calculation of PAF is displayed in Figure 51, below.

Figure 51: mathematical expression for the population attributable fraction

$$PAF\ \% = 100 * \frac{p\ (RR - 1)}{p(RR - 1) + 1}$$

Once again, where the outcome is rare enough that OR approximates RR (as in this case), this formula can be rewritten as: PAF = 100*p(OR – 1)/p(OR – 1) +1.

9.3 Results

9.3.1 Describing total study participants

The 988 study participants have been described previously. In brief, half were cases with HRJL and half were matched controls. The median age was 58.21 years (IQR 53.36 to 60.89 years), at the point of analysis. 44.5% were men, 98.1% were white, 68.9% were married, and 7.8% were single. 22.6% had a university-level qualification and 19.6% had no qualifications. Finally, 35.8% were working in higher managerial or professional class occupations, 27.5% in intermediate occupations, and 36.7% in routine or manual occupations.

Of these participants, 22.1% had chronic MSDs, 24.4% had recent MSD pain, 17.9% had primary-care-level MHPs, 1.0% had psychiatric-care-level MHPs, 5.2% had recent sleep disorders, 22.0% had hypertension, 5.2% had ischaemic heart disease, 5.9% had heart failure, 0.7% had structural heart disease, 1.2% had peripheral atherosclerotic disease, 0.1% had venous thromboembolic disease, 0.8% had cardiac arrhythmias, 7.9% had asthma, 2.0% had COPD, 2.1% had cerebrovascular accident, 1.0% had epilepsy, and 9.2% had diabetes. The prevalence of multimorbidity (two or more CPRD-defined health disorders) was 33.2%.

9.3.2 The independent association of MSDs with HRJL, adjusting for other specific health disorders

Using purposeful selection methods and known demographic, occupational, lifestyle, and health variables, a model was built for the prediction of HRJL.

At the univariable level (using a p=0.25 threshold) the following factors were found to be associated with HRJL: level of education, single relationship status, history of heavy alcohol intake, chronic musculoskeletal disorders, recent musculoskeletal pain, primary care level mental health problems, sleep disturbances, psychiatric mental health problems, hypertension, heart failure, ischaemic heart disease, peripheral arterial disease, arrythmias, asthma, COPD, CVA, epilepsy, and diabetes. Ethnicity and smoking did not meet the threshold and were not initially entered into statistical models. As in previous chapters, participants with any musculoskeletal disorders were modelled together, as well as chronic musculoskeletal disorders and recent musculoskeletal pain disorders in separate models.

In the first model, I considered participants with any MSD (chronic MSD or recent MSD pain). After iterative backward selection, the following variables were removed: educational attainment, sleep disorders, psychiatric-care-level MHPs, and COPD. Variables not initially included in the model (smoking and white ethnicity) were tested however no further important variables were found. Results from the final model are displayed in Table 138, below.

The following health disorders remained significantly associated with HRJL in this preliminary main effects model: any musculoskeletal disorder (aOR 1.86 95%CI 1.35 to 2.56), primary-care-level MHP (aOR 3.49 95%CI 2.26 to 5.40), hypertension (aOR 1.58 95%CI 1.07 to 2.32), heart failure (aOR 5.02 95%CI 2.14 to 11.77), asthma (aOR 2.18 95%CI 1.24 to 3.82), cerebrovascular accident (aOR 3.88 95%CI 1.17 to 12.94), epilepsy (aOR 5.74 95%CI 1.02 to 32.45), and diabetes (aOR 1.93 95%CI 1.06 to 3.52).

From this model, I could also calculate the estimated combined effects of having both a musculoskeletal disorder and primary-care-level mental health disorder (aOR 6.49), MSD and hypertension (aOR 2.94), MSD and heart failure (aOR 9.34), MSD and asthma (aOR 4.05), MSD and CVA (aOR 7.22), MSD and epilepsy (aOR 10.68), and MSD and diabetes (aOR 3.59).

Table 138: Multivariable model of important health disorders and their association with HRJL, including any MSD to define musculoskeletal disorders

Explanatory variable	*Association with HRJL, aOR (95%CI)*
Single relationship status	1.78 (0.99 to 3.19)
History of heavy alcohol intake	2.72 (0.87 to 8.51)
Musculoskeletal disorder	**1.86 (1.35 to 2.56)**
Primary-care mental health problem	**3.49 (2.26 to 5.40)**
Hypertension	**1.58 (1.07 to 2.32)**
Heart failure	**5.02 (2.14 to 11.77)**
Ischaemic heart disease	0.45 (0.20 to 1.01)
Peripheral arterial disease	8.46 (0.93 to 77.22)
Arrhythmias	6.90 (0.71 to 67.09)
Asthma	**2.18 (1.24 to 3.82)**
Cerebrovascular accident	**3.88 (1.17 to 12.94)**
Epilepsy	**5.74 (1.02 to 32.45)**
Diabetes	**1.93 (1.06 to 3.52)**

In the second model, I considered participants with chronic MSDs. After iterative backward selection, the following variables were removed: level of education, sleep disturbance, psychiatric-level mental health problems, and arrhythmias. Variables not initially included in the model (smoking and white ethnicity) were tested however no further important variables were found. Results from the final model are displayed in Table 139, below.

The following health disorders remained significantly associated with HRJL in the preliminary main effects model: chronic musculoskeletal disorders (aOR 1.69 95%CI 1.19 to 2.41), primary-care-level mental health disorders (aOR 3.25 95%CI 1.10 to 5.54), hypertension (aOR 1.66 95%CI 1.13 to 2.42), heart failure (aOR 4.50 95%CI 1.94 to 10.45), asthma (aOR 1.80 95%CI 1.02 to 3.20), cerebrovascular accident (aOR: 4.12 95%CI 1.23 to 13.77), and diabetes (aOR 2.10 95%CI 1.10 to 3.67).

From this model, I could also calculate the estimated combined effects of having both a chronic musculoskeletal disorder and primary-care-level MHP (aOR 6.05), chronic MSD and hypertension (aOR 2.81), chronic MSD and heart failure (aOR 7.61), chronic MSD and asthma (aOR 3.04), chronic MSD and CVA (aOR 6.96), and a chronic MSD and diabetes (aOR 3.40).

Table 139: Multivariable model of important health disorders and their association with HRJL, using chronic MSDs to define musculoskeletal disorders

Explanatory variable	*Association with HRJL, aOR (95%CI)*
Single relationship status	**1.80 (1.01 to 3.22)**
History of heavy alcohol intake	**3.25 (1.10 to 9.63)**
Chronic MSD	**1.69 (1.19 to 2.41)**
Primary-care-level MHP	**3.58 (2.32 to 5.54)**
Hypertension	**1.66 (1.13 to 2.42)**
Heart failure	**4.50 (1.94 to 10.45)**
Ischaemic heart disease	0.48 (0.22 to 1.04)
Peripheral arterial disease	7.78 (0.89 to 68.12)
Asthma	**1.80 (1.02 to 3.20)**
COPD	3.58 (0.86 to 14.92)
Cerebrovascular accident	**4.12 (1.23 to 13.77)**
Epilepsy	5.59 (0.98 to 31.76)
Diabetes	**2.01 (1.10 to 3.67)**

In the third model, participants with recent MSD pain were considered. After iterative backward selection, the following variables were removed: psychiatric-level mental health problems, level of education, sleep disorders, single relationship status, ischaemic heart disease and cardiac arrhythmias. Once again, variables not initially included in the model (smoking and white ethnicity) were tested however no further important variables were found. Results from the final model are displayed in Table 140, below.

The following health disorders remained significantly associated with HRJL in the preliminary main effects model: recent musculoskeletal pain (aOR 2.14 95%CI 1.48 to 3.09), primary-care-level MHPs (aOR 3.41 95%CI 2.24 to 5.20), hypertension (aOR 1.56 95%CI 1.07 to 2.28), heart failure (aOR 3.82 95%CI 1.78 to 8.10), cerebrovascular accident (aOR 3.93 95%CI 1.13 to 13.63), epilepsy (aOR 5.92 95%CI 1.06 to 33.17), and diabetes (aOR 2.04 95%CI 1.14 to 3.63).

From this model, I could also calculate the estimated combined effects of having both recent musculoskeletal pain and a primary-care-level MHP (aOR 7.30), recent MSD pain and hypertension (aOR 3.34), recent MSD pain and heart failure (aOR 8.17), recent MSD pain and CVA (aOR 8.41), recent MSD pain and epilepsy (aOR 12.67), and recent MSD pain and diabetes (aOR 4.37).

Table 140: Multivariable model of important health disorders and their association with HRJL, using recent MSD pain to define musculoskeletal disorders

Explanatory variable	*Association with HRJL, aOR (95%CI)*
History of heavy alcohol intake	**3.30 (1.07 to 10.14)**
Musculoskeletal pain	**2.14 (1.48 to 3.09)**
Primary-care-level MHP	**3.41 (2.24 to 5.20)**
Hypertension	**1.56 (1.07 to 2.28)**
Heart failure	**3.82 (1.78 to 8.10)**
Peripheral arterial disease	7.47 (0.90 to 62.04)
Asthma	1.73 (0.97 to 3.06)
COPD	3.34 (0.89 to 12.56)
Cerebrovascular accident	**3.93 (1.13 to 13.63)**
Epilepsy	**5.92 (1.06 to 33.17)**
Diabetes	**2.04 (1.14 to 3.63)**

9.3.3 The statistical interaction between musculoskeletal disorders and other CPRD-defined health disorders associated with HRJL

I examined the first, second, and third preliminary effects models above for the presence of statistical interactions between musculoskeletal health disorders and other CPRD-defined health disorders that were significantly associated with HRJL. Interactions on the additive and multiplicative scale were considered, as recommended by VanderWeele et al.(484) See Tables 78, 79, and 80, Appendix, for a full examination of preliminary main effects model interactions.

In the second model, a significant interaction was observed between chronic MSDs and diabetes on the multiplicative scale (aOR 0.24 95%CI 0.07 to 0.82) but not the additive scale (RERI -2.53 95%CI -5.13 to 0.07). On the multiplicative scale, this appeared to show a slightly protective interaction, i.e. the combined effect of having both diabetes and a chronic MSD appeared to have a smaller association with HRJL than the product of the effects of the two disorders individually.

No interaction between musculoskeletal disorders and any other health problem was observed across all three models.

9.3.4 The Population Attributable Fraction

The population attributable fraction (PAF) of HRJL was calculated for each of the CPRD-defined health disorders that were significantly associated with HRJL in the preliminary main-effects model(s) outlined above. As described in the methods, PAF was calculated using two metrics 1) an estimate of the association between a CPRD-defined health disorder and HRJL and 2) an estimate of the prevalence of this CPRD-defined health disorder in the population of interest (UK older-age workers).

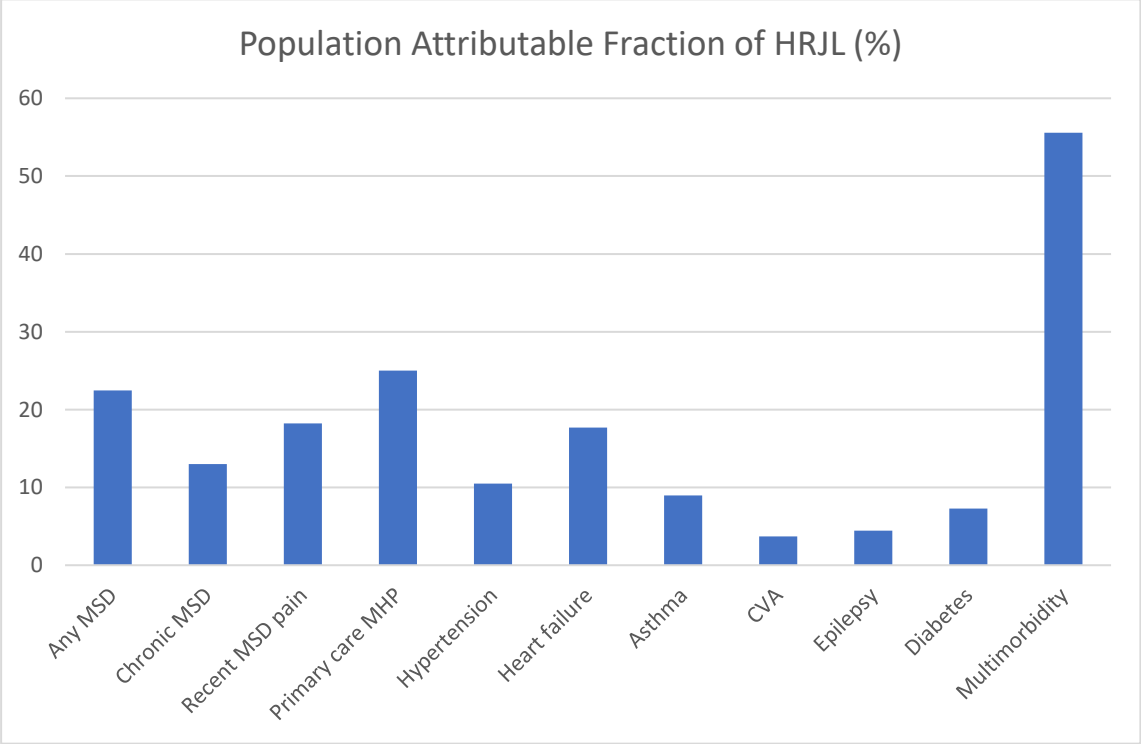
Prevalence estimates were calculated using the baseline HEAF study population (n=8109), a UK-representative population.(201) Effect estimates for musculoskeletal disorders (chronic or pain), primary-care-level MHPs, hypertension, heart failure, asthma, cerebrovascular accident, epilepsy, or diabetes was derived from the first main-effects model. The effect estimate for chronic MSDs was derived from the second main-effects model; and the effect estimate for recent MSD pain was derived from the third main-effects model. Finally, the effect estimate for multimorbidity was derived from a separate model of the association between multimorbidity (two or more CPRD-defined health disorders) and HRJL, compared to not having multimorbidity, adjusted for single status, qualification level, and history of heavy alcohol intake.

Of the individual health disorders, primary care-level MHPs had the largest PAF (25.0%). Recent musculoskeletal pain was found to have a PAF of 18.2% and chronic MSDs had a PAF of 13.0%, although, together, musculoskeletal disorders had the second largest PAF of 22.5%. Heart failure had the next largest PAF at 17.7% as it was strongly associated with HRJL and its prevalence was 5.4% in the HEAF baseline population. This was followed by hypertension (10.5%), asthma (9.0%), diabetes (7.3%), epilepsy (4.4%), and cerebrovascular accident (3.7%). However, multimorbidity was observed to have a greater PAF than any individual condition, which was estimated to be 55.6% for the UK older-working age population. See Table 141 and Figure 52, below.

Table 141: Population Attributable Fraction of HRJL for CPRD-defined health disorders

CPRD defined health disorder	Prevalence in HEAF baseline population	Independent association with HRJL	Population Attributable Fraction (%)
Any MSD	33.7%	1.86 (1.35 to 2.56)	22.5%
Chronic MSD	21.6%	1.69 (1.18 to 2.42)	13.0%
Recent MSD pain	19.6%	2.14 (1.48 to 3.09)	18.2%
Primary care MHP	13.4%	3.49 (2.26 to 5.40)	25.0%
Hypertension	20.2%	1.58 (1.07 to 2.32)	10.5%
Heart failure	5.4%	5.02 (2.14 to 11.77)	17.7%
Asthma	8.4%	2.18 (1.24 to 3.82)	9.0%
CVA	1.3%	3.88 (1.17 to 12.94)	3.7%
Epilepsy	1.0%	5.74 (1.02 to 32.45)	4.4%
Diabetes	8.5%	1.93 (1.06 to 3.52)	7.3%
Multimorbidity	**41.4%**	**4.02 (2.87 to 5.64)**	**55.6%**

Figure 52: the estimated population attributable fraction of CPRD-defined health disorders and multimorbidity for HRJL in the older working age population



9.4 Summary

- Musculoskeletal disorders, including chronic MSDs and recent MSD pain, remained independently associated with HRJL after adjustment for other important CPRD-defined health disorders.

- Primary care-level MHPs, hypertension, heart failure, cerebrovascular accident, and diabetes were also observed to be independently and significantly associated with HRJL, in all analyses.

- Musculoskeletal disorders comorbid with primary-care-level MHPs, heart failure, cerebrovascular accident, or epilepsy were estimated to have a particularly strong association with HRJL.

- Of the individual health disorders, primary-care-level MHPs and musculoskeletal disorders (chronic or pain) had the largest estimated population attributable fraction of HRJL in the UK older working-age population (PAF 25.0% and 22.5%, respectively). However, multimorbidity was estimated to account for over half of all HRJL in the UK older working-age population (PAF 55.6%).

9.5 Discussion

In the previous chapter, participants with MSDs were found to have a high degree of comorbidity (58.7%) compared to the level of multimorbidity in the general study population (33.2%). This chapter contributed important data helping establish the independent effect of musculoskeletal disorders (chronic and/or pain) on HRJL, after adjusting for the presence of other common health disorders. The independent effect estimates generated in multivariable modelling were then used to estimate the proportion of HRJL that could be attributed to these CPRD-defined health disorders in the UK older working-age population. Findings confirm that musculoskeletal disorders and mental health problems are the two greatest contributors to HRJL, however results also suggested that considerably more HRJL could be attributed to multimorbidity than any individual health disorder. These findings should encourage a greater interest in research focussed on multimorbidity, both for its role as a predictor of adverse work outcomes and to develop interventions to support people with multimorbidity to remain at work.

Across all three preliminary main effects models, chronic MSDs (aOR 1.69 95%CI 1.19 to 2.41), recent MSD pain (aOR 2.14 95%CI 1.48 to 3.09), primary care-level MHPs (aOR 3.49 95%CI 2.26 to 5.40), hypertension (aOR 1.58 95%CI 1.07 to 2.32), heart failure (aOR 5.02 95%CI 2.14 to 11.77), cerebrovascular accident (aOR 3.88 95%CI 1.17 to 12.94), and diabetes (aOR 1.93 95%CI 1.06 to 3.52) remained independently and significantly associated with HRJL after adjustment for other CPRD-defined health problems. Asthma may also have a weak-moderate independent association with HRJL (aOR 1.73 to 2.18),

epilepsy may have a strong independent association (aOR 5.59 to 5.92), COPD may have a strong independent association (aOR 3.34 to 3.58), and peripheral atherosclerotic disease may have a very strong association (aOR 7.47 to 8.46), although this effect was not statistically significant across all models. Cardiac arrhythmias were included in only the first model and may also have a strong association with HRJL, although effect estimates were very uncertain (aOR 6.90 95%CI 0.71 to 67.09).

In Chapter 6, CPRD-defined ischaemic heart disease was found to have a mild, but non-significant, association with HRJL, after adjustment for educational attainment, single relationship status, and history of heavy alcohol intake (aOR 1.32 95%CI 0.74 to 2.37). In this chapter, ischaemic heart disease was included in two preliminary main effects models but tended towards a more protective effect (aOR 0.45 and 0.48). Although running a statistical test of multicollinearity (VIF) in these models did not suggest substantial intercorrelation between ischaemic heart disease and other covariables, it was found that when other indicators of cardiometabolic disease (hypertension, heart failure, peripheral arterial disease, cardiac arrhythmias, and diabetes) were adjusted for, the estimated direction of effect for ischaemic heart disease reversed. Therefore, it is possible that other indicators of the "cardiometabolic syndrome" were acting as the primary mediators of the relationship between ischaemic heart disease and HRJL. Participants with particularly severe forms of ischaemic heart disease (i.e. myocardial infarction) may not have taken part in the HEAF study to begin with, or, where occurring, may have been better captured by other CPRD-defined disorders relating to severe cardiovascular disorders e.g. heart failure and peripheral arterial disease.

In Chapter 6, sleep disorders were also moderately associated with HRJL after adjustment for educational attainment, single relationship status, and history of heavy alcohol intake (aOR 2.74 95%CI 1.40 to 5.38). These also occurred commonly alongside primary-care-level MHPs in cluster analysis (see Chapter 7). However, sleep disorders were non-significantly associated with HRJL after adjustment for the presence of primary care-level MHPs (aOR 1.43 95%CI 0.70 to 2.93) and, as a result, did not achieve inclusion in any of the preliminary main effects models in this chapter. Since 72.6% of participants with sleep disorders also had a recent primary-care-level MHP, it seems likely that MHPs are the primary mediator of the previously observed relationship between sleep disorders and HRJL.

In Chapter 8, among participants with musculoskeletal disorders, the mental health problem comorbidity cluster was found to have the strongest association with HRJL. From

the preliminary main effect models, it was possible to estimate the combined effects of having both a musculoskeletal disorder and a primary care-level MHP specifically, which was associated with a 6.05- to 7.30-fold increased odds of HRJL. Previous studies have considered musculoskeletal-mental health comorbidity and its relationship to adverse work outcomes. I've commented on the heterogeneity of such studies in the systematic review chapter of this thesis (Chapter 4, Section 4.3.2), which makes direct comparisons difficult. However, among studies using the general population as the reference group, the relationship between musculoskeletal-mental health comorbidity and sickness absence or "work-loss" days,(335,364,489) work cut-back days,(335) reduced physical work ability,(385) thoughts of early retirement,(385) and disability retirement,(490) has been reported. In all cases, these studies found that the combination of musculoskeletal disorders with mental health problems resulted in considerably worse work outcomes than for participants with purely musculoskeletal or mental health morbidity. For example, Kaila-Kangas et al. presented a longitudinal analysis of disability retirement in 3943 working Finns, aged 30 to 63 years old. Over follow up, participants with MSDs (including low back pain and osteoarthritis) had a hazard ratio of 2.2 (95%CI 1.8 to 2.7), participants with common mental health problems (including mostly primary care-level MHPs) had a hazard ratio of 2.4 (95%CI 1.7 to 2.7), and participants with both conditions had a hazard ratio of 4.1 (95%CI 2.9 to 5.7) for the receipt of disability pension.

Identified studies also considered the possibility of an interaction between comorbid musculoskeletal and mental health problems for adverse work outcomes. Kaila-Kangas et al., the most comparable study, found no such interaction for receipt of disability pension on the additive or multiplicative scale.(490) In contrast, synergistic behaviour has been observed between musculoskeletal pain and depression for self-reported thoughts of early retirement;(385) and between chronic back pain and mental health disorders for work loss days in the past 12 months.(364) In this chapter, no such interactions were observed on the additive or multiplicative scale for HRJL, meaning I found no evidence that the impact of these conditions together was more than the combination of their individual effects. However, analysis may have been underpowered to detect this effect.

Interaction effects were also used to explore any modification of the relationship between MSDs and HRJL by other co-occurring health conditions. A negative multiplicative interaction between chronic musculoskeletal disorders and diabetes was observed. In other words, the combined impact was less than the product of their individual effects. One possible reason for this could involve increased monitoring and contact with healthcare

professionals leading to overall improved care and outcomes for both musculoskeletal and diabetic health problems. However, no such interaction was observed on the additive scale, and it is possible that statistical significance occurred by chance (as may occur periodically with multiple testing). No other significant interactions were observed between musculoskeletal disorders and other health disorders, however the sample size may have been underpowered to confidently assess interactions between MSDs and cerebrovascular accident or epilepsy.

Finally, results from the preliminary main effects models were used to calculate the population attributable fraction of HRJL for each CPRD-defined health disorder. In order to avoid extremely skewed estimates of PAF, I focussed on conditions that had a statistically significant association with HRJL in the final adjusted models of this chapter. In order of importance, the following health disorders were estimated to account for the greatest proportion of HRJL among the UK older working-age population: Primary-care-level MHP (25.0%), any MSD (22.5%), recent MSD pain (18.2%), heart failure (17.7%), chronic MSD (13.0%), hypertension (10.5%), asthma (9.0%), diabetes (7.3%), epilepsy (4.4%), and CVA (3.7%). As mentioned previously, it is known that common mental health disorders, musculoskeletal disorders, and cardio-respiratory disorders are, together, responsible for the majority of work disability.(48) This is reflected in the results of this chapter. However, the quantity of health-related work loss that can be attributed to multimorbidity has been previously unexplored. In this study, an estimated 55.6% of HRJL could be attributed to the presence of two or more CPRD-defined health disorders, a fraction that was at least double that of any individual condition. In Chapter 8, it was shown how the odds of HRJL increases precipitously with number of comorbid health conditions. In this chapter, the large PAF observed for multimorbidity also suggests that a significant proportion of premature work loss in the population could be avoided by preventing multimorbidity. It has already been shown that a large proportion of this multimorbidity is due to musculoskeletal-mental health comorbidity, which has a particularly strong association with HRJL. Therefore, the avoidance of mental health comorbidity in musculoskeletal disorders (and vice versa) should be considered a priority area for preventive interventions to support the older working-age population to remain in work. In addition, populations with musculoskeletal-mental health comorbidity should be examined to manage additional risks to their physical, mental, and occupational health that occur as a direct result of their comorbidity. This will encourage person-centred, rather than disease-centred, solutions that go beyond the management of isolated clinical health disorders.

An assessment of population attributable fractions resulted in some surprising results. Particularly, the large PAF observed for heart failure, which is discussed below, as well as the considerable PAF observed for hypertension and asthma. As previously discussed, despite being a generally symptomless condition, hypertension is likely associated with other health disorders that were unmeasured in this thesis, for example, obesity.(423) The 1.56 to 1.66-fold increased odds of HRJL observed in the multivariable models for hypertension was in line with its previously reported risk of disability pension (RR 1.50 95%CI 1.31-1.72).(421) However, it is certainly the high prevalence of hypertension that drives its importance among the older working age population (PAF 10.5%).

Asthma too, was associated with a considerable PAF (9.0%). This condition may be more complicated among older adults, as a result of age-related deterioration of lung function, degenerative changes in respiratory musculature, and immunological and inflammatory changes. At older ages, asthma also associates with several comorbidities, some of which were unmeasured in this thesis, such as obesity, gastro-intestinal reflux disease, cataracts, and osteoporosis.(491) In addition, as alluded to in earlier chapters, an overlap syndrome exists between asthma and COPD at older ages. The extent of such a syndrome is not insignificant, such that after the age of 65 years, most people with obstructive airway disease have both asthma and COPD diagnoses.(492,493) It should also be noted that a stricter classification of asthma was employed in this study, requiring that participants were continuing to receive treatments for asthma in the year prior. This may have ruled out very mild presentations of asthma.

The population attributable fraction observed for heart failure was very large (PAF 17.7%) which was a similar level to that observed for recent musculoskeletal pain (PAF 18.2%) and a greater level than that observed for chronic MSDs (13.0%). I had previously thought the high prevalence of heart failure observed in this study (5.9%) was due to the number of study participants with health-related job loss (and therefore worse health than the general population). However, the prevalence of this CPRD-defined disorder was also high in the HEAF baseline population (5.4%). As a result, I reviewed the Read codes that had been used to classify heart failure in this study (see Appendix Table 4). Unfortunately, despite the Read codes having been proofed by two personnel (myself and Professor Keith Palmer), one diagnostic code “seen in cardiac clinic” had been sorted into the heart failure category. Although all other Read codes in this category were heart failure specific, it cannot be ruled out that this code was particularly noisy, and it must be assumed, was the cause of the large prevalence and, by extension, PAF for HRJL. CPRD-defined heart failure was strongly

associated with HRJL throughout this thesis, however, this measurement error must now be taken into account in the interpretation of this finding. In the UK, cardiac clinic is where diagnostic cardiac investigations (such as echocardiography, tilt testing, and ECG) occur, as well as Rapid Access Chest Pain Clinic, cardiac monitoring, cardiac rehabilitation, and services related to the management of heart failure and atrial fibrillation. As such, this variable is unlikely to be heart failure specific, and more likely represents a cross-section of the study sample with more severe kinds of cardiovascular disease, including heart failure. It should also be noted, that to be classified as having heart failure participants were required to have received a prescription for treatments used in heart failure. This improves specificity of CPRD-defined heart failure, although such drugs may have multiple indications.

Other than the limitations already outlined above and in other chapters of the thesis, one of the major limitations of this study was the sample size which, in many cases, was underpowered to assess the impact of having two specific concomitant disorders on HRJL. Instead, I estimated the combined effects of exposure to musculoskeletal disorders and other health disorders from the preliminary main effects models constructed in this chapter. It is also possible that analysis was underpowered for the detection of statistical interactions between health exposures in these models. This was particularly true for rarer diseases.

In recognition of the fact that health disorders do not occur in isolation, the strengths of this chapter included its adjusted analyses of the impact of health disorders on HRJL. These analyses accounted for the presence of several other prevalent and important health disorders and included an examination of how these health disorders interact with one another in their association with HRJL. While it is commonplace in the literature to adjust for the presence of comorbidity, or number of comorbidities, when considering the association between a specific health problem and work status, few studies examined several conditions concurrently. In addition, the reporting of population attributable fractions will help the reader to judge the public health impact of these exposures among the older working-age population. I found only one other similar study, looking at the relationship between several chronic conditions and being out of the labour force for health reasons.(494) This paper used self-report data from the representative Canadian Community Health Survey to classify health-related worklessness and the presence of seven physical chronic conditions: arthritis, hypertension, back problems, migraine, diabetes, heart disease, and thyroid disorders. However, PAF was calculated using prevalence figures

derived from participants with health-related worklessness, and included participants as young as 25 years old, therefore results are not comparable. Unlike the work in this chapter, this study also did not consider mental health problems which have been shown to be a key health exposure in worklessness.

In conclusion, musculoskeletal disorders (chronic and/or recent pain) remained independently associated with health-related job loss after adjustment for the presence of other common health conditions. Primary-care-level MHPs, hypertension, heart failure, cerebrovascular accident, diabetes, asthma, epilepsy, COPD, and peripheral atherosclerotic disease also remained independently and significantly associated with HRJL in multivariable modelling. At the population level, a large proportion of HRJL was estimated to be attributable to musculoskeletal disorders and mental health disorders, individually. These conditions, in previous chapters, have also been shown to commonly co-occur in clusters with very strong association to HRJL. Overall, far more HRJL could be attributed to multimorbidity than to any individual condition, which suggests a stronger public health focus on co-occurring health problems is required for the prevention of premature exit from work.

Chapter 10- discussion and conclusions

10.1 Introduction

In this chapter, I summarise the major research findings across the entire thesis and discuss their significance both for the individual and the UK population as a whole. In relation to the wider scientific literature, I discuss how the work of this thesis has added to previous findings, the strengths and limitations, and I highlight important research gaps to prioritise areas for future research. Next, I examine relevant policy at a national and local level and consider where the findings of this thesis buttress current recommendations or suggest the need for change. Lastly, I discuss interventions and strategies that could be used to help support high-risk groups identified in this thesis to remain in work.

10.2 Summary of findings in the context of previous research

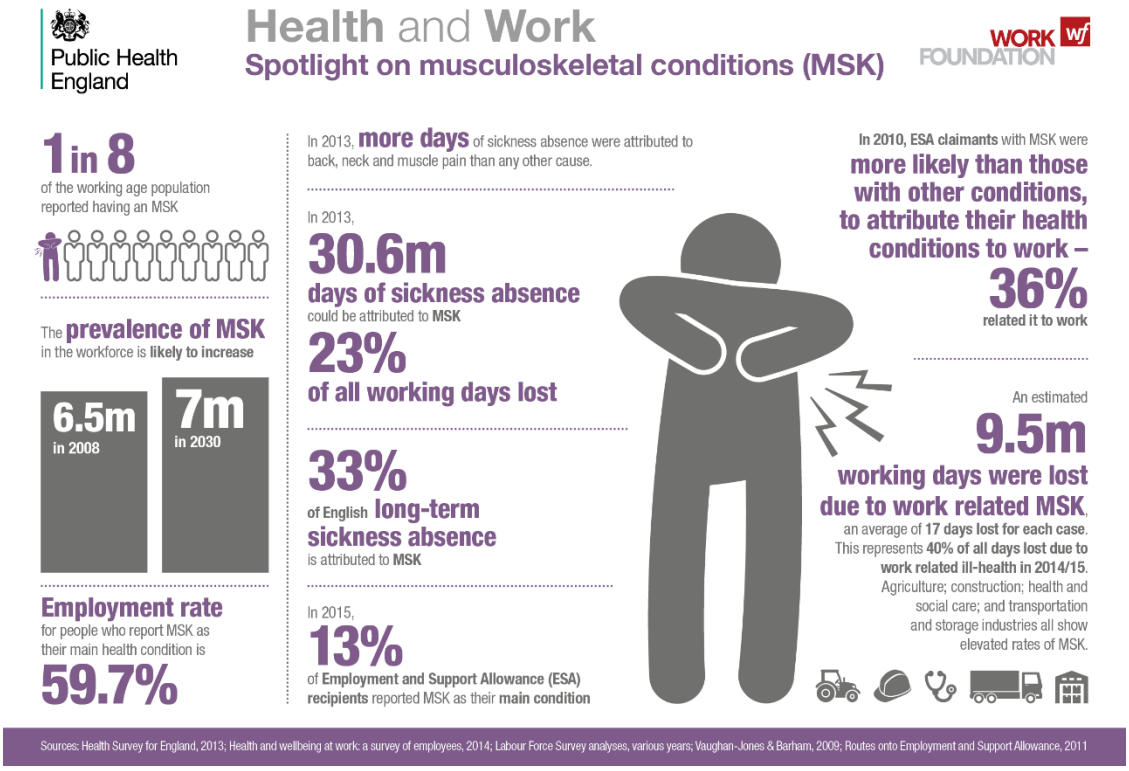
The thesis began with a narrative review chapter introducing musculoskeletal disorders, multimorbidity, and the work and health context. From this review work, research questions were generated. Using a systematic review, I explored what is currently known about the impact of comorbidity upon work outcomes among people with musculoskeletal disorders. Then, using linked data from the English population-based Health and Employment After Fifty (HEAF) study and the Clinical Practice Research Datalink (CPRD) among the older working-age population (aged 50 – 65 years old) 1) I described a representative sample of participants with HRJL 2) I explored factors associated with the development and persistence of HRJL 3) I found patterns of multimorbidity that feature commonly within this population, and 4) I considered the importance of these multimorbidity patterns in relation to HRJL. Finally, 5) I considered the population attributable fraction of HRJL for each of the studied health disorders, and of multimorbidity itself.

Chapter 4: systematic review

In the first results chapter, a systematic review was performed to answer the question, "how does comorbidity impact work outcomes in musculoskeletal disease?" Compared to having a musculoskeletal disorder alone, comorbidity, and specifically comorbid mental health problems, were consistently associated with a range of adverse work outcomes

across different MSD populations. While a statistically significant impact was observed in most studies, reported effect sizes varied considerably, reflecting differences in underlying study populations, classification of work outcomes, and criteria for comorbidity. However, overall, the direction of effect was very consistent (see Figures 26 and 27). The detrimental impact of comorbidity on work was an important finding in this key disease group for work disability in the UK (see Figure 53).(118) MSDs are highly prevalent among the working-age population, and interventions that help support people to remain in work can be expensive and time-consuming. Therefore, the identification of high-risk groups within MSD populations can help to focus efforts towards the patients who are most likely to struggle to remain in work.

Figure 53: Health and Work infographic: spotlight on musculoskeletal disorders. Contains public sector information licensed under the Open Government Licence v3.0. (118)



One of the primary findings of the systematic review concerned the limitations of the evidence base. Weaknesses included inconsistencies in the classification of the study population, the exposure of interest, and the work outcome of interest.

Few included papers studied participants with osteoarthritis (the most common chronic musculoskeletal disorder) or low back pain (the most common type of musculoskeletal pain

condition) which meant indirectness was an issue when applying results to the entire MSD population.

Comorbidity was poorly and inconsistently defined. While some studies used validated comorbidity checklists, these were validated against criteria unrelated to work ability, such as mortality or healthcare utilisation.(9,13,334,341,343,361–363) In analysis, comorbidity exposure was also often reduced to a simplified yes/no criteria with no exploration of a gradient in effect, or the common patterns of comorbidity.(10,11,199,342,348,349,353,357,359,366)

Reported work outcomes were also inconsistently defined, to the extent that grouping them together for the purposes of review was challenging. For example, classifications of work disability, sickness absence, and health-related productivity loss may be so broadly defined that definitions overlap.(12,199,338,353,365) For these and other work outcomes, particularly return to work following disability,(345–348,351,355,356,364,366) the timeframe over which the outcome was assessed differed by months or years between studies.

Studies reporting the impact of specific comorbidities upon work in MSD populations, mostly focussed on comorbid mental health problems (frequently depression), which were generally associated with worse work outcomes. Additionally, some studies observed a multiplicative interaction, whereby musculoskeletal disorders and mental health problems worked synergistically in association with sickness absence and impaired work ability.(335,357,364,385) Other comorbid disorders were under-reported, which was surprising particularly for health problems such as diabetes and cardiovascular disorders, which commonly co-occur with musculoskeletal disorders in the general population.(388,389) Importantly, few studies compared the effect of multiple specific comorbidities in the same musculoskeletal population, which made it difficult to determine which comorbid health disorders were likely to be the most impactful.

Overall, this review found strong and consistent evidence that comorbidity, and comorbid mental health problems, are important risk factors for the development of a range of poor work outcomes across various musculoskeletal populations. The scope of this review was considerably broader than previous work in this area: only two previous systematic reviews had looked at comorbidities and occupational outcomes in MSD populations. One of these studies (Baumeister et al.) found a mixture of supportive and inconclusive evidence regarding the detrimental impact of comorbid mental health problems on return to work

and sickness absence in a low back pain population; the other (Lloyd et al.), found depression was linked to worsened return-to-work rates when comorbid with MSDs.(330,331) Both of these studies were old (published 2008 – 2012), were limited in their focus on comorbid mental health problems alone, and only considered selected work outcomes. To my knowledge, no previous review has been completed looking at the impact of any comorbidity on work-related outcomes in MSDs, covering all major employment outcomes including work disability, unemployment, job loss, return-to-work time, and productivity. To consider all of these outcomes was important in order to get a sense of the continuum of work-health interactions which may begin in the workplace with presenteeism, leading to absenteeism, job loss, and finally permanent work disability.(495,496) By showing that comorbidity impacts work at each of these stages, my review suggests a rationale for addressing comorbidity (and mental health problems) at an early stage in people with musculoskeletal disorders, while it is still possible to maintain their work situation. The Department of Work and Pensions have found less than 50% of people with 6 months sickness absence ever return to work and few people return to any form of work after 1-2 years absence, irrespective of further treatment.(47) Therefore early identification of high risk groups needing support is key, something that this review can help to inform.

Finally, this review chapter highlighted the little that is known about non-psychiatric disorders and their impact upon work in MSDs. The convincing evidence showing that higher comorbidity scores (all of which included non-psychiatric disorders in their classifications) were associated with poorer work outcomes, suggests that non-psychiatric health problems may also have an important role to play in the work ability of people with MSDs. Study of the impact of these disorders on work in MSDs is an important omission from the evidence base identified by this review. As described below, this has implications for the direction of future research.

Chapter 5: describing a cohort of older workers with HRJL

Participants of HEAF with HRJL, for whom CPRD data was available around the time of their job loss, were described for known demographic, lifestyle, and health-factors. These participants commonly had been working in occupations such as teaching, administration, and service industries. Certain health problems were particularly prevalent in this cohort such as musculoskeletal disorders (recent MSD pain and chronic MSDs), primary care-level mental health problems, hypertension, ischaemic heart disease, heart failure, asthma, and

diabetes. These findings provided important descriptive evidence showing the types of health problems commonly affecting those with health-related exit from work in the UK, and the kinds of employment they were unable to maintain.

It was observed that participants in whom HRJL occurred at an earlier age were broadly less well educated, less likely to have chronic musculoskeletal disorders and cardiovascular disorders, but more likely to have mental health problems. Whereas those who experienced HRJL at older ages were more likely to be diagnosed with age-associated conditions such as MSDs and cardiovascular disorders. This finding helped to delineate two distinct groups within the study sample, those with long-term HRJL from a younger age, and those with HRJL that occurred between 50 – 65 years of age (the focus of this thesis). The differences between these subgroups, only hinted at in this chapter, may encourage further research to consider whether different approaches are required to support employment for those with HRJL at younger ages.

An interesting distinction was also observed between men and women with HRJL for the types of jobs previously worked. For example, men were predominantly in careers such as construction and trade, agriculture, electronics, and transport while participants in healthcare, management, administration, caring, service, and sales occupations were mostly women. Men with HRJL were also more likely to have lost work from routine and manual-type jobs compared to women with HRJL. Aside from the much-debated drivers of these gender differences,(497) this was an important observation which showed that the work environments of older working-age men and women were, on average, quite distinct. In addition, men and women (with HRJL) had broadly different disease profiles: cardiovascular problems were more prevalent in men and primary-care level mental health disorders were more prevalent among women. Similar findings have been well observed in the literature.(235,395) However, for the purposes of this thesis, the observed differences in occupational environment and disease burden between men and women prompted the use of stratified analysis by gender. By extension, this finding also provides support for exploration of gender-influences upon health-related work outcomes in future research. In the reviewed literature, stratification of results by gender was uncommon, even in recent publications,(200,340) although most studies adjusted for gender statistically.

Primarily, the strength of this chapter lies in its description of a contemporary and representative UK-based population who have fallen out of work for health reasons. Few UK-based studies of health-related job loss amongst the older working-age have been

conducted. Yet this is an important research gap since those aged over 50 are highest risk for leaving the work force.(46) As such, understanding the profile and health status of this unique cohort is key to understanding the interplay of factors leading to their poor work outcomes, and to inform the design of policy and workplace interventions to support employment.

Chapter 6: case-control study of CPRD-defined health disorders and HRJL

In Chapter 6, participants with HRJL were matched to controls for important confounders including age, gender, and GP practice, and a case-control analysis was performed. Differences were assessed between participants with HRJL (the cases) and matched participants who remained working at the point of time that cases lost their jobs (the controls). Using conditional logistic regression, several CPRD-defined health disorders were significantly associated with the development of HRJL, after statistical adjustment for other known confounders. These included: chronic musculoskeletal disorders, recent musculoskeletal pain, primary care-level mental health problems, sleep disorders, hypertension, heart failure, peripheral arterial disease, COPD, cerebrovascular accident, and diabetes (see Figure 36, Chapter 6). The effect estimates of other CPRD-defined health disorders suggested that they may also be associated with HRJL, however analysis was underpowered to show a statistically significant effect, these included: psychiatric-level mental health disorders, cardiac arrythmias, and epilepsy. Structural heart disease is also likely to be important at the individual level since all seven participants with this condition were cases. However, for this reason, I was also unable to generate an effect estimate for this variable in conditional logistic regression.

Studied health disorders appeared to have a broadly consistent association with HRJL after stratification by gender. For certain progressive age-related conditions, such as chronic MSDs, heart failure, and COPD, the strength of association was larger among those with HRJL at older ages, in whom these diseases were more prevalent and possibly more severe. The association between primary care-level MHPs or recent musculoskeletal pain and HRJL seemed more marked in the younger age groups. However, in all cases following stratification, confidence intervals were wide.

A considerable amount of research has already outlined the relationship between mental health problems and musculoskeletal disorders for disability pension, although these studies largely included broader age groups and non-UK nationalities (and used heterogeneous classifications for exposures and outcomes). For example, a systematic

review and meta-analysis by van Rijn et al. (2014) pooled estimates of effect from 17 studies of mental health problems and 12 studies of musculoskeletal disorders, and found these conditions were significantly associated with disability pension (RR 1.80 95%CI 1.41 to 2.31 and RR 2.23 (1.93 to 2.56, respectively),(115) these estimates of association were comparable to those observed for HRJL in this thesis. However, the work of this chapter contributes to these findings by confirming the importance of these conditions in a contemporary and narrowly-defined population of pivotal importance to UK policymakers.(46)

For conditions unrelated to musculoskeletal disorders or mental health problems, the available research for comparison was scarce. This represents a considerable research gap which the work of this chapter can help to fill: cardiovascular disorders, diabetes, and some respiratory conditions, such as asthma and COPD, occur frequently among older workers,(329) yet their impact upon health-related work loss is not yet sufficiently accounted for. The systematic review by van Rijn et al. found only four studies considering the association between other health disorders and disability pension (including two studies of "chronic bronchitis", and two studies considering low resolution categories of health problems such as "circulatory disease" and "respiratory disease") for which point estimates suggested an important relationship.(115) In addition, one recent prospective study from the Netherlands, among older workers, also suggested cardiovascular and respiratory disorders have an important impact upon work disability (SHR 2.13 95%CI 1.44 to 3.16 and 2.11 95%CI 1.45 to 3.07, respectively)(498) – these findings, and those of this thesis, suggest cardiovascular disorders and respiratory disorders deserve closer attention in future research. In this chapter, however, cardiovascular disorders (hypertension, heart failure, ischaemic heart disease, peripheral arterial disease) and respiratory disorders (asthma, COPD) were considered at a greater resolution, allowing for differences between distinct clinical conditions to be considered.

This chapter also found the presence of diabetes to be detrimental for maintaining work to older ages, a finding that is both supported(420,426) and contradicted(498) in existing research. The lack of association between diabetes and disability benefits observed in the Netherlands cohort study may have been due to the adjustment of analysis for cardiovascular disorders (which may have adjusted for participants with more severe diabetic disorders), however, diabetes remained importantly associated with HRJL in this thesis, even after adjustment for other cardiovascular disorders (see Chapter 9). More work

is needed to study the contribution of this condition to work outcomes, particularly addressing common clinical sequelae within diabetic populations.

Finally, this chapter considered specific health disorders that, to my knowledge, have not yet been studied for their association with HRJL in the older working age population: these included epilepsy, cerebrovascular accident, peripheral arterial disease, COPD, cardiac arrythmias, structural heart disease, and asthma. The direction of effect observed suggested that these conditions, also, have an important role to play in HRJL among older workers. Future research, with greater statistical power is needed to confirm the relationship between these conditions and premature exit from work.

Chapter 7: describing patterns of multimorbidity

Using the 16 health disorder variables, for which CPRD-data was available, I explored common patterns of co-occurrence across the total study sample (cases and controls). The most common comorbid pairs were comprised of highly prevalent conditions in the population; for example, musculoskeletal disorders with hypertension, musculoskeletal disorders with primary-care level mental health problems, and diabetes with hypertension.

Recognising the overlap between chronic MSDs and recent MSD pain (34.9% of participants with chronic MSDs had recent MSD pain. 31.5% of participants with recent MSD pain had a chronic MSD disorder), cluster analysis to study patterns of multimorbidity were run separately for these two musculoskeletal groups. The generated multimorbidity clusters were similar regardless of whether chronic MSDs or recent MSD pain groups were included. The following multimorbidity clusters appeared consistent: large clusters of participants with mental health disorders and musculoskeletal disorders, primarily; small clusters of participants with ischaemic heart disease, heart failure, and hypertension, primarily; large clusters of participants with hypertension and musculoskeletal disorders (and a high prevalence of diabetes), primarily; and small clusters of participants with asthma and COPD, primarily.

Among multimorbid men the clusters that formed were similar to those that had occurred among all participants with multimorbidity, these included: a cluster of participants with mental health disorders and musculoskeletal disorders, primarily; a cluster of participants with hypertension, musculoskeletal disorders, and diabetes, primarily; a cluster of participants with other cardio-metabolic disorders, primarily; and a cluster of participants with asthma and COPD, primarily. Among women, two main clusters formed consistently,

including: a cluster of participants with hypertension and musculoskeletal disorders, primarily; and a cluster of participants with mental health disorders and musculoskeletal disorders, primarily.

Lastly, a cluster analysis of comorbid health disorders was performed among participants with musculoskeletal disorders (chronic or pain). A cluster of participants with musculoskeletal disorders and no other known health disorders formed. Other prominent clusters included participants with comorbid hypertension, primarily (and a high prevalence of comorbid diabetes); participants with comorbid cardiovascular disorders, primarily (ischaemic heart disease and heart failure); participants with comorbid asthma, primarily; and participants with comorbid mental health problems. Among people with musculoskeletal disorders, the two most prominent comorbidity clusters were those formed by comorbid hypertension and by comorbid mental health problems.

The descriptive analyses outlined in this chapter revealed a high degree of multimorbidity in this older working age sample. Multimorbidity, classified as two or more CPRD-defined health disorders, was present in approximately a third of all participants (33.2%). It is difficult to compare this prevalence to figures reported in the literature, which are often based on very different classifications of multimorbidity (using different constituent diseases). However, findings supported the high degree of multimorbidity observed for the older working-age group in other UK population-based studies, most notably, the Scottish epidemiological study of multimorbidity produced by Barnett et al.(438) Also, among those with a known health problem, approximately half (47.9%) had multimorbidity. Importantly, this result suggests that the health disorders studied here should not be viewed in isolation when assessing their role as catalysts of adverse work outcomes in older workers. An increased focus on multimorbidity by researchers and policymakers will promote holistic work solutions for older working-age people in a system that too often targets single illnesses alone. For example, researchers and policymakers considering employment outcomes and musculoskeletal disorders should be aware that these conditions frequently overlap with mental health problems and hypertensive disorders.

Similarly, it was difficult to compare the multimorbidity patterns observed in this chapter to those of existing research describing patterns of multimorbidity. Identified studies differed for number, demographics, and selectivity of recruited participants; the data sources and classifications used to define health disorders; the number of health disorders considered; and the statistical techniques used (cluster and factor analysis were common approaches).

Nevertheless, a well-cited systematic review of 14 such studies (Prados-Torres, 2014) found three broad patterns, or clusters, of diseases were commonly reported: 1) cardiovascular and metabolic disorders 2) disorders related to mental health and 3) disorders related to musculoskeletal problems.(442) The results reported in this chapter show some similarities. For instance, mental health disorders were observed to naturally cluster together, as did cardiovascular-metabolic disorders. By design, the formation of a musculoskeletal disease cluster was prohibited since only one MSD variable was entered into cluster analysis at a time (see Section 7.2.2). However, this was advantageous as it made it possible to observe how musculoskeletal disorders (the focus of this thesis) commonly overlap with other prominent disease clusters. Importantly, little of the work reviewed by Prados-Torres et al. was age- or sex-stratified, and no studies had a focus on the older-working-age population, or participants with MSDs. The work of this chapter can contribute to existing knowledge by outlining how multimorbidity patterns differ within older working-age men and women, and within those with MSDs. Therefore, these results can guide the design of tailored interventions to support employment among the multimorbid, within these important subgroups.

Chapter 8: the impact of multimorbidity upon HRJL

Crude indicators of multimorbidity burden were examined. Having two or more known health disorders was strongly associated with HRJL compared to participants with no known health disorders and the strength of association increased as the number of disorders increased (see Figure 46, Chapter 8). Likewise, the number of GP consultations in the year prior and the number of drug prescriptions were significantly associated with the development of HRJL.

Next, I explored the association between generated multimorbidity clusters and HRJL. Compared to participants with no known health disorders, being part of any multimorbidity cluster appeared to be important and generally had a strong statistically significant increased odds of HRJL (range OR 2.26 to 10.68). The clusters that formed between musculoskeletal disorders and cardiovascular disorders, or musculoskeletal disorders and mental health problems, were the largest clusters. Multimorbidity clusters formed by musculoskeletal disorders and mental health problems appeared to be very strongly associated with HRJL (range OR 7.56 to 10.68), although confidence intervals were wide (see Figures 47 and 48, Chapter 8).

After stratification by gender, number of health disorders, number of GP consultations, and number of drug prescriptions in the prior year remained significantly associated with HRJL. Compared to participants with no known health disorders, being part of any multimorbidity cluster was observed to have a strong association with HRJL among men or women (range OR 3.40 to 15.00). Once again, comorbidity clusters formed by musculoskeletal disorders and mental health problems were common (especially among women) and consistently had the strongest association with HRJL (range OR 6.62 to 15.00), although confidence intervals were wide.

Finally, the analysis was restricted to participants with musculoskeletal disorders. Compared to participants with CPRD-defined musculoskeletal disorders but no known comorbidities, number of comorbid health disorders was significantly associated with HRJL. Being part of any comorbidity cluster had a strong association with HRJL (range OR 4.25 to 16.18). Once again, a large cluster formed by participants with comorbid mental health problems was observed to have the strongest association with HRJL (OR: 16.18 95%CI 6.52 to 40.25), although confidence intervals were wide.

There is currently little published about the impact of multimorbidity on work outcomes and where present, this is often restricted to the study of two specific types of diseases in combination.(476,477) To my knowledge, this was the first study of the impact of multimorbidity upon health-related job loss in the literature, although the direction of effect broadly correlated with other previously reported work outcomes: Several other cross-sectional studies among western (non-UK) working populations observed that number of health disorders was correlated with sickness absence,(450,451) increased work impairment scores,(199) and presenteeism.(450) This chapter contributed further unique analyses by exploring the relationship between frequency of GP consultation and HRJL, and number of drug prescriptions (as a proxy for polypharmacy) and HRJL. These factors may prove to be additional “red flags” that can be used to identify those at imminent risk of job loss due to poor health. With approximately, one third of sample participants experiencing multimorbidity, the results of this chapter suggested that those who are dealing with multiple health problems may represent one of the most common high-risk groups for premature work exit among the older working-age population.

In addition, to my knowledge, this was the first study to consider common disease clusters among multimorbid older workers, and to consider the relative occupational health impact of these clusters. Given the large proportion of participants with multimorbidity, it was

desirable to characterise this group further by considering the specific groups of diseases with the strongest association to HRJL. At the population level, findings represented supportive evidence that the co-occurrence of mental health disorders and musculoskeletal disorders, particularly, is of key importance to HRJL in this cohort. This was true also when considering comorbidity clusters among those with musculoskeletal disorders. Previous studies have considered musculoskeletal-mental health comorbidity and its relationship to adverse work outcomes. Using the general population as the reference group, the relationship between musculoskeletal-mental health comorbidity and sickness absence or "work-loss" days,(335,364,489) work cut-back days,(335) reduced physical work ability,(385) thoughts of early retirement,(385) and disability retirement,(490) has been reported. In all cases, these studies found that the combination of musculoskeletal disorders with mental health problems resulted in considerably worse work outcomes than for participants with purely musculoskeletal or mental health morbidity. However, the work of this chapter represents an important next step, showing not only that musculoskeletal-mental health comorbidity is detrimental to employment longevity, but also that it is important *relative to other common multimorbidity clusters* in the older working age population.

Chapter 9: the population attributable fraction of HRJL for CPRD-defined health disorders

In the final chapter, multivariable conditional logistic models were constructed using purposeful selection. These models were informative in numerous ways. Firstly, they could be used to estimate the independent impact of CPRD-defined health disorders on HRJL, after adjustment for other known health disorders. Secondly, models could be used to estimate the impact of having a combination of musculoskeletal disorders and other CPRD-defined health problems. Thirdly, models were used to assess multiplicative or additive interactions between musculoskeletal disorders and other health problems. Finally, effect sizes from these adjusted models were used to estimate the HRJL population attributable fraction (PAF) in the broader population from which these participants were drawn (the English older-working-age population).

After purposeful selection, chronic MSDs (aOR 1.69 95%CI 1.19 to 2.41), recent MSD pain (aOR 2.14 95%CI 1.48 to 3.09), primary-care-level MHPs (aOR 3.49 95%CI 2.26 to 5.40), hypertension (aOR 1.58 95%CI 1.07 to 2.32), heart failure (aOR 5.02 95%CI 2.14 to 11.77), cerebrovascular accident (aOR 3.88 95%CI 1.17 to 12.94), and diabetes (aOR 1.93 95%CI 1.06 to 3.52) remained independently and significantly associated with HRJL after

adjustment for other CPRD-defined health problems and confounding factors in the final preliminary effects model. A significant interaction was observed between chronic MSDs and diabetes on the multiplicative scale (aOR 0.24 95%CI 0.07 to 0.82) but not the additive scale (RERI -2.53 95%CI -5.13 to 0.07). However, no other significant positive multiplicative or additive interactions were identified between musculoskeletal disorders and other health disorders. From one model, the combination of musculoskeletal disorders with primary-care-level mental health problems (aOR 6.49), heart failure (aOR 9.34), epilepsy (aOR 10.68), or cerebrovascular accident (aOR 7.22) was estimated to be particularly strongly associated with inability to stay in work.

Lastly, I estimated the PAF of HRJL associated with each of the CPRD-defined health disorders that remained significantly associated with HRJL after adjustment (see Figure 52, Chapter 9). Primary-care level MHPs accounted for the greatest PAF of any individual health disorder (25.0%). Recent MSD pain disorders had a considerable PAF (18.2%) which was greater than that for having ever been diagnosed with a chronic MSD (13.0%). However, combined, musculoskeletal disorders had an estimated PAF of 22.5%. This was followed by heart failure (PAF 17.7%), although the unusually large prevalence of this variable in the sample population may have been due to the erroneous inclusion of one broad cardiology Read code in its classification. In order of PAF, the remaining conditions were hypertension (10.5%), asthma (9.0%), diabetes (7.3%), epilepsy (4.4%), and CVA (3.7%). However, the prevalence of multimorbidity and the strength of its relationship with HRJL, meant that the PAF due to multimorbidity was more than double that of any individual condition (55.6%).

In recognition of the finding that health problems commonly do not occur in isolation, the strengths of this chapter included its adjusted analyses of the impact of individual health disorders on HRJL. Multivariable analyses accounted for the presence of several other prevalent and important health disorders and included an examination of how these health disorders interact with one another in their association with HRJL. While it is commonplace in the literature to adjust for the presence of “comorbidity”, or “number of comorbidities”, when considering the association between a specific health problem and work status, few studies have examined several conditions concurrently. Participants with MSDs, for example, were found to have a high degree of comorbidity (58.7%) compared to the level of multimorbidity in the general study population (33.2%). This chapter contributed important data helping establish the independent effect of musculoskeletal disorders (chronic and/or pain) on HRJL, after adjusting for the presence of other common health disorders.

In addition, the reporting of population attributable fractions was an important aspect of this work that can help to judge the public health impact of these health disorders among the older working-age population. I found only one other similar study by Smith et al., looking at the relationship between several chronic conditions and being out of the labour force for health reasons.(494) This cross-sectional paper used self-report data from the representative Canadian Community Health Survey to classify health-related worklessness and the presence of seven physical chronic conditions: arthritis, hypertension, back problems, migraine, diabetes, heart disease, and thyroid disorders. Authors attributed the highest PAF to arthritis (29.0%) and back problems (23.8%). However, PAF was calculated using prevalence figures derived from a cohort with health-related worklessness, and included participants as young as 25 years old, therefore results are not comparable. Unlike the work in this chapter, the study also did not consider mental health problems which have been shown to be a key health exposure in worklessness.

Among the health disorders studied in this chapter, findings confirmed that musculoskeletal disorders and mental health problems are the two greatest contributors to HRJL, however results also suggested that considerably more HRJL could be attributed to multimorbidity than to any individual health disorder. The dramatically large PAF observed for multimorbidity was a key finding of this chapter, suggesting that more than half of all health-related job loss among older workers could be avoided by preventing multimorbidity. These findings should encourage a greater interest in research focussed on multimorbidity, both for its role as a predictor of adverse work outcomes and to develop interventions to support people with multimorbidity to remain at work.

As has already been discussed above, a large proportion of this multimorbidity is due to musculoskeletal-mental health comorbidity, which has a particularly strong association with HRJL. Therefore, these results also suggest that the avoidance of mental health comorbidity in musculoskeletal disorders (and vice versa) should be considered a priority area for preventive interventions to support the older working-age population to remain in work. In addition, populations with musculoskeletal-mental health comorbidity should be identified early to manage additional risks to their physical, mental, and occupational health as well as those that occur as a direct result of their comorbidity. This will encourage person-centred, rather than disease-centred, solutions that go beyond the management of isolated clinical health disorders.

10.3 Limitations of this work

After summarising the results of this thesis, and their significance, I reflect on some limitations, below.

Sample population

Included study participants were from the Health and Employment after Fifty (HEAF) study. As often occurs with questionnaire postal studies, the percentage of participants approached for the HEAF study who agreed to participate was low: 39,359 people were contacted and 8,134 returned a valid questionnaire (20.7%). While this study recruited participants that were broadly representative of the 50 – 65 years old English population, there were some notable differences. Participants were drawn from relatively less deprived catchment areas than the population of England as a whole. Additionally, responding participants were generally older, more often women, Caucasian, married, and home owners than in the general English population aged 50 – 65 years old.(6)

Survival bias was also an issue: People who had experienced particularly severe diseases such as stroke or myocardial infarction were less likely to have been recruited into the HEAF study. Possibly because they had died prior to recruitment but also because a person with disabling disease, e.g. stroke, may find it more physically challenging to fill out a questionnaire.

Another considerable limitation of this study was the sample size. As described in the methods section (Chapter 3), and Chapter 6, the available statistical power was sufficient to observe, at minimum, a small to moderate association with HRJL for most of the health exposures of interest. However, analyses were more often underpowered to assess the impact of these exposures in subpopulations of interest (e.g. analysis stratified by gender) due to the reduced number of case-control pairs available. Despite this, statistically significant associations were frequently observed at sufficient statistical power in subgroup analyses (see Tables 97 – 99, Chapter 6) often due to the strong associations observed. Statistical power was also limited to assess the impact of having two specific comorbid disorders on HRJL because of the low prevalence of these comorbidities. Instead, this thesis mainly considered multimorbidity at the level of the larger disease clusters that formed in cluster analysis. The combined effects of exposure to musculoskeletal disorders and other health disorders were also estimated using preliminary main effects models constructed in Chapter 9. While it was not possible to increase the number of case participants for this

thesis, one method of increasing statistical power is to increase the number of matched control participants from a 1:1 ratio to 1:2 or even 1:3 ratio as recommended in standard epidemiology textbooks (the benefit to cost of increasing the ratio of matched controls drops off above 1:3).(217) However, after matching for age, gender, and GP practice the number of available control participants was limited in the HEAF study. As a result, achieving a greater control-to-case ratio would have required broadening the matching criteria for age. Since age has a well-documented influence on both health and work outcomes, the judgement was made to remain at 1:1 matching in order to preserve the comparability of case and control participants for this important confounder. Instead, throughout the thesis, care was taken not to overinterpret non-significant results as evidential of lack of association where statistical power was low, i.e. less than 80%.

Classification of case participants from HEAF questionnaire data

Cases included participants who reported HRJL at HEAF baseline, however, a HEAF participant who had previously lost work for health reasons, and was later reemployed before HEAF baseline, would not be identified as a case. This means the classification of cases was influenced by duration of health-related job loss, and not only occurrence, and cases were more likely to reflect those who have had a longer duration of HRJL. Therefore, data would be more likely to show an association between a health disorder and job loss, if that health disorder puts people out of work for a longer time (i.e. is chronic or the cause of long-standing disability). Additionally, it is possible that some control participants had experienced HRJL in the past, but had later gained re-employment. Where this occurred, it would result in a bias effect towards the null.

Secondly, with cross-sectional data, it is often unclear whether the health condition was first present before or after the event of interest. This is less of an issue for the current project since CPRD diagnostic codes were date-stamped and patients also reported the date of HRJL. Health exposures were therefore only “counted” if they were active prior, and in proximity, to the event of interest (job loss). However, errors in the self-reported date of job loss are possible and may have led to unreliable information regarding health status prior to work loss.

Classifying exposures of interest using HEAF questionnaire data

Similarly, some data used to classify exposures of interest were derived from the HEAF baseline questionnaire and were therefore susceptible to recall bias. Data on ethnicity,

qualifications, occupations, and marital status were self-reported but also unlikely to be strongly affected by recall bias. However, participants also reported when they started smoking, and when they stopped, this information was used to assess whether a study participant were currently smoking or were an ex-smoker at the time of HRJL. Since people are unlikely to know the precise date of their stopping smoking, if it were some time ago, this variable may have been more strongly affected by recall bias.

Classifying exposures of interest using CPRD data

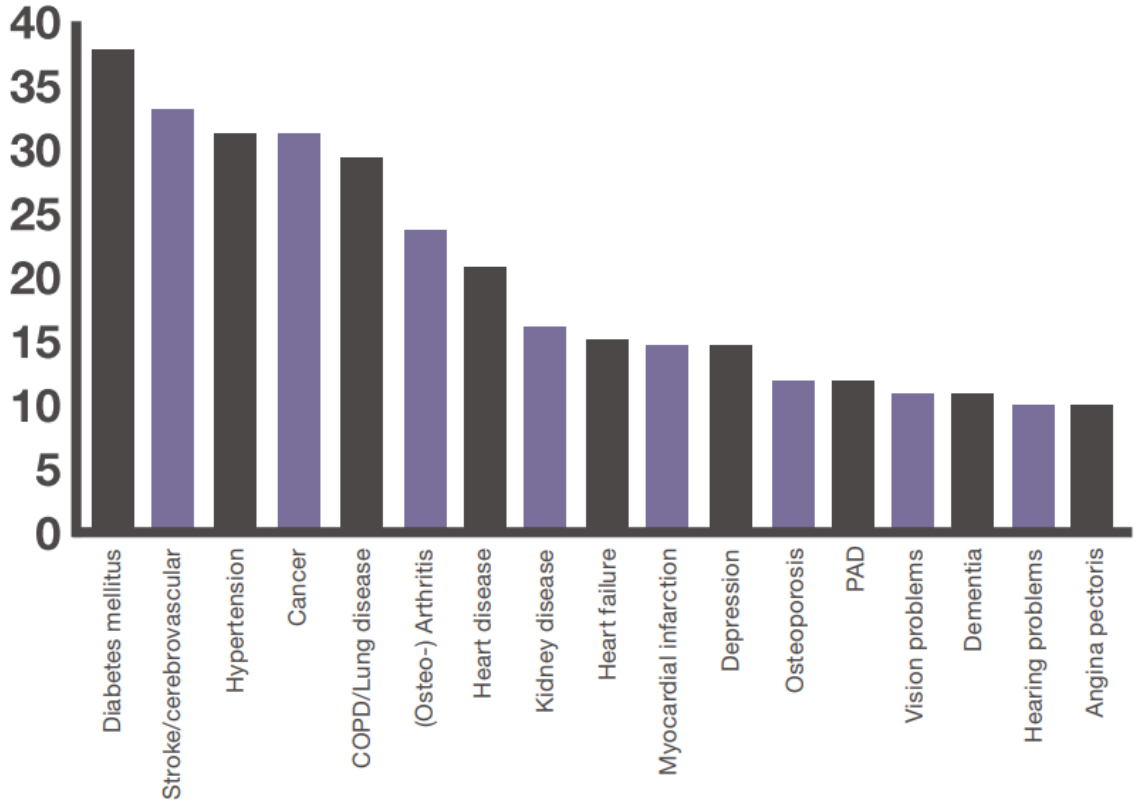
The use of CPRD data was both a strength of this work, and a limitation. While use of CPRD carried some inherent advantages over self-reported data (see below), there were also some weaknesses. Detailed diagnostic information is not available in CPRD, which may not be a problem in conditions for which there is clear accepted national diagnostic criteria but can create uncertainty otherwise.(214) For example, one doctor's diagnosis of anxiety disorder may be coded as an affective disorder by another doctor. Similarly, CPRD allows the coding of symptoms as well as diagnoses, so for example, a knee osteoarthritis diagnosis may be coded as "knee pain" depending on the practitioner's level of confidence in the diagnosis. Additionally, conditions may have been initially misdiagnosed and later recoded.(499) Even if a participant received their true diagnosis at a later date, they could still have appeared to have the initial incorrect diagnosis in the studied dataset.

I mitigated against these weaknesses using CPRD prescription codes to validate diagnostic data wherever possible, however, even when this was possible some uncertainty remained since drug prescriptions often have multiple indications other than for the disease code being validated. Additionally, drugs primarily prescribed in hospital settings or over-the-counter, rather than in primary care, were less likely to be coded.(214) Where confidence in the diagnostic distinction between CPRD-defined health disorders was in doubt, such as for mood disorders, anxiety disorders, and affective disorders, groups were merged for analysis. Of course, this approach can also be problematic as important distinctions between clinical sub-groups may be concealed.

Missing data was also a concern in CPRD: new diagnoses are manually recorded and may be missed from time to time. Available literature reporting validation outcomes for CPRD diagnostic data mostly reports positive predicative values, therefore, it is not clear how often clinical diagnoses are missed.(499) Secondly, the range of CPRD health disorders for which information was available was specified prior to this work and was not comprehensive for all diagnoses. Those included were: all musculoskeletal disorders; all

cardiovascular disorders; all mental health problems; and selected respiratory (asthma and COPD), endocrine (diabetes), and neurological conditions (CVA and epilepsy), but not other common and important conditions such as kidney disease or cancer, which have previously been included in published multimorbidity indices (see Figure 54). Since I classified multimorbidity according to these variables, it is probable that there were multimorbid participants who were not identified in this study. It is worth considering that the multivariable models constructed in Chapter 9 only achieved a Pseudo R^2 of 0.20 which, while not unusual for statistical models in public health, suggests that there are other important unmeasured factors affecting the development of HRJL among older workers. However, musculoskeletal disorders, mental health problems, and cardio-respiratory conditions are reported to account for two-thirds of sickness absence and long-term incapacity in the UK,(47) therefore it is likely that the major health predictors of HRJL were captured by this dataset, although not exhaustively. To address the problem of unavailable CPRD diagnostic codes, plans have been made to use future follow-up work in the HEAF study to gather additional information about diagnosed health problems via a validated self-report questionniare (see Section 10.5). Doing so will have dual benefits: 1) being able to identify more participants with multimorbidity, and therefore to study work outcomes in multimorbidity using a more sensitive classification 2) to study the contribution of other common comorbid disorders to poor work outcomes in the older working-age population, and among those with musculoskeletal disorders.

Figure 54: list of diseases which were considered across 39 different multimorbidity indices, from a Systematic review by Diederichs et al.(500,501)



It is recognised that the results of this thesis were based on health exposure variables which were defined using a novel classification system. I grouped Read codes for classification with the input of experts in occupational and musculoskeletal medicine, however, face validity was ultimately relied upon to define these study variables. Therefore, the classifications used here ideally require their own validation study. Resources were limited to accomplish this within the timeframe of the PhD. Instead, plans have been made to produce formal validation of these CPRD-defined health exposures using future follow-up work in the HEAF study (see Section 10.5). It is possible that validation work may result in revisions to the coding criteria used in this study, however, this is unlikely to impact the key findings of this research, which have both confirmed and built upon prior research findings: for example, that musculoskeletal disorders and mental health problems have the most significant impact on work outcomes at the population level, and that this is compounded by their comorbidity. Some CPRD-defined variables may be more likely to undergo revision than others. For example, I found that the prevalence of heart failure in this study was notably higher than that reported elsewhere.(329) As described previously, this is likely due to a known misclassification error which was taken

into account when interpreting findings. However, the prevalence of other health exposures studied in this thesis were within the expected range when compared to those reported in other UK population-based studies such as the Age UK almanac of disease profiles in later life.(329) In addition, the study variables broadly behaved in expected ways, for example, rare but debilitating conditions such as stroke were found to have a low prevalence but a strong association with HRJL (OR 4.82 95%CI 1.57 to 14.76), while common and less debilitating conditions such as hypertension were found to have a high prevalence and weak association with HRJL (OR 1.79 95%CI 1.28 to 2.50). Results like these are encouraging and suggest that the conclusions drawn from this study can be trusted – something that future validation work will be able to confirm.

Finally, the back-record of CPRD data was not equally available for all HEAF study participants and depended on 1) how long a GP practice had been contributing CPRD data 2) whether that data was "up to standard" for the whole period and 3) how long the participant themselves had been attending the contributing GP practice. Cases or controls who did not have available health data at least a year prior to the date of HRJL were not included. Over a long period of time this is likely to have favoured entry into the study of case participants who had left work more recently, since CPRD data was unlikely to be available from several decades prior to HEAF baseline. However, this effect was favourable to this thesis as the focus of this work was primarily participants who had lost work at a later (more recent) age, between the ages of 50 – 65 years old, as this is the age group in which the majority of premature exit from work occurs.(46)

10.4 Strengths of this work

HEAF study population

Despite acknowledgement of the limitations outlined above, the underlying population data had important strengths. The HEAF study, from which this study sample was drawn, was rigorously performed and reasonably representative over a broad geographic area within England. Data attained from the HEAF questionnaires underwent several stages of cleaning to identify inconsistencies in participant responses and errors in data entry.

The HEAF study also focussed on English older working-age participants, the group of primary interest for the study of premature exit from work.(45) The fact that these participants were recently recruited is important. Health is not the only influential factor when it comes to job loss (most employees with chronic diseases continue to work).(63)

Socioeconomic, political, and cultural context can have pivotal effects on a person's ability, expectations, and need to leave work. As a result, research into the causes of work disability can be time-specific and may date quickly; therefore contemporary study populations, like the HEAF study, are desirable.(63) UK-specific data was also necessary since occupational and social welfare systems vary considerably by country.

Study Design

A common limitation of matched case-control design is the susceptibility to bias inherent in the selection of cases and controls i.e. participants may have been favourably selected based on prior knowledge of their exposure status. However, this case-control study was nested within the broader HEAF prospective population-based cohort study and participants within HEAF were not selected directly by administrators with prior in-depth knowledge of the study or it's variables of interest. Rather, GPs, who were unaware of the hypotheses being tested, were asked to mail requests to all participants who fit the inclusion criteria for HEAF. By design, this should rule out the possibility of a case being chosen based on prior exposure.

In addition, the method of recruitment was the same for both cases and controls. Certain diseases may make a person less likely to be recruited to the whole study, for example, if the condition was disabling or associated with fatigue. Other conditions could increase the likelihood of recruitment e.g. because a participant is more motivated to contribute to research. However, it seems unlikely that such factors would unevenly affect recruitment between cases and controls given the HEAF methodology.

Lastly, matching cases to working controls at HEAF study baseline would have led to control participants who are inherently healthier since they remain in work till older ages. This could cause a work survivor bias, whereby observed effect sizes are accentuated. To avoid this bias in the current study, cases were matched to controls who were working at the point of time that HRJL occurred and may or may not have continued working up until HEAF study baseline thereafter.

Health-related job loss

It was necessary that the main work outcome under study reflected aspects of both work and health. Health-related job loss was an ideal work outcome since it was health-specific (unlike unemployment and job loss, for instance) and captured a work event of primary importance to the patient and society, i.e. permanent loss of employment. Other work

outcomes which are health-specific often focus on factors impairing a participant who is still employed (e.g. sickness absence and presenteeism) although these may be predictors of permanent work disability.(502) Health-related job loss captures participants who prematurely exit work for health reasons and may or may not successfully attain disability benefits. Individuals who do not receive direct payments from the government for their ill health still represent a cost to society in terms of the lost opportunities to contribute economically. Additionally, there is a cost to the individual in terms of their role, income, and ability to support their families.(48,52) Therefore, it is a strength of HRJL that it captures all forms of employment loss with a contributing health problem. I am unaware of any other UK-based study of health-related job loss in the older working age population.

Clinical Practice Research Datalink

Despite the weaknesses of CPRD data outlined above, CPRD had numerous strengths. Firstly, it was an objective clinical data source that did not rely on the memory of study participants. At one time, CPRD covered 6.4% of the population of England and is considered broadly representative since almost all members of the population are registered with a GP.(214) CPRD has also been collecting health information for over 30 years, which facilitated the retrospective aspect of this thesis. It's date-stamped clinical records help to evaluate temporality and reduce the likelihood of making a "correlation proves causation" fallacy. To date, over 2000 peer-reviewed research papers have been published using this data source.(212)

CPRD also undertakes internal data-quality assessments both at the patient and practice level.(213) "Acceptable" patients are identified after excluding those for whom there is non-contiguous follow up or poor data recording (e.g. missing vital information such as first registration date, or errors such as age >115 years).(213) Participating GP practices are required to record a minimum of 95% of prescribing events and patient-consultations and are routinely validated by internal checks and sent a validation report after data collection. These checks will look at completeness of prescribing, demographic, registration, referrals, and cause of death data. Practices not meeting CPRD standards are removed from the database.(214) Therefore, the clinical diagnostic data used in this study were robust and rigorously collected. Such is the validity of CPRD data, that it has been used to investigate important public health problems such as a possible link between the measles, mumps and rubella (MMR) vaccine and autism.(503)

One systematic review of validation studies for clinical diagnostic information in the CPRD found that the median proportion of cases with a confirmed diagnosis was 89% (range 24 – 100%). For this study, validation methods included external methods such as requesting GP medical records or sending the GP a questionnaire, and internal methods such as the use of a diagnostic algorithm using other CPRD data.(499) Importantly, this review also undertook sub-group analysis by type of health disorder: for musculoskeletal and connective tissue disorders the median proportion of cases confirmed was 80% (range 33 – 97); for mental and behavioural disorders, 83% (range 52 – 100); for circulatory system disorders, 85% (range 48 – 100); for respiratory disorders, 88% (range 26 – 100); for endocrine, nutritional and metabolic disorders, 88% (53 – 100); and for nervous system disorders, 81% (range 39 – 100).(499) While these positive predictive values do not account for health diagnoses that have been missed, the high median values suggest that the large majority of CPRD diagnosed cases were true cases and a high degree of confidence in these data is possible. This review also recommended the use of internal diagnostic algorithms (e.g. using prescription data) to boost diagnostic accuracy, methods that I used in this thesis wherever appropriate and possible.

By design, this case-control study was not prospective, however, I had the advantage of using date-stamped CPRD information. Using this information I could ensure independent variables preceded HRJL and was thus able to show evidence of temporality - one of the key elements of the Bradford-Hill criteria for causation.(504) As described, participants supplied the date at which they had left work on the HEAF questionnaire and I considered CPRD-defined health disorders that had occurred prior to the date of job loss. Certain health problems, such as osteoarthritis, are chronic and, once diagnosed, are permanent and degenerative. However, for other potentially short-term health problems, e.g. depression, I could define a parameter within which participants needed to have been diagnosed or treated for the condition e.g. a year prior to the job loss. This way, the measurement of health exposures was restricted only to those that could conceivably have had an impact upon work, improving the validity of study observations.

Multiple health exposures and cluster analysis

In this thesis, it was possible to study the relative importance of common and important health disorders, such as musculoskeletal disorders, mental health problems, and cardio-respiratory conditions, for their association with HRJL. I found few existing studies that

evaluated the impact of multiple individual health problems upon work,(340,344,347,351–353,365,494) with most focussing on single health exposures.

Even fewer studies have considered the impact of multimorbidity upon work. However, multimorbidity research takes a more patient-centred approach that focusses less on individual diseases,(505) and thereby reflects the common experience of older-age patients, in whom diseases more often occur alongside other health problems than in isolation.(153) Another strength of this piece of work is the use of cluster analysis to characterise patterns of multimorbidity. While cluster analysis has been used before to describe how health disorders group together within a population,(164,442) this was the first study to then assess the relationship between these multimorbidity clusters and the development of adverse work outcomes. It is certainly the first piece of work of its kind among older-age workers.

10.5 Future research in the HEAF study

Work is currently underway to validate the preliminary findings of this nested case-control study, although prospective data will not be available for a couple of years. The HEAF study has a motivated cohort of participants who have good response rates at follow-up (exceeding 80%).(506) In the broader HEAF study, I contributed to the questionnaire design for the fourth annual follow up in order to improve on areas where the work of this thesis is lacking, and also to answer new questions specific to participants with musculoskeletal disorders.

Figure 55: Cover designs for the HEAF study baseline questionnaire and four annual follow-up questionnaires.(507)

Following HEAF baseline, many GP practices moved their clinical records system from CPRD over to Egton Medical Information Systems (EMIS).(508) Concurrently, CPRD could no longer supply prospective clinical data for the HEAF study. To continue to explore the relationship between clinical health disorders, multimorbidity, and work outcomes, a new

source of diagnostic health information was needed. Therefore, with agreement from the rest of the HEAF study team, I included a modified version of the Self-Administered Comorbidity Questionnaire (SACQ) (509) in the fourth annual follow-up questionnaire for the HEAF study. The SACQ contains both a self-reported checklist of common health problems and also indicators of disease severity, such as: whether a doctor was consulted for the problem; if there had been a hospital visit for the problem; if the participant was prescribed medicine for the problem; and whether the problem has limited a participant's activity. Although self-reported, this data is more detailed than the information provided by CPRD which, as I have found, could not provide clear indicators of disease severity. Data from the SACQ can improve on the work of this thesis in three main ways: 1) allowing validation of the CPRD-defined health disorders used in this thesis, as has been recommended by Herrett et al.(499) 2) allowing an assessment of how the underlying severity of health exposures relates to HRJL, and to look for a dose-response relationship, or "biological-gradient."(504) 3) Finally, facilitating a more comprehensive analysis of patterns of multimorbidity in the HEAF study population, as additional disorders for which CPRD information was not available are included in the SACQ, such as gastrointestinal disorders or ulcers, kidney disease, liver disease, anaemia and other blood diseases, cancer, and lung diseases (other than asthma and COPD).

In this thesis, it was observed that participants with musculoskeletal disorders were more likely to have had HRJL as their number of comorbidities increased. However, participants with musculoskeletal disorders and comorbidity may also have had more severe underlying musculoskeletal disease e.g. more severe pain can lead to increased risk of depression.(470–472) Therefore, to explore this possibility, in the HEAF fourth annual follow-up questionnaire, validated indicators of musculoskeletal disease severity (disability, pain, and fatigue) were included. Disability was measured using the Disability Rating Index (DRI) which assesses many aspects of musculoskeletal function such as dressing, walking, and climbing stairs.(510) Musculoskeletal pain was measured using the Von Korff Chronic Pain Scale which measures chronic musculoskeletal pain, containing items about: current pain; average pain intensity; worst pain intensity over the previous 6 months; and chronic pain limiting work and activities.(511) Lastly, fatigue was measured using the Fatigue Assessment Scale, which contains several questions about how fatigued a participant usually feels.(512) Using the new questionnaire data it should be possible to explore the relationship between musculoskeletal disability, pain, and fatigue and poor work outcomes. In addition, the relationship between comorbidity and work outcomes in people with

musculoskeletal disorders can be assessed, with adjustment or stratification for underlying musculoskeletal disease severity.

While the primary work outcome of focus for this thesis was HRJL, in the HEAF fourth annual follow-up questionnaire, additional work outcomes were collected. These included: job satisfaction, job security, optimism for being able to continue working, sickness absence in the prior year, and questions relating to the struggle to perform work due to health problems. Additionally, this questionnaire includes items from the validated and widely used Work Productivity and Activity Impairment questionnaire,(380) from which it will be possible to assess whether a person's health problems, or multimorbidity, impacts productivity, leading to "presenteeism," while at work. The additional work outcomes available in the new questionnaire will give new insights about the experience of older employed workers with multiple health disorders.

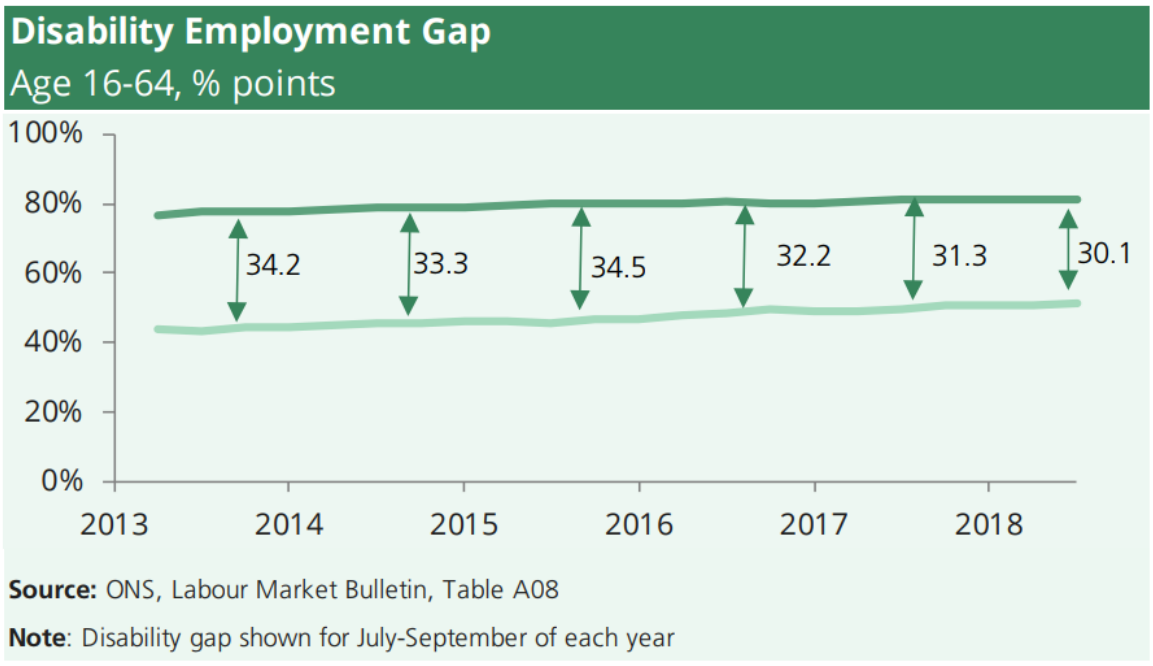
10.6 Recommendations for research

The disability employment gap (defined by the Office of National Statistics) represents the difference in the employment rate between people with and without disabilities. As described in the introductory chapter, reducing this figure is economically desirable for society while employment may also improve the material and psychosocial wellbeing of disabled individuals.(52) However, the UK disability employment gap has been consistently greater than 30% over the past decade (albeit with a 4.1% improvement overall, see Figure 56).(513) This suggests that much work still remains to encourage and enable people with disabling health problems to remain in employment. Initially, more research is needed to understand the journey that a person takes to becoming permanently work disabled, and the key risk factors involved.

The systematic review (Chapter 4) highlighted the need for higher quality, and more consistently reported, research exploring the impact of comorbidities upon work among people with musculoskeletal disorders. Some work has already been done to encourage a unified approach to absenteeism and productivity-loss outcomes used in rheumatology research.(383) Future studies can help aid consistency and interpretability by adopting these recommended outcome measures wherever possible. For research questions relating to adverse work outcomes as a result of poor health, health-specific work outcomes should also be used where possible (rather than e.g. unemployment or job loss which may occur for reasons unrelated to health). Chapter 4 also identified several common comorbidities that remain unexplored for their impact upon work outcomes among people with MSDs.

This thesis has also highlighted the importance of multimorbidity, and particularly musculoskeletal-mental health comorbidity, for health-related job loss in the older working age population; however, prospective data is needed to support these findings. As mentioned already, the Pseudo R^2 achieved in the multivariable models constructed in Chapter 9, while not unusual, suggested that there were remaining important unmeasured factors affecting the development of HRJL among older workers. Future research can explore these unknown factors by using a more comprehensive measure of multimorbidity, that considers other common health disorders in the UK population e.g. cancer and gastrointestinal disorders. Given enough statistical power, this research could also be used to explore interactions between these comorbid conditions in their relationship to adverse work outcomes. If certain comorbid conditions are found to have a strong additive or multiplicative interaction with poor work outcomes, this may have implications for preventative or targeted occupational interventions.

Figure 56: The UK Disability Employment Gap, from 2013 to 2018. Contains Parliamentary information licensed under the Open Parliament Licence v3.0. (513)



This thesis has highlighted the importance of multimorbidity for work, however, at the time of writing, there is very little research discussing the effectiveness of interventions specifically for improving occupational outcomes in multimorbidity. Existing literature mostly focusses on specific health problems. For example: there is reasonably strong evidence for CBT-based therapies for low back pain; workplace-based interventions such as ergonomic interventions, flexible working environment, and workplace rehabilitation have

been tested for musculoskeletal disorders and low back pain conditions; psychological interventions have been used for depression, such as occupational therapy and mindfulness-based interventions; and supported employment (including, individual placement and support) have been explored in people with severe mental health problems.(514,515) Studies of occupational outcomes for workplace interventions among people with musculoskeletal disorders mostly focusses on low back pain, and evidence is of weak quality among people with mental health problems;(514,516,517) Research concerning the effectiveness of occupational interventions to help people with cardio-respiratory disorders or other common conditions to remain in work is particularly scarce.(514) To summarise, important research gaps remain for supportive occupational interventions in many specific health disorders, but particularly for people with multimorbidity. Additionally, cost-effectiveness outcomes have rarely been explored, evidence about which is desperately needed if governments and employers are to be encouraged to adopt these interventions.

Prior to developing occupational support strategies for people with multimorbidity, preliminary research may be advisable. In 2017, “Work Matters” a UK-wide survey conducted by the National Rheumatoid Arthritis Society, took a focussed look at the impact of rheumatoid arthritis and juvenile idiopathic arthritis upon work. Participants with these conditions were asked about their main barriers and facilitators to staying in work.(518) A similar piece of research, particularly using qualitative face-to-face interviews, would be useful to better understand the challenges of managing multiple health conditions while working. Such research should focus on: perceived support at work; the advantages and challenges to staying in work in employed participants with multimorbidity; and the experience of multimorbid people who are no longer employed because of their health problems. For the unemployed with multimorbidity, such a survey should include information about benefits claimed and barriers and facilitators to returning to work (including ability and willingness). Given the complex nature of multimorbidity discussed throughout this thesis, the classification of multimorbidity used should be carefully considered and results stratified by number of concurrent health problems, and the type of multimorbidity (e.g. purely physical or mental-physical?). Research should facilitate the development of interventions and policy changes specifically aimed to support people with multimorbidity who want to remain in work.

10.7 Summary: research recommendations

- To validate the findings of this thesis: A comprehensive analysis of the relationship between multimorbidity and health-related job loss should be undertaken using prospective data and a validated measure of multimorbidity including all common and important disorders in the UK older working-age population.

- To validate the findings of this thesis: Using a validated measure of multimorbidity, patterns of multimorbidity, and relationship of these patterns to health-related job loss, should be explored in the older working-age population. Other indicators of disease burden should be explored where possible, such as healthcare utilisation and polypharmacy.

- To continue the work of this thesis and study the impact of comorbidity upon work outcomes among people with musculoskeletal disorders, future research should: be prospective and capture incident comorbidity; consider the comparative impact of several common comorbid disorders; be powered to assess important interactions; and should adjust for the severity of the underlying musculoskeletal disorders.

- Work should be considered an important health outcome and its reporting encouraged in the literature. To facilitate consistency in how these outcomes are classified and analysed, a standardised set of core work outcomes for effectiveness studies should be agreed. Future research studies can aid consistency and interpretability by adopting recommended work outcome measures wherever possible.

- More research is needed to study the impact of multimorbidity on currently employed workers, using validated measures of presenteeism, sickness absence, or time to return to work following long-term sickness absence. For return to work outcomes, length of follow up should be consistent with existing studies to aid comparison.

- Qualitative research is needed that considers the experience of working-age people with multimorbidity. Such research should focus on: perceived support at work; the advantages and challenges to staying in work amongst the employed; and the experience of people who are no longer employed because of their multiple health

problems (including information about benefits claimed and barriers and facilitators to returning to work).

- Study authors should take care to stratify their results by gender wherever possible, in consideration of the differences in occupational environment and disease burden observed in this thesis.

- Evidence is needed to support the use of workplace interventions for improving occupational outcomes in multimorbidity (and numerous other specific health disorders). Particularly needed is an assessment of cost-effectiveness for these interventions, which considers: the effectiveness of the intervention; the cost of the intervention; the cost of work-time lost; and the cost of replacing a worker who has left employment for health reasons.

10.8 Policy Recommendations

The need for workplace support among people with multimorbidity in England

The work of this thesis has highlighted the powerful influence of multimorbidity upon early exit from work among older workers. While, little is known about the experience of people with multimorbidity at work, some survey data is available. The Work Foundation wrote a report on the complexities and challenges of working with multiple health conditions, using data from the 2013 Health Survey for England (HSE).(519,520) This report found that the employment rate among responders decreased with the number of concurrent health disorders. An additional telephone questionnaire survey was then conducted among a subsample of participants reporting multimorbidity in the 2011 – 2014 HSE. Questions were asked about disclosure of health problems to the employer, perceived support from employers, adjustments made by the employer, and use of occupational health services.(520) I consider some findings from this work, how they relate to the people with multimorbidity studied in this thesis, and how they may influence changes in policy or targets for interventions, below.

According to the report, 20% of participants with multimorbidity had not told their employer about any of their long-term health conditions, while 23% of multimorbid employees had only disclosed one condition. Participants commonly reported “not seeing the point” and it “does not affect my work” as the most common reasons for not disclosing their health conditions. Public health initiatives may therefore focus on education for employers and employees, to try and encourage people with multiple health problems to

disclose their health problems to their employers at a stage where some support may gradually be put in place to reduce presenteeism and prevent sickness absences and health-related job loss. Of course, multimorbid workers who did not disclose may have been reluctant to tell their employers of their health problems for fear of threat to work relationships or job security. Encouragingly, of those who did disclose their condition, 73% felt their employer had been supportive, only 14% did not.(520) These results may not be representative however, since the telephone questionnaire survey was conducted only among people who were still in employment and did not include participants who had already fallen out of work, such as the "case" participants in this thesis.

Among the participants who had disclosed, 53% had not had any adjustments made at work, 34% said the employer had made some form of adjustment, and 13% reported they did not require adjustments. Physical comorbidity, number of health disorders, frequency of symptoms experienced, and pain/discomfort were significantly associated with whether the employer had made workplace adjustments. Throughout this thesis, mental health problems appeared to be more strongly associated with HRJL than musculoskeletal disorders (although both were important). The results from the Work Foundation report suggest one possible mechanism for this finding: workplaces may be more equipped and willing to provide support for people with health problems if their condition is physical or painful.

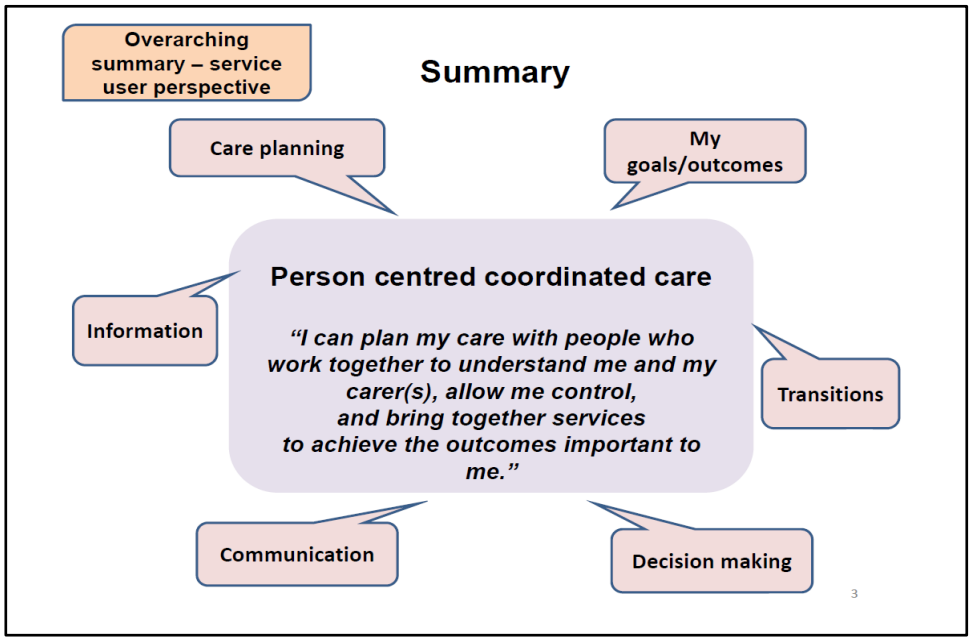
In the work foundation report, of those who had received adjustment to their workplace, "changes to working hours, breaks, or shift patterns" was considered the "most helpful to stay in work." Overall, 60% of participants had access to an occupational health service, and of those who used it, 66% agreed that the occupational health service was "helpful in managing all of my health conditions at work," only 13% did not.(520) This suggests that the role of occupational health services may be important in maintaining employment for people with multiple health problems. However, currently less than 50% of employees in the UK may have access to these services.(521) Interestingly, the fact that changes to working hours, breaks, or shift patterns were considered the most helpful is encouraging, since, depending on the work, these changes may be relatively inexpensive for employers but impactful for the employee with health problems.

Recommendations for management of multimorbidity in the workplace

The clinical management of multimorbidity is complex, as reflected in the National Institute for Health and Care Excellence (NICE) Guideline "Multimorbidity: clinical assessment and

management" published in 2016. This guideline recommends several aspects of good clinical management for people with two or more long-term health conditions. Healthcare professionals are recommended to provide a tailored approach to care that takes into account: difficulty managing treatments or daily activities; the need to receive care from multiple healthcare services; the possible presence of a combination of both physical and mental health conditions, or frailty; the possibility of a frequent need to seek unplanned or emergency care; the possibility of requiring multiple regular medications.(192) Management for people with multimorbidity should follow a person-centred, biopsychosocial approach incorporating the six desirable elements of care identified by people with long-term conditions (see Figure 57).(522) These elements can be enabled through systems to support self-management and shared decision-making, and the implementation of care and support planning. Models of managing people with health problems in the workplace can take inspiration from these systems by encouraging communication and shared decision making between the employer and employee, and by tailored forward planning that takes into account the possibility of needing to attend multiple healthcare appointments, or unplanned fluctuations in symptoms.

Figure 57: A narrative for person-centred coordinated care.(522)



Although evidence is lacking for the management of multimorbidity in the workplace, employers should be aware of health issues that could affect the ability of employees to cope with their workload and are required by law to provide "reasonable adjustments" wherever possible to help support people with disabling multimorbidity to remain

working.(523) Employers could help to support people with multimorbidity through the use of workplace interventions targeted at health disorders which are common contributors to multimorbidity. For example, as outlined in this thesis, musculoskeletal disorders were found to commonly exist alongside other health conditions.(181) There is some evidence that these conditions may be managed at work with CBT-based therapies for low back pain; and ergonomic interventions, flexible working arrangements, and workplace rehabilitation for general musculoskeletal disorders.(514)

One intervention which may prove a useful approach for supporting people with multimorbidity in the workplace is "case management", which involves person-centred co-ordination between employers and healthcare and rehabilitation professionals, with an identifiable and accountable case manager.(514,524) Specific aspects of this intervention include motivation, goal setting, and return to work planning. This is an intervention with some evidence of benefits for people with long-term health conditions generally and therefore may be a useful approach for participants with multimorbidity.(514)

Some management strategies can be time and resource intensive because of the complexity of care needed, and resources are increasingly stretched because of the growing number of individuals who need such services. For example, UK health and social care costs average nearly £8,000 per year to care for a person living with three or more long-term conditions as compared with an estimated £3,000 for a person living with only one long-term condition.(162) Therefore, such interventions may only be cost-effective among people at highest risk for work disability, or for whom there is strong evidence of benefit. However, the work cited above by the Work Foundation suggests that there may be inexpensive options that can be attempted before using more costly interventions, for example, employing a flexible approach to working hours, breaks, or shift patterns.

The work of this thesis has contributed important evidence to suggest the highest risk of health-related job loss is among older workers with concurrent musculoskeletal and mental health problems. This suggests that a person developing mental health problems with pre-existing musculoskeletal disorders (and vice versa) should be given priority occupational support to preserve their employment. For such a person, occupational support could include mindfulness-based interventions which have shown some benefit for anxiety, depression, and burnout in the workplace.(515) Supportive interventions should be employed promptly before periods of long sickness absence, based on evidence that

suggests that the longer a person remains out of work due to sickness, the greater the likelihood that they will never return to paid work.(47)

10.9 Policy recommendations: summary

- Public health initiatives should focus on education for employers and employees, to try and encourage people with multiple health problems to disclose their health problems to their employers at a stage where some support may be offered. Healthcare professionals can facilitate this in clinical appointments by asking about health struggles at work in people with multimorbidity.

- Recommended clinical management for people with multimorbidity follows a person-centred, biopsychosocial approach. Likewise, systems that support multimorbid people at work should encourage communication and shared decision making between the employer and employee, as well as tailored forward planning that takes into account the possibility of needing to attend multiple healthcare appointments, or unplanned fluctuations in symptoms.

- Employers should be aware that permitting flexibility in working hours, break times, or shift patterns is often inexpensive and may be particularly helpful to the employee to support remaining in work, especially for people with multimorbidity who may be managing multiple health appointments and fluctuations in disease symptom severity.

- Odds of premature exit from work due to health problems appear to be considerably higher among people with multiple health problems. Employers should be aware that musculoskeletal disorders and mental health problems pose the greatest threat, particularly if occurring together. Certain workplace interventions such as CBT-based therapies, ergonomic interventions, flexible working arrangements, and workplace rehabilitation may be helpful for these conditions specifically, although there are few studies reporting cost-effectiveness. These interventions should be provided promptly in a person with concurrent musculoskeletal and mental health disorders in the workplace, in order to reduce the likelihood of long-term sickness absence and permanent loss of paid work.

10.10 Conclusions

These results support the primary importance of common mental health problems and musculoskeletal disorders for health-related job loss in the older working-age UK population. In addition, the novel work conducted in this thesis was the first to study the relationship between multimorbidity and health-related job loss in this cohort. Multimorbidity (by the classification used in this thesis) was strongly associated with HRJL and accounted for a significantly greater proportion of HRJL than any individual health disorder. This stresses the importance of treating an individual holistically when managing their occupational health by considering the influence of comorbidity on their work situation. At a population level, the recognition of people with multimorbidity as a group at particularly high risk of premature job loss is crucial in order for policymakers to focus resources where they are needed. Another unique feature of this work was the use of cluster analysis to characterise multimorbidity among older workers. Musculoskeletal disorders were found to frequently co-occur with hypertension, and with mental health problems and these comprised the most common multimorbidity patterns. In men, a cluster of participants with cardio-metabolic disorders was also prominent. Most multimorbidity clusters identified were strongly associated with HRJL, however, clusters formed by musculoskeletal disorders and mental health problems appeared to have the greatest impact. Previous research has suggested the possibility of a synergistic relationship between musculoskeletal disorders and mental health problems for poor work outcomes. Therefore, policymakers and healthcare professionals who are concerned about supporting older working-age people in employment should be cautious to prevent, and treat, the occurrence of mental health disorders in persons with musculoskeletal disease (and vice versa) since the long term impact on employment may be dramatic. Future research will be undertaken to validate the findings of this thesis and to understand how a broader range of health problems interact to influence work outcomes among the older working age.

Glossary

ABS - Australian Bureau of Statistics

ACR - American College of Rheumatology

aOR - adjusted Odds Ratio

ARDS - Adult Respiratory Distress Syndrome

AS - Ankylosing Spondylitis

BNF - British National Formulary

BSRBR - British Society for Rheumatology Biologics Registers

CI - Confidence interval

COPD - Chronic Obstructive Pulmonary Disease

CPRD - Clinical Practice Research Datalink

CVA - Cerebrovascular accident

ERAS - Early Rheumatoid Arthritis Study

GP- General Practice

HEAF - Health and Employment After Fifty (study)

HES – Hospital Episode Statistics

HND - Higher National Diploma

HR - Hazard ratio

HTN - Hypertension

ICD - International Classification of Disease

IHD - Ischaemic Heart Disease

IRD - Inflammatory Rheumatic Disorder

IRR - Incidence Rate Ratio

JL - Job loss

LTC - Long Term Condition

LTSA - Long Term Sickness Absence

MHP - Mental Health Problem

MRC- Medical Research Council

MSD - Musculoskeletal Disorder

MSpain - musculoskeletal pain

NA - Not Applicable

NE – Not Estimable

NOS - Newcastle-Ottawa Score

NSLBP - Non-Specific Low Back Pain

NS-SEC - National Statistics Socio-Economic Classification

OA - Osteoarthritis

OECD - Organisation for Economic Co-operation and Development

OMERACT - Outcome Measures in Rheumatology

ONS - Office of National Statistics

OPD - Obstructive Pulmonary Disease

OR - Odds Ratio

PAD - Peripheral Arterial Disease

Pres - Presenteeism

PsA - Psoriatic Arthritis

RA - Rheumatoid Arthritis

RDCI - Rheumatic Disease Comorbidity Index

RR - Risk Ratio

RTW - Return to Work (time to return to work after work disability)

SA - Sickness absence

SHR – Standardised Hazard Ratio

SLE - Systemic Lupus Erythematous

SOC - Standard Occupational Classification

SOC-10 - Standard Occupational Classification 2010

SSRI - Selective Serotonin Reuptake Inhibitors

SpA - Spondyloarthritis

TIA - Transient Ischemic Attack

UE - Unemployment

VTE - Venous Thromboembolism

WAI - Work Ability Index

WALS - Workplace Activity Limitations Scale

WD - Work Disability

WLQ PDmod - Work Limitations Questionnaire with modified physical demands scale

WPAI - Work Productivity and Activity Impairment questionnaire

WPS - Work Productivity Survey

WT - Work Transition

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Appendix

Appendix to Chapter 3

Appendix Table 1: Excluded Read codes by body system

Body system	Excluded Read codes
Musculoskeletal disorders	Acute rheumatic fever O/E - knee joint abnormal O/E - shoulder joint abnormal H/O: rheumatic fever O/E - finger joint abnormal O/E - wrist joint abnormal O/E - elbow joint abnormal O/E - joint abnormal O/E - neck joint abnormal O/E - toe joint abnormal O/E - hip joint abnormal O/E - hand joint abnormal Rheumatoid factor Back X-ray Adverse reaction to analgesics, antipyretics, antirheumatics [D]Head and neck symptoms O/E - ankle joint abnormal [X]Cervicogenic headache
Mental health problems	Flashing lights seen O/E - irritable Tantrums O/E - disorientated Speech problem Nightmares Nervous system symptoms Mental disorders Floaters seen Anxious mother School refusal H/O: psychiatric disorder Irritable - symptom Jet lag syndrome Restless [D]Physical violence Sexual symptom Dreams Night terrors Nightmares - symptom Speech problem - symptom [V]Other or unspecified general psychiatric examination Bruxism (teeth grinding) Post-concussion syndrome [D]Visual hallucinations

	Problem situation [D]Hallucinations, auditory Nervous system symptoms NOS Nervous system symptom Guilty ideas CNS symptom Blunted affect Flight of ideas On lithium Stage fright Morbid thoughts [D]Strange and inexplicable behaviour [X]Mild mental/behav disorder assoc with the puerperium NEC [X]Severe mental and behav disorder assoc wth puerperium NEC Hypnagogic hallucination
Cardiovascular disorders	[SO]Coronary artery Cardiovascular event risk Cardiac event recording [D]Functional heart murmur [D]Other abnormal heart sounds Primary pulmonary hypertension Ocular hypertension Portal hypertension Benign intracranial hypertension Chronic peripheral venous hypertension Sinus arrhythmia Transient neurological symptoms Pulmonary sarcoidosis Diffuse pulmonary fibrosis Pulmonary rehabilitation programme completed [SO]Pulmonary vein Pulmonary rehabilitation Referral to pulmonary rehabilitation Assessment for pulmonary rehabilitation completed Pulmonary rehabilitation declined Pulmonary rehabilitation offered Temporal artery biopsy Carotid artery doppler abnormal [SO]Common iliac artery Percutaneous embolisation of uterine artery [SO]Renal artery [SO]Ophthalmic artery Ligation of haemorrhoidal artery [SO]Basilar artery Atrial premature depolarization Atrial dilatation [SO]Valve of heart [SO]Aortic valve
Respiratory	Pulmonary tuberculosis Respiratory disease monitoring

	Wheezing symptom Referred to chest physician Asthma screening Seen by respiratory physician Referral to chest physician At risk of chronic obstructive pulmonary disease Seen by chest physician Referral to respiratory physician Referral to thoracic physician Pulmonary aspergillus disease Inhaler technique - moderate Private referral to chest physician [V] Personal history of pulmonary tuberculosis Seen by respiratory physician Referral to respiratory nurse specialist CPAP - Continuous positive airways pressure Pulmonary eosinophilia Referral to respiratory rapid response team CPAP - Continuous positive airways pressure Seen by thoracic physician Pulmonary tuberculosis NOS Discharge by respiratory physician Continuous positive airways pressure Seen in respiratory clinic Referral to respiratory physician Pulmonary fibrosis Seen by respiratory nurse specialist Prescription of respiratory disease rescue medication
Epilepsy	Contraceptiv advice for patients with epilepsy not indicated Pre-conception advic fr patients with epilepsy not indicated Pregnancy advice for patients with epilepsy not indicated Epilepsy screen invite 3
Diabetes	Diabetic monitoring not required

Appendix Table 2: Read codes used to compose musculoskeletal health disorder sub-group categories

Health disorder category and group number	**Clinical diagnostic codes (Read codes) used**
1. Rheumatoid arthritis	Rheumatoid arthritis Intramuscular gold therapy Rheumatoid factor positive Rheumatoid nodule H/O: rheumatoid arthritis Seronegative rheumatoid arthritis Flare of rheumatoid arthritis Seropositive errosive rheumatoid arthritis Rheumatoid lung Seropositive rheumatoid arthritis, unspecified Rheumatoid arthrit. monitoring Rheumatoid bursitis

	Swan-neck finger deformity Rheumatoid arthritis and other inflammatory polyarthropathy Rheumatoid arthritis annual review Except rheumatoid arthritis qual indicator: informed dissent Exception reporting: rheumatoid arthritis quality indicators Except rheumatoid arthritis quality indicator: pt unsuitable Rheumatoid arthritis monitoring invitation Rheumatoid arthritis monitoring invitation first letter Rheumatoid arthritis monitoring invitation second letter Rheumatoid arthritis monitoring verbal invitation Rheumatoid arthritis monitoring invitation third letter Rheumatoid arthritis monitoring telephone invitation
2. Inflammatory arthritis/juvenile arthritis	Psoriatic arthropathy Synovitis or tenosynovitis NOS Synovitis and tenosynovitis Polyarthritis Spondylitis NOS Ankylosing spondylitis Synovitis of hip Reactive arthropathy, unspecified Chronic post-rheumatic arthropathy Sero negative arthritis Arthropathy associated with infections Palindromic rheumatism Sero negative polyarthritis Acute arthritis Psoriatic arthropathy NOS Other synovitis and tenosynovitis Rheumat.dis.- joints affected Shoulder synovitis Behcet's syndrome Arthropathy associated with other viral diseases Arthropathy in Crohn's disease Inflammatory polyarthropathy Oligoarticular osteoarthritis, unspecified Reactive arthropathies Enthesopathy of the hip region Disease modifying antirheumatic drug monitoring Hip enthesopathy NOS Juvenile rheumatoid arthritis Inflammatory spondylopathies Sarcoid arthropathy Palindromic rheumatism NOS Adverse reaction to antirheumatics NOS Arthropathy associated with dermatological disorders Reactive arthropathy of knee Rheumat. drug side effect BASDAI - Bath ankylosing spondylitis disease activity index Suspected inflammatory arthritis Seen in GP DMARD monitoring clinic Psoriatic arthritis

	DNA GP disease modifying antirheumatic drug monitor clinic
3. Probable osteoarthritis (OA) unclear site	Osteoarthritis Arthritis H/O: arthritis Joint degeneration Osteoarthritis and allied disorders Unspecified monoarthritis Generalised osteoarthritis - OA Chronic arthritis Osteoarthritis NOS H/O: osteoarthritis Generalised arthritis [X]Arthrosis Localised, primary osteoarthritis of other specified site Primary generalized osteoarthrosis Osteoarthritis NOS Localised, primary osteoarthritis Osteoarthritis NOS, of unspecified site Erosive osteoarthrosis Unspecified monoarthritis of other specified site
4. OA back	Lumbar disc degeneration Lumbar spondylosis Degeneration of lumbar spine Narrowing intervertebral disc space Plain X-ray lumbar spine abnormal Thoracic disc degeneration Thoracic spondylosis Lumbosacral instability Lumbar spinal stenosis Collapse of lumbar vertebra Lumbosacral spondylosis without myelopathy Spinal stenosis, excluding cervical region Dorsal spondylosis without myelopathy Thoracic spondylosis without myelopathy Other lumbar disc disorders Congenital lumbosacral spondylolysis Osteoarthritis of thoracic spine
5. OA neck	Cervical spondylosis Cervical spondylosis without myelopathy Plain X-ray cervical spine abnormal Cervical spinal stenosis Osteoarthritis cervical spine Cervical spine instability Degenerative cervical spinal stenosis Cervical spondylosis
6. OA shoulder and elbow	Osteoarthritis NOS, of acromioclavicular joint Osteoarthritis NOS, of shoulder region Joint ankylosis of the shoulder region Osteoarthritis NOS, of shoulder Shoulder arthritis NOS

	Unspecified monoarthritis of the shoulder region Elbow arthritis NOS Localised, primary osteoarthritis of the shoulder region Localised, primary osteoarthritis of the upper arm
7. OA hip	Hip osteoarthitis NOS Hip osteoarthritis NOS Osteoarthritis NOS, of hip Hip arthritis NOS [X]Other primary coxarthrosis
8. OA knee	Knee osteoarthritis NOS Patellofemoral osteoarthritis Osteoarthritis NOS, of knee Knee arthritis NOS Arthritis associated with other disease, knee
9. OA lower limb, not specified or other than hip or knee	Foot osteoarthritis NOS Foot arthritis NOS Localised osteoarthritis, unspecified, of the ankle and foot Toe osteoarthritis NOS Osteoarthritis NOS, of 1st MTP joint Osteoarthritis NOS, of ankle Ankle arthritis NOS Osteoarthritis NOS, of the lower leg Osteoarthritis NOS, of ankle and foot Localised, primary osteoarthritis of the lower leg Localised, primary osteoarthritis of toe Ankle osteoarthritis NOS Arthritis associated with other disease, 1st MTP joint
10. OA back or neck, not specified	Degenerative disc disease NOS Osteoarthritis spine Spondylosis and allied disorders Arthritis of spine Spinal stenosis Spondylosis NOS Osteoarthritis of spine Osteoarthritis of spine Osteoarthritis of lumbar spine
11. OA hand, wrist, digits	Osteoarthritis NOS, of the hand Thumb osteoarthritis NOS Wrist arthritis NOS Heberdens' nodes Finger osteoarthritis NOS Osteoarthritis NOS, of MCP joint Hand arthritis NOS Osteoarthritis NOS, of wrist Osteoarthritis NOS, of DIP joint of finger Osteoarthritis NOS, of PIP joint of finger Wrist osteoarthritis NOS Periarthritis of wrist Localised, primary osteoarthritis of the hand Heberden's nodes with arthropathy Localised, primary osteoarthritis of the wrist

	Generalised osteoarthritis of the hand Arthritis associated with other disease, PIP joint of finger
12. OA pelvis	Osteoarthritis NOS, pelvic region/thigh Localised, primary osteoarthritis of the pelvic region/thigh Sacroiliac ankylosis
13. Crystal arthritis	Gout Crystal arthropathies Gouty arthritis H/O: gout Pseudogout Gouty tophi of other sites Gouty arthropathy Gouty arthritis NOS Gout monitoring Gout NOS Gout treatment changed Gouty arthritis of the ankle and foot Gouty tophi of ear
14. Infective arthritis/arthropathy	Septic arthritis Pyogenic arthritis
15. Non-specific disorder of joints	Arthralgia of unspecified site Injection of therapeutic substance into joint Effusion of joint Injection into joint NEC O/E - joint swelling Arthralgia of multiple joints Arthropathy NOS Joint disorders NOS Arthropathies NOS Pain in joint - arthralgia O/E - joint effusion present Other and unspecified joint disorders O/E - reduced joint movement O/E - swelling - joint Swelling of joint - effusion Polyarthropathy NEC Transient arthropathy Arthropathies and related disorders Other specified joint disorders NOS Ankylosis of joint Swollen joint Arthropathy NOS, of the lower leg Unspecified polyarthropathy or polyarthritis Swollen joint count Other specified arthropathies Unspecified polyarthropathy or polyarthritis NOS O/E - joint movement painful Other and unspecified arthropathies Other joint symptoms NOS Unspecified polyarthropathy of unspecified site

16. Back pain	Backache Low back pain Backache, unspecified Pain in lumbar spine Sacroiliac strain Lumbago Therapeutic lumbar epidural injection Backache symptom Back pain without radiation NOS C/O - low back pain Spasm of back muscles Pain in thoracic spine Acute back pain - lumbar C/O - a back symptom C/O - lumbar pain Acute back pain - thoracic Acute back pain - unspecified Back stiffness C/O - upper back ache Backache symptom NOS Back disorders NOS H/O: back problem Back pain, unspecified Backache with radiation Referral to back pain clinic Lumbar traction Chronic low back pain Mechanical low back pain Lumbalgia Other back symptoms
17. Discogenic nerve root pain	Sciatica Intervertebral disc disorders Prolapsed lumbar intervertebral disc Slipped intervertebral disc Cervical disc degeneration Lumbar disc displacement Lumbosacral neuritis, unspecified Cervical disc displacement Acute back pain - disc Acute back pain with sciatica Cervical disc disorder with radiculopathy Intervertebral disc prolapse NOS Cervical disc displacement without myelopathy Cervical spondylosis with myelopathy Prolapsed lumbar intervertebral disc with sciatica Myelopathy due to spondylosis Cervical disc disorder with myelopathy Exploratory thoracic laminectomy Lumbosacral spondylosis with radiculopathy Cervical spondylosis with radiculopathy Disc prolapse with radiculopathy Lumbar disc prolapse with myelopathy

	Prolapsed intervertebral disc without myelopathy Cervicobrachial syndrome Lumbago with sciatica Thoracic and lumbosacral neuritis Thoracic spondylosis with radiculopathy Cervical nerve root injury Disc prolapse with myelopathy Lumbar disc prolapse with radiculopathy Lumbosacral root lesions NEC Lumbar disc prolapse with cauda equina compression Thoracic disc displacement without myelopathy Thoracic and lumbosacral neuritis NOS Cervical disc prolapse with radiculopathy Disc disorder with myelopathy Prolapsed cervical intervertebral disc without myelopathy Lumbar nerve root injury Lumbar disc disorder with myelopathy Lumbosacral plexus injury Nerve root and plexus compressions in intervert disc disord Other cervical disc disorders
18. Spinal surgery	Primary laminectomy excision of lumbar intervertebral disc Primary laminectomy excision of cervical intervert disc Laminectomy approach to cervical spine Revisional lumbar microdiscectomy Exploratory cervical laminectomy Laminectomy approach to thoracic spine Primary posterior laminectomy decompression lumbar spine Laminectomy approach to lumbar spine Revision posterior laminectomy decompression lumbar spine Other specified operations on lumbar spine Decompression operations on unspecified spine Other specified primary foraminoplasty of spine
19. Neck pain	Cervicalgia - pain in neck Stiff neck Spasmodic torticollis Wry neck Torticollis unspecified Cervical and neck disorders NOS C/O - a neck symptom Stiff neck symptom Torticollis - symptom [V]Problems with neck Stiff neck NOS Torticollis NOS Wry neck/torticollis Neck sprain, unspecified Wry neck symptom Crick in neck Torticollis - traumatic Pain in cervical spine

	Cervicalgia
20. Hip pain	Hip pain Hip joint pain Arthralgia of the pelvic region and thigh Arthralgia of hip
21. Knee pain	H/O: significant knee disorder Knee joint pain Arthralgia of knee Anterior knee pain Knee pain Anterior knee pain
22. Lower limb pain unspecified or other than hip or knee	Arthralgia of the ankle and foot
23. Knee bursitis	Prepatellar bursitis Bursitis of the knee NOS Housemaids' knee Infrapatellar bursitis Subpatellar bursitis Suprapatellar bursitis Beat knee [X]Other bursitis of knee
24. Knee joint swelling or effusion	Knee joint effusion Swollen knee Rupture of Baker's cyst - knee Effusion of knee
25. Widespread pain	Fibromyalgia Myalgic encephalomyelitis Myalgia or myositis NOS Myalgic encephalomyelitis Chronic fatigue syndrome Fibromyalgia Fibrositis of neck CFS - Chronic fatigue syndrome Generalised pain [symptom] Myofascial pain syndrome [X]Chronic pain personality syndrome Myofascial pain syndrome Referral to chronic fatigue syndrome specialist team Chronic pain review
26. Connective tissue disease	Polymyalgia rheumatica Musculoskeletal and connective tissue diseases NOS Sicca (Sjogren's) syndrome Discoid lupus erythematosus Polymyalgia Temporal arteritis Lupus erythematosus Arteritis unspecified Wegener's granulomatosis Dermatomyositis

	Myositis unspecified Lupus erythematosus NOS Systemic lupus erythematosus Cranial arteritis Giant cell arteritis Sjogren - Larsson syndrome Polymyositis Disseminated lupus erythematosus Lupus nephritis Subacute cutaneous lupus erythematosus Systemic sclerosis Lupus erythematosus profundus History of connective tissue disease
27. Shoulder pain	Shoulder pain Shoulder joint pain Shoulder stiff Shoulder pain Arthralgia of sternoclavicular joint Stiff joint NEC, of the shoulder region Other joint symptoms of the shoulder region Arthralgia of the shoulder region Arthralgia of the upper arm Arthralgia of shoulder Arthralgia of acromioclavicular joint Shoulder joint painful on movement
28. Elbow pain	Elbow joint pain Arthralgia of elbow Pain in elbow Elbow pain
29. Wrist/hand or forearm pain	Wrist joint pain Arthralgia of wrist Arthralgia of the hand Arthralgia of the forearm Arthralgia of DIP joint of finger Hand joint pain Arthralgia of PIP joint of finger Pain in wrist
30. Specific disorders of the shoulder & shoulder girdle (not OA)	Painful arc syndrome Bicepital tendonitis Supraspinatus tendonitis Adhesive capsulitis of the shoulder Frozen shoulder Scapulohumeral fibrositis Rotator cuff shoulder syndrome and allied disorders Subacromial bursitis Supraspinatus tendinitis Capsulitis NOS Shoulder tendonitis Bursitis - shoulder O/E - painful arc Subacromial impingement

	Impingement syndrome of shoulder Subacromial bursitis Biceps tendinitis Bicipital tenosynovitis Subdeltoid bursitis Tendonitis bicepital Rotator cuff syndrome, unspecified Rotator cuff syndrome NOS
31. Specific disorders of the elbow (not OA)	Tennis elbow Olecranon bursitis Golfer's elbow Lateral epicondylitis of the elbow Medial epicondylitis of the elbow
32. Specific disorders of the forearm, hand, wrist, or digits (not OA)	De Quervain's disease Other tenosynovitis of the wrist Other tenosynovitis of hand or wrist
33. Shoulder surgery & other procedures	Injection of steroid into shoulder joint Shoulder joint operations Hemiarthroplasty of head of humerus Injection of hydrocortisone acetate into shoulder joint Plastic repair of rotator cuff of shoulder Bursitis of shoulder Pain due to shoulder joint prosthesis Prosthetic uncemented hemiarthroplasty of shoulder Shoulder joint operations NOS Other specified operations on shoulder joint Primary uncemented hemiarthroplasty of shoulder Total prosthetic replacement of shoulder joint using cement Resurfacing hemiarthroplasty of head of humerus NEC Arthroscopic subacromial decompression Plastic repair of rotator cuff of shoulder NEC Plastic repair of multiple tears of rotator cuff of shoulder Diagnostic arthroscopy of shoulder joint
34. Elbow injections	Injection of steroid into elbow joint
35. Wrist injection/splinting	None in study sample
36. Other procedures upper limb (not shoulder)	Injection of steroid into wrist joint Injection of steroid into carpometacarpal joint of thumb
37. Upper limb pain not specified	Pain in upper limb
38. Non-specific sprain/injury group	Sprains and strains of joints and adjacent muscles Ligament sprain NOS Joint sprain NOS Tendon sprain NOS Muscle sprain NOS Sprain - late effect Sprains and strains NOS Nontraumatic tendon rupture Other specified sprains and strains

	Other and ill-defined sprains and strains Complex regional pain syndrome type I Complex regional pain syndrome
39. Neck injury	Whiplash injury Neck sprain Whiplash injury Dislocations, sprains and strains involving head with neck
40. Back injury	Back sprain NOS Sprain, lumbosacral ligament Lumbar sprain Pulled back muscle Sacroiliac ligament sprain Coccyx sprain Disloc,sprains + strains involv thorax wth lwr back + pelvis Thoracic sprain Lumbosacral strain Sprain & strain of oth & unsp parts of lumb spine & pelv
41. Shoulder/upper limb injury	Elbow sprain NOS Sprain wrist ligament Sprain finger Sprain thumb Rotator cuff sprain Sprain, acromio-clavicular ligament Hand and wrist extensor tendon rupture Shoulder strain Sprain tendon wrist or hand Sprain of shoulder and upper arm Complete tear, shoulder joint Sprain tendon of thumb Wrist sprain unspecified Hand and wrist flexor tendon rupture Hand sprain Biceps tendon rupture Sternoclavicular sprain Wrist and hand sprain NOS Sprain of elbow and forearm Sprain, supraspinatus tendon Forearm sprain Other shoulder sprain Sprain, biceps tendon Sprain, triceps tendon Rotator cuff complete rupture Sprain, infraspinatus tendon Sprain, subscapularis tendon Shoulder sprain NOS Sprain, elbow joint, medial collateral ligament Sprain, shoulder joint Sprain of wrist and hand Sprain tendon of finger Wrist sprain NOS Sprain & strain of oth & unspecif parts of should girdle

	Finger sprain
42. Hip injury	Hip sprain Sprain of hip and thigh
43. Knee injury (including ligament tears)	Knee sprain Complete tear, knee ligament Knee sprain NOS Acute meniscal tear, medial Sprain of cruciate ligament of knee Partial tear, knee, anterior cruciate ligament Complete tear, knee, posterior cruciate ligament Complete tear, knee, anterior cruciate ligament Sprain or partial tear, knee, lateral collateral ligament Sprain of medial collateral ligament of knee Partial tear, knee, medial collateral ligament Complete tear, knee, medial collateral ligament Adhesions of knee joint
44. Other lower limb injury	Foot sprain Ankle sprain Groin sprain Quadriceps tendon rupture Hamstring sprain Sprain, tendocalcaneus (Achilles tendon) Toe sprain Leg sprain NOS Ankle sprain NOS Sprain gastrocnemius Leg sprain Sprain, patellar tendon Sprain, hamstring tendon Sprain of superior tibiofibular ligament Sprain, quadriceps tendon Sprain of knee and leg Sprain of ankle and foot Foot sprain NOS Sequelae of dislocation, sprain and strain of lower limb Sprain, inter-phalangeal joint, toe Complete tear, ankle or foot ligament
45. Specific disorder that does not fit anywhere	Tendonitis NOS Rib sprain Xiphoid cartilage sprain Intercostal myalgia Temporomandibular joint disorder NOS Sternum sprain Effusion of ankle
46. Arthroplasty of the hip	Total prosthetic replacement of hip joint NOS THR - Total prosthetic replacement hip joint without cement Hip joint operations Revision of total prosthetic replacement of hip joint NEC THR - Total prosthetic replacement of hip joint using cement THR - Other total prosthetic replacement of hip joint

	Hip replacement planned Total prosthetic replacement of hip joint using cement Hemiarthroplasty of head of femur NEC Revision cemented total hip replacement Prosthetic hemiarthroplasty of head of femur using cement Other total prosthetic replacement of hip joint Other arthroplasty of hip joint Primary hybrid total replacement of hip joint NEC Primary cemented total hip replacement Pain due to hip joint prosthesis Hip joint operations NOS Total prosthetic replacement of hip joint not using cement Exeter total replacement of hip joint using cement Primary prosthetic hemiarthroplasty of hip NEC Primary total prosthetic replacement of hip joint NEC Total prosthetic replacement of hip joint using cement OS Closed reduction dislocated total prosthet replace hip joint Primary uncemented total hip replacement Primary hybrid total replacement of hip joint NEC Revision one component total prosthet replace hip joint NEC H/O hip replacement
47. Other hip procedures	Other specified operations on hip joint Injection of steroid into hip joint
48. Arthroplasty of knee	Other total prosthetic replacement of knee joint NOS Total prosthetic replacement of knee joint using cement TKR - Other total prosthetic replacement of knee joint TKR -Total prosthetic replacement of knee joint using cement Other total prosthetic replacement of knee joint TKR - Total prosthetic replacement knee joint without cement Other arthroplasty of knee joint Revision cemented total knee replacement Cemented unicompartmental knee replacement Revision of total knee replacement NEC Total prosthetic replacement of knee joint not using cement Primary cemented total knee replacement Primary total knee replacement NEC Primary cemented unicompartmental knee replacement Unicompartmental knee replacement NOS Prosthetic arthroplasty of the patellofemoral joint H/O knee replacement
49. Other knee procedures	Diagnostic arthroscopy of knee Open total meniscectomy of knee Knee joint operations Therapeutic arthroscopic operations on cavity of knee joint Therapeutic arthroscopy on knee joint Arthroscopic removal of loose body from knee joint Injection of steroid into knee joint Partial meniscectomy of knee Arthroscopic debridement of knee joint

	Arthroscopic synovectomy knee joint Arthroscopic irrigation of knee joint Open meniscectomy of knee NEC Endoscopic washout of knee joint Diagnostic arthroscopy of knee NOS Lateral release of contracture of knee joint Knee joint operations NOS Therapeutic arthroscopic op on cavity of knee joint NOS Release of contracture of knee joint Endoscopic lavage of knee joint Other specified operations on knee joint Arthroscopic partial medial meniscectomy Arthroscopy of knee
50. Referral/ seen by/ under care of rheum/ orthopaed/ musculoskeletal special interest/ GP/musculoskeletal clinic/physio	Physiotherapy Orthopaedic referral Refer to physiotherapist Referred to rheumatologist Refer to pain clinic Physiotherapy/remedial therapy Seen in physiotherapy dept Physiotherapy manipulation Under care of community-based physiotherapist Arthritis monitoring Refer to physiotherapist Refer to domiciliary physiotherapy Seen by orthopaedic surgeon Seen by rheumatologist Referral to physiotherapist Referral to rheumatologist Discharge by physiotherapist Refer to osteopath Referral to community-based physiotherapist Referral to rheumatology clinic Referral to hospital physiotherapist Private referral to orthopaedic surgeon Referral to hand surgeon Private referral to rheumatologist Private referral to physiotherapist Referral to community physiotherapist Referral to hand surgeon Rheumatism monitoring Physiotherapy Under care of rheumatologist Discharge from physiotherapy service Other physiotherapy Seen by physiotherapist Discharge by hospital-based physiotherapist Seen in physiotherapy department Refer to community physiotherapist Referral to musculoskeletal clinic Referral to hospital-based physiotherapist Rheumat. initial assessment

	Rheumat. follow-up assessment Referral to orthopaedic physiotherapist practitioner Referral to musculoskeletal special interest GP Physiotherapy self-referral Referral to spinal surgeon Referral to orthopaedic surgeon Discharge from physiotherapy service Private referral to spinal surgeon Private referral to hand surgeon
51. "Rheumatism" not specified	Rheumatism unspecified Myalgia unspecified [D]Musculoskeletal pain [D]General aches and pains Viral myalgia C/O: stiffness Tendinitis NOS O/E - joint stiffness Joint stiffness NEC Rheumatic pain Morning stiffness - joint Musculoskeletal pain - joints Musculoskeletal and connective tissue diseases Menopausal arthritis Muscular rheumatism Rheumatol. disorder monitoring Hand rheumatism Arthralgia NOS [X]Other chronic pain Rheumatology drug monitoring Rheumatic disorder annual review invitation

Appendix Table 3: Read codes used to compose mental health disorder sub-group categories.

Health disorder category and group number	Clinical diagnostic codes (Read codes) used
1 Disorders usually first diagnosed in infancy, childhood, or adolescence	Stammering or stuttering [X]Asperger's syndrome Childhood hyperkinetic syndrome Stuttering Tics Stammer - symptom [X]Autistic disorder Seen by child and adolescent psychiatrist Stutter - symptom Has a stammer/stutter
2 Delirium, dementia, and amnestic and other cognitive disorders	Confusion Acute confusional state [X] Unspecified dementia [D]Confusion Mild memory disturbance

	[X]Acute / subacute confusional state, nonalcoholic [X]Dementia in other diseases classified elsewhere Senile and presenile organic psychotic conditions Dementia care plan Dementia care plan agreed Dementia medication review Cerebral atrophy
3 Mental disorders due to a general medical condition not elsewhere classified	Toxic confusional state Organic delusional syndrome [X]Organic emotionally labile [asthenic] disorder [X]Organic delusional [schizophrenia-like] disorder [X]Organic mood [affective] disorders Organic affective syndrome [X]Organic dissociative disorder
4 Substance-related disorders	[X]Alcohol withdrawal-induced seizure
5 Schizophrenia and other psychotic disorders	[X]Psychosis NOS Schizophrenic disorders Paranoid schizophrenia Hallucinations Delusions [X]Paranoid psychosis Schizo-affective schizophrenia Psychotic episode NOS Chronic schizophrenic Paranoid states [X]Paranoia H/O: schizophrenia Schizophrenia NOS [X]Schizoaffective disorders [X]Paranoid state H/O: psychosis Affective psychoses Acute paranoid reaction [X]Schizophrenia, schizotypal and delusional disorders Delusion Psychosis, schizophrenia + bipolar affective disord resolved [X]Mania with psychotic symptoms [X]Acute and transient psychotic disorders [X]Brief reactive psychosis NOS Paranoid schizophrenia in remission Schizo-affective schizophrenia in remission Schizophrenia in remission Psychosis resolved [X]Nonorganic psychosis in remission
6 Mood disorders or Depressive disorders	Depressive disorder NEC [X]Depression NOS Endogenous depression Anxiety with depression Agitated depression Neurotic depression reactive type

	Brief depressive reaction O/E - depressed Depressed Postnatal depression H/O: depression Puerperal depression [X]Depressive episode, unspecified Postviral depression [X]Depressive disorder NOS [X]Recurrent depressive disorder Chronic depression [X]Depressive episode C/O - feeling depressed [X]Mood - affective disorders Agitated depression [X] Reactive depression NOS Recurrent depression Endogenous depression first episode [X]Other depressive episodes Endogenous depression - recurrent Endogenous depression first episode Single major depressive episode NOS [X]Single episode of reactive depression [X]Neurotic depression [X]Mild anxiety depression [X]Dysthymia [X]Depressive neurosis [X]SAD - Seasonal affective disorder [X]Recurrent episodes of depressive reaction [X]Recurrent episodes of reactive depression Low mood [X]Single episode of depressive reaction Masked depression [X]Moderate depressive episode [X]Severe depressive episode without psychotic symptoms Symptoms of depression Depressed mood Depressive symptoms Single major depressive episode [X]Mild depression Seasonal affective disorder [X]Endogenous depression without psychotic symptoms [X]Mild depressive episode [X]Mixed anxiety and depressive disorder [X]Severe depressive episode with psychotic symptoms Depression medication review Depression annual review [X]Postnatal depression NOS Recurrent major depressive episodes, moderate Recurrent major depressive episode [X]Persistant anxiety depression Single major depressive episode, mild

	Prolonged depressive reaction Psychotic reactive depression Depression resolved [X]Single episode major depression w'out psychotic symptoms Recurrent major depressive episodes, severe, with psychosis Advice regarding symptoms on discontinuation of SSRI [X]Prolonged single episode of reactive depression Excepted from depression quality indicators: Patient unsuita [X]Recurrent depressive disorder, current episode moderate [X]Recurrent depressive disorder, current episode mild Depression interim review Patient given advice about management of depression [X]Recurr depress disorder cur epi severe without psyc sympt [X]Persistent mood affective disorders On depression register Excepted from depression quality indicators: Informed dissen [X]Recurrent depressive disorder, unspecified Removed from depression register [X]Recurrent depress disorder cur epi severe with psyc symp Exception reporting: depression quality indicators [X]Other single mood affective disorders Depression monitoring administration Depression monitoring first letter Depression monitoring second letter [X]Single major depr ep, severe with psych, psych in remiss
7 Bipolar disorders	[X]Manic-depressive illness [X]Hypomania Rebound mood swings [X]Mania NOS [X]Bipolar affective disorder Bipolar psychoses [X]Bipolar disorder, single manic episode H/O: manic depressive disorder [X]Manic episode [X]Mania without psychotic symptoms Unspecified bipolar affective disorder Manic-depressive - now manic [X]Cyclothymia Unspecified bipolar affective disorder, in full remission Single manic episode in full remission
8 Anxiety disorders	Panic attack Tension - nervous Anxiety states [X]Anxiety neurosis Chronic anxiety Obsessional neurosis [D]Hyperventilation Hysteria [D]Nervousness Obsessive-compulsive disorders General nervous symptoms

	H/O: anxiety state 'Nerves' [X]Panic state [X]Post - traumatic stress disorder Anxiety state NOS Recurrent anxiety Generalised anxiety disorder [X]Obsessive - compulsive disorder [X]Other anxiety disorders Compulsive neurosis [X]Panic attack Anxiety state unspecified [D]Restlessness and agitation Anxiety counselling [X]Panic disorder [episodic paroxysmal anxiety] Anxiety management training [X]Generalized anxiety disorder C/O - panic attack Neurotic disorder NOS Obsessive-compulsive disorder NOS [D]Nerves [X]Mixed obsessional thoughts and acts [X]Predominantly obsessional thoughts or ruminations [X]Obsessive-compulsive neurosis Compulsive behaviour [X]Anxiety disorder, unspecified [X]Anxiety NOS [X]Traumatic neurosis
9 Somatoform disorders	Hypochondriasis [D]Debility, unspecified Neurasthenia - nervous debility Writer's cramp neurosis Psychogenic dyspepsia Aphonia - hysterical Globus hystericus Hysterical fugue Psychogenic aerophagy Psychosomatic disorder NOS [X]Psychogenic vomiting [X]Fatigue syndrome Cardiac neurosis Somatization disorder Psychogenic pruritus Hysterical seizures [X]Psychogenic IBS [X]Psychogenic pruritis Psychogenic hyperventilation Acute situational disturbance [X]Globus hystericus [X]Psychogenic headache Hysterical paralysis

10 Factitious disorders	No codes in study sample
11 Dissociative disorders	Depersonalisation syndrome [X]Depersonalization - derealization syndrome Other conversion disorder
12 Sexual and gender identity disorders	Psychosexual disorder NOS [X]Sex dysfunction not caused by organic disorder or disease Psychosexual dysfunction Psychogenic vaginismus [X]Excessive sexual drive
13 Eating disorders	[D]Anorexia Anorexia nervosa Bulimia (non-organic overeating) [X]Eating disorders Other and unspecified non-organic eating disorders H/O: anorexia nervosa [X]Bulimia nervosa Referral to eating disorders clinic [X]Anorexia nervosa
14 Sleep disorders	[D]Insomnia NOS Initial insomnia Insomnia NOS C/O - insomnia Late insomnia Non-organic sleep disorders C/O - somnolence [D]Insomnia - symptom Hypersomnia NOS Transient insomnia [X]Dream anxiety disorder Cannot sleep - insomnia [X]Nonorganic sleep disorders [D]Insomnia with sleep apnoea
15 Impulse-Control Disorders Not Elsewhere Classified	[X]Trichotillomania [X]Compulsive gambling
16 Adjustment disorders	Acute reaction to stress Nervous breakdown Grief reaction Adjustment reaction Bereavement counselling Stress related problem Bereavement reaction [X]Reaction to severe stress, and adjustment disorders [X]Adjustment disorders [X]Grief reaction Adjustment reaction NOS
17 Personality disorders (Axis II)	Psychopathic personality Obsessional personality Behaviour disorder Immature personality disorder

	[V]Behavioural problems Personality disorders Neurotic personality Adolescent - emotional problem Emotionally unstable personality Inadequate personality disorder Hysterical personality disorders Paranoid personality disorder Aggressive personality [X]Emotionally unstable personality disorder [X]Anxious [avoidant] personality disorder Neurotic, personality and other nonpsychotic disorders Depressive personality disorder Cyclothymic personality disorder Personality disorder NOS Other personality disorder NOS Obsessional thoughts Borderline personality disorder Dependent personality Explosive personality disorder [X]Cyclothymic personality [X]Dependent personality disorder Introverted personality [X]Immature personality disorder Schizotypal personality
18 Self-harm, suicidal actions or ideations	[X]Deliberate drug overdose / other poisoning Suicidal ideation Suicide + selfinflicted poisoning by drug or medicine NOS Attempted suicide Injury - self-inflicted Suicidal plans [X]Self mutilation Suicide risk Cause of overdose - deliberate H/O: deliberate self harm [X]Para-suicide Suicidal - symptom Deliberate self-harm Self-harm Poisoning - self-inflicted [X]Self inflicted injury H/O: attempted suicide Self inflicted lacerations to wrist Suicide + selfinflicted poisoning by analgesic/antipyretic Suicidal [X]Intentional self-harm [X]Attempted suicide [X]Overdose - paracetamol At risk of DSH - deliberate self harm Cutting own wrists [X]Intent self poison/exposure to nonopioid analgesic Suicide + selfinflicted poisoning by other drugs/medicines

	[X]Intentional self harm by sharp object Suicide + selfinflicted poisoning by solid/liquid substances [X]Intentional self harm by unspecified means
19 Referral to a support service	Psychotherapy Refer to psychologist Seen in psychology clinic Refer to CPN Psychological counselling Refer to community psych.nurse Counselling offered Referral to counsellor Counselling by other agency Psychiatric monitoring Stress counselling Mental health assessment Refer to counsellor Seen by psychologist Counselling requested Seen by nurse behavioural therapist Refer to counsellor Referral to psychotherapist Referral to mental health counsellor Mental health review Refer to psychologist Referral to psychologist Cognitive-behaviour therapy Seen by mental health counsellor Seen by psychotherapist Under care of counsellor Counselling Referral to psychotherapist Mental health medication review Referral to primary care mental health gateway worker Mental health personal health plan Referral to psychosexual clinic Referral to non NHS mental health community service Counselling carried out Under care of community psychiatric nurse Seen by psychologist Mental therapy follow-up Refer to mental health worker Seen by counsellor Counselled by a counsellor Mental health review follow-up Under care of mental health counsellor Mental health monitoring first letter Mental health monitoring second letter Mental health monitoring third letter Referral for mental health self-help literature Mental health monitoring verbal invitation Seen by primary care graduate mental health worker Seen by mental health triage nurse

	Seen by primary care mental health gateway worker In-house counselling first appointment Referral for cognitive behavioural therapy Review of mental health care plan Agreeing on mental health care plan
20 under the psychiatrist's team	Psychiatric referral Seen in psychiatry clinic Non-urgent psychiatric admisn. Referral to psychogeriatrician Seen by community psychiatric nurse Seen by CPN Seen by CPN Seen by psychiatrist Referral to psychiatric nurse Referral to psychiatrist Referral to community mental health team Under care of mental health team Under care of psychiatrist Referral to mental health team Psychiatry care plan Private referral to psychiatrist Under care of CPN Under care of psychiatrist Psychiatry D.V. done Seen by psychiatric nurse Discharge by psychiatrist Seen by community psychiatric nurse Seen by forensic psychiatrist Seen by liaison psychiatrist Seen by rehabilitation psychiatrist Referral to liaison psychiatrist Under care of hospital psychiatric team Psychiatry Referral to primary care mental health team Seen in mental health clinic Mental Health Care Programme Approach Electroconvulsive therapy
21 Crisis admission, section, on a severe mental health register	Mental Health Act examination Section 2 form - compulsory admission for assessment Admit psychiatric emergency Section 3 form - compulsory admission for treatment On severe mental illness register Referral to mental health crisis team Removed from severe mental illness register Mental health crisis plan [X]Crisis state Completion of mental health crisis plan
22 Symptoms of psychological distress (with no diagnosis specified)	Anxiousness Domestic stress Marital stress Stress at work

	Emotional problem Nervous exhaustion Stress at home [V]Psychological problems Poor self esteem Work worries Worried Tenseness - symptom Aggressive outburst Crying, excessive Tearful C/O - feeling unhappy Emotional upset Irritable Agitated Fear Agitated - symptom [D]Lassitude Anxiousness - symptom Anger reaction [V]Stressful work schedule [D]Work stress Loss of confidence [D]Irritability and anger O/E - distressed C/O weepiness [D]State of emotional shock and stress, unspecified Life crisis Feeling stressed Anger management [X]Acute reaction to stress [D]Nervous tension Stress management [X]Acute stress reaction Anger management counselling O/E - angry O/E - anxious O/E - agitated [D]Demoralization and apathy Frightened H/O: low self-esteem Acknowledging anxiety [D]Unhappiness Acute stress reaction NOS [X]Reaction to severe stress, unspecified Stress monitoring admin. [D]Hostility Anxious Anger

Appendix Table 4: Read codes used to compose cardiovascular disorder sub-group categories.

Health disorder category and group number	Clinical diagnostic codes (Read codes) used
1 Myocardial infarction/unstable angina	Acute myocardial infarction MI - acute myocardial infarction Inferior myocardial infarction NOS Old myocardial infarction Other specified anterior myocardial infarction Acute non-ST segment elevation myocardial infarction Acute ST segment elevation myocardial infarction Acute myocardial infarction NOS Anterior myocardial infarction NOS H/O: myocardial infarct <60 History of myocardial infarction Coronary thrombosis Acute coronary syndrome Unstable angina Crescendo angina Unstable angina Post infarct angina Angina at rest Cardiac enzymes abnormal Heart attack Acute inferolateral infarction Acute non-Q wave infarction Acute anteroseptal infarction Acute Q-wave infarct
2 Myocardial ischaemia/atherosclerosis/angina	ECG: myocardial ischaemia Coronary artery disease Single coronary vessel disease Double coronary vessel disease Coronary atherosclerosis Acute coronary insufficiency Coronary heart disease medication review Angina on effort Angina pectoris H/O: angina pectoris Stable angina Angina control Angina control - improving Angina control - poor Worsening angina Angina control - good New onset angina Angina pectoris NOS Angina control - worsening Cardiac syndrome X Ischaemic heart disease Triple vessel disease of the heart Ischaemic heart disease NOS

	IHD - Ischaemic heart disease Coronary heart disease review Asymptomatic coronary heart disease Arteriosclerotic heart disease Coronary heart disease monitoring 1st letter Suspected ischaemic heart disease Coronary heart disease monitoring 2nd letter Coronary heart disease monitoring 3rd letter Attends coronary heart disease monitoring Coronary heart disease monitoring verbal invitation Coronary heart disease monitoring check done Coronary heart disease monitoring telephone invite Atherosclerotic cardiovascular disease Other chronic ischaemic heart disease NOS Other specified ischaemic heart disease Other chronic ischaemic heart disease [X]Other forms of chronic ischaemic heart disease Coronary artery spasm Referred to acute chest pain clinic
3 Cardiology/vascular investigations	Myocardial perfusion scan Coronary arteriograph.abnormal Coronary arteriography Coronary arteriography NEC Diagnostic transluminal operations on coronary artery Cardiac catheterisation Cardiac computed tomography angiography Catheterisation of heart Catheterisation of heart NOS Percut translum electrophysiol studies on heart conduct syst Heart monitoring Cardiovascular sys.angiography Vascular studies performed Cardiovascular stress test using Bruce protocol 72 hour ambulatory electrocardiographic monitoring Arteriography of cerebral artery Arteriography of carotid artery Carotid artery angiography
4 Coronary angioplasty/ bypass/ stent	Transluminal balloon angioplasty of coronary artery NOS Coronary artery bypass graft operations [V]Presence of coronary artery bypass graft [V]Presence of coronary artery bypass graft - CABG Percutaneous balloon coronary angioplasty Open angioplasty of coronary artery Coronary artery operations Other autograft bypass of coronary artery Saphenous vein graft replacement of coronary artery OS Saphenous vein graft replacement of three coronary arteries Saphenous vein graft replacement of two coronary arteries

	Coronary arteriogr.-general Saphenous vein graft replacement of one coronary artery Insertion of coronary artery stent Autograft replacement of three coronary arteries NEC Coronary artery operations NOS Saphenous vein graft replacement of four+ coronary arteries Coronary artery bypass graft occlusion Saphenous vein graft replacement of coronary artery Percut transluminal balloon angioplasty one coronary artery Rotary blade coronary angioplasty Percut translum balloon angioplasty mult coronary arteries Other bypass of coronary artery Transluminal balloon angioplasty of coronary artery OS Insertion of drug-eluting coronary artery stent Perc translumin balloon angioplasty stenting coronary artery Percutaneous coronary intervention Peroperative angioplasty Perc translum ball angio insert 1-2 drug elut stents cor art Patch angioplasty of renal artery Cardiac operations Cardiothoracic surgery Heart operations Percutaneous operations on heart Transluminal balloon angioplasty of coronary artery
5 Cardiovascular problem non-specific	[D]Echocardiogram abnormal Cardiac treatment changed Cardiac dis.-treatment changed Patient advised about cardiovascular disorder Heart disease NOS Suspected heart disease H/O: heart disorder Heart symptoms Heart diseases Cardiovascular symptoms H/O: cardiovascular disease Cardiovascular disease, unspecified [D]Cardiovascular system symptoms Cardiovascular procedures Occlusion of artery Operation on pulmonary vein Artery and vein operations NOS Other specified operations on artery or vein H/O: thrombosis Vein graft thrombectomy Thrombolytic therapy Prosthetic graft thrombectomy

	Atherosclerosis ECG:left ventricle hypertrophy Admit cardiology emergency Circulatory system diseases
6 Pulmonary embolism	Embolism and thrombosis NOS H/O: embolism Pulmonary embolism Pulmonary embolus H/O: pulmonary embolus [V] Personal history of pulmonary embolism Post operative pulmonary embolus Suspected pulmonary embolism
7 Referrals/FU cardiac clinic/surgeon/GPSI and other follow up/monitoring	Cardiac disease monitoring Follow-up cardiac assess. Cardiac rehabilitation Referral to cardiac rehabilitation nurse Cardiac rehabilitation class DNA - Did not attend cardiac clinic Seen by cardiac rehabilitation nurse Under care of cardiac rehabilitation nurse Cardiac rehabilitation declined Seen by cardiac surgeon Cardiac drug monitoring Referral to cardiac rehabilitation nurse Seen in cardiothoracic surgery clinic Heart disease monitoring Seen by vascular surgeon Seen in vascular clinic Cardiovascular clinic Referral to vascular surgeon Peripheral vascular disease monitoring Under care of vascular surgeon Private referral to vascular surgeon Discharge from vascular surgery service Stroke/transient ischaemic attack monitoring verbal invitati Cardiological referral Seen in cardiology clinic Seen by cardiologist Referral to cardiologist Referred to vascular surgeon Referral to rapid access chest pain clinic Private referral to cardiologist Referral to Cardiothoracic surgeon Attending cardiology clinic Discharge by cardiologist Referral for warfarin monitoring Referral to cardiology special interest general practitioner In-house cardiology first appointment Cardiology

	Seen by private cardiologist Referral to community cardiology service
8 Heart failure	Seen in cardiac clinic Congestive cardiac failure Fast track HF referral for transthoracic 2D echocardiogram Congestive heart failure Heart failure Heart failure confirmed Seen in heart failure clinic New York Heart Association classification - class II New York Heart Association classification - class I New York Heart Association classification - class III Heart failure annual review Heart failure monitoring first letter Heart failure education Referral to rapid access heart failure clinic Pulmonary congestion Pulmonary oedema NOS Left ventricular failure
9 Probable/possible heart failure	Left ventricular hypertrophy Ventricular hypertrophy Impaired left ventricular function Impaired left ventricular function Left ventricular systolic dysfunction Echocardiogram shows left ventricular systolic dysfunction Left ventricular diastolic dysfunction Left ventricular cardiac dysfunction
10 Diseases of the endocardium and valves	Endocarditis, valve unspecified, NOS Subacute bacterial endocarditis - SBE Acute and subacute endocarditis Other diseases of endocardium Prosthetic replacement of valve of heart NEC H/O: artificial heart valve Mechanical complication of heart valve prosthesis Aortic stenosis, non-rheumatic Mitral stenosis Aortic stenosis alone, cause unspecified Rheumatic aortic stenosis Aortic stenosis Stenosis of unspecified heart valve Pulmonary stenosis, cause unspecified Pulmonary infundibular stenosis Pulmonary valve disorders Open pulmonary valvotomy Pulmonary incompetence, cause unspecified Percutaneous transluminal balloon angioplasty pulmonary vein Atrial septal defect NOS Ostium secundum atrial septal defect

	Other specified atrial septal defect Ventricular septal defect Closure of defect of interventricular septum NOS Closure of defect of interventricular septum Mitral valve prolapse Replacement of aortic valve Mitral valve incompetence Bicuspid aortic valve Aortic valve disorders [SO]Mitral valve Plastic repair of mitral valve Mitral valve regurgitation Plastic repair of aortic valve Diseases of mitral and aortic valves Replacement of aortic valve NEC Tricuspid valve disease NEC Rheumatic mitral valve disease Open heart valvotomy Open mitral valvotomy Aortic valve disorders NOS Aortic valve sclerosis Aortic valvuloplasty Prosthetic replacement of aortic valve Mitral valvuloplasty Aortic valve calcification Patent ductus arteriosus Open correction of patent ductus arteriosus NOS
11 Arrythmia other than AF or treated	Paroxysmal tachycardia NOS Cardiac dysrhythmia NOS Cardiac arrhythmias Other cardiac dysrhythmias Heart beats irregular Heart block Fluttering of heart ECG: heart block [D] Other and unspecified abnormalities of heart beat Other heart block NOS Cardiac dysrhythmias Suspected arrhythmia Paroxysmal ventricular tachycardia Ventricular fibrillation ECG: ventricular tachycardia Ventricular tachycardia First degree atrioventricular block Anomalous atrioventricular excitation Mobitz type I (Wenckebach) atrioventricular block History of ventricular tachycardia
12 Cardiomyopathies	Cardiomegaly Cardiomyopathy Hypertrophic non-obstructive cardiomyopathy Primary dilated cardiomyopathy

	Hypertrophic obstructive cardiomyopathy Secondary dilated cardiomyopathy Myocarditis NOS Acute myocarditis Cardiomyopathy NOS
13 Pericardial diseases	Acute pericarditis Viral pericarditis NOS Other and unspecified acute pericarditis Acute pericarditis - unspecified Pericardial effusion
14 Possible/probable acute coronary syndrome	No codes in study sample
15 Vascular/ atherosclerotic/ peripheral arterial disease (non-coronary)	Peripheral arterial disease Claudication Peripheral vascular disease NOS Peripheral vascular disease NOS Arteriosclerotic vascular disease NOS Other specified peripheral vascular disease NOS Peripheral ischaemic vascular disease Other peripheral vascular disease Vascular calcification Small vessel cerebrovascular disease Intermittent claudication Carotid artery stenosis Claudication distance Extremity artery atheroma Therapeutic transluminal operation on other artery NOS Thrombosis - arterial
16 Aneurysms (all body)- only one rupture code (n=1)	Aortic aneurysm Abdominal aortic aneurysm without mention of rupture Dissecting aortic aneurysm Transluminal coil embolisation of aneurysm Cerebral aneurysm, nonruptured Percutaneous coil embolisation of cerebral artery aneurysm Aneurysm NOS Clipping of aneurysm of cerebral artery Other aneurysm NOS Aneurysm of common carotid art Operation on aneurysm of carotid artery
17 Heart transplant	Other transplantation of heart Other transplantation of heart NOS
19 Hypertension	Hypertensive disease High blood pressure Essential hypertension Benign essential hypertension H/O: hypertension On treatment for hypertension Hypertension NOS Seen in hypertension clinic Systolic hypertension

	Referral to hypertension clinic Hypertensive retinopathy Hypertensive disease NOS BP - hypertensive disease Cardiomegaly - hypertensive Essential hypertension NOS Patient on maximal tolerated antihypertensive therapy Hypertension clinical management plan Hypertensive treatm.changed Malignant essential hypertension Hypertensive heart disease Good hypertension control Antihypertensive therapy Hypertension six month review Moderate hypertension control Hypertension annual review Hypertension treatm. started Suspected hypertension Poor hypertension control Seen in hypertension clinic Hypertens.monitor phone invite Hypertension:follow-up default Hypertens.monitor.1st letter Hypertens.monitor 2nd letter Hypertens.monitor 3rd letter Hypertens.monitoring admin.NOS DNA - Did not attend hypertension clinic Hypertension monitor.chck done Hypertens.monitor verbal inv. Attends hypertension monitor. Diastolic hypertension Hypertension 9 month review Stage 1 hypertension
20 DVT	Deep vein thrombosis Post operative deep vein thrombosis DVT - Deep vein thrombosis Deep vein phlebitis and thrombophlebitis of the leg H/O: Deep Vein Thrombosis Deep vein thrombosis, leg Deep vein thrombophlebitis of the leg unspecified Thrombophlebitis of the posterior tibial vein Suspected deep vein thrombosis Referral to deep vein thrombosis clinic Axillary vein thrombosis On deep vein thrombosis care pathway
21 Stoke/CVA	Stroke and cerebrovascular accident unspecified H/O: stroke Stroke monitoring Excepted from stroke quality indicators: Patient unsuitable

	Excepted from stroke quality indicators: Informed dissent Stroke / transient ischaemic attack referral Stroke/CVA annual review Referral to stroke clinic Seen in stroke clinic Delivery of rehabilitation for stroke Suspected stroke Infarction - cerebral Cerebrovascular disease Cerebral infarction NOS Intracerebral haemorrhage CVA - cerebral artery occlusion CVA - Cerebrovascular accident unspecified Stroke due to cerebral arterial occlusion CVA - cerebrovascular accid due to intracerebral haemorrhage Evacuation of intracerebral haematoma NEC Cerebral arterial occlusion Left sided cerebral infarction Cerebral infarct due to thrombosis of precerebral arteries Cerebral infarction due to embolism of cerebral arteries Sequelae of cerebral infarction Suspected cerebrovascular disease CVA unspecified H/O: CVA Left sided CVA Cerebrovascular disease NOS Right sided CVA Suspected cerebrovascular accident Cerebellar infarction Infarction of basal ganglia
22 Cardiac arrest, cardiopulmonary resuscitation	Cardiac arrest O/E - collapse -cardiac arrest Sudden cardiac death, so described Cardiac arrest-ventricular fibrillation Cardiac arrest with successful resuscitation Cardiopulmonary resuscitation
23 Superficial vein thrombus	Thrombosis of vein NOS Thrombophlebitis NOS Phlebitis and thrombophlebitis of the leg NOS Thrombosed haemorrhoids NOS Phlebitis and thrombophlebitis External thrombosed haemorrhoids Thrombosis of vein of leg Superficial vessel phlebitis and/or thrombophlebitis of leg Evacuation of thrombosed haemorrhoid Thrombophlebitis of a superficial leg vein NOS Other phlebitis and thrombophlebitis NOS

	Phlebitis and thrombophlebitis NOS Superficial thrombophlebitis in pregnancy and the puerperium Thrombophlebitis after infusion Superficial phlebitis and thrombophlebitis of the leg NOS
24 AF, SVT	History of supraventricular tachycardia Paroxysmal atrial fibrillation ECG: supraventricular arrhythmia Paroxysmal atrial tachycardia Atrial fibrillation Atrial flutter Atrial fibrillation and flutter ECG: atrial fibrillation H/O: atrial fibrillation ECG: atrial flutter ECG: paroxysmal atrial tachy. Atrial fibrillation monitoring Atrial fibrillation and flutter NOS Atrial fibrillation resolved Excepted from atrial fibrillation qual indic: Inform dissent Atrial fibrillation annual review Atrial fibrillation monitoring first letter History of atrial flutter Persistent atrial fibrillation Permanent atrial fibrillation Supraventricular tachycardia NOS Paroxysmal supraventricular tachycardia Paroxysmal supraventricular tachycardia NOS
25 Ectopics	Ventricular ectopic beats Supraventricular ectopic beats Ventricular premature depolarization
26 Arrhythmia requiring cardioversion/ablation/pacemaker	[V]Cardiac pacemaker in situ [V]Fitting or adjustment of cardiac pacemaker Implantation of intravenous cardiac pacemaker system Direct current cardioversion Introduction of cardiac pacemaker system via vein Cardioversion and stimulation Internal electrode cardioversion Implantation of permanent intravenous cardiac pacemaker Implantation of cardiac pacemaker system NEC Seen by cardiac pacemaker technician H/O: cardiac pacemaker Implantation of internal cardiac defibrillator Other cardiac pacemaker system Other cardiac pacemaker system NOS Removal of cardiac pacemaker system NEC Implantation of dual chamber cardiac pacemaker system Percutaneous transluminal internal cardioversion NEC Renewal of cardioverter defibrillator Electrical cardioversion planned

	Patient with internal cardiac defibrillator pacemaker Percut transluminal ablation of heart conducting system NEC Perc transluminal ablation of atrial wall for atrial flutter Percutaneous transluminal ablation of atrial wall Percutaneous transluminal ablation of atrial wall NEC Percutaneous transluminal ablation of atrioventricular node Open ablation of atrioventricular node
27 Vascular atherosclerotic events/occlusions/surgery (non-coronary)	External cardioversion NEC Embolism and thrombosis of the femoral artery Arterial embolism and thrombosis Embolisation of arteriovenous abnormality Embolism and thrombosis of the axillary artery Ischaemic optic neuropathy Ischaemic toe Ischaemic foot Retinal vascular occlusion NOS Retinal arterial branch occlusion Carotid artery occlusion Femoral artery occlusion Central retinal artery occlusion Iliac artery occlusion Percutaneous transluminal angioplasty of artery NEC Other bypass of femoral artery or popliteal artery NOS Endarterectomy of carotid artery NEC Aorto biiliac graft Percutaneous transluminal angioplasty of femoral artery Insertion of iliac artery stent Percutaneous transluminal angioplasty of iliac artery Other bypass of popliteal artery Other artery operations Carotid, cerebral and subclavian artery operations Other bypass of femoral artery Operation on artery NEC Endarterectomy of femoral artery NEC Other bypass of femoral artery or popliteal artery Percutaneous transluminal angioplasty of renal artery Repair of popliteal artery NEC Percutaneous transluminal angioplasty of carotid artery Percutaneous transluminal angioplasty of brachial artery Percutaneous transluminal embolisation of renal artery Endarterectomy of common iliac artery NEC Endarterectomy of iliac artery NEC Repair of iliac artery NEC Reconstruction of iliac artery NOS Percutaneous transluminal insertion of stent femoral artery Dissection of artery

28 Secondary hypertension including gestational/pre-eclampsia	Unspecified hypertension in preg/childb/puerp - not deliv Secondary hypertension Hypertension complicating pregnancy/childbirth/puerperium Pre-eclampsia or eclampsia with pre-existing hypertension
29 TIA	Stroke/transient ischaemic attack monitoring first letter Stroke/transient ischaemic attack monitoring administration Stroke/transient ischaemic attack monitoring second letter Stroke/transient ischaemic attack monitoring third letter Transient cerebral ischaemia Transient ischaemic attack Transient ischaemic attack clinical management plan [V]Personal history of transient ischaemic attack Suspected transient ischaemic attack
30 Venous occlusions (not superficial)	Other venous embolism and thrombosis Percutaneous transluminal embolisation of vein Central retinal vein occlusion Retinal venous branch occlusion Branch retinal vein occlusion Retinal vein thrombosis Portal vein thrombosis Nonpyogenic venous sinus thrombosis

Appendix Table 5: Read codes used to compose other health disorder sub-group categories

Epilepsy	
1 epilepsy	Epilepsy Grand mal (major) epilepsy Petit mal (minor) epilepsy Temporal lobe epilepsy Fit (in known epileptic) NOS H/O: epilepsy Traumatic epilepsy Epileptic seizures - myoclonic Epileptic seizures - tonic Grand mal seizure [X]Epileptic psychosis NOS Epilepsy monitoring O/E - petit mal fit O/E - grand mal fit Absence seizure Tonic-clonic epilepsy Epilepsy resolved Epilepsy medication review Jacksonian, focal or motor epilepsy

	Epilepsy NOS Locl-rlt(foc)(part)idiop epilep&epilptic syn seiz locl onset Other forms of epilepsy NOS Complex partial epileptic seizure Excepted from epilepsy quality indicators: Patient unsuitabl Excepted from epilepsy quality indicators: Informed dissent Patient on maximal tolerated anticonvulsant therapy Suspected epilepsy Epilepsy resolved 2 to 4 seizures a month Epileptic seizures - clonic Daily seizures 1 to 7 seizures a week Epilepsy control good Epilepsy does not limit activities Epilepsy confirmed Epileptic seizures - atonic Generalised convulsive epilepsy Follow-up epilepsy assessment Epilepsy treatment changed 1 to 12 seizures a year Partial epilepsy with impairment of consciousness Epilepsy screen administration Epilepsy screen invite 1 Epilepsy screen invite 2 Epilepsy monitoring NOS Many seizures a day O/E - Jacksonian fit Simple partial epileptic seizure Generalised convulsive epilepsy NOS Exception reporting: epilepsy quality indicators Emergency epilepsy treatment since last appointment Epilepsy society member Seen in epilepsy clinic No epilepsy drug side effects [X]Dissociative convulsions Epilepsy monitoring call first letter Epilepsy monitoring call second letter Contraceptive advice for patients with epilepsy Pre-conception advice for patients with epilepsy Contraceptive advice for patients with epilepsy declined Pregnancy advice for patients with epilepsy declined Pre-conception advice for patients with epilepsy declined Pregnancy advice for patients with epilepsy
2 fit/seizure (non-specific)	[D]Convulsions [D]Seizure NOS Had a fit Fit - had one, symptom O/E - a seizure Last fit Convulsion - symptom Fit frequency

	Seizure free >12 months Trigger factor for seizure No seizures on treatment [D]Convulsion NOS O/E - a fit Post-ictal state
Respiratory	
1 asthma or probable asthma	Asthma Asthma monitoring Acute exacerbation of asthma Asthma attack H/O: asthma Childhood asthma Bronchial asthma Allergic asthma Mild asthma Occasional asthma Late onset asthma Asthma unspecified Exercise induced asthma Intrinsic asthma Seen in asthma clinic Hay fever with asthma Exercise induced asthma Extrinsic asthma with asthma attack Extrinsic (atopic) asthma Asthma limiting activities Asthma prophylactic medication used Asthma management plan given Asthma disturbing sleep Pollen asthma Asthma attack NOS Asthma monitored Number of asthma exacerbations in past year Airways obstruction reversible Change in asthma management plan Step up change in asthma management plan Asthma annual review Asthma medication review Suspected asthma Asthma resolved Asthma trigger Asthma confirmed Refuses asthma monitoring Excepted from asthma quality indicators: Patient unsuitable Excepted from asthma quality indicators: Informed dissent Asthma resolved Late-onset asthma Asthma severity Moderate asthma Asthma - currently dormant

	Asthma not disturbing sleep Asthma not limiting activities Asthma disturbs sleep frequently Asthma follow-up Hay fever with asthma Asthma NOS Asthma monitoring admin. Asthma control step 2 Asthma control step 1 Asthma monitoring due Allergic bronchitis NEC Step down change in asthma management plan Asthma control step 3 Exception reporting: asthma quality indicators Referral to asthma clinic Asthma monitoring by nurse Asthma treatment compliance unsatisfactory Asthma treatment compliance satisfactory Asthma monitoring check done Asthma control step 5 Asthma control step 4 Occupational asthma Asthma causes daytime symptoms 1 to 2 times per week Asthma restricts exercise Asthma monitor 3rd letter Asthma monitor 2nd letter Asthma monitor 1st letter Mixed asthma Health education - asthma Asthma never causes daytime symptoms Asthma causes daytime symptoms most days Asthma never restricts exercise Asthma sometimes restricts exercise Asthma control step 0 DNA - Did not attend asthma clinic Asthma monitoring admin.NOS Asthma monitoring by doctor Asthma causing night waking Asthma monitor phone invite Asthma night-time symptoms Asthma causes daytime symptoms 1 to 2 times per month Hyperreactive airways disease Asthma monitor verbal invite Asthma never disturbs sleep Asthma limits walking up hills or stairs Asthma limits walking on the flat Asthma disturbs sleep weekly Asthma causes night symptoms 1 to 2 times per month Asthma monitor offer default Asthma daytime symptoms Extrinsic asthma NOS Attends asthma monitoring

	Asthma accident and emergency attendance since last visit Asthma control test Patient has a written asthma personal action plan Health education - asthma self management Asthma review using Roy Colleg of Physicians three questions Asthma trigger - seasonal Asthma trigger - pollen Asthma causes symptoms most nights Asthma causes night time symptoms 1 to 2 times per week Asthma trigger - respiratory infection Asthma limits activities 1 to 2 times per month Asthma trigger - exercise Asthma limits activities 1 to 2 times per week Asthma trigger - warm air Asthma trigger - animals Asthma never causes night symptoms Asthma trigger - cold air Asthma trigger - airborne dust Asthma trigger - damp Asthma trigger - emotion Asthma trigger - tobacco smoke Asthma limits activities most days Chronic asthma with fixed airflow obstruction
2 severe asthma	Severe asthma attack Severe asthma Status asthmaticus NOS Emergency admission, asthma Extrinsic asthma without status asthmaticus Emergency asthma admission since last appointment Asthma severely restricts exercise
3 acute bronchitis	Acute bronchitis Acute viral bronchitis unspecified Laryngotracheobronchitis Acute wheezy bronchitis Acute bronchitis NOS Acute bronchitis due to parainfluenza virus
4 chronic bronchitis	Chronic bronchitis Simple chronic bronchitis Mucopurulent chronic bronchitis NOS Aspergillus bronchitis
5 bronchitis NOS	Bronchitis unspecified Wheezy bronchitis Tracheobronchitis NOS Bronchitis NOS Recurrent wheezy bronchitis
6 COPD or emphysema	Emphysema Chronic obstructive airways disease Chronic obstructive pulmonary disease Acute exacerbation of chronic obstructive airways disease Chronic obstructive airways disease NOS Chronic obstructive pulmonary disease monitoring

	Severe chronic obstructive pulmonary disease Moderate chronic obstructive pulmonary disease Mild chronic obstructive pulmonary disease Admit COPD emergency Excepted from COPD quality indicators: Patient unsuitable Excepted from COPD quality indicators: Informed dissent Chronic obstructive pulmonary disease annual review COPD follow-up COPD self-management plan given Chronic obstructive pulmonary disease follow-up Exception reporting: COPD quality indicators Chronic obstructive pulmonary disease monitoring admin Emergency COPD admission since last appointment COPD accident and emergency attendance since last visit Suspected chronic obstructive pulmonary disease Chronic obstructive pulmonary disease leaflet given Chronic obstructive pulmonary disease monitoring by nurse Chronic bullous emphysema Number of COPD exacerbations in past year Chronic obstructive pulmonary disease monitoring 1st letter Emphysema NOS Chronic obstructive pulmonary disease monitoring 2nd letter Chronic obstructive pulmonary disease monitoring 3rd letter DNA - Did not attend COPD clinic Chronic obstructive pulmonary disease NOS Chronic obstructive pulmonary disease monitor phone invite Chronic obstructive pulmonary disease monitoring verb invite Health education - chronic obstructive pulmonary disease Chronic obstructive pulmonary disease clini management plan Multiple COPD emergency hospital admissions Very severe chronic obstructive pulmonary disease At risk of chronic obstructive pulmonary diseas exacerbation Chronic obstructive pulmonary disease assessment test Issue of chronic obstructive pulmonary disease rescue pack Chronic obstructive pulmonary disease 3 monthly review Chronic obstructive pulmonary disease 6 monthly review History of chronic obstructive pulmonary disease Referral to COPD community nursing team COPD self-management plan agreed COPD self-management plan review Has chronic obstructive pulmonary disease care plan Chronic obstructive pulmonary disease rescue pack declined Chronic obstructive pulmon dis wr self managem plan declined Chronic obstruct pulmonary disease management plan declined Chron obstruct pulmonary dis wth acute exacerbation, unspec
Diabetes	
1 Diabetes	Non-insulin dependent diabetes mellitus Follow-up diabetic assessment Diabetes mellitus Type 2 diabetes mellitus Glycosuria

	Insulin dependent diabetes mellitus Diabetic retinopathy Insulin treated Type 2 diabetes mellitus Type 1 diabetes mellitus Insulin dependent diabetes mellitus Diabetes mellitus with ketoacidosis Diabetic on oral treatment Diabetic neuropathy Diabetic - poor control Seen in diabetic clinic Hypoglycaemic coma Diabetic nephropathy Gestational diabetes mellitus Preproliferative diabetic retinopathy Proliferative diabetic retinopathy Diabetic monitoring Diabetic maculopathy Non-insulin dependent diabetes mellitus NIDDM - Non-insulin dependent diabetes mellitus Diabetic annual review Attending diabetes clinic H/O: diabetes mellitus Admit diabetic emergency Background diabetic retinopathy Diabetic on diet only Referral to diabetologist Diabetes mellitus with neuropathy Referral to diabetes nurse Non-insulin dependent diabetes mellitus - poor control Pt advised re diabetic diet Gestational diabetes mellitus Seen by diabetic liaison nurse Diabetes management plan given Diabetic on insulin Unstable diabetes DNA - Did not attend diabetic clinic [X]Hyperglycaemia, unspecified O/E - diabetic maculopathy present both eyes Diabetes monitoring admin. Hb. A1C - diabetic control Seen in diabetic eye clinic Advanced diabetic maculopathy Type 1 diabetes mellitus with nephropathy Dietary advice for diabetes mellitus Type 1 diabetes mellitus with ketoacidosis Non proliferative diabetic retinopathy Seen in diabetic foot clinic Diabetic peripheral neuropathy screening Excepted from diabetes qual indicators: Patient unsuitable Conversion to insulin Under care of diabetic foot screener O/E - left eye background diabetic retinopathy

	Excepted from diabetes quality indicators: Informed dissent Diabetes mellitus during pregnancy/childbirth/puerperium O/E - right eye background diabetic retinopathy Diabetes medication review Pan retinal photocoagulation for diabetes Diabetic retinopathy NOS Refer to diabetic foot screener Under care of diabetes specialist nurse Referral to diabetes nurse Diabetes monitoring 3rd letter Patient on maximal tolerated therapy for diabetes Refer, diabetic liaison nurse Diabetic foot examination not indicated Diabetic retinopathy screening refused Diabetes care by hospital only Diabetes: practice programme Type 2 diabetes mellitus with nephropathy Diabetes: shared care programme Patient offered diabetes structured education programme Diabetic monitoring NOS Initial diabetic assessment Diabetic - good control Diabetic diet Diabetic weight reducing diet O/E - right eye proliferative diabetic retinopathy O/E - right eye preproliferative diabetic retinopathy O/E - no right diabetic retinopathy O/E - left eye proliferative diabetic retinopathy O/E - right eye diabetic maculopathy O/E - left eye preproliferative diabetic retinopathy O/E - no left diabetic retinopathy O/E - left eye diabetic maculopathy Diabetes clinic administration Diabetes monitor. check done Diabetes monitoring 1st letter Diabetes monitoring 2nd letter Fundoscopy - diabetic check Attends diabetes monitoring Referral to diabetic liaison nurse HbA1 - diabetic control Diabetes mellitus, adult onset, no mention of complication Maturity onset diabetes Diabetes mellitus with neurological manifestation Diabetic treatment changed Diabetes mellitus with renal manifestation Autonomic neuropathy due to diabetes O/E - Right diabetic foot at risk H/O: insulin therapy Self monitoring of blood glucose Type 1 diabetes mellitus Type 2 diabetes mellitus Diabetic - follow-up default

	Annual diabetic blood test Insulin treated Type 2 diabetes mellitus Diabetic retinopathy screening Type 1 diabetes mellitus with retinopathy Type 2 diabetes mellitus with persistent microalbuminuria Type 2 diabetes mellitus with retinopathy IDDM-Insulin dependent diabetes mellitus Diabetic retinopathy screening not indicated Diabetic foot examination declined Referral to diabetic eye clinic Diabetic retinopathy screening offered Injection sites - diabetic Diabetes monitored Diabetic lipid lowering diet Diabetes monitoring default Diabetic foot examination Type II diabetes mellitus Ischaemic ulcer diabetic foot Diabetic stabilisation Dietary advice for type II diabetes Diabetic diet - poor compliance Type 2 diabetes mellitus with persistent proteinuria Diabetic diet - good compliance O/E - Left diabetic foot at risk O/E - Right diabetic foot at low risk O/E - Left diabetic foot at low risk Diabetic Charcot arthropathy Foot abnormality - diabetes related Exception reporting: diabetes quality indicators Diabetic on insulin and oral treatment Diabetic 6 month review Did not attend diabetic retinopathy clinic Diabetes monitor.phone invite O/E - Left diabetic foot at moderate risk O/E - Right diabetic foot at moderate risk O/E - Right diabetic foot at high risk O/E - Left diabetic foot at high risk Diabetes monitor.verbal invite Diabetes monitoring admin.NOS [V]Dietary counselling in hypoglycaemia Perceived control of insulin-dependent diabetes Patient diabetes education review Type 2 diabetes mellitus with ketoacidosis Seen in community diabetes specialist clinic Private referral to diabetologist O/E - Left diabetic foot - ulcerated O/E - Right diabetic foot - ulcerated Diabetic patient unsuitable for digital retinal photography Insulin lipohypertrophy Understands diet - diabetes Seen in diabetic nurse consultant clinic Type 1 diabetes mellitus with hypoglycaemic coma

	Type 1 diabetes mellitus with retinopathy Diabetes mellitus NOS with ketoacidosis Referral to diabetes structured education programme Diabetes care plan agreed O/E - diabetic maculopathy absent both eyes Diabetic crisis monitoring Type 1 diabetes mellitus with ophthalmic complications Type 2 diabetes mellitus without complication Type II diabetes mellitus with retinopathy Diabetic foot risk assessment O/E - left eye stable treated prolif diabetic retinopathy Patient held diabetic record issued Referral to diabetic register Discharge by diabetic liaison nurse Referral for diabetic retinopathy screening Referral to community diabetes specialist nurse Insulin dose changed Diabetes type 2 review Diabetes type 1 review Attended DAFNE diabetes structured education programme DESMOND diabetes structured education programme completed XPERT diabetes structured education programme completed Referral to DESMOND diabetes structured education programme Referral to DAFNE diabetes structured education programme Diabetes structured education programme declined Referral to XPERT diabetes structured education programme Attended XPERT diabetes structured education programme Referral to diabetes special interest general practitioner Did not attend XPERT diabetes structured education programme Did not complete DESMOND diabetes structured educat program Diabetes screening invitation Did not attend DESMOND diabetes structured education program Latent autoimmune diabetes mellitus in adult Other hypoglycaemia Diabetic foot screen Insulin treatment initiated Insulin initiation - enhanced services administration Diabetic dietary review Diabetic dietary review declined Type II diabetic dietary review Suspected diabetes mellitus Diabetic erectile dysfunction review Diabetic assessment of erectile dysfunction Type I diabetic dietary review Hypoglycaemic management discussed Referral to DESMOND structured programme declined Insulin alert pat information booklet information discussed Insulin passport completed Insulin passport given Insulin alert patient information booklet given Provision of diabetes clinical summary Type 1 diabetic dietary review

	Insulin passport checked Referral to community diabetes clinic Proteinuric diabetic nephropathy O/E - Left diabetic foot at increased risk O/E - Right diabetic foot at increased risk Referral to community diabetes specialist nurse declined Declined diabetic retinopathy screening Diabetic retinopathy screening administrative status Hypoglycaemia education Erectile dysfunction due to diabetes mellitus Provision of written information about diabetes and driving Referral to DAFNE diabetes structured educn prog declined Education about diabetes and driving Diabetes Year of Care annual review Diabetic foot care education
2 Diabetes with eye involvement	Diabetic retinopathy Preproliferative diabetic retinopathy Proliferative diabetic retinopathy Diabetic maculopathy Background diabetic retinopathy O/E - diabetic maculopathy present both eyes Seen in diabetic eye clinic Advanced diabetic maculopathy Non proliferative diabetic retinopathy O/E - left eye background diabetic retinopathy O/E - right eye background diabetic retinopathy Pan retinal photocoagulation for diabetes Diabetic retinopathy NOS O/E - right eye proliferative diabetic retinopathy O/E - right eye preproliferative diabetic retinopathy O/E - left eye proliferative diabetic retinopathy O/E - right eye diabetic maculopathy O/E - left eye preproliferative diabetic retinopathy O/E - left eye diabetic maculopathy Type 1 diabetes mellitus with retinopathy Type 2 diabetes mellitus with retinopathy Referral to diabetic eye clinic Did not attend diabetic retinopathy clinic Type 1 diabetes mellitus with retinopathy Type 1 diabetes mellitus with ophthalmic complications Type II diabetes mellitus with retinopathy O/E - left eye stable treated prolif diabetic retinopathy
3 Diabetes with poor control	Diabetes mellitus with ketoacidosis Diabetic - poor control Hypoglycaemic coma Admit diabetic emergency Non-insulin dependent diabetes mellitus - poor control Unstable diabetes Hb. A1C - diabetic control Type 1 diabetes mellitus with ketoacidosis HbA1 - diabetic control

	Diabetic diet - poor compliance [V]Dietary counselling in hypoglycaemia Type 2 diabetes mellitus with ketoacidosis Type 1 diabetes mellitus with hypoglycaemic coma Diabetes mellitus NOS with ketoacidosis Diabetic crisis monitoring Other hypoglycaemia
4 Diabetes with other complication	Diabetic neuropathy Diabetic nephropathy Diabetes mellitus with neuropathy Type 1 diabetes mellitus with nephropathy Type 2 diabetes mellitus with nephropathy Diabetes mellitus with neurological manifestation Diabetes mellitus with renal manifestation Autonomic neuropathy due to diabetes Type 2 diabetes mellitus with persistent microalbuminuria Type 2 diabetes mellitus with persistent proteinuria Diabetic Charcot arthropathy O/E - Left diabetic foot - ulcerated O/E - Right diabetic foot - ulcerated Diabetic assessment of erectile dysfunction Proteinuric diabetic nephropathy Erectile dysfunction due to diabetes mellitus

Appendix Table 6: Read codes used to compose CPRD-derived lifestyle factors

History of heavy alcohol intake	
1 Heavy alcoholic	Heavy drinker - 7-9u/day Very heavy drinker - >9u/day Suspect alcohol abuse - denied Increasing risk drinking Feels should cut down drinking Higher risk drinking Alcohol intake above recommended sensible limits Heavy drinker Very heavy drinker Binge drinker Hazardous alcohol use Harmful alcohol use Alcohol misuse Alcohol units consumed on heaviest drinking day Drinks in morning to get rid of hangover Alcoholics anonymous Disqualified from driving due to excess alcohol H/O: alcoholism Alcohol induced hallucinations Replaces meals with drinks Alcohol dependence resolved O/E - breath - alcohol smell SADQ - Severity of alcohol dependence questionnaire

	Clinical Institute Withdrawal Assessment for Alcohol, revisd Alcohol disorder monitoring Alcohol abuse monitoring Delivery of rehabilitation for alcohol addiction Alcohol detoxification Alcohol harm reduction programme Advised to contact primary care alcohol worker Specialist alcohol treatment service signposted Aversion therapy - alcoholism Admitted to alcohol detoxification centre Referral to community alcohol team Referral to community drug and alcohol team Referral to specialist alcohol treatment service Referral to alcohol brief intervention service Declined referral to specialist alcohol treatment service Extended interven for excessive alcohol consumption declined Referral to community alcohol team declined Refer to MH services deferred until alcohol misuse resolved Police:venesect-alcohol Police:venesect-alcohol Alcohol misuse - enhanced services administration Alcohol consumption counselling Alcohol misuse - enhanced service completed Alcohol counselling by other agencies Brief intervention for excessive alcohol consumptn completed Extended intervention for excessive alcohol consumptn complt Withdrawn from alcohol detoxification programme Under care of community alcohol team Hospital attendance related to personal alcohol consumption Alcohol-induced pseudo-Cushing's syndrome Alcoholic psychoses Alcohol withdrawal delirium Alcohol amnestic syndrome Korsakov's alcoholic psychosis Korsakov's alcoholic psychosis with peripheral neuritis Alcohol amnestic syndrome NOS Other alcoholic dementia Alcoholic dementia NOS Chronic alcoholic brain syndrome Alcohol withdrawal hallucinosis Pathological alcohol intoxication Alcoholic paranoia Other alcoholic psychosis Alcohol withdrawal syndrome Other alcoholic psychosis NOS Alcoholic psychosis NOS Alcohol dependence syndrome Alcoholism Alcohol problem drinking Acute alcoholic intoxication in alcoholism Alcohol dependence with acute alcoholic intoxication Acute alcoholic intoxication, unspecified, in alcoholism

	Continuous acute alcoholic intoxication in alcoholism Episodic acute alcoholic intoxication in alcoholism Acute alcoholic intoxication in remission, in alcoholism Acute alcoholic intoxication in alcoholism NOS Chronic alcoholism Unspecified chronic alcoholism Continuous chronic alcoholism Episodic chronic alcoholism Chronic alcoholism in remission Chronic alcoholism NOS Alcohol dependence syndrome NOS Nondependent alcohol abuse Hangover (alcohol) Intoxication - alcohol Nondependent alcohol abuse, unspecified Nondependent alcohol abuse, continuous Nondependent alcohol abuse, episodic Nondependent alcohol abuse in remission Nondependent alcohol abuse NOS [X]Mental and behavioural disorders due to use of alcohol [X]Mental & behav dis due to use alcohol: acute intoxication [X]Acute alcoholic drunkenness [X]Mental and behav dis due to use of alcohol: harmful use [X]Mental and behav dis due to use alcohol: dependence syndr [X]Alcohol addiction [X]Chronic alcoholism [X]Mental and behav dis due to use alcohol: withdrawal state [X]Men & behav dis due alcohl: withdrawl state with delirium [X]Delirium tremens, alcohol induced [X]Mental & behav dis due to use alcohol: psychotic disorder [X]Alcoholic hallucinosis [X]Alcoholic jealousy [X]Alcoholic paranoia [X]Alcoholic psychosis NOS [X]Mental and behav dis due to use alcohol: amnesic syndrome [X]Korsakov's psychosis, alcohol induced [X]Alcoholic dementia NOS [X]Chronic alcoholic brain syndrome [X]Men & behav dis due to use alcohol: oth men & behav dis [X]Ment & behav dis due use alcohol: unsp ment & behav dis Alcoholic encephalopathy Cerebellar ataxia due to alcoholism Alcoholic polyneuropathy Alcoholic myopathy Oesophageal varices in alcoholic cirrhosis of the liver Maternal care for (suspected) damage to fetus from alcohol [D]Alcohol blood level excessive Alcohol deterrent poisoning Alcohol causing toxic effect Other alcohol causing toxic effect Alcohol causing toxic effect NOS [X]Toxic effect of other alcohols

	Accidental poisoning by alcohol NOS Adverse reaction to alcohol deterrents [X]Accident poisoning/exposure to alcohol [X]Accident poison/exposure to alcohol at home [X]Acc poison/expos alcohol school/pub admin area [X]Accid pois/expos alcohol in sport/athletic area [X]Accid poison/expos alcohol in street/highway [X]Accid poison/expos alcohol trade/service area [X]Accid pois/expos to alcohol other spec place [X]Accid poison/expos to alcohol unspecif place [X]Intent self poison/exposure to alcohol [X]Int self poison/exposure to alcohol at home [X]Int self poison alcohol other spec place [X]Intent self poison alcohol unspecif place [X]Poisoning/exposure, ? intent, to alcohol [X]Poison/exposure ?intent, to alcohol at home [X]Pois/exp ?intent alcohol school/pub admin area [X]Pois/expos ?intent alcohol in street/highway [X]Pois/expos ?intent to alcohol unspecif place [X]Alcohol deterrents caus adverse effects in therapeut use [X] Adverse reaction to alcohol deterrents [X]Evid of alcohol involv determind by level of intoxication Alcohol detoxification Alcohol withdrawal regime Planned reduction of alcohol consumption Alcohol reduction programme Alcoholism counselling Advice to change alcoholic drink intake Advice to change alcohol intake Alcohol dependence scale ADS - Alcohol dependence scale Alcohol use disorders identification test SADQ - Severity of alcohol dependence questionnaire Short alcohol dependence data SADD - Short alcohol dependence data HoNOS item 3 - alcohol/drug problem [V]Personal history of alcoholism [V]Problems related to lifestyle alcohol use [V]Alcohol rehabilitation [V]Alcohol abuse counselling and surveillance [V]Blood-alcohol and blood-drug test
2 Ex drinker - heavy	Ex-heavy drinker - (7-9u/day) Ex-very heavy drinker-(>9u/d)

Appendix to Chapter 4

Appendix Table 7: Do comorbidities increase the risk of unemployment or work disability in a person with MSK disease?

Table 2: Do comorbidities increase the risk of unemployment or work disability in a person with MSK disease?									
Reference	Design	MSD population (criteria used)	Number of Study Patients with MSD (n)	Age in years; Median (IQR)/ Mean ± SD/ Mean	Number of Females (%) in the Study	Adjustments (covariables)	Comorbidity (definition)	Work outcome (definition)	Measure of association (95%CI)
Work disability or disability pension									
Abrai'do-Lanza (2006) (12)	CS	Arthritis (ICD-codes: including inflammatory and osteoarthritis types)	1,734	Latino: 63.66 ± 1.20 Non-latino: 65.81 ± 0.26	Latino: 169 (75.4) Non-latino: 2057 (70.6)	Age, sex, education, family income, Latino ethnicity, duration of illness, physician visit for arthritis 6 months ago, limitations in ADL, limitations in IADL, functional limitations.	Number of comorbid conditions	Work disability-self-report: does a health problem prevent working a job or limit the type or amount of work they can perform.	OR: 1.22 (1.13–1.33)
Callahan (1992) (339)	Cross-sectional	Rheumatoid arthritis (American Rheumatism Association criteria)	128	Median 55.0	52 (41)	Age, sex, marital status, education, occupation type, duration of disease, rheumatoid factor, total radiographic score, total joint count	Number of comorbid conditions	Work disability-receiving work disability payments	OR: 1.5 (0.85-2.15)* *confidence intervals imputed by reviewer using

						score, ADL difficulty score.			P-value and point estimates Reported values: partial odds 1.5 (p value 0.32)
Boonen (2001) (11)	Cohort	Ankylosing spondylitis (rheumatologist diagnosed AS)	658	Range 16 to 60 years	234 (35.6)	Age, sex, education, profession, presence of peripheral arthritis, or history of total hip replacement.	Presence of comorbidity	Work disability-certified (official) work disability	OR: 3.15 (1.96 to 5.09)
Castillo-Ortiz (2016) (9)	Cohort	Ankylosing Spondylitis (rheumatologist diagnosed AS)	216	43.56 ± 12.7	62 (29)	Age and BASFI	Rheumatic Disease Comorbidity Index (RDCI) score	Work disability-certified (official) work disability	OR: 2.2 (1.2-4.0)
Hansen (2016) (357)	Cohort	Rheumatoid arthritis (inflammatory rheumatic disease biologics registry)	6677	18 to 59 years	4914 (73.6)	Age, sex, ethnicity, urbanization, season, family type, calendar year, highest obtained education, physical job exposure, psychiatric comorbidity, somatic comorbidity and significant interactions.	Presence of somatic comorbidity (i.e. not a mental comorbidity) (using selected ICD-8 and ICD-10 codes)	Long-term sickness absence (≥3 weeks) during the first year after diagnosis. (public register)	HR: 1.2 (1.0 to 1.5)
Hansen (2016) (357)	Cohort	Rheumatoid arthritis (inflammatory rheumatic	6677	Range 18 to 59 years	RA: 4914 (73.6)	Age, sex, ethnicity, urbanization, season, family type, calendar year, highest obtained education, physical	Presence of somatic comorbidity (i.e. not a mental	Long-term sickness absence (≥3 weeks) more than one year	HR: 1.3 (1.1 to 1.4)

		disease biologics registry)				job exposure, psychiatric comorbidity, somatic comorbidity and significant interactions.	comorbidity) (using selected ICD-8 and ICD-10 codes)	after diagnosis with RA. (public register)	
Hudson (2009) (13)	CS	Scleroderma (rheumatologist diagnosed scleroderma)	365	Working: 48.4 ± 9.4, not-working: 50.2 ± 8.2	167 (45.8)	Age, female, white ethnicity, education, disease duration, diffuse skin involvement, disease severity.	Self-Administered Comorbidity Questionnaire (SCQ) 12-comorbidity score	Work disability-self report: currently disabled or on sick leave	OR: 1.135 (1.072 to 1.202)
Ward (2001) (10)	Retrospective Cohort	Ankylosing spondylitis (modified New York criteria)	234	Age at diagnosis: 27.4 ± 11.0	69 (29.5)	Age, education, current or former smoker, initial job as a professional/manager, physical activity of work.	Presence of comorbidity	Work disability-self-report: permanent work disability (disability retirement)	HR: 2.62 (0.58–11.86)
Ward (2001) (10)	Retrospective Cohort	Ankylosing spondylitis (modified New York criteria)	234	Age at diagnosis: 27.4 ± 11.0	69 (29.5)	Age, sex, education, current or former smoker, initial job as a professional/manager, physical activity of work.	Presence of comorbidity	Work disability-self-report: receiving payments for work disability	HR: 4.07 (1.23–13.43)
Sickness absence									
Kessler (2001)(199)	CS	Arthritis (self-reported)	~261	Range 25 to 74	NR	Age, sex, education and occupational status.	Number of comorbid chronic conditions.	how many days out of the past 30 “totally unable to work or carry out normal work activities	Unstandardized linear regression coefficient; SE, standard error of the

								because of your physical health or mental health"; and how many additional days out of the past 30 that respondents had to "cut back on work or how much you got done because of physical health or mental health").	regression coefficient. Total number of conditions in those with arthritis: 0-2: 0.9 (0.3) 3 or more: 4.0 (1.9) P=<0.05
Nikiphorou (2018)(361)	CS	Spondyloarthritis (ASAS criteria)	3370	43 ± 14	2221 (34.1)	Age, sex, ASDAS, BASFI, presence of peripheral enthesitis	Rheumatic Disease Comorbidity Index (RDCI) score	Absenteeism (percentage of working hours absent- work productivity and activity impairment questionnaire)	Odds ratio (95% CI). 1.18 (1.04 to 1.34)
Van de Zee-Neuen (2017) (341)	CS	Rheumatoid arthritis (1987 American College of Rheumatology classification criteria)	2395	48 ± 9.2	1972 (84%) excluding controls	Age, gender, mHAQ, DAS28, Country GDP	Rheumatic Disease Comorbidity Index (scored 0-8)	Absenteeism (percentage of working hours absent- work productivity and activity	Odds ratio (95% CI). All countries 1.44 (1.25 to 1.68)

								impairment questionnaire)	
Webers (2018) (362)	Cohort	Ankylosing spondylitis (modified New York criteria)	139	38.7 ± 10.00	34 (24.5%)	Age, sex, BASDAI	Rheumatic Disease Comorbidity Index (scored 0-9)	Ankylosing Spondylitis-related sick leave, no minimum duration (self-reported questionnaire, 6 year follow up)	Odds ratio (95% CI) Participants with a high educational attainment 1.58 (0.34 to 7.38) Participants with a low educational attainment 1.52 (1.00 to 2.29)
Employment status or job loss									
Furunes (2018)(359)	Cohort	Degenerative disc and chronic low back pain treated with lumbar total disc replacement (orthopaedic surgeon and physician defined)	82	41 (25 – 54)	40 (48.8)	Education, duration of sick leave (<12 months vs >12 months), Oswestry Disability Index ≥ 50 (no/yes)	Comorbidities (absence of comorbidity)	Employment at follow up (minimum 3 years)	Odds ratio (95% CI). 7.7 (2.0 – 30.5)
Manders (2014) (349)	Cohort	Rheumatoid arthritis (with moderate to high disease activity	508	48.30 ± 9.45	368 (72.4)	Baseline HAQ and response to treatment HAQ	Comorbidities (presence of comorbidity)	Stopping work participation after 2 years of treatment.	OR: 2.67 (p:0.007) Imputed OR

		on TNFi treatment)							2.67 (2.14-3.20)* *confidence intervals imputed by reviewer using P-value and point estimate
Marengo (2008) (342)	Case-control	Ankylosing Spondylitis (modified New York criteria, 1984)	157	43 (33–52)	22 (14)	Age, age of onset, BASDAI, BASFI, HAQ, fatigue, depression, ASQoL.	Comorbidities (presence of comorbidity)	Current unemployment	Odds ratio (95% CI). 2.5 (0.23–26.5)
Nikiphorou (2018)(361)	CS	Spondyloarthritis (ASAS criteria)	3370	43 ± 14	2221 (34.1)	Age, sex, ASDAS, BASFI, education	Rheumatic Disease Comorbidity Index (RDCI) score	Current employment	Odds ratio (95% CI). 0.83 (0.76 to 0.91)
Schofield (2014)(352)	CS	Arthritis (survey-ICD-10 codes "arthritis and related disorders")	1,414	45 to 64 years	NR	Age, sex, and highest level of education	Comorbid conditions (one, two or three or more other health conditions, see results) (survey- ICD-10 codes)	Not being in the labour force (self-report)	OR: Arthritis only: 1.00 One other health condition: **1.67 (1.06–2.64)** Two other health conditions: **1.73 (1.06–2.86)**

									Three or more other health conditions: **3.68 (2.43–5.58)**
Van der Zee-Neuen (2017) (341)	CS	Rheumatoid arthritis (1987 American College of Rheumatology classification criteria)	2395	48 ± 9.2	1972 (84%) excluding controls	Age, gender, level of education, HAQ, DAS28	Rheumatic Disease Comorbidity Index (scored 0-8)	Current employment	OR: All countries 0.93 (0.85 to 1.02) High gross domestic product (GDP) countries. **0.89 (0.81 to 0.97)** Low GDP countries **0.80 (0.70 to 0.91)**
Return to work									
Nordin (2002) (350)	Cohort	Non-specific low back pain (defined by occupational health physician-work administrative records)	2,382	Range 15-65 years	329 (13.8)	Age, sex, type of company, heavy lifting	Comorbidity (per every additional comorbidity)	Estimated first return to work from work disability episodes.	HR: 1.31 (1.12-1.52)
Kausto (2017) (366)	CS	Intervertebral disc disorders (insurance register)	14,170	Men: 43.1 ± 10.2	11,953 (84.4)	Age, occupational group, country region, sickness absence during previous year, purchase of	Comorbid conditions (due to diabetes, rheumatoid	Return to sustained work time from the initial day of work absence	HR: Men: 0.93 (0.71 to 1.23) Women: 1.00 (0.88 to 1.13)

				Women: 42.7 ± 10.3		antidepressants or hospitalisation for mental disorders, reimbursed purchase of medication for MSD pain or hospitalisation due to MSD.	arthritis, asthma/COPD or coronary heart disease, ICD-10 codes: Sickness Insurance Register)	until the end of the compensation period.	
Lee (2017) (348)	Cohort	Spinal surgery (including, disk herniation, stenosis, spondylolisthesis, degenerative scoliosis, and traumatic injuries- electronic medical records)	326	Range 18-75 years	185 (56.7)	Age, sex, alcohol use, smoking status, employment before surgery, surgery characteristics, complications of surgery.	Comorbidity (presence of a "significant medical comorbidity" in medical records)	Return to full employment within 1 year of surgery and still working on last follow up (follow-up for 2 years after surgery).	OR: 0.19 (0.04 to 0.85)
Presenteeism									
Kennedy (2014) (334)	CS	Psoriatic arthritis (rheumatologist-confirmed)	186	50.5 ± 10.7	74 (39.8)	Age, sex, duration of PsA, education, PASI, AJC, DJC, Erythrocyte Sedimentation Rate (ESR), FCI, medications, physical labour at work, work schedule control, and support at work.	Functional Comorbidity Index score	Patients completed the 25-item self-administered WLQ as well as the WLQ 2-Question Time Loss Module. Outcome: risk of moderate-severe work impairment.	Odds ratios (95% CI) 2.31 (1.19, 4.50)

Agaliotis (2013) (343)	Cohort	Knee Pain (knee pain on most days in the past month and mild-to-moderate medial tibio-femoral joint space narrowing-physician diagnosed)	360	Range 45 to 75 years	194 (53.9)	Age, type of work, maximum knee pain, SF-12.	Number of comorbidities (odds per every unit increase of comorbidities)	Presenteeism (percentage impairment while working-Work Productivity and Activity Impairment Questionnaire (WPAI))	OR (95% CI) 0: reference 1-3: 1.27 (0.64-2.50) 4 or more: 2.15 (0.91-5.09)
Joshi (2015) (365)	CS	Arthritis (self-reported)	167,068	>18 years	111,707 (67.2)	Age, sex, race, income, geographic region, employment status, health insurance, marital status, education, weight status (BMI categorisation), smoking status, drinking status, time since previous health check-up, general health status, depression status.	number of chronic comorbidities (odds per every unit increase of chronic comorbidities)	Work limitation (presenteeism)-Self report: "Do arthritis or joint symptoms now affect whether you work, the type of work you do, or the amount of work you do?''	Odds ratio (95% CI). 1.01 (0.99–1.03)
Nikiphorou (2018)(361)	CS	Spondyloarthritis (ASAS criteria)	3370	43 ± 14	2221 (34.1)	Age, sex, ASDAS, BASFI, BMI	Rheumatic Disease Comorbidity Index (RDCI) score	Presenteeism (percentage impairment while working-Work Productivity and Activity Impairment	Odds ratio (95% CI). 1.42 (1.26–1.61)

								Questionnaire (WPAI))	
Wilkie (2013) (353)	Cohort	Osteoarthritis (self-reported and defined as hip, knee, or foot pain for 1 day or more during the past year)	716	Range 50 to 59 years	392 (54.7)	Age, sex, severity of lower limb pain, number of painful sites, anxiety, depression, BMI, cognitive impairment.	Comorbidity (presence of 1-4 comorbidities)	Work restriction- Keele Assessment of Participation (KAP): ''During the past 4 weeks, if you work, have you taken part in paid or voluntary work as and when you have wanted?''- answered some/a little or none of the time.	Odds ratio (95% CI) None: 1 1–4: 1.28 (0.81, 2.02)
Work transitions									
Agaliotis (2017) (363)	CS	Knee Pain (knee pain on most days in the past month)	129	Range 45 to 75 years	64 (37.4)	Age, sex, maximum knee pain, physical workload, social support	Self-Administered Comorbidity Questionnaire (categorised as 0-1 comorbidities; 2-3 comorbidities and 4 or more comorbidities.)	Work transitions scale. A ten item scale evaluating loss of work hours or interruptions, change in type or nature of work, or	Odds ratio (95% CI) Comorbidity score 0: reference 1 to 3: 3.49 (0.84 to 14.46) 4 or more: 4.44 (1.02 to 19.32).

								permanent change of work hours over 6 months	

Appendix Table 8: Psychiatric disease and MSK disease related work disability

Table 2: Do co-occurring psychiatric diseases increase the risk of unemployment or work disability in a person with MSK disease?									
Reference	Design	MSD population (criteria used)	Number of Study Patients with MSD (n)	Age in years; Median (IQR)/ Mean ± SD/ Mean	Number of Females (%) in the Study	Adjustments (covariables)	Psychiatric disease (definition)	Work outcome (definition)	Measure of association (95%CI)
Work disability or disability pension									
Csupak (2018)(358)	CS	Arthritis (self-report)	25113 (5465 with arthritis)	48.5 ± 0.1	13773 (50.7)	Age, sex ethnicity, household income, education, marital status	Generalised anxiety disorder (World Health Organisation Mental Health Composite International Diagnostic Interview WMH-CIDI)	Permanent inability to work (work disability- self report)	OR: 5.38 (2.44 to 11.84)
Csupak (2018) (358)	CS	Back pain (self-report)	25113 (5205 with back pain)	48.5 ± 0.1	13773 (50.7)	Age, sex ethnicity, household income,	Generalised anxiety disorder (World Health Organisation Mental Health	Permanent inability to work (work disability- self report)	OR: 4.26 (2.06 to 8.81)

						education, marital status	Composite International Diagnostic Interview WMH-CIDI)		
Hansen (2016) (357)	Cohort	Rheumatoid arthritis (inflammatory rheumatic disease biologics registry)	6677	18 to 59 years	4914 (73.6)	Age, sex, ethnicity, urbanization, season, family type, calendar year, highest obtained education, physical job exposure, psychiatric comorbidity, somatic comorbidity and significant interactions.	Psychiatric comorbidity. (using selected ICD-8 and ICD-10 codes)	Long-term sickness absence (≥3 weeks) during the first year after diagnosis (public register)	HR: 2.2 (2.0 to 2.5)
Hansen (2016) (357)	Cohort	Rheumatoid arthritis (inflammatory rheumatic disease biologics registry)	6677	Range 18 to 59 years	4914 (73.6)	Age, sex, ethnicity, urbanization, season, family type, calendar year, highest obtained education, physical job exposure, psychiatric comorbidity,	Psychiatric comorbidity. (using selected ICD-8 and ICD-10 codes)	Long-term sickness absence (≥3 weeks) more than one year after diagnosis with RA. (public register)	HR: 1.9 (1.8 to 2.0)

						somatic comorbidity and significant interactions.			
Lowe (2004) (336)	CS	Inflammatory rheumatic diseases (ACR 1987 for RA, Tan et al criteria for SLE and ICD-10 for other IRD)	356	42.7 ± 11.7	263 (73.9)	Physical functioning, depression severity, severity of illness (physician rating).	Depression (Patient health questionnaire defined: PHQ-9)	Work disability (self-report: receiving temporary or permanent disability pension OR employed (full-time or part-time) with a sick leave of at least 4 weeks OR unemployed and unable to do their usual activities for at least 4 weeks because of medical illness. [disability pension was verified using insurance statements].	OR: 1.6 (1.1 to 2.3)

Olofsson (2017) (351)	Cohort	RA (biologics register-ACR, 1987)	857	45 ± 11	753 (72)	Year of biologics-start, disease duration, sex, age at bio-start, education, HAQ, DAS28.	Depression or anxiety (medical records-National Patient Register combined with drug information from the Prescribed Drug Register)	LTSA (Time to lose 15 days of 30 with sick leave or disability pension over follow up (maximum 3 years))	HR: 1.7 (1.1 to 2.6)
Panopalis (2007) (338)	CS	SLE (met at least 4/11 ACR revised criteria (1997))	832	Memory intact: 45.5 ± 10.6 Mild to moderate impairment : 46.1 ± 11.1 Severe impairment : 46.3 ± 11.2	Memory intact: 425 (94.0) Mild to moderate impairment : 188 (93.1) Severe impairment : 76 (87.4)	age, sex, race, marital status, education, depressive symptoms, disease duration, and disease activity.	Depression symptoms (Center for Epidemiologic Studies Depression Scale (CES-D))	Unable to work (self-report that they are "unable to work")	OR: 1.71 (1.15, 2.54)
Sickness absence									
Buist-Bouwman (2005) (364)	Retrospective randomised survey	Rheumatism (checklist (y/n) self-reported rheumatism or inflammation of joints in past 12m and treated for the condition by a healthcare	587	Range 18 to 64 years	NR	Sex, age and educational attainment.	Anxiety (Composite International Diagnostic Interview: DSM-III-R criteria in prior 12m), mood disorder (Composite International Diagnostic Interview: DSM-	Number of work-loss days over the past 12 months (self-report: how many days in the past 12 months were you unable to work due to	Unstandardized linear regression coefficients, standard error of the mean, and P values only reported. Rheumatism and anxiety 18.7 (6.3) <0.01

		professional or medication had been prescribed).					III-R criteria in prior 12m), substance use disorder (Composite International Diagnostic Interview: DSM-III-R criteria in prior 12m)	mental health problems or substance use disorders or physical health problems?)	Rheumatism and mood disorder 30.5 (7.5) <0.001 Rheumatism and Substance use disorder 7.4 (9.6) >0.05 The additive effect of mental comorbidities on work days lost was 1.7 (3.3) (>0.05)
Buist-Bouwman (2005) (364)	Retrospective randomised survey (7076)	Chronic back trouble (checklist (y/n) self-reported chronic back pain in past 12m and treated for the condition by a healthcare professional or medication had been prescribed).	631	Range 18 to 64 years	NR	Sex, age and educational attainment.	Anxiety (Composite International Diagnostic Interview: DSM-III-R criteria in prior 12m), mood disorder (Composite International Diagnostic Interview: DSM-III-R criteria in prior 12m), substance use disorder (Composite International Diagnostic	Number of work-loss days over the past 12 months (self-report: how many days in the past 12 months were you unable to work due to mental health problems or substance use disorders or physical health problems?)	Unstandardized linear regression coefficients, standard error of the mean, and P values only reported. Chronic Back trouble and anxiety 23.8 (6.3)<0.001 Chronic Back trouble and mood disorder 39.7 (7.4) <0.001 Chronic Back trouble and

							Interview: DSM-III-R criteria in prior 12m)		Substance use disorder 5.4 (10.0) >0.05 The additive effect of mental comorbidities on work days lost was 10.4 (3.2) <0.001
Csupak (2018) (358)	CS	Arthritis (self-report)	25113 (5465 with arthritis)	48.5 ± 0.1	13773 (50.7)	Age, sex ethnicity, household income, education, marital status	Generalised anxiety disorder (World Health Organisation Mental Health Composite International Diagnostic Interview WMH-CIDI)	Absent from work in the past week (absenteeism-self report)	OR: 1.90 (0.67 to 5.36)
Csupak (2018) (358)	CS	Back pain (self-report)	25113 (5205 with back pain)	48.5 ± 0.1	13773 (50.7)	Age, sex ethnicity, household income, education, marital status	Generalised anxiety disorder (World Health Organisation Mental Health Composite International Diagnostic Interview WMH-CIDI)	Absent from work in the past week (absenteeism-self report)	OR: 1.48 (0.61 to 3.64)
Kessler (2003) (335)	CS	Arthritis and related conditions	382	Range 15 to 54	NR	age, sex, education, and	comorbid mental disorder (interview-	Number of work loss days (self-report:	Mean difference and (SE).

		(checklist- self reported in the past 12 months)				employment status	Diagnostic and Statistical Manual, 3rd edition, revised (DSM-III-R))	days unable to work out of past 30).	Arthritis: -0.1 (0.4) Arthritis and comorbid mental disorder: 2.5* (0.7) Mental disorder additional component: 0.5 (0.4) Additional effect of comorbidity on effect of mental disorder and arthritis alone: 2.3* (0.8) *P=<0.05
Melkevik (2018)(360)	Cohort	Musculoskeletal pain (self-reported- in the low back, neck/shoulders, or knees)	6572	45.9 ± 10.5	6572 (100)	Age, seniority, cohabitation, job group	Comorbid depression (Major Depression Inventory (MDI) mean score, multiplied by 10: 0 – 12.99 low, 13 – 20.99 moderate, >21 high)	Onset of long term sickness absence (self-report: any sickness absence for four consecutive weeks or more during 550 days)	Musculoskeletal pain in 1 location, low depressive symptoms: 1.00 Medium depressive symptoms: HR 0.79 (0.50 to 1.25) High depressive symptoms: HR 1.55 (0.95 to 2.55)

									Musculoskeletal pain in 2 locations, low depressive symptoms: 1.00 Medium depressive symptoms: HR 1.30 (0.96 to 1.77) High depressive symptoms: HR 0.97 (0.62 to 1.50) Musculoskeletal pain in 3 locations, low depressive symptoms: 1.00 Medium depressive symptoms: HR 0.91 (0.62 to 1.32) High depressive symptoms: HR 1.31 (0.87 to 1.98)
Munce (2007) (337)	CS	Chronic pain condition, (self report: chronic	9,238,593	Absenteeism Y: 44.7 ± 10.2	Absenteeism Y: 68.2%	Age, sex, marital status, income adequacy, and	Major depressive event (lay interview	Absenteeism in the past week (self	"The presence of major depression

		pain diagnosed by a health care professional and present for at least 6 months-included fibromyalgia, arthritis, rheumatism, back problems and migraine).		Absenteeism N:52.8 ± 17.4	Absenteeism N: 67.7%	level of education.	using: World Mental Health 2000 version of the Composite International Diagnostic Interview (WMH-CIDI))	report: absent from work in the last week, mainly due to illness or disability)	emerged as the strongest predictor among all the variables examined. Persons with a MDE in the past 12 months were 2.9 times (95% CI 2.825 to 2.915) more likely to be absent from their job or business than their non-depressed counterparts.”
Unemployment status or job loss									
De Buck (2006) (354)	Cohort	RA, AS, or SLE (RA: ARA classification criteria; AS: modified New York criteria, 1984. reactive arthritis or psoriatic arthritis; SLE: ARA criteria (Tan et al. 1982), or scleroderma.)	112	43.9 ± 9.0	66 (59)	RAND summary scales for physical and mental health, complete sick leave.	Depression (hospital anxiety and depression scale (HADS))	Job loss (self-report: receiving a full work disability pension or unemployed)	OR: 1.18 (1.02–1.36)

Panopalis (2007) (338)	CS	SLE (met at least 4/11 ACR revised criteria (1997))	832	Memory intact: 45.5 ± 10.6 Mild to moderate impairment : 46.1 ± 11.1 Severe impairment : 46.3 ± 11.2	Memory intact: 425 (94.0) Mild to moderate impairment : 188 (93.1) Severe impairment : 76 (87.4)	age, sex, race, marital status, education, depressive symptoms, disease duration, and disease activity.	Depression symptoms (Center for Epidemiologic Studies Depression Scale (CES-D))	Employed (self-report that they have a job or paid work)	OR: 0.64 (0.44, 0.94)
Schofield (2014) (352)	Cross-sectional study (8,864)	Arthritis (ICD-10 codes "arthritis and related disorders")	1,414	45 to 64 years	NR	Age, sex, and highest level of education	Depression/mood affective disorders (survey- ICD-10 codes)	Not being in the labour force (survey-self report)	Odds ratio (95% CI) 5.42 (2.61–11.26)
Schofield (2014) (352)	CS	Arthritis (ICD-10 codes "arthritis and related disorders")	1,414	45 to 64 years	NR	Age, sex, and highest level of education	Mental health and related disorders (survey- ICD-10 codes)	Not being in the labour force (survey-self report)	Odds ratio (95% CI) 3.46 (1.92–6.23)
Time to return to work									
Anderson (2016) (345)	Cohort	Workers who underwent anterior, posterior, or 360° lumbar fusion for spondylolisthesis. (identified using ICD-9 codes)	686	RTW: 43.2±9.7 No RTW: 45.1±10.5	RTW: 56 (27.3) No RTW: 153 (31.8)	Out of work for longer than 1 year, single-level vs multilevel fusion, decompression with fusion, receipt of permanent disability benefits, age	Preoperative diagnosis of depression (Workers compensation database-identified using ICD-9 codes)	Return to work (Workers compensation database-RTW within 2 years after fusion and remained working for >6 months).	Clinically diagnosed with depression OR: <0.01 (confidence interval (<0.01)?* [no subjects with depression RTW after fusion.]

						older than 50 years, sex, obesity, approximated income less than the 25th percentile for the study population, isthmic vs degenerative spondylolisthesis, individual lumbar and psychiatric comorbidities, lumbar diskography, use of physical therapy, use of chiropractic care, supplied with opioid analgesics for longer than 1 year, daily opioid load above the 75th percentile for the study population, and legal			

						representation, type of fusion surgery, instrumentation, and graft used.			
Brede (2012) (346)	Prospective cohort study	Occupational musculoskeletal injury (disabled as a result of their injury for at least 4 months and completed rehabilitation)	1850	45.9 ± 9.4	875 (47.3)	Age, sex, not working at discharge, MVAS≥100 at admission, antisocial personality, receiving social security disability allowance at admission, opiate dependence, attorney retained at admission, MVAS≥100 at discharge, pretreatment surgery, not working at admission, major depressive disorder, BDI≥20 at discharge, BDI≥20 at	The Beck Depression Inventory (BDI), a measure of depressive symptoms (BDI >20).	Failure to retain work at 12 months (interview-self-report)	OR (95% CI) Rehab admission: 1.06 (0.77–1.45) Rehab discharge: 1.18 (0.76–1.86)

						admission, pain≥8 at admission.			
Brede (2012) (346)	Prospective cohort study	Occupational musculoskeletal injury (disabled as a result of their injury for at least 4 months and completed rehabilitation)	1850	45.9 ± 9.4	875 (47.3)	Age, sex, not working at discharge, MVAS≥100 at admission, antisocial personality, receiving social security disability allowance at admission, opiate dependence, attorney retained at admission, MVAS≥100 at discharge, pretreatment surgery, not working at admission, major depressive disorder, BDI≥20 at discharge, BDI≥20 at admission,	Major depressive disorder (medical records)	Failure to retain work at 12 months (interview-self-report)	OR (95% CI) At admission: 1.21 (0.89–1.64)

						pain≥8 at admission.			
Cote (2001) (356)	Prospective cohort study	Sustained road traffic injury (whiplash-self reported via questionnaire using directed questions)	2377 (tort) 3021 (no fault)	Tort insurance system 36.3 ± 14.9 No-fault insurance system 37.4 ± 15.2	Tort insurance system 1360 (57.2) No-fault insurance system 1875 (62.1)	Age, gender, baseline percent body in pain, baseline neck pain intensity.	Depressive symptomology (self-report: questionnaire CES-D)	Time to claim closure (similar to return to work time-insurance company database)	Hazard rate ratios: tort insurance period: 0.628 (0.514, 0.769) No-fault insurance period: 0.636 (0.537, 0.753)
Kausto (2017) (366)	CS	Intervertebral disc disorders (insurance register)	14,170	Men: 43.1 ± 10.2 Women: 42.7 ± 10.3	11,953 (84.4)	Age, occupational group, country region, sickness absence during previous year, purchase of antidepressants or hospitalisation for mental disorders, reimbursed purchase of medication for MSD pain or hospitalisation due to MSD.	Purchase of antidepressants or hospitalization period for mental disorders. (medical codes-Drug Reimbursement Register)	Return to sustained work time from the initial day of work absence until the end of the compensation period.	Hazard ratio (95% CI) Men: 0.82 (0.74 to 0.91) Women: 0.86 (0.82 to 0.90)

Olofsson (2017) (351)	Cohort	RA (biologics register- ACR, 1987)	753	53 ± 8	601 (80)	Year of biologics-start, disease duration, sex, age at bio-start, education, HAQ, DAS28.	Depression or anxiety (medical records- National Patient Register combined with drug information from the Prescribed Drug Register)	Return to work (time to regain ≥16 days of 30 without sick leave or disability pension over follow up (maximum 3 years))	HR 0.62 (0.37 to 1.03)
Schade (1999) (355)	Cohort	Discectomy patients (surgical assessment, independent radiologists)	46	Range 20 to 50 years	NR	Preoperative pain and/or disability in daily activities, occupational mental stress.	Depression (self-report: Psychological general well-being index)	Return to work at 2 years (self-report: any work).	Beta 0.43 R2 change 0.16 Fchange: 9.00*** Final Beta 0.37 T 2.63*** ***=P<0.01 Imputed: standard error of the regression coefficient (0.16)
Presenteeism									
Joshi (2015) (365)	CS	Arthritis (self-reported)	167,068	>18 years	111,707 (67.2)	Age, sex, race, income, geographic region, employment status, health insurance, marital status, education,	Depression (self report- “have you been told by a doctor that you have a depressive disorder including…”)	Work limitation (presenteeism)- Self report: “Do arthritis or joint symptoms now affect	OR (95% CI). 1.51 (1.41–1.60)

						weight status (BMI categorisation), smoking status, drinking status, time since previous health check-up, general health status, depression status.		whether you work, the type of work you do, or the amount of work you do?''	
Kessler (2003) (335)	CS	Arthritis and related conditions (checklist- self reported in the past 12 months)	382	Range 15 to 54	NR	age, sex, education, and employment status	comorbid mental disorder (interview-Diagnostic and Statistical Manual, 3rd edition, revised (DSM-III-R))	Role impairment score taking into account work loss days and number of days out of the past 30, when able to work but needed to cut back on what (they) did or did not get as much done as usual because of problems with physical or mental health	Mean difference and (SE). Arthritis: 0.0 (0.4) Arthritis and comorbid mental disorder: 3.4* (0.7) Additional effect of comorbidity on effect of mental disorder and arthritis alone: 2.6 (0.8)* *P=<0.05
Kessler (2003) (335)	CS	Arthritis and related	382	Range 15 to 54	NR	age, sex, education, and	comorbid mental disorder	Number of work cutback	Mean difference and (SE).

		conditions (checklist- self reported in the past 12 months)				employment status	(interview- Diagnostic and Statistical Manual, 3rd edition, revised (DSM-III-R))	days (self-report: days cut back on work or did less than usual out of past 30).	Arthritis: 0.2 (0.3) Arthritis and comorbid mental disorder: 2.3* (0.6) Additional effect of comorbidity on effect of mental disorder and arthritis alone: 0.8 (0.6) *P=<0.05
Wilkie (2013) (353)	Cohort	Osteoarthritis (self-reported and defined as hip, knee, or foot pain for 1 day or more during the past year)	716	Range 50 to 59 years	392 (54.7)	Age, sex, severity of lower limb pain, number of painful sites, anxiety, depression, BMI, cognitive impairment.	Anxiety (hospital anxiety and depression scale- HADS)	Work restriction- Keele Assessment of Participation (KAP): ‘‘During the past 4 weeks, if you work, have you taken part in paid or voluntary work as and when you have wanted?’’- answered	OR (95% CI) Anxiety Non-case (0–7): 1 Possible/probable case (8–21): 0.95 (0.57, 1.56)

								some/a little or none of the time.	
Wilkie (2013) (353)	Cohort	Osteoarthritis (self-reported and defined as hip, knee, or foot pain for 1 day or more during the past year)	716	Range 50 to 59 years	392 (54.7)	Age, sex, severity of lower limb pain, number of painful sites, anxiety, depression, BMI, cognitive impairment.	Depression (hospital anxiety and depression scale- HADS)	Work restriction- Keele Assessment of Participation (KAP): ‘‘During the past 4 weeks, if you work, have you taken part in paid or voluntary work as and when you have wanted?’’- answered some/a little or none of the time.	Odds ratio (95% CI) Depression Non-case (0–7): 1 Possible/probable case (8–21): 2.11 (1.13, 3.95)

Appendix Table 9: Cardiovascular comorbidity and MSK disease related work disability

Table 2: Do co-occurring cardiovascular diseases increase the risk of unemployment or work disability in a person with MSK disease?									
Reference	Design	MSD population (criteria used)	Number of Study Patients with MSD (n)	Age in years; Median (IQR)/ Mean ± SD/ Mean	Number of Females (%) in the Study	Adjustments (covariables)	Cardiovascular disease (definition)	Work outcome (definition)	Measure of association (95%CI)
Work disability or disability pension									
Al Dhanhani (2009) (344)	Cohort	Systemic Lupus Erythematosus (ACR criteria tan et al, 1982)	432	35.9 ± 13.6	379 (88)	Age at diagnosis, Female sex, Finished high school, Sjogren's syndrome, Avascular necrosis, Diabetes, Arthritis, Neuropsychiatric lupus, Fibromyalgia.	Hypertension (registry-rheumatologist diagnosed)	Work disability (self-report: being unemployed due to disability)	OR: 2.23 (1.16–4.32)
Olofsson (2017) (351)	Cohort	RA (biologics register-ACR, 1987)	857 (in analysis)	45 ± 11	753 (72)	Year of biologics-start, disease duration, sex, age at bio-start, education, HAQ, DAS28.	Hypertension (medical records-National Patient Register combined with drug information from the Prescribed Drug Register)	LTSA (Time to lose 15 days of 30 with sick leave or disability pension over follow up (maximum 3 years))	HR: 1.25 (0.85 to 1.85)
Sickness absence									

Ven den Berg (2017) (340)	Cross-sectional study, questionnaire	Musculoskeletal disorders (self-report: work ability index)	3271	49 ± 13.6	2722 (83.2%)	Age, sex, and educational level	Obesity (self-reported height and weight: BMI ≥ 30 kg/m^2)	Any sickness absence in the year prior (self-report: 1-365 days vs 0 days)	OR (95% CI) 1.37 (1.10 to 1.71)
Time to return to work									
Kuijer (2016) (347)	Cohort study, retrospective (167)	Total knee arthroplasty (multicentre, two Dutch hospitals)	167	59.7 ± 8.4	85 (50.9)	Female, difference in follow up time, work-relatedness of knee symptoms, medium knee-demanding job	Obesity (medical records: BMI ≥ 30.0)	Return to work after a follow up of at least 2 years. (self-report: questionnaire)	OR: 2.8 (1.1 to 7.1)
Olofsson (2017) (351)	Cohort	RA (biologics register-ACR, 1987)	599 (in analysis)	53 ± 8	601 (80)	Year of biologics-start, disease duration, sex, age at bio-start, education, HAQ, DAS28.	Hypertension (medical records-National Patient Register combined with drug information from the Prescribed Drug Register)	Return to work (time to regain ≥16 days of 30 without sick leave or disability pension over follow up (maximum 3 years))	HR: 0.90 (0.56 to 1.45)
Unemployment status or job loss									
Schofield (2014) (352)	CS	Arthritis (ICD-10 codes “arthritis and related disorders”)	1,414	45 to 64 years	NR	Age, sex, and highest level of education	Other diseases of the circulatory system. (survey-ICD-10 codes)	Not being in the labour force (survey- self report)	Odds ratio (95% CI) Arthritis only: reference Other circulatory diseases: 6.95 (2.76–17.51)

Schofield (2014) (352)	CS	Arthritis (ICD-10 codes "arthritis and related disorders")	1,414	45 to 64 years	NR	Age, sex, and highest level of education	Heart disease (survey- ICD-10 codes)	Not being in the labour force (survey- self report)	Odds ratio (95% CI) Arthritis only: reference Heart disease: 4.31 (1.94–9.55)
Schofield (2014) (352)	CS	Arthritis (ICD-10 codes "arthritis and related disorders")	1,414	45 to 64 years	NR	Age, sex, and highest level of education	Hypertension (survey- ICD-10 codes)	Not being in the labour force (survey- self report)	Odds ratio (95% CI) Arthritis only: reference Hypertension: 2.44 (1.55–3.83)
Presenteeism									
Joshi (2015) (365)	CS	Arthritis (self-reported)	167,068	>18 years	111,707 (67.2)	Age, sex, race, income, geographic region, employment status, health insurance, marital status, education, weight status (BMI categorisation), smoking status, drinking status, time since previous health check-up, general health status, depression status.	Obesity/overweight (self-report: (BMI ≥25 kg/m^2 and above))	Work limitation (presenteeism)- Self report: "Do arthritis or joint symptoms now affect whether you work, the type of work you do, or the amount of work you do?''	Odds ratio (95% CI) 1.07 (1.01–1.14)
Wilkie (2013) (353)	Cohort	Osteoarthritis (self-reported	716	Range 50 to	392 (54.7)	Age, sex, severity of lower limb pain,	Obesity (self-reported: height and	Work restriction- Keele	Odds ratio (95% CI)

		and defined as hip, knee, or foot pain for 1 day or more during the past year)		59 years		number of painful sites, anxiety, depression, BMI, cognitive impairment.	weight BMI ≥30 kg/m^2)	Assessment of Participation (KAP): ''During the past 4 weeks, if you work, have you taken part in paid or voluntary work as and when you have wanted?''- answered some/a little or none of the time.	Normal weight (BMI: 20 to 24.9 kg/m^2): 1 Obesity (BMI ≥30 kg/m^2): 1.36 (0.74, 2.52)

Appendix Table 10: Diabetes and MSK disease related work disability

Table 2: Does co-occurring diabetes increase the risk of unemployment or work disability in a person with MSK disease?									
Reference	Design	MSD population (criteria used)	Number of Study Patients with MSD (n)	Age in years; Median (IQR)/ Mean ± SD/ Mean	Number of Females (%) in the Study	Adjustments (covariables)	Diabetes (definition)	Work outcome (definition)	Measure of association (95%CI)
Work disability or disability pension									
Al Dhanhani (2009) (344)	Cohort	Systemic Lupus Erythematosus	432	35.9 ± 13.6	379 (88)	Age at diagnosis, Female sex, Finished high school, Sjogren's syndrome,	Diabetes (registry-	Work disability (self-report: being	OR (95% CI)

		(ACR criteria tan et al, 1982)				Hypertension, Avascular necrosis, Arthritis, neuropsychiatric lupus, Fibromyalgia.	rheumatologist diagnosed)	unemployed due to disability)	Diabetes **1.00 (0.41–2.44)**
Unemployment status or job loss									
Schofield (2014) (352)	CS	Arthritis (ICD-10 codes "arthritis and related disorders")	1,414	45 to 64 years	NR	Age, sex, and highest level of education	Diabetes (survey- ICD-10 codes)	Not being in the labour force (survey- self report)	Odds ratio (95% CI) Arthritis only: reference Diabetes: 2.55 (1.29–5.02)

Appendix Table 11: Respiratory disease and MSK disease related work disability

Table 2: Do co-occurring respiratory diseases increase the risk of unemployment or work disability in a person with MSK disease?									
Reference	Design	MSD population (criteria used)	Number of Study Patients with MSD (n)	Age in years; Median (IQR)/ Mean ± SD/ Mean	Number of Females (%) in the Study	Adjustments (covariables)	Respiratory disease (definition)	Work outcome (definition)	Measure of association (95%CI)
Unemployment status or job loss									
Schofield (2014) (352)	CS	Arthritis (ICD-10 codes "arthritis and related disorders")	1,414	45 to 64 years	NR	Age, sex, and highest level of education	Diseases of the respiratory system (survey- ICD-10 codes)	Not being in the labour force (survey- self report)	Odds ratio (95% CI) Arthritis only: reference Diseases of the respiratory system:

									3.16 (1.35–7.43)
Schofield (2014) (352)	CS	Arthritis (ICD-10 codes "arthritis and related disorders")	1,414	45 to 64 years	NR	Age, sex, and highest level of education	Asthma (survey- ICD-10 codes)	Not being in the labour force (survey- self report)	Odds ratio (95% CI) Arthritis only: reference Asthma: 2.46 (1.37–4.42)

Appendix Table 12: Other disease and MSK disease related work disability

Table 2: Do other co-occurring diseases increase the risk of unemployment or work disability in a person with MSK disease?									
Reference	Design	MSD population (criteria used)	Number of Study Patients with MSD (n)	Age in years; Median (IQR)/ Mean ± SD/ Mean	Number of Females (%) in the Study	Adjustments (covariables)	Other disease (definition)	Work outcome (definition)	Measure of association (95%CI)
Unemployment status or job loss									
Schofield (2014) (352)	CS	Arthritis (ICD-10 codes "arthritis and related disorders")	1,414	45 to 64 years	NR	Age, sex, and highest level of education	Diseases of the eye and adnexa (survey- ICD-10 codes)	Not being in the labour force (survey- self report)	Odds ratio (95% CI) Arthritis only: reference Diseases of the eye and adnexa: 3.86 (1.13–13.14)
Schofield (2014) (352)	CS	Arthritis (ICD-10 codes "arthritis and related disorders")	1,414	45 to 64 years	NR	Age, sex, and highest level of education	Diseases of the skin and subcutaneous tissue (survey- ICD-10 codes)	Not being in the labour force (survey- self report)	Odds ratio (95% CI) Arthritis only: reference

									Diseases of the skin and subcutaneous tissue: 3.75 (1.31–10.72)
Schofield (2014) (352)	CS	Arthritis (ICD-10 codes "arthritis and related disorders")	1,414	45 to 64 years	NR	Age, sex, and highest level of education	Diseases of the digestive system (survey- ICD-10 codes)	Not being in the labour force (survey- self report)	Odds ratio (95% CI) Arthritis only: reference Diseases of the digestive system: 3.63 (1.91–6.89)
Schofield (2014) (352)	CS	Arthritis (ICD-10 codes "arthritis and related disorders")	1,414	45 to 64 years	NR	Age, sex, and highest level of education	Diseases of the nervous system (survey- ICD-10 codes)	Not being in the labour force (survey- self report)	Odds ratio (95% CI) Arthritis only: reference Diseases of the nervous system: 3.30 (1.72–6.32)
Schofield (2014) (352)	CS	Arthritis (ICD-10 codes "arthritis and related disorders")	1,414	45 to 64 years	NR	Age, sex, and highest level of education	Other endocrine/nutritional and metabolic disorders (survey- ICD-10 codes)	Not being in the labour force (survey- self report)	Odds ratio (95% CI) Arthritis only: reference Other endocrine/nutritional and metabolic disorders: 2.06 (0.92–4.58)
Schofield (2014) (352)	CS	Arthritis (ICD-10 codes "arthritis and related disorders")	1,414	45 to 64 years	NR	Age, sex, and highest level of education	Neoplasms (tumours/cancers) (survey- ICD-10 codes)	Not being in the labour force (survey- self report)	Odds ratio (95% CI) Arthritis only: reference Neoplasms (tumours/cancers): 2.60 (0.84–7.99)
Schofield (2014) (352)	CS	Arthritis (ICD-10 codes "arthritis	1,414	45 to 64 years	NR	Age, sex, and highest level of education	Diseases of the genitourinary system (survey- ICD-10 codes)	Not being in the labour force	Odds ratio (95% CI) Arthritis only: reference

		and related disorders")						(survey- self report)	Diseases of the genitourinary system: 1.65 (0.71–3.81)
Schofield (2014) (352)	CS	Arthritis (ICD-10 codes "arthritis and related disorders")	1,414	45 to 64 years	NR	Age, sex, and highest level of education	"Other" comorbidity (survey- ICD-10 codes)	Not being in the labour force (survey- self report)	Odds ratio (95% CI) Arthritis only: reference "Other": 2.64 (0.76–9.17)
Presenteeism									
Wilkie (2013) (353)	Cohort	Osteoarthritis (self-reported and defined as hip, knee, or foot pain for 1 day or more during the past year)	716	Range 50 to 59 years	392 (54.7)	Age, sex, severity of lower limb pain, number of painful sites, anxiety, depression, BMI, cognitive impairment.	Cognitive impairment (self-reported: Cognitive and Alertness behaviour subscale of the Functional Limitations Profile: No impairment (score of 0) and cognitive impairment (score>0))	Work restriction- Keele Assessment of Participation (KAP): ''During the past 4 weeks, if you work, have you taken part in paid or voluntary work as and when you have wanted?''- answered some/a little or none of the time.	Odds ratio (95% CI) Cognitive impairment None (0): 1 Cognitive impairment (0.1–100): 1.09 (0.67, 1.75)

Appendix Table 13: Newcastle-Ottawa Score: cross-sectional studies

Reference	**Outcome:** Assessment of the outcome	**Selection:** Representativeness of the sample	**Selection:** Sample size	**Comparability** Confounding factors are controlled for	**Selection:** ascertainment of the exposure	**Outcome:** Statistical test	**Selection:** Non-respondents comparable	**Quality**
ABRAI´DO-LANZA (2006) (12)	1	1	0	2	1	1	0	6/10
Agaliotis (2017) (363)	1	0	0	2	2	1	1	7/10
Buist-Bouwman (2005)(364)	1	1	0	1	1	1	0	5/10
CASTILLO-ORTIZ (2016)(9)	1	0	0	2	2	1	0	6/10
Csupak (2018) (358)	1	1	0	2	2	1	1	8/10
Hudson (2009) (13)	1	1	0	2	2	1	0	7/10
Joshi (2015)(365)	1	1	0	2	1	1	0	6/10
Kausto (2017) (366)	2	1	0	2	1	1	0	7/10
Kennedy (2014)(334)	1	1	0	2	2	1	0	7/10
Kessler (2001)(199)	1	1	0	1	2	1	0	6/10
Kessler (2003)(335)	1	1	0	1	2	1	1	7/10
Loewe (2004)(336)	1	1	1	1	1	1	0	6/10
Munce (2007)(337)	1	1	0	1	2	1	0	6/10
Nikiphorou (2018)(361)	1	1	0	2	2	1	0	7/10
Panopalis (2007)(338)	2	0	0	2	2	1	0	7/10

Callahan (1992)(339)	1	1	0	2	1	1	0	6/10
Van den Berg (2017) (340)	1	0	0	2	1	1	0	5/10
Van der Zee-Neuen (2017)(341)	1	1	1	2	2	1	0	8/10

Appendix Table 14: Newcastle-Ottawa Score: case-control studies

Reference	**Selection** Is the case definition adequate?	**Selection** Representativeness of the cases	**Selection** Selection of Controls	**Selection** Definition of Controls	**Comparability** Comparability of cases and controls on the basis of the design or analysis	**Outcome** Ascertainment of exposure	**Outcome** Same method of ascertainment for cases and controls	**Outcome** Non-Response rate	**Quality**
Marengo (2008) (342)	0	0	1	0	1	0	1	0	3/9

Appendix Table 15: Newcastle-Ottawa Score: cohort studies

Reference	**Selection** Representativeness of the exposed cohort	**Selection** Selection of the non-exposed cohort	**Selection** Ascertainment of exposure	**Selection** Demonstration that outcome of interest was not present at start of study	**Comparability** Comparability of cohorts on the basis of the design or analysis	**Outcome** Assessment of outcome	**Outcome** Was follow-up long enough for outcomes to occur	**Outcome** Adequacy of follow up of cohorts	**Quality**
Agaliotis (2013) (343)	0	1	1	1	1	0	1	1	6/9
Al Dhanhani (2009) (344)	0	1	1	1	2	0	1	0	7/9
Anderson (2016)(345)	0	1	1	1	2	1	1	0	7/9
Boonen (2001)(11)	1	1	0	1	1	0	0	1	5/9

Brede (2012)(346)	1	1	1	1	2	0	1	0	7/9
Furunes (2018)(359)	0	1	0	0	2	0	1	1	5/9
Kuijer (2017)(347)	0	1	1	0	1	0	1	1	5/9
Lee (2017) (348)	0	1	0	1	1	0	1	0	4/9
Manders (2014)(349)	0	1	1	1	2	1	1	0	7/9
Melkevik (2018)(360)	0	1	0	0	1	1	1	1	5/9
Nordin (2002)(350)	1	1	1	1	1	1	0	0	6/9
Olofsson (2016)(351)	1	1	1	1	1	1	1	0	7/9
Schofield (2014)(352)	0	1	1	0	1	1	1	1	6/9
Ward (2001)(10)	0	1	0	1	2	0	1	1	6/9
Webers (2018)(362)	1	1	1	1	2	0	1	1	8/9
Wilkie (2013)(353)	0	1	0	1	2	0	1	0	5/9
De Buck (2006)(354)	1	1	1	1	0	0	1	1	6/9
Schade (1999)(355)	1	1	1	1	0	0	1	1	6/9
Cote (2001)(356)	1	1	0	1	1	1	1	0	7/9
Hansen (2016)(357)	1	0	1	0	1	1	1	0	5/9

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Appendix Table 16: Strata of SOC-10 sub-major occupational groups among people with HRJL, in total and by gender.

Variable	Skill level	Total with HRJL, 494 (100.0%)	Male with HRJL, 220 (44.5%)	Female with HRJL, 274 (55.5%)
Corporate managers and directors	Level 4	18 (3.6)	5 (2.3)	13 (4.7)
Science, research, engineering, and technology professionals		9 (1.8)	7 (3.2)	2 (0.7)
Health professionals		28 (5.7)	2 (0.9)	26 (9.5)
Teaching and educational professionals		48 (9.7)	18 (8.2)	30 (11.0)
Business, media and public service professionals		14 (2.8)	9 (4.1)	5 (1.8)
Other managers and proprietors	Level 3	15 (3.0)	5 (2.3)	10 (3.7)
Science, engineering, and technology associate professionals		9 (1.8)	5 (2.3)	4 (1.5)
Health and social care associate professionals		10 (2.0)	4 (1.8)	6 (2.2)
Protective service occupations		7 (1.4)	6 (2.7)	1 (0.4)
Culture, media, and sports occupations		3 (0.6)	2 (0.9)	1 (0.4)
Business and public service associate professionals		15 (3.0)	8 (3.6)	7 (2.6)
Skilled agricultural and related trades		9 (1.8)	8 (3.6)	1 (0.4)
Skilled metal, electrical and electronic trades		16 (3.2)	16 (7.3)	0 (0.0)
Skilled construction and building trades		15 (3.0)	14 (6.4)	1 (0.4)
Textiles, printing, and other skilled trades		13 (2.6)	9 (4.1)	4 (1.5)
Administrative occupations	Level 2	65 (13.2)	18 (8.2)	47 (17.2)
Secretarial and related occupations		12 (2.4)	1 (0.5)	11 (4.0)
Caring personal service occupations		34 (6.9)	5 (2.3)	29 (10.6)
Leisure, travel and related personal service occupations		13 (2.6)	3 (1.4)	10 (3.7)
Sales occupations		30 (6.1)	5 (2.3)	25 (9.1)
Customer service occupations		5 (1.0)	2 (0.9)	3 (1.1)
Process, plant and machine operatives		16 (3.2)	12 (5.5)	4 (1.5)
Transport and mobile machine drivers and operatives		19 (3.9)	19 (8.6)	0 (0.0)
Elementary trade and related occupations	Level 1	10 (2.0)	8 (3.6)	2 (0.7)
Elementary administration and service occupations		53 (10.7)	27 (12.3)	26 (9.5)

Appendix Table 17: Strata of SOC-10 sub-major occupational groups among case participants, by age at HRJL

Variable	Skill level	HRJL <50 years old (%)	HRJL 50 to <60 years (%)	HRJL 60+ years old (%)
11 Corporate managers and directors	Level 4	2 (3.1)	13 (4.9)	3 (1.8)
21 Science, research, engineering, and technology professionals		2 (3.1)	5 (1.9)	2 (1.2)
22 Health professionals		4 (6.3)	12 (4.6)	12 (7.2)
23 Teaching and educational professionals		3 (4.7)	33 (12.5)	12 (7.2)
24 Business, media and public service professionals		1 (1.6)	8 (3.0)	5 (3.0)
12 Other managers and proprietors	Level 3	3 (4.7)	7 (2.7)	5 (3.0)
31Science, engineering, and technology associate professionals		0 (0.0)	6 (2.3)	3 (1.8)
32 Health and social care associate professionals		0 (0.0)	4 (1.5)	6 (3.6)
33 Protective service occupations		1 (1.6)	6 (2.3)	0 (0.0)
34 Culture, media, and sports occupations		1 (1.6)	2 (0.8)	0 (0.0)
35 Business and public service associate professionals		1 (1.6)	10 (3.8)	4 (2.4)
51 Skilled agricultural and related trades		4 (6.3)	1 (0.4)	4 (2.4)
52 Skilled metal, electrical and electronic trades		1 (1.6)	6 (2.3)	9 (5.4)
53 Skilled construction and building trades		0 (0.0)	8 (3.0)	7 (4.2)
54 Textiles, printing, and other skilled trades		2 (3.1)	9 (3.4)	2 (1.2)
41 Administrative occupations	Level 2	5 (7.8)	34 (12.9)	26 (15.7)
42 Secretarial and related occupations		0 (0.0)	9 (3.4)	3 (1.8)
61 Caring personal service occupations		4 (6.3)	17 (6.4)	13 (7.8)
62 Leisure, travel and related personal service occupations		1 (1.6)	9 (3.4)	3 (1.8)
71 Sales occupations		7 (10.9)	15 (5.7)	8 (4.8)
72 Customer service occupations		0 (0.0)	3 (1.1)	2 (1.2)
81 Process, plant and machine operatives		1 (1.6)	7 (2.7)	8 (4.8)
82 Transport and mobile machine drivers and operatives		3 (4.7)	4 (1.5)	3 (1.8)
91 Elementary trade and related occupations	Level 1	3 (4.7)	4 (1.5)	3 (1.8)
92 Elementary administration and service occupations		13 (20.3)	25 (9.5)	15 (9.0)

Appendix Table 18: Strata of SOC-10 sub-major occupational groups among people with HRJL, in total and by type of HRJL.

Variable	Skill level	Total with HRJL, 494 (100.0%)	Health main reason, 220 (46.6%)	Health part reason, 274 (53.4%)
Corporate managers and directors	Level 4	18 (3.6)	8 (3.5)	10 (3.8)
Science, research, engineering, and technology professionals		9 (1.8)	3 (1.3)	6 (2.3)
Health professionals		28 (5.7)	14 (6.1)	14 (5.3)
Teaching and educational professionals		48 (9.7)	11 (4.8)	37 (14.0)
Business, media and public service professionals		14 (2.8)	7 (3.0)	7 (2.7)
Other managers and proprietors	Level 3	15 (3.0)	8 (3.5)	10 (3.8)
Science, engineering, and technology associate professionals		9 (1.8)	3 (1.3)	6 (2.3)
Health and social care associate professionals		10 (2.0)	1 (0.4)	9 (3.4)
Protective service occupations		7 (1.4)	4 (1.7)	3 (1.1)
Culture, media, and sports occupations		3 (0.6)	2 (0.9)	1 (0.4)
Business and public service associate professionals		15 (3.0)	8 (3.5)	7 (2.7)
Skilled agricultural and related trades		9 (1.8)	4 (1.7)	5 (1.9)
Skilled metal, electrical and electronic trades		16 (3.2)	7 (3.0)	9 (3.4)
Skilled construction and building trades		15 (3.0)	14 (6.1)	1 (0.4)
Textiles, printing, and other skilled trades		13 (2.6)	6 (2.6)	7 (2.7)
Administrative occupations	Level 2	65 (13.2)	22 (9.6)	43 (16.3)
Secretarial and related occupations		12 (2.4)	4 (1.7)	8 (3.0)
Caring personal service occupations		34 (6.9)	16 (7.0)	18 (6.8)
Leisure, travel and related personal service occupations		13 (2.6)	7 (3.0)	6 (2.3)
Sales occupations		30 (6.1)	15 (6.5)	15 (5.7)
Customer service occupations		5 (1.0)	3 (1.3)	2 (0.8)
Process, plant and machine operatives		16 (3.2)	8 (3.5)	8 (3.0)
Transport and mobile machine drivers and operatives		19 (3.9)	12 (5.2)	7 (2.7)
Elementary trade and related occupations	Level 1	10 (2.0)	6 (2.6)	4 (1.5)
Elementary administration and service occupations		53 (10.7)	32 (13.9)	21 (8.0)

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Appendix Table 19: Strata of SOC-10 major occupational groups and association with HRJL

Variable	Total participants, 988 (%)	Control, n (%)	Case, n (%)	Association with HRJL OR (95% CI)
Managers, directors and senior officials	82 (8.3)	49 (9.9)	33 (6.7)	0.65 (0.41 to 1.03)
Professional occupations	198 (20.0)	99 (20.0)	99 (20.0)	1.00 (0.73 to 1.36)
Associate professional and technical occupations	91 (9.2)	47 (9.5)	44 (8.9)	0.93 (0.61 to 1.43)
Administrative and secretarial occupations	168 (17.0)	91 (18.4)	77 (15.6)	0.82 (0.59 to 1.14)
Skilled trades occupations	98 (9.9)	45 (9.1)	53 (10.7)	1.21 (0.79 to 1.84)
Caring, leisure, and other service occupations	86 (8.7)	39 (7.9)	47 (9.5)	1.24 (0.79 to 1.96)
Sales and customer service occupations	74 (7.5)	39 (7.9)	35 (7.1)	0.88 (0.54 to 1.44)
Process, plant and machine operatives	71 (7.2)	36 (7.3)	35 (7.1)	0.97 (0.57 to 1.62)
Elementary occupations	105 (10.6)	42 (8.5)	63 (12.8)	**1.58 (1.04 to 2.40)**

Appendix Table 20: Strata of SOC-10 sub-major occupational groups and association with HRJL

Variable	Skill level	Total participants, 988 (%)	Control, n (%)	Case, n (%)	Association with HRJL OR (95% CI)
11 Corporate managers and directors	Level 4 (n=237)	39 (4.0)	21 (4.3)	18 (3.6)	0.86 (0.46 to 1.61)
21 Science, research, engineering, and technology professionals		26 (2.6)	17 (3.4)	9 (1.8)	0.53 (0.24 to 1.19)
22 Health professionals		55 (5.6)	27 (5.5)	28 (5.7)	1.04 (0.59 to 1.82)
23 teaching and educational professionals		80 (8.1)	32 (6.5)	48 (9.7)	1.52 (0.96 to 2.39)
24 business, media and public service professionals		37 (3.7)	23 (4.7)	14 (2.8)	0.61 (0.31 to 1.18)
12 other managers and proprietors	Level 3 (n=232)	43 (4.4)	28 (5.7)	15 (3.0)	**0.48 (0.24 to 0.96)**
31 Science, engineering, and technology associate professionals		16 (1.6)	7 (1.4)	9 (1.8)	1.29 (0.48 to 3.45)

32 Health and social care associate professionals		20 (2.0)	10 (2.0)	10 (2.0)	1.00 (0.42 to 2.40)
33 Protective service occupations		10 (1.0)	3 (0.6)	7 (1.4)	2.33 (0.60 to 9.02)
34 Culture, media, and sports occupations		7 (0.7)	4 (0.8)	3 (0.6)	0.75 (0.17 to 3.35)
35 Business and public service associate professionals		38 (3.9)	23 (4.7)	15 (3.0)	0.64 (0.33 to 1.24)
51 Skilled agricultural and related trades		19 (1.9)	10 (2.0)	9 (1.8)	0.90 (0.37 to 2.21)
52 Skilled metal, electrical and electronic trades		32 (3.2)	16 (3.2)	16 (3.2)	1.00 (0.50 to 2.00)
53 Skilled construction and building trades		25 (2.5)	10 (2.0)	15 (3.0)	1.56 (0.67 to 3.59)
54 Textiles, printing, and other skilled trades		22 (2.2)	9 (1.8)	13 (2.6)	1.44 (0.62 to 3.38)
41 Administrative occupations	Level 2 (n=399)	134 (13.6)	69 (14.0)	65 (13.2)	0.94 (0.66 to 1.33)
42 Secretarial and related occupations		34 (3.4)	22 (4.5)	12 (2.4)	0.50 (0.23 to 1.07)
61 Caring personal service occupations		63 (6.4)	29 (5.9)	34 (6.9)	1.20 (0.71 to 2.04)
62 Leisure, travel and related personal service occupations		23 (2.3)	10 (2.0)	13 (2.6)	1.33 (0.56 to 3.16)
71 Sales occupations		64 (6.5)	34 (6.9)	30 (6.1)	0.86 (0.50 to 1.47)
72 Customer service occupations		10 (1.0)	5 (1.0)	5 (1.0)	1.00 (0.29 to 3.45)
81 Process, plant and machine operatives		30 (3.0)	14 (2.8)	16 (3.2)	1.17 (0.54 to 2.52)
82 Transport and mobile machine drivers and operatives		41 (4.2)	22 (4.5)	19 (3.9)	0.85 (0.45 to 1.62)
91 Elementary trade and related occupations	Level 1 (n=105)	17 (1.7)	7 (1.4)	10 (2.0)	1.43 (0.54 to 3.75)
92 Elementary administration and service occupations		88 (8.9)	35 (7.1)	53 (10.7)	**1.55 (1.00 to 2.39)**

Appendix Table 21: Association between structural heart disease and health-related job loss, across total study population and by gender

Variable	Number of "exposed" controls, n (%)	Number of "exposed" cases, n (%)	Association with HRJL, unadjusted. OR (95% CI)	Association with HRJL, adjusted for education level, single status, history of heavy alcohol use. OR (95% CI)
No structural heart disease	494 (100.0)	487 (98.6)	1.00	1.00
Structural heart disease	0 (0)	7 (1.4)	NR	NR
Men				
No structural heart disease	220 (100.0)	213 (96.8)	1.00	1.00
Structural heart disease	0 (0.0)	7 (3.2)	NR	NR
Women				
No structural heart disease	274 (100.0)	274 (100.0)	1.00	1.00
Structural heart disease	0 (0.0)	0 (0.0)	NR	NR

Appendix Table 22: Association between cardiac arrhythmias and health-related job loss, across total study population and by gender

Variable	Number of "exposed" controls, n (%)	Number of "exposed" cases, n (%)	Association with HRJL, unadjusted. OR (95% CI)	Association with HRJL, adjusted for education level, single status, history of heavy alcohol use. OR (95% CI)
No arrhythmias	493 (99.8)	487 (98.6)	1.00	1.00
Cardiac arrhythmias	1 (0.2)	7 (1.4)	7.00 (0.86 to 56.89)	6.83 (0.83 to 56.47)
Men				
No arrhythmias	220 (100.0%)	214 (97.3)	1.00	1.00
Cardiac arrhythmias	0 (0.0)	6 (2.7)	NR	NR
Women				
No arrhythmias	273 (99.6)	273 (99.6)	1.00	1.00
Cardiac arrhythmias	1 (0.4)	1 (0.4)	1.00 (0.06 to 15.99)	1.14 (0.07 to 18.32)

Appendix Table 23: Association between psychiatric-level mental health problems and health-related job loss, by age at HRJL

Variable	Number of "exposed" controls, n (%)	Number of "exposed" cases, n (%)	Association with HRJL, unadjusted. OR (95% CI)	Association with HRJL, adjusted for education level, single status, history of heavy alcohol use. OR (95% CI)
Aged <50				
No psychiatric-level MHPs	63 (98.4)	63 (98.4)	1.00	1.00
Psychiatric-level MHPs	1 (1.6)	1 (1.6)	1.00 (0.06 to 15.99)	0.72 (0.04 to 11.86)
Aged 50 - <60				
No psychiatric-level MHPs	263 (99.6)	258 (97.7)	1.00	1.00
Psychiatric-level MHPs	1 (0.38)	6 (2.3)	6.00 (0.72 to 49.84)	6.22 (0.69 to 55.86)
Aged >60				
No psychiatric-level MHPs	166 (100.0)	165 (99.4)	1.00	1.00
Psychiatric-level MHPs	0 (0.0)	1 (0.6)	NE	NE

Appendix Table 24: Association between peripheral atherosclerotic disease and health-related job loss, by age at HRJL

Variable	Number of "exposed" controls, n (%)	Number of "exposed" cases, n (%)	Association with HRJL, unadjusted. OR (95% CI)	Association with HRJL, adjusted for education level, single status, history of heavy alcohol use. OR (95% CI)
Aged <50				
No PAD	64 (100.0)	63 (98.4)	1.00	1.00
PAD	0 (0.0)	1 (1.6)	NE	NE
Aged 50 - <60				
No PAD	263 (99.6)	257 (97.4)	1.00	1.00
PAD	1 (0.4)	7 (2.7)	7.00 (0.86 to 56.89)	7.12 (0.82 to 61.51)
Aged >60				
No PAD	166 (100.0)	163 (98.2)	1.00	1.00
PAD	0 (0.0)	3 (1.8)	NE	NE

Appendix Table 25: Association between cardiac arrhythmias and health-related job loss, by age at HRJL

Variable	Number of "exposed" controls, n (%)	Number of "exposed" cases, n (%)	Association with HRJL, unadjusted. OR (95% CI)	Association with HRJL, adjusted for education level, single status, history of heavy alcohol use. OR (95% CI)
Aged <50				
No arrhythmias	64 (100.0)	64 (100.0)	1.00	1.00
Cardiac arrhythmias	0 (0.0)	0 (0.0)	NE	NE
Aged 50 - <60				
No arrhythmias	264 (100.0)	259 (98.1)	1.00	1.00
Cardiac arrhythmias	0 (0.0)	5 (1.9)	NE	NE
Aged >60				
No arrhythmias	165 (99.4)	164 (98.8)	1.00	1.00
Cardiac arrhythmias	1 (0.6)	2 (1.2)	2.00 (0.18 to 22.06)	2.58 (0.23 to 29.12)

Appendix Table 27: Association between structural heart disease and health-related job loss, by age at HRJL

Variable	Number of "exposed" controls, n (%)	Number of "exposed" cases, n (%)	Association with HRJL, unadjusted. OR (95% CI)	Association with HRJL, adjusted for education level, single status, history of heavy alcohol use. OR (95% CI)
Aged <50				
No structural heart disease	64 (100.0)	64 (100.0)	1.00	1.00
Structural heart disease	0 (0.0)	0 (0.0)	NE	NE
Aged 50 - <60				
No structural heart disease	264 (100.0)	261 (98.9)	1.00	1.00
Structural heart disease	0 (0.0)	3 (1.1)	NE	NE
Aged >60				
No structural heart disease	166 (100.0)	162 (97.6)	1.00	1.00
Structural heart disease	0 (0.0)	4 (2.4)	NE	NE

Appendix Table 27: Association between epilepsy and health-related job loss, by age at HRJL

Variable	Number of "exposed" controls, n (%)	Number of "exposed" cases, n (%)	Association with HRJL, unadjusted. OR (95% CI)	Association with HRJL, adjusted for education level, single status, history of heavy alcohol use. OR (95% CI)
Aged <50				
No epilepsy	64 (100.0)	62 (96.9)	1.00	1.00
Epilepsy	0 (0.0)	2 (3.1)	NE	NE
Aged 50 - <60				
No epilepsy	261 (98.9)	260 (98.5)	1.00	1.00
Epilepsy	3 (1.1)	4 (1.5)	1,50 (0.25 to 8.98)	2.08 (0.30 to 14.57)
Aged >60				
No epilepsy	166 (100.0)	165 (99.4)	1.00	1.00
Epilepsy	0 (0.0)	1 (0.6)	NE	NE

Appendix Table 28: Association between association between chronic MSD and health-related job loss, by age at HRJL

Variable	Prevalence among controls, n (%)	Prevalence among cases, n (%)	Association with HRJL, unadjusted. OR (95% CI)	Association with HRJL, adjusted for education level, single status, history of heavy alcohol use. OR (95% CI)
Aged <50				
No chronic MSD	60 (93.8)	55 (85.9)	1.00	1.00
Chronic MSD	4 (6.3)	9 (14.1)	2.25 (0.69 to 7.31)	2.55 (0.63 to 10.33)
Aged 50 - <60				
No chronic MSD	217 (82.2)	195 (73.9)	1.00	1.00
Chronic MSD	47 (17.8)	69 (26.1)	**1.59 (1.06 to 2.41)**	**1.58 (1.04 to 2.41)**
Aged >60				
No chronic MSD	135 (81.3)	108 (65.1)	1.00	1.00
Chronic MSD	31 (18.7)	58 (34.9)	**2.42 (1.42 to 4.13)**	**2.25 (1.31 to 3.88)**

Appendix Table 29: Association between musculoskeletal pain and health-related job loss, by age at HRJL

Variable	Prevalence among controls, n (%)	Prevalence among cases, n (%)	Association with HRJL, unadjusted. OR (95% CI)	Association with HRJL, adjusted for education level, single status, history of heavy alcohol use. OR (95% CI)
Aged <50				
No MSD pain	56 (87.5)	41 (64.1)	1.00	1.00
MSD pain	8 (12.5)	23 (35.9)	**4.00 (1.50 to 10.66)**	**4.40 (1.48 to 13.08)**
Aged 50 - <60				
No MSD pain	222 (84.1)	182 (68.9)	1.00	1.00
MSD pain	42 (15.9)	82 (31.1)	**2.48 (1.59 to 3.88)**	**2.33 (1.46 to 3.71)**
Aged >60				
No MSD pain	128 (77.1)	118 (71.1)	1.00	1.00
MSD pain	38 (22.9)	48 (28.9)	1.48 (0.85 to 2.57)	1.51 (0.85 to 2.67)

Appendix Table 30: Association between primary-care-level mental health problems and health-related job loss, by age at HRJL

Variable	Prevalence among controls, n (%)	Prevalence among cases, n (%)	Association with HRJL, unadjusted. OR (95% CI)	Association with HRJL, adjusted for education level, single status, history of heavy alcohol use. OR (95% CI)
Aged <50				
No primary-care-level MHP	59 (92.2)	44 (68.8)	1.00	1.00
Primary-care-level MHP	5 (7.8)	20 (31.3)	**16.00 (2.12 to 120.65)**	**29.70 (2.78 to 317.56)**
Aged 50 - <60				
No primary-care-level MHP	233 (88.3)	182 (68.9)	1.00	1.00
Primary-care-level MHP	31 (11.7)	82 (31.1)	**3.55 (2.16 to 5.83)**	**3.61 (2.14 to 6.09)**
Aged >60				
No primary-care-level MHP	154 (92.8)	139 (83.7)	1.00	1.00
Primary-care-level MHP	12 (7.2)	27 (16.3)	**2.36 (1.17 to 4.78)**	**2.04 (0.98 to 4.25)**

Appendix Table 31: Association between sleep disturbance and health-related job loss, by age at HRJL

Variable	Prevalence among controls, n (%)	Prevalence among cases, n (%)	Association with HRJL, unadjusted. OR (95% CI)	Association with HRJL, adjusted for education level, single status, history of heavy alcohol use. OR (95% CI)
Aged <50				
No sleep disorders	61 (95.3)	58 (90.6)	1.00	1.00
Sleep disorders	3 (4.7)	6 (9.4)	**2.00 (0.50 to 8.00)**	**2.71 (0.46 to 16.05)**
Aged 50 - <60				
No sleep disorders	256 (97.0)	246 (93.2)	1.00	1.00
Sleep disorders	8 (3.0)	18 (6.8)	**2.67 (1.04 to 6.81)**	**2.45 (0.94 to 6.42)**
Aged >60				
No sleep disorders	163 (98.2)	153 (92.2)	1.00	1.00
Sleep disorders	3 (1.8)	13 (7.8)	**4.33 (1.23 to 15.21)**	**4.34 (1.18 to 15.97)**

Appendix Table 32: Association between severe mental health disorders and health-related job loss, by age at HRJL

Variable	Prevalence among controls, n (%)	Prevalence among cases, n (%)	Association with HRJL, unadjusted. OR (95% CI)	Association with HRJL, adjusted for education level, single status, history of heavy alcohol use. OR (95% CI)
Aged <50				
No severe MHPs	63 (98.4)	57 (89.1)	1.00	1.00
Severe MHPs	1 (1.6)	7 (10.9)	NE	NE
Aged 50 - <60				
No severe MHPs	258 (97.7)	240 (90.9)	1.00	1.00
Severe MHPs	6 (2.3)	24 (9.1)	**4.00 (1.64 to 9.79)**	**4.00 (1.49 to 10.76)**
Aged >60				
No severe MHPs	163 (98.2)	160 (96.4)	1.00	1.00
Severe MHPs	3 (1.8)	6 (3.6)	2.50 (0.49 to 12.89)	3.09 (0.57 to 16.80)

Appendix Table 33: Association between hypertension and health-related job loss, by age at HRJL

Variable	Prevalence among controls, n (%)	Prevalence among cases, n (%)	Association with HRJL, unadjusted. OR (95% CI)	Association with HRJL, adjusted for education level, single status, history of heavy alcohol use. OR (95% CI)
Aged <50				
No hypertension	61 (95.3)	55 (85.9)	1.00	1.00
Hypertension	3 (4.7)	9 (14.1)	3.00 (0.81 to 11.08)	3.52 (0.77 to 16.01)
Aged 50 - <60				
No hypertension	219 (83.0)	194 (73.5)	1.00	1.00
Hypertension	45 (17.1)	70 (26.5)	**1.86 (1.19 to 2.92)**	**1.90 (1.19 to 3.04)**
Aged >60				
No hypertension	130 (78.3)	112 (67.5)	1.00	1.00
Hypertension	36 (21.7)	54 (32.5)	**1.78 (1.07 to 2.97)**	**1.64 (0.97 to 2.76)**

Appendix Table 34: Association between heart failure and health-related job loss, by age at HRJL

Variable	Prevalence among controls, n (%)	Prevalence among cases, n (%)	Association with HRJL, unadjusted. OR (95% CI)	Association with HRJL, adjusted for education level, single status, history of heavy alcohol use. OR (95% CI)
Aged <50				
No heart failure	64 (100.0)	63 (98.4)	1.00	1.00
Heart failure	0 (0.0)	1 (1.6)	NE	NE
Aged 50 - <60				
No heart failure	257 (97.4)	251 (95.1)	1.00	1.00
Heart failure	7 (2.7)	13 (4.9)	1.86 (0.74 to 4.65)	1.83 (0.71 to 4.72)
Aged >60				
No heart failure	159 (95.8)	136 (81.9)	1.00	1.00
Heart failure	7 (4.2)	30 (18.1)	**6.75 (2.36 to 19.29)**	**7.63 (2.52 to 23.11)**

Appendix Table 35: Association between ischaemic heart disease and health-related job loss, by age at HRJL

Variable	Prevalence among controls, n (%)	Prevalence among cases, n (%)	Association with HRJL, unadjusted. OR (95% CI)	Association with HRJL, adjusted for education level, single status, history of heavy alcohol use. OR (95% CI)
Aged <50				
No IHD	64 (100.0)	63 (98.4)	1.00	1.00
IHD	0 (0.0)	1 (1.6)	NE	NE
Aged 50 - <60				
No IHD	254 (96.2)	250 (94.7)	1.00	1.00
IHD	10 (3.8)	14 (5.3)	1.40 (0.62 to 3.15)	1.25 (0.55 to 2.88)
Aged >60				
No IHD	155 (93.4)	151 (91.0)	1.00	1.00
IHD	11 (6.6)	15 (9.0)	1.40 (0.62 to 3.15)	1.23 (0.52 to 2.93)

Appendix Table 36: Association between asthma and health-related job loss, by age at HRJL

Variable	Prevalence among controls, n (%)	Prevalence among cases, n (%)	Association with HRJL, unadjusted. OR (95% CI)	Association with HRJL, adjusted for education level, single status, history of heavy alcohol use. OR (95% CI)
Aged <50				
No asthma	60 (93.8)	60 (93.8)	1.00	1.00
Asthma	4 (6.3)	4 (6.3)	1.00 (0.25 to 4.00)	1.12 (0.24 to 5.17)
Aged 50 - <60				
No asthma	244 (92.4)	234 (88.6)	1.00	1.00
Asthma	20 (7.6)	30 (11.4)	1.67 (0.88 to 3.16)	1.94 (0.99 to 3.81)
Aged >60				
No asthma	60 (93.8)	60 (93.8)	1.00	1.00
Asthma	4 (6.3)	4 (6.3)	1.86 (0.74 to 4.65)	2.19 (0.84 to 5.72)

Appendix Table 37: Association between COPD and health-related job loss, by age at HRJL

Variable	Prevalence among controls, n (%)	Prevalence among cases, n (%)	Association with HRJL, unadjusted. OR (95% CI)	Association with HRJL, adjusted for education level, single status, history of heavy alcohol use. OR (95% CI)
Aged <50				
No COPD	64 (100.0)	64 (100.0)	1.00	1.00
COPD	0 (0.0)	0 (0.0)	NE	NE
Aged 50 - <60				
No COPD	261 (98.9)	257 (97.4)	1.00	1.00
COPD	3 (1.1)	7 (2.7)	2.33 (0.60 to 9.02)	2.67 (0.54 to 13.30)
Aged >60				
No COPD	164 (98.8)	158 (95.2)	1.00	1.00
COPD	2 (1.2)	8 (4.8)	4.00 (0.85 to 18.84)	6.12 (1.14 to 32.74)

Appendix Table 38: Association between cerebrovascular accident and health-related job loss, by age at HRJL

Variable	Prevalence among controls, n (%)	Prevalence among cases, n (%)	Association with HRJL, unadjusted. OR (95% CI)	Association with HRJL, adjusted for education level, single status, history of heavy alcohol use. OR (95% CI)
Aged <50				
No CVA	64 (100.0)	64 (100.0)	1.00	1.00
CVA	0 (0.0)	0 (0.0)	NE	NE
Aged 50 - <60				
No CVA	262 (99.2)	254 (96.2)	1.00	1.00
CVA	2 (0.8)	10 (3.8)	**5.00 (1.10 to 22.82)**	**5.76 (1.19 to 27.79)**
Aged >60				
No CVA	164 (98.8)	159 (95.8)	1.00	1.00
CVA	2 (1.2)	7 (4.2)	3.50 (0.73 to 16.85)	3.33 (0.67 to 16.48)

Appendix Table 39: Association between diabetes and health-related job loss, by age at HRJL

Variable	Prevalence among controls, n (%)	Prevalence among cases, n (%)	Association with HRJL, unadjusted. OR (95% CI)	Association with HRJL, adjusted for education level, single status, history of heavy alcohol use. OR (95% CI)
Aged <50				
No diabetes	64 (100.0)	59 (92.2)	1.00	1.00
Any diabetes	0 (0.0)	5 (7.8)	NE	NE
Aged 50 - <60				
No diabetes	248 (93.9)	233 (88.3)	1.00	1.00
Any diabetes	16 (6.1)	31 (11.7)	**2.25 (1.14 to 4.44)**	**2.07 (1.03 to 4.19)**
Aged >60				
No diabetes	151 (91.0)	142 (85.5)	1.00	1.00
Any diabetes	15 (9.0)	24 (14.5)	1.90 (0.88 to 4.09)	1.77 (0.81 to 3.87)

Appendix Table 40: Association between psychiatric-level mental health problems and health-related job loss, by "type" of HRJL

Variable	Number of "exposed" controls, n (%)	Number of "exposed" cases, n (%)	Association with HRJL, unadjusted. OR (95% CI)	Association with HRJL, adjusted for education level, single status, history of heavy alcohol use. OR (95% CI)
Mainly due to a health problem				
No psychiatric-level MHPs	228 (99.1)	227 (98.7)	1.00	1.00
Psychiatric-level MHPs	2 (0.9)	3 (1.3)	1.50 (0.25 to 8.98)	1.63 (0.25 to 10.59)
Partly due to a health problem				
No psychiatric-level MHPs	264 (100.0)	259 (98.1)	1.00	1.00
Psychiatric-level MHPs	0 (0.0)	5 (1.9)	NE	NE

Appendix Table 41: Association between peripheral atherosclerotic disease and health-related job loss, by "type" of HRJL

Variable	Number of "exposed" controls, n (%)	Number of "exposed" cases, n (%)	Association with HRJL, unadjusted. OR (95% CI)	Association with HRJL, adjusted for education level, single status, history of heavy alcohol use. OR (95% CI)
Mainly due to a health problem				
No PAD	229 (99.6)	226 (98.3)	1.00	1.00
PAD	1 (0.4)	4 (1.7)	4.00 (0.45 to 35.79)	2.43 (0.25 to 23.94)
Partly due to a health problem				
No PAD	264 (100.0)	257 (97.4)	1.00	1.00
PAD	0 (0.0)	7 (2.7)	NE	NE

Appendix Table 42: Association between cardiac arrhythmias and health-related job loss, by "type" of HRJL

Variable	Number of "exposed" controls, n (%)	Number of "exposed" cases, n (%)	Association with HRJL, unadjusted. OR (95% CI)	Association with HRJL, adjusted for education level, single status, history of heavy alcohol use. OR (95% CI)
Mainly due to a health problem				
No arrhythmias	230 (100.0)	224 (97.4)	1.00	1.00
Cardiac arrhythmias	0 (0.0)	6 (2.6)	NE	NE
Partly due to a health problem				
No arrhythmias	263 (99.6)	263 (99.6)	1.00	1.00
Cardiac arrhythmias	1 (0.4)	1 (0.4)	1.00 (0.06 to 15.99)	0.85 (0.05 to 14.22)

Appendix Table 43: Association between structural heart disease and health-related job loss, by "type" of HRJL

Variable	Number of "exposed" controls, n (%)	Number of "exposed" cases, n (%)	Association with HRJL, unadjusted. OR (95% CI)	Association with HRJL, adjusted for education level, single status, history of heavy alcohol use. OR (95% CI)
Mainly due to a health problem				
No structural heart disease	230 (100.0)	226 (98.3)	1.00	1.00
Structural heart disease	0 (0.0)	4 (1.7)	NE	NE

Partly due to a health problem				
No structural heart disease	264 (100.0)	261 (98.9)	1.00	1.00
Structural heart disease	0 (0.0)	3 (1.1)	NE	NE

Appendix Table 44: Association between COPD and health-related job loss, by "type" of HRJL

Variable	Number of "exposed" controls, n (%)	Number of "exposed" cases, n (%)	Association with HRJL, unadjusted. OR (95% CI)	Association with HRJL, adjusted for education level, single status, history of heavy alcohol use. OR (95% CI)
Mainly due to a health problem				
No COPD	230 (100.0)	220 (95.7)	1.00	1.00
COPD	0 (0.0)	10 (4.4)	NE	NE
Partly due to a health problem				
No COPD	259 (98.1)	259 (98.1)	1.00	1.00
COPD	5 (1.9)	5 (1.9)	1.00 (0.29 to 3.45)	1.28 (0.32 to 5.13)

Appendix Table 45: Association between epilepsy and health-related job loss, by "type" of HRJL

Variable	Number of "exposed" controls, n (%)	Number of "exposed" cases, n (%)	Association with HRJL, unadjusted. OR (95% CI)	Association with HRJL, adjusted for education level, single status, history of heavy alcohol use. OR (95% CI)
Mainly due to a health problem				
No epilepsy	229 (99.6)	226 (98.3)	1.00	1.00
Epilepsy	1 (0.4)	4 (1.7)	4.00 (0.45 to 35.79)	5.83 (0.62 to 54.96)
Partly due to a health problem				
No epilepsy	262 (99.2)	261 (98.9)	1.00	1.00
Epilepsy	2 (0.8)	3 (1.1)	2.00 (0.18 to 22.06)	1.77 (0.16 to 20.05)

Appendix Table 46: Association between chronic MSD and health-related job loss, by "type" of HRJL

Variable	Prevalence among controls, n (%)	Prevalence among cases, n (%)	Association with HRJL, unadjusted. OR (95% CI)	Association with HRJL, adjusted for education level, single status, history of heavy alcohol use. OR (95% CI)
Mainly due to a health problem				
No chronic MSD	203 (88.3)	168 (73.0)	1.00	1.00
Chronic MSD	27 (11.7)	62 (27.0)	**2.75 (1.65 to 4.59)**	**2.71 (1.60 to 4.57)**
Partly due to a health problem				
No chronic MSD	209 (79.2)	190 (72.0)	1.00	1.00
Chronic MSD	55 (20.8)	74 (28.0)	1.48 (0.99 to 2.20)	1.47 (0.98 to 2.22)

Appendix Table 47: Association between musculoskeletal pain and health-related job loss, by "type" of HRJL

Variable	Prevalence among controls, n (%)	Prevalence among cases, n (%)	Association with HRJL, unadjusted. OR (95% CI)	Association with HRJL, adjusted for education level, single status, history of heavy alcohol use. OR (95% CI)
Mainly due to a health problem				
No MSD pain	186 (80.9)	151 (65.7)	1.00	1.00
MSD pain	44 (19.1)	79 (34.4)	**2.13 (1.39 to 3.26)**	**2.01 (1.30 to 3.12)**
Partly due to a health problem				
No MSD pain	220 (83.3)	190 (72.0)	1.00	1.00
MSD pain	44 (16.7)	74 (28.0)	**2.36 (1.44 to 3.89)**	**2.42 (1.44 to 4.07)**

Appendix Table 48: Association between primary-care-level mental health problems and health-related job loss, by "type" of HRJL

Variable	Prevalence among controls, n (%)	Prevalence among cases, n (%)	Association with HRJL, unadjusted. OR (95% CI)	Association with HRJL, adjusted for education level, single status, history of heavy alcohol use. OR (95% CI)
Mainly due to a health problem				
No primary-care-level MHPs	214 (93.0)	161 (70.0)	1.00	1.00
Primary-care-level MHPs	16 (7.0)	69 (30.0)	**6.89 (3.42 to 13.86)**	**6.93 (3.37 to 14.25)**

Partly due to a health problem				
No primary-care-level MHPs	232 (87.9)	204 (77.3)	1.00	1.00
Primary-care-level MHPs	32 (12.1)	60 (22.7)	**2.22 (1.36 to 3.63)**	**2.08 (1.24 to 3.46)**

Appendix Table 49: Association between sleep disturbance and health-related job loss, by "type" of HRJL

Variable	Prevalence among controls, n (%)	Prevalence among cases, n (%)	Association with HRJL, unadjusted. OR (95% CI)	Association with HRJL, adjusted for education level, single status, history of heavy alcohol use. OR (95% CI)
Mainly due to a health problem				
No sleep disorders	224 (97.4)	211 (91.7)	1.00	1.00
Sleep disorders	6 (2.6)	19 (8.3)	**3.60 (1.34 to 9.70)**	**3.57 (1.27 to 10.04)**
Partly due to a health problem				
No sleep disorders	256 (97.0)	246 (93.2)	1.00	1.00
Sleep disorders	8 (3.0)	18 (6.8)	**2.43 (1.01 to 5.86)**	2.18 (0.89 to 5.33)

Appendix Table 50: Association between severe mental health disorders and health-related job loss, by "type" of HRJL

Variable	Prevalence among controls, n (%)	Prevalence among cases, n (%)	Association with HRJL, unadjusted. OR (95% CI)	Association with HRJL, adjusted for education level, single status, history of heavy alcohol use. OR (95% CI)
Mainly due to a health problem				
No severe MHPs	225 (97.8)	210 (91.3)	1.00	1.00
Severe MHPs	5 (2.2)	20 (8.7)	**4.75 (1.62 to 13.96)**	**4.29 (1.42 to 12.92)**
Partly due to a health problem				
No severe MHPs	259 (98.1)	247 (93.6)	1.00	1.00
Severe MHPs	5 (1.9)	17 (6.4)	**4.00 (1.34 to 11.96)**	**4.46 (1.27 to 15.72)**

Appendix Table 51: Association between hypertension and health-related job loss, by "type" of HRJL

Variable	Prevalence among controls, n (%)	Prevalence among cases, n (%)	Association with HRJL, unadjusted. OR (95% CI)	Association with HRJL, adjusted for education level, single status, history of heavy alcohol use. OR (95% CI)
Mainly due to a health problem				
No hypertension	189 (82.2)	177 (77.0)	1.00	1.00
Hypertension	41 (17.8)	53 (23.0)	**1.44 (0.88 to 2.36)**	**1.34 (0.80 to 2.22)**
Partly due to a health problem				
No hypertension	221 (83.7)	184 (69.7)	1.00	1.00
Hypertension	43 (16.3)	80 (30.3)	**2.32 (1.49 to 3.62)**	**2.26 (1.44 to 3.55)**

Appendix Table 52: Association between heart failure and health-related job loss, by "type" of HRJL

Variable	Prevalence among controls, n (%)	Prevalence among cases, n (%)	Association with HRJL, unadjusted. OR (95% CI)	Association with HRJL, adjusted for education level, single status, history of heavy alcohol use. OR (95% CI)
Mainly due to a health problem				
No heart failure	224 (97.4)	208 (90.4)	1.00	1.00
Heart failure	6 (2.6)	22 (9.6)	**5.00 (1.71 to 14.63)**	**4.34 (1.46 to 12.95)**
Partly due to a health problem				
No heart failure	256 (97.0)	242 (91.7)	1.00	1.00
Heart failure	8 (3.0)	22 (8.3)	**3.00 (1.28 to 7.06)**	**3.42 (1.38 to 8.44)**

Appendix Table 53: Association between ischaemic heart disease and health-related job loss, by "type" of HRJL

Variable	Prevalence among controls, n (%)	Prevalence among cases, n (%)	Association with HRJL, unadjusted. OR (95% CI)	Association with HRJL, adjusted for education level, single status, history of heavy alcohol use. OR (95% CI)
Mainly due to a health problem				
No IHD	221 (96.1)	216 (93.9)	1.00	1.00
Ischaemic Heart Disease	9 (3.9)	14 (6.1)	1.56 (0.67 to 3.59)	1.32 (0.56 to 3.12)
Partly due to a health problem				

No IHD	252 (95.5)	248 (93.9)	1.00	1.00
Ischaemic Heart Disease	12 (4.6)	16 (6.1)	1.36 (0.63 to 2.97)	1.34 (0.61 to 2.97)

Appendix Table 54: Association between asthma and health-related job loss, by "type" of HRJL

Variable	Prevalence among controls, n (%)	Prevalence among cases, n (%)	Association with HRJL, unadjusted. OR (95% CI)	Association with HRJL, adjusted for education level, single status, history of heavy alcohol use. OR (95% CI)
Mainly due to a health problem				
No asthma	218 (94.8)	208 (90.4)	1.00	1.00
Asthma	12 (5.2)	22 (9.6)	2.03 (0.99 to 4.18)	**2.18 (1.05 to 4.55)**
Partly due to a health problem				
No asthma	245 (92.8)	239 (90.5)	1.00	1.00
Asthma	19 (7.2)	25 (9.5)	1.41 (0.76 to 2.64)	1.51 (0.79 to 2.87)

Appendix Table 55: Association between cerebrovascular accident and health-related job loss, by "type" of HRJL

Variable	Prevalence among controls, n (%)	Prevalence among cases, n (%)	Association with HRJL, unadjusted. OR (95% CI)	Association with HRJL, adjusted for education level, single status, history of heavy alcohol use. OR (95% CI)
Mainly due to a health problem				
No CVA	229 (99.6)	218 (94.8)	1.00	1.00
CVA	1 (0.4)	12 (5.2)	**12.00 (1.56 to 92.29)**	**13.49 (1.71 to 106.34)**
Partly due to a health problem				
No CVA	261 (98.9)	259 (98.1)	1.00	1.00
CVA	3 (1.1)	5 (1.9)	1.67 (0.40 to 6.97)	2.09 (0.46 to 9.60)

Appendix Table 56: Association between diabetes and health-related job loss, by "type" of HRJL

Variable	Prevalence among controls, n (%)	Prevalence among cases, n (%)	Association with HRJL, unadjusted. OR (95% CI)	Association with HRJL, adjusted for education level, single status, history of heavy alcohol use. OR (95% CI)
Mainly due to a health problem				
No diabetes	219 (95.2)	204 (88.7)	1.00	1.00
diabetes	11 (4.8)	26 (11.3)	**2.88 (1.29 to 6.43)**	**2.48 (1.08 to 5.70)**
Partly due to a health problem				
No diabetes	244 (92.4)	230 (87.1)	1.00	1.00

diabetes	20 (7.6)	34 (12.9)	**2.00 (1.05 to 3.80)**	**1.79 (0.93 to 3.44)**

Appendix to Chapter 7

Appendix Table 57: frequency of comorbidity pairs

Health problem (Index disorder =col)	MSDs (chronic or recent pain)	Chronic MSD	MSD pain	Primary care MHP	Psychiatric MHP	Sleep disorders	Hypertension	Heart failure	Ischaemic heart disease	Diabetes	Peripheral atherosclerosis
MSDs (chronic or recent pain)	x	x	x	89 (50.3)	6 (60.0)	31 (60.8)	111 (51.2)	24 (41.4)	22 (43.1)	39 (42.9)	7 (58.3)
Chronic MSD	X	x	76 (31.5)	48 (27.1)	4 (40.0)	21 (41.2)	63 (29.0)	12 (20.7)	11 (21.6)	27 (29.7)	5 (41.7)
MSD pain	X	76 (34.9)	X	76 (31.5)	5 (50.0)	17 (33.3)	72 (33.2)	17 (29.3)	16 (31.4)	20 (22.0)	3 (25.0)
Primary care MHP	89 (23.2)	48 (22.0)	59 (24.5)	x	6 (60.0)	37 (72.6)	34 (15.7)	9 (15.5)	9 (17.7)	17 (18.7)	3 (25.0)
Psychiatric MHP	6 (1.6)	4 (1.8)	5 (2.1)	6 (3.4)	x	2 (3.9)	3 (1.4)	1 (1.7)	1 (2.0)	1 (1.1)	1 (8.3)
Sleep disorders	31 (8.1)	21 (9.6)	17 (7.1)	37 (20.9)	2 (20.0)	x	5 (2.3)	6 (10.3)	3 (5.9)	4 (4.4)	1 (8.3)
Hypertension	111 (29.0)	63 (28.9)	72 (29.9)	34 (19.2)	3 (30.0)	5 (9.8)	x	23 (39.7)	27 (52.9)	46 (50.6)	9 (75.0)
Heart failure	24 (6.3)	12 (5.5)	17 (7.1)	9 (5.1)	1 (10.0)	6 (11.8)	23 (10.6)	x	26 (51.0)	14 (15.4)	0 (0.0)
Ischaemic heart disease	22 (5.7)	11 (5.1)	16 (6.6)	9 (5.1)	1 (10.0)	3 (5.9)	27 (12.4)	26 (44.8)	X	14 (15.4)	2 (16.7)
Diabetes	39 (10.2)	27 (12.4)	20 (8.3)	17 (9.6)	1 (10.0)	4 (7.8)	46 (21.2)	14 (24.1)	14 (27.5)	x	5 (41.7)
Peripheral atherosclerosis	7 (1.8)	5 (2.3)	3 (1.2)	3 (1.2)	1 (10.0)	1 (2.0)	9 (4.2)	0 (0.0)	2 (3.9)	5 (5.5)	X
Cardiac arrythmias	3 (0.8)	2 (0.9)	2 (0.8)	1 (0.6)	1 (10.0)	0 (0.0)	3 (1.4)	2 (3.5)	3 (5.9)	2 (2.2)	0 (0.0)
Venous thrombus	1 (0.3)	1 (0.4)	1 (0.4)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Structural heart disease	2 (0.5)	1 (0.5)	1 (0.4)	1 (0.6)	0 (0.0)	0 (0.0)	4 (1.8)	4 (6.9)	3 (5.9)	0 (0.0)	0 (0.0)
CVA	8 (2.1)	3 (1.4)	7 (2.9)	4 (2.3)	0 (0.0)	1 (2.0)	8 (3.7)	5 (8.6)	2 (3.9)	3 (3.3)	1 (8.3)
Epilepsy	4 (1.0)	2 (0.9)	3 (1.2)	2 (1.1)	1 (10.0)	0 (0.0)	1 (0.5)	2 (3.5)	1 (2.0)	0 (0.0)	0 (0.0)
Asthma	34 (8.9)	19 (8.7)	21 (8.7)	14 (7.9)	0 (0.0)	6 (11.8)	21 (9.7)	6 (10.3)	5 (9.8)	6 (6.6)	0 (0.0)
COPD	8 (2.1)	5 (2.3)	5 (2.1)	6 (3.4)	0 (0.0)	3 (5.9)	3 (1.4)	3 (5.2)	1 (2.0)	1 (1.1)	0 (0.0)

Appendix Table 58: frequency of comorbidity pairs

	Cardiac arrhythmias	Venous thrombus	Structural heart disease	CVA	Epilepsy	Asthma	COPD
MSDs (chronic or recent pain)	3 (37.5)	1 (100.0)	2 (28.6)	8 (38.1)	4 (40.0)	34 (43.6)	8 (40.0)
Chronic MSD	2 (25.0)	0 (0.0)	1 (14.3)	3 (14.3)	2 (20.0)	19 (24.4)	5 (25.0)
MSD pain	2 (25.0)	1 (100.0)	1 (14.3)	7 (33.3)	3 (30.0)	21 (26.9)	5 (25.0)
Primary care MHP	1 (12.5)	1 (100.0)	1 (14.3)	4 (19.1)	2 (20.0)	14 (18.0)	6 (30.0)
Psychiatric MHP	1 (12.5)	0 (0.0)	0 (0.0)	0 (0.0)	1 (10.0)	0 (0.0)	0 (0.0)
Sleep disorders	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.8)	0 (0.0)	6 (7.7)	3 (15.0)
Hypertension	3 (37.5)	0 (0.0)	4 (57.1)	8 (38.1)	1 (10.0)	21 (26.9)	3 (15.0)
Heart failure	2 (25.0)	0 (0.0)	4 (57.1)	5 (23.8)	2 (20.0)	6 (7.7)	3 (15.0)
Ischaemic heart disease	3 (37.5)	0 (0.0)	3 (42.9)	2 (9.5)	1 (10.0)	5 (6.4)	1 (5.0)
Diabetes	2 (25.0)	0 (0.0)	0 (0.0)	3 (14.3)	0 (0.0)	6 (7.7)	1 (5.0)
Peripheral atherosclerosis	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.8)	0 (0.0)	0 (0.0)	0 (0.0)
Cardiac arrythmias	x	0 (0.0)	1 (14.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Venous thrombus	0 (0.0)	x	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Structural heart disease	1 (12.5)	0 (0.0)	x	2 (9.5)	0 (0.0)	0 (0.0)	0 (0.0)
CVA	0 (0.0)	0 (0.0)	2 (28.6)	x	0 (0.0)	1 (1.3)	0 (0.0)
Epilepsy	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	x	0 (0.0)	0 (0.0)
Asthma	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.8)	0 (0.0)	x	12 (60.0)
COPD	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	12 (15.4)	x

Appendix Table 59: clusters formed from total population cluster analysis using chronic MSDs to define MSDs

	Cluster 1	**Cluster 2**	**Cluster 3**	**Cluster 4**	**Cluster 5**	**Cluster 6**	**Cluster 7**	**Cluster 8**	**Cluster 9**	**Cluster 10**
Total	404 (40.9)	140 (14.2)	59 (6.0)	41 (4.2)	14 (1.4)	13 (1.3)	44 (4.5)	141 (14.3)	113 (11.4)	11 (1.1)
Chronic musculoskeletal disorders	0 (0.0)	50 (35.7)	13 (22.0)	2 (4.9)	0 (0.0)	0 (0.0)	0 (0.0)	40 (28.4)	113 (100.0)	0 (0.0)
Hypertension	0 (0.0)	139 (99.3)	35 (59.3)	24 (58.5)	0 (0.0)	4 (30.8)	13 (29.6)	2 (1.4)	0 (0.0)	0 (0.0)
Primary care mental health problems	0 (0.0)	19 (13.6)	6 (10.2)	3 (7.3)	4 (28.6)	3 (23.1)	3 (6.8)	139 (98.6)	0 (0.0)	0 (0.0)
Diabetes	0 (0.0)	2 (1.4)	59 (100.0)	11 (26.8)	0 (0.0)	2 (15.4)	0 (0.0)	10 (7.1)	7 (6.2)	0 (0.0)
Asthma	0 (0.0)	5 (3.6)	2 (3.4)	3 (7.3)	3 (21.4)	0 (0.0)	44 (100.0)	9 (6.4)	11 (9.7)	1 (9.1)
Heart failure	0 (0.0)	7 (5.0)	4 (6.8)	27 (65.9)	14 (100.0)	0 (0.0)	0 (0.0)	2 (1.4)	3 (2.7)	1 (9.1)
Ischaemic heart disease	0 (0.0)	6 (4.3)	0 (0.0)	38 (92.7)	0 (0.0)	0 (0.0)	0 (0.0)	6 (4.3)	1 (0.9)	0 (0.0)
Sleep disorders	0 (0.0)	0 (0.0)	1 (1.7)	1 (2.4)	2 (14.3)	0 (0.0)	1 (2.3)	34 (24.1)	1 (0.9)	11 (100.0)
Cerebrovascular accident	0 (0.0)	2 (1.4)	0 (0.0)	2 (4.9)	1 (7.1)	13 (100.0)	1 (2.3)	0 (0.0)	2 (1.8)	0 (0.0)
COPD	0 (0.0)	1 (0.7)	0 (0.0)	1 (2.4)	2 (14.3)	0 (0.00)	8 (18.2)	5 (3.6)	2 (1.8)	0 (0.0)
Peripheral atherosclerotic disease	0 (0.0)	3 (2.1)	5 (8.5)	0 (0.0)	0 (0.0)	1 (7.7)	0 (0.0)	2 (1.4)	0 (0.0)	0 (0.0)
Psychiatric care mental health problems	0 (0.0)	1 (0.7)	1 (1.7)	1 (2.4)	0 (0.0)	0 (0.0)	0 (0.0)	5 (3.6)	0 (0.0)	0 (0.0)
Epilepsy	0 (0.0)	1 (0.7)	0 (0.0)	1 (2.4)	1 (7.1)	0 (0.0)	0 (0.0)	2 (1.4)	1 (0.9)	0 (0.0)
Arrythmias	0 (0.0)	0 (0.0)	1 (1.7)	4 (9.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.8)	0 (0.0)
Structural heart disease	0 (0.0)	1 (0.7)	0 (0.0)	5 (12.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)
Venous thrombus	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)

Appendix Table 60: clusters formed from total population cluster analysis using recent MSD pain to define musculoskeletal disorders

	Cluster 1	**Cluster 2**	**Cluster 3**	**Cluster 4**	**Cluster 5**	**Cluster 6**	**Cluster 7**	**Cluster 9**
Total	396 (40.1)	163 (16.5)	56 (5.7)	42 (4.3)	106 (10.7)	150 (15.2)	14 (1.4)	45 (4.6)
Musculoskeletal pain	0 (0.0)	59 (36.2)	9 (16.1)	5 (11.9)	10 (9.4)	150 (100.0)	5 (35.7)	0 (0.0)
Hypertension	0 (0.0)	161 (98.8)	29 (51.8)	6 (14.3)	4 (3.8)	4 (2.7)	0 (0.0)	12 (26.7)
Primary care mental health problems	0 (0.0)	23 (14.1)	2 (3.6)	12 (28.6)	106 (100.0)	33 (22.0)	0 (0.0)	0 (0.0)
Diabetes	0 (0.0)	27 (16.6)	16 (28.6)	42 (100.0)	4 (3.8)	0 (0.0)	0 (0.0)	2 (4.4)
Asthma	0 (0.0)	4 (2.5)	4 (7.1)	0 (0.0)	8 (7.6)	15 (10.0)	2 (14.3)	45 (100.0)
Heart failure	0 (0.0)	2 (1.2)	44 (78.6)	0 (0.0)	6 (5.7)	5 (3.3)	1 (7.1)	0 (0.0)
Ischaemic heart disease	0 (0.0)	6 (3.7)	35 (62.5)	1 (2.4)	3 (2.8)	5 (3.3)	0 (0.0)	1 (2.2)
Sleep disorders	0 (0.0)	1 (0.6)	1 (1.8)	0 (0.0)	35 (33.0)	0 (0.0)	14 (100.0)	0 (0.0)
Cerebrovascular accident	0 (0.0)	1 (0.6)	4 (7.1)	3 (7.1)	4 (3.8)	1 (0.7)	0 (0.0)	0 (0.0)
COPD	0 (0.0)	3 (1.8)	3 (5.4)	0 (0.0)	4 (3.8)	3 (2.0)	0 (0.0)	7 (15.6)
Peripheral atherosclerotic disease	0 (0.0)	7 (4.3)	2 (3.6)	1 (2.4)	2 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)
Psychiatric care mental health problems	0 (0.0)	1 (0.6)	0 (0.0)	1 (2.4)	3 (2.8)	3 (2.0)	0 (0.0)	0 (0.0)
Epilepsy	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	3 (2.0)	0 (0.0)	0 (0.0)
Arrythmias	0 (0.0)	1 (0.6)	4 (7.1)	1 (2.4)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)
Structural heart disease	0 (0.0)	2 (1.2)	4 (7.1)	0 (0.0)	1 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)
Venous thrombus	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)

Appendix Table 61: total population demographics (chronic MSD only)

	Cluster 1	Cluster 2	Cluster 3	Cluster 4	Cluster 5	Cluster 6	Cluster 7	Cluster 8	Cluster 9	Cluster 10
Total	404 (40.9)	140 (14.2)	59 (6.0)	41 (4.2)	14 (1.4)	13 (1.3)	44 (4.5)	141 (14.3)	113 (11.4)	11 (1.1)
Age at HRJL, y, median (IQR)	56.74 (51.73 to 60.33)	59.69 (56.05 to 61.46)	58.91 (53.41 to 61.41)	60.22 (58.50 to 62.36)	60.78 (58.35 to 62.82)	58.67 (53.65 to 60.89)	56.14 (54.45 to 60.42)	55.96 (51.71 to 59.99)	59.10 (55.40 to 61.02)	56.25 (49.86 to 59.54)
Sex (m)	161 (39.9)	76 (54.3)	38 (64.4)	35 (85.4)	4 (28.6)	8 (61.5)	19 (43.2)	48 (34.0)	39 (34.5)	5 (45.5)
Ethnicity (white)	395 (97.8)	138 (98.6)	58 (98.3)	40 (97.6)	13 (92.9)	13 (100.0)	43 (97.7)	139 (98.6)	111 (98.2)	11 (100.0)
Married/Civil partnership	278 (69.9)	100 (71.4)	46 (79.3)	27 (65.9)	6 (42.9)	9 (69.2)	26 (60.5)	90 (64.3)	80 (70.8)	7 (63.6)
Single	30 (7.5)	7 (5.0)	4 (6.9)	7 (17.1)	2 (14.3)	3 (23.1)	4 (9.3)	13 (9.3)	4 (3.5)	2 (18.2)
Divorced	71 (17.8)	24 (17.1)	3 (5.2)	6 (14.6)	3 (21.4)	1 (7.7)	11 (25.6)	31 (22.1)	20 (17.7)	2 (18.2)
Widowed	19 (4.8)	9 (6.4)	5 (8.6)	1 (2.4)	3 (21.4)	0 (0.0)	2 (4.7)	6 (4.3)	9 (8.0)	0 (0.0)
University degree	98 (24.3)	30 (21.4)	7 (11.7)	7 (17.1)	1 (7.1)	3 (23.1)	14 (31.8)	35 (24.8)	22 (19.5)	5 (45.5)
Vocational qualifications/higher professional	162 (40.1)	61 (43.6)	23 (39.0)	17 (41.5)	2 (14.3)	3 (23.1)	17 (38.6)	46 (32.6)	49 (43.4)	3 (27.3)
High school qualifications	77 (19.1)	24 (17.1)	13 (22.0)	5 (12.2)	9 (64.3)	3 (23.1)	6 (13.6)	28 (19.9)	16 (14.2)	1 (9.1)
No qualifications	67 (16.6)	25 (17.9)	16 (27.1)	12 (29.3)	2 (14.3)	4 (30.8)	7 (15.9)	32 (22.7)	26 (23.0)	2 (18.2)
Cases	134 (33.2)	78 (55.7)	41 (69.5)	25 (61.0)	10 (71.4)	10 (76.9)	25 (56.8)	100 (70.9)	60 (53.1)	6 (54.6)

Appendix Table 62: total population demographics (musculoskeletal pain only)

	Cluster 1	Cluster 2	Cluster 3	Cluster 4	Cluster 5	Cluster 6	Cluster 7	Cluster 9
Total	396 (40.1)	163 (16.5)	56 (5.7)	42 (4.3)	106 (10.7)	150 (15.2)	14 (1.4)	45 (4.6)
Age at HRJL, y, median (IQR)	57.48 (52.42 – 60.28)	59.13 (55.82 – 61.22)	61.36 (58.72 – 63.66)	59.54 (55.18 – 61.49)	56.84 (51.72 – 59.86)	55.98 (51.71 – 61.03)	57.41 (50.47 – 61.15)	58.08 (55.37 – 59.86)
Sex (m)	149 (37.6)	92 (56.4)	43 (76.8)	25 (59.5)	34 (32.1)	62 (41.3)	7 (50.0)	18 (40.0)
Ethnicity (white)	389 (98.2)	161 (98.8)	54 (96.4)	42 (100.0)	104 (98.1)	146 (97.3)	14 (100.00)	43 (95.6)
Married/Civil partnership	270 (68.9)	117 (72.2)	37 (66.1)	32 (76.2)	69 (65.7)	103 (69.6)	10 (71.4)	27 (61.4)
Single	24 (6.1)	11 (6.8)	8 (14.3)	3 (7.1)	8 (7.6)	14 (9.5)	2 (14.3)	3 (6.8)
Widowed	26 (6.6)	9 (5.6)	4 (7.1)	3 (7.1)	5 (4.7)	3 (2.0)	0 (0.0)	4 (9.1)
Divorced	72 (18.4)	25 (15.4)	7 (12.5)	4 (9.5)	23 (21.9)	28 (18.9)	2 (14.3)	10 (22.7)
University degree	94 (23.7)	33 (20.3)	7 (12.5)	7 (16.7)	23 (21.7)	33 (22.0)	6 (42.9)	16 (35.6)
Vocational qualifications/higher professional	159 (39.9)	68 (41.7)	24 (42.9)	16 (38.1)	30 (28.3)	67 (44.7)	5 (35.7)	14 (31.1)
High school qualifications	77 (19.4)	30 (18.4)	11 (19.6)	8 (19.1)	23 (21.7)	25 (16.7)	1 (7.1)	5 (11.1)
No qualifications	67 (16.9)	32 (19.6)	14 (25.0)	11 (26.2)	30 (28.3)	25 (16.7)	2 (14.3)	10 (22.2)
Cases	134 (33.8)	93 (57.1)	41 (73.2)	26 (61.9)	73 (68.9)	85 (56.7)	8 (57.1)	23 (51.1)

Appendix Table 63: multimorbid population demographics (chronic MSD only)

	Cluster 1	Cluster 2	Cluster 3	Cluster 5
Total	88 (32.2)	35 (12.8)	109 (39.9)	32 (11.7)
Age at HRJL, y, median (IQR)	57.30 (54.12 to 60.17)	61.13 (58.50 to 62.44)	59.63 (56.42 to 61.27)	57.43 (53.96 to 61.37)
Sex (m)	29 (33.0)	29 (82.9)	61 (56.0)	14 (43.8)
Ethnicity (white)	87 (98.9)	34 (97.1)	106 (97.3)	30 (93.8)
Married/Civil partnership	51 (58.6)	25 (71.4)	85 (78.7)	18 (58.1)
Single	11 (12.6)	6 (17.1)	6 (5.6)	6 (19.4)
Divorced	19 (21.8)	3 (8.6)	11 (10.2)	6 (19.4)
Widowed	6 (6.9)	1 (2.9)	6 (5.6)	1 (3.2)
University degree	18 (20.5)	5 (14.3)	17 (15.6)	6 (18.8)
Vocational qualifications/higher professional	29 (33.0)	13 (37.1)	44 (40.4)	13 (40.6)
High school qualifications	21 (23.9)	5 (14.3)	19 (17.4)	5 (15.6)
No qualifications	20 (22.7)	12 (34.3)	29 (26.6)	8 (25.0)
Cases	68 (77.3)	21 (60.0)	78 (71.6)	23 (71.9)

Appendix Table 64: multimorbid population constituent health disorders (chronic MSD only)

	Cluster 1	Cluster 2	Cluster 3	Cluster 5
Total	88 (32.2)	35 (12.8)	109 (39.9)	32 (11.7)
Chronic musculoskeletal disorders	44 (50.0)	1 (2.9)	80 (73.4)	1 (3.1)
Hypertension	21 (23.9)	22 (62.9)	84 (77.1)	13 (40.6)
Primary care mental health problems	85 (96.6)	3 (8.6)	7 (6.4)	12 (37.5)
Diabetes	8 (9.1)	11 (31.4)	47 (43.1)	2 (6.3)

Asthma	2 (2.3)	3 (8.6)	18 (16.5)	30 (93.8)
Heart failure	8 (9.1)	26 (74.3)	13 (11.9)	3 (9.4)
Ischaemic heart disease	5 (5.7)	33 (94.3)	7 (6.4)	1 (3.1)
Sleep disorders	35 (39.8)	1 (2.9)	2 (1.8)	4 (12.5)
Cerebrovascular accident	4 (4.6)	2 (5.7)	8 (7.3)	1 (3.1)
COPD	2 (2.3)	1 (2.9)	3 (2.8)	13 (40.6)
Peripheral atherosclerotic disease	2 (2.3)	0 (0.0)	9 (8.3)	0 (0.0)
Psychiatric care mental health problems	5 (5.7)	0 (0.0)	2 (1.8)	0 (0.0)
Epilepsy	2 (2.3)	0 (0.0)	0 (0.0)	0 (0.0)
Arrythmias	0 (0.0)	1 (2.9)	2 (1.8)	0 (0.0)
Structural heart disease	1 (1.1)	4 (11.4)	1 (0.9)	0 (0.0)
Venous thrombus	1 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)

Appendix Table 65: multimorbid population demographics (musculoskeletal pain only)

	Cluster 1	**Cluster 2**	**Cluster 3**	**Cluster 4**	**Cluster 5**
Total	95 (32.5)	36 (12.3)	35 (12.0)	110 (37.7)	12 (4.1)
Age at HRJL, y, median (IQR)	59.10 (55.37 – 61.72)	59.18 (54.88 – 61.01)	60.09 (58.39 – 62.36)	56.04 (51.99 – 60.00)	61.23 (58.21 – 63.99)
Sex (m)	56 (59.0)	23 (63.9)	30 (85.7)	35 (85.7)	75 (68.2)
Ethnicity (white)	91 (95.8)	36 (100.0)	34 (97.1)	109 (99.1)	10 (83.3)
Married/Civil partnership	70 (73.7)	29 (82.9)	23 (65.7)	64 (58.7)	4 (36.4)
Single	7 (7.4)	1 (2.9)	6 (17.1)	15 (13.8)	3 (27.3)
Widowed	6 (6.3)	3 (8.6)	1 (2.9)	6 (5.5)	1 (9.1)
Divorced	12 (12.6)	2 (5.7)	5 (14.3)	24 (22.0)	3 (27.3)
University degree	12 (12.6)	4 (11.1)	6 (17.1)	27 (24.6)	2 (16.7)
Vocational qualifications/higher professional	44 (46.3)	12 (33.3)	14 (40.0)	34 (30.9)	5 (41.7)

High school qualifications	20 (21.1)	9 (25.0)	5 (14.3)	25 (22.7)	3 (25.0)
No qualifications	19 (20.0)	11 (30.6)	10 (28.6)	24 (21.8)	2 (16.7)
Cases	64 (67.4)	26 (72.2)	24 (68.6)	90 (81.8)	6 (50.0)

Appendix Table 66: multimorbid population constituent health disorders (recent musculoskeletal pain only)

	Cluster 1	**Cluster 2**	**Cluster 3**	**Cluster 4**	**Cluster 5**
Total	95 (32.5)	36 (12.3)	35 (12.0)	110 (37.7)	12 (4.1)
Musculoskeletal pain	74 (77.9)	0 (0.0)	6 (17.1)	59 (53.6)	3 (25.0)
Hypertension	73 (76.8)	26 (72.2)	20 (57.1)	27 (24.6)	0 (0.0)
Primary care mental health problems	2 (2.1	11 (30.6)	3 (8.6)	103 (93.6)	1 (8.3)
Diabetes	16 (16.8)	36 (100.0)	12 (34.3)	4 (3.6)	0 (0.0)
Asthma	26 (27.4)	1 (2.8)	1 (2.9)	14 (12.7)	10 (83.3)
Heart failure	13 (13.7)	4 (11.1)	24 (68.6)	8 (7.3)	3 (25.0)
Ischaemic heart disease	10 (10.5)	1 (2.8)	34 (97.1)	4 (3.6)	0 (0.0)
Sleep disorders	0 (0.0)	0 (0.0)	1 (2.9)	43 (39.1)	0 (0.0)
Cerebrovascular accident	7 (7.4)	3 (8.3)	2 (5.7)	4 (3.6)	0 (0.0)
COPD	2 (2.1)	0 (0.0)	1 (2.9)	5 (4.6)	11 (97.7)
Peripheral atherosclerotic disease	3 (3.2)	5 (13.9)	2 (5.7)	2 (1.8)	0 (0.0)
Psychiatric care mental health problems	2 (2.1)	1 (2.8)	0 (0.0)	5 (4.6)	0 (0.0)
Epilepsy	3 (3.2)	0 (0.0)	0 (0.0)	2 (1.8)	0 (0.0)
Arrythmias	1 (1.1)	0 (0.0)	3 (8.6)	0 (0.0)	0 (0.0)
Structural heart disease	3 (3.2)	0 (0.0)	4 (11.4)	0 (0.0)	0 (0.0)
Venous thrombus	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)

Appendix Table 67: multimorbid men population demographics (chronic MSD only)

	Cluster 1	Cluster 4	Cluster 5	Cluster 6
Total	21 (15.1)	54 (38.9)	37 (26.6)	17 (12.2)
Age at HRJL, y, median (IQR)	56.07 (51.71 to 62.03)	58.84 (56.05 to 60.72)	61.13 (58.67 to 63.47)	59.10 (55.82 to 63.47)
Ethnicity (white)	21 (100.0)	54 (100.0)	35 (94.6)	16 (94.1)
Married/Civil partnership	15 (71.4)	41 (77.4)	21 (56.8)	13 (76.5)
Single	2 (9.5)	3 (5.7)	9 (24.3)	2 (11.8)
Divorced	3 (14.3)	7 (13.2)	5 (13.5)	2 (11.8)
Widowed	1 (4.8)	2 (3.8)	2 (5.4)	0 (0.0)
University degree	4 (19.1)	11 (20.4)	11 (29.7)	4 (23.5)
Vocational qualifications/higher professional	7 (33.3)	22 (40.7)	13 (35.1)	12 (70.6)
High school qualifications	4 (19.1)	8 (14.8)	6 (16.2)	0 (0.0)
No qualifications	4 (19.1)	11 (20.4)	11 (29.7)	4 (23.5)
Cases	18 (85.7)	39 (72.2)	23 (62.2)	12 (70.6)

Appendix Table 68: multimorbid men population constituent health disorders (chronic MSD only)

	Cluster 1	Cluster 4	Cluster 5	Cluster 6
Total	21 (15.1)	54 (38.9)	37 (26.6)	17 (12.2)
Chronic musculoskeletal disorders	14 (66.7)	26 (48.2)	3 (8.1)	7 (41.2)
Hypertension	1 (4.8)	52 (96.3)	23 (62.2)	7 (41.2)
Primary care mental health problems	19 (90.5)	13 (24.1)	0 (0.0)	1 (5.9)
Diabetes	5 (23.8)	24 (44.4)	13 (35.1)	0 (0.0)

Asthma	3 (14.3)	1 (1.9)	3 (8.1)	16 (94.1)
Heart failure	1 (4.8)	4 (7.4)	26 (70.3)	0 (0.0)
Ischaemic heart disease	2 (9.5)	1 (1.9)	31 (83.8)	0 (0.0)
Sleep disorders	11 (52.4)	0 (0.0)	0 (0.0)	0 (0.0)
Cerebrovascular accident	0 (0.0)	6 (11.1)	2 (5.4)	1 (5.9)
COPD	2 (9.5)	1 (1.9)	1 (2.7)	7 (41.2)
Peripheral atherosclerotic disease	2 (9.5)	6 (11.1)	0 (0.0)	0 (0.0)
Psychiatric care mental health problems	0 (0.0)	2 (3.7)	0 (0.0)	0 (0.0)
Epilepsy	0 (0.0)	1 (1.9)	0 (0.0)	0 (0.0)
Arrythmias	0 (0.0)	1 (1.9)	2 (5.4)	0 (0.0)
Structural heart disease	1 (4.8)	2 (3.7)	4 (10.8)	0 (0.0)
Venous thrombus	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Appendix Table 69: multimorbid men population demographics (recent musculoskeletal pain only)

	Cluster 1	**Cluster 2**	**Cluster 3**	**Cluster 4**
Total	64 (41.6)	31 (20.1)	36 (23.4)	19 (12.3)
Age at HRJL, y, median (IQR)	59.29 (55.98 – 61.29)	60.09 (58.39 – 62.36)	55.90 (50.44 – 60.05)	59.45 (54.19 – 63.70)
Ethnicity (white)	63 (98.4)	30 (96.8)	36 (100.0)	18 (94.7)
Married/Civil partnership	48 (76.2)	18 (58.1)	24 (66.7)	14 (73.7)
Single	5 (7.9)	6 (19.4)	6 (16.7)	1 (5.3)
Widowed	3 (4.8)	1 (3.2)	1 (2.8)	1 (5.3)
Divorced	7 (11.1)	6 (19.4)	5 (13.9)	3 (15.8)
University degree	11 (17.2)	6 (19.4)	9 (25.0)	2 (10.5)
Vocational qualifications/higher professional	28 (43.8)	12 (38.7)	11 (30.6)	13 (68.4)

High school qualifications	15 (23.4)	5 (16.1)	7 (19.4)	1 (5.3)
No qualifications	10 (15.6)	8 (25.8)	9 (25.0)	3 (15.8)
Cases	44 (68.8)	21 (67.7)	29 (80.6)	12 (63.2)

Appendix Table 70: multimorbid men population constituent health disorders (recent musculoskeletal pain only)

	Cluster 1	**Cluster 2**	**Cluster 3**	**Cluster 4**
Total	64 (41.6)	31 (20.1)	36 (23.4)	19 (12.3)
Musculoskeletal pain	40 (62.5)	4 (12.9)	16 (44.4)	9 (47.4)
Hypertension	47 (73.4)	17 (54.8)	14 (38.9)	8 (42.1)
Primary care mental health problems	1 (1.6)	1 (3.2)	36 (100.0)	1 (5.3)
Diabetes	28 (43.8)	11 (35.5)	7 (19.4)	1 (5.3)
Asthma	0 (0.0)	1 (3.2)	3 (8.3)	18 (94.7)
Heart failure	10 (15.6)	21 (67.7)	2 (5.6)	1 (5.3)
Ischaemic heart disease	3 (4.7)	30 (96.8)	1 (2.8)	2 (10.5)
Sleep disorders	3 (4.7)	0 (0.0)	9 (25.0)	0 (0.0)
Cerebrovascular accident	6 (9.4)	2 (6.5)	1 (2.8)	1 (5.3)
COPD	1 (1.6)	1 (3.2)	2 (5.6)	7 (36.8)
Peripheral atherosclerotic disease	7 (10.9)	1 (3.2)	2 (5.6)	0 (0.0)
Psychiatric care mental health problems	2 (3.1)	1 (3.2)	1 (2.8)	0 (0.0)
Epilepsy	1 (1.6)	1 (3.2)	0 (0.0)	0 (0.0)
Arrythmias	2 (3.1)	2 (6.5)	0 (0.0)	0 (0.0)
Structural heart disease	3 (4.7)	4 (12.9)	0 (0.0)	0 (0.0)
Venous thrombus	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Appendix Table 71: multimorbid women population demographics (chronic MSD only)

	Cluster 1	**Cluster 2**
Total	71 (53.0)	59 (44.0)
Age at HRJL, y, median (IQR)	59.86 (56.42 – 61.48)	56.80 (52.65 – 60.00)
Ethnicity (white)	69 (97.2)	58 (98.3)
Married/Civil partnership	51 (71.8)	38 (65.5)
Single	5 (7.0)	6 (10.3)
Divorced	10 (14.1)	11 (19.0)
Widowed	5 (7.0)	3 (5.2)
University degree	11 (15.5)	7 (11.9)
Vocational qualifications/higher professional	27 (38.0)	19 (32.2)
High school qualifications	13 (18.3)	15 (25.4)
No qualifications	20 (28.2)	18 (30.5)
Cases	51 (71.8)	44 (74.6)

Appendix Table 72: multimorbid women population constituent health disorders (chronic MSD only)

	Cluster 1	**Cluster 2**
Total	71 (53.0)	59 (44.0)
Chronic musculoskeletal disorders	46 (64.8)	25 (42.4)
Hypertension	55 (77.5)	5 (8.5)
Primary care mental health problems	18 (25.4)	55 (93.2)
Diabetes	23 (32.4)	2 (3.4)
Asthma	17 (23.9)	10 (17.0)

Heart failure	4 (5.6)	10 (17.0)
Ischaemic heart disease	6 (8.5)	7 (11.9)
Sleep disorders	2 (2.8)	28 (47.5)
Cerebrovascular accident	3 (4.2)	3 (5.1)
COPD	0 (0.0)	4 (6.8)
Peripheral atherosclerotic disease	2 (2.8)	0 (0.0)
Psychiatric care mental health problems	0 (0.0)	4 (6.8)
Epilepsy	1 (1.4)	3 (5.1)
Arrythmias	1 (1.4)	1 (1.7)
Structural heart disease	0 (0.0)	0 (0.0)
Venous thrombus	0 (0.0)	1 (1.7)

Appendix Table 73: multimorbid women population demographics (musculoskeletal pain only)

	Cluster 1	**Cluster 2**
Total	67 (48.6)	62 (44.9)
Age at HRJL, y, median (IQR)	59.06 (55.24 – 61.21)	56.28 (52.35 – 60.00)
Ethnicity (white)	65 (97.0)	61 (98.4)
Married/Civil partnership	47 (70.2)	36 (59.0)
Single	4 (6.0)	7 (11.5)
Widowed	6 (9.0)	4 (6.6)
Divorced	10 (14.9)	14 (23.0)
University degree	6 (9.0)	15 (24.2)
Vocational qualifications/higher professional	25 (37.3)	19 (30.7)
High school qualifications	16 (23.9)	16 (25.8)
No qualifications	20 (29.9)	12 (19.4)
Cases	49 (73.1)	50 (80.7)

Appendix Table 74: multimorbid women population constituent health disorders (recent musculoskeletal pain only)

	Cluster 1	**Cluster 2**
Total	67 (48.6)	62 (44.9)
Musculoskeletal pain	38 (56.7)	34 (54.8)
Hypertension	54 (80.6)	4 (6.5)
Primary care mental health problems	20 (29.9)	61 (98.4)
Diabetes	19 (28.4)	3 (4.8)
Asthma	20 (29.9)	6 (9.7)
Heart failure	2 (3.0)	7 (11.3)
Ischaemic heart disease	6 (9.0)	5 (8.1)
Sleep disorders	3 (4.5)	28 (45.2)
Cerebrovascular accident	2 (3.0)	3 (4.8)
COPD	2 (3.0)	2 (3.2)
Peripheral atherosclerotic disease	2 (3.0)	0 (0.0)
Psychiatric care mental health problems	0 (0.0)	4 (6.5)
Epilepsy	0 (0.0)	2 (3.2)
Arrythmias	1 (1.5)	1 (1.6)
Structural heart disease	0 (0.0)	0 (0.0)
Venous thrombus	0 (0.0)	1 (1.6)

Appendix Table 75: musculoskeletal disorder population cluster demographics

	Cluster 1	**Cluster 2**	**Cluster 4**	**Cluster 5**	**Cluster 8**
Total	96 (25.1)	25 (6.5)	86 (22.5)	10 (2.6)	159 (41.5)
Age at HRJL, y, median (IQR)	59.72 (55.98 – 61.39)	59.45 (56.07 – 61.85)	55.99 (52.36 – 60.07)	60.59 (57.26 – 62.13)	58.10 (53.36 – 60.99)

Ethnicity (white)	94 (97.9)	23 (92.0)	85 (98.8)	10 (100.0)	156 (98.1)
Married/Civil partnership	70 (72.9)	20 (80.0)	53 (62.4)	7 (70.0)	109 (69.4)
Single	5 (5.2)	1 (4.0)	10 (11.8)	0 (0.0)	9 (5.7)
Widowed	7 (7.3)	2 (8.0)	5 (5.9)	0 (0.0)	9 (5.7)
Divorced	14 (14.6)	2 (8.0)	17 (20.0)	3 (30.0)	30 (19.1)
University degree	14 (14.6)	4 (16.0)	17 (19.8)	0 (0.0)	35 (22.0)
Vocational qualifications/higher professional	42 (43.8)	12 (48.0)	29 (33.7)	4 (40.0)	70 (44.0)
High school qualifications	18 (18.8)	3 (12.0)	21 (24.4)	3 (30.0)	23 (14.5)
No qualifications	22 (22.9)	6 (24.0)	19 (22.1)	3 (30.0)	31 (19.5)
Cases	60 (62.5)	17 (68.0)	72 (83.7)	7 (70.0)	69 (43.4)

Appendix Table 76: musculoskeletal disorder population cluster constituent health disorders

	Cluster 1	**Cluster 2**	**Cluster 3**	**Cluster 4**	**Cluster 5**	**Cluster 6**	**Cluster 7**	**Cluster 8**
Total	96 (25.1)	25 (6.5)	3 (0.8)	86 (22.5)	10 (2.6)	1 (0.3)	3 (0.8)	159 (41.5)
Chronic musculoskeletal disorders	59 (61.5)	16 (64.0)	2 (66.7)	43 (50.0)	5 (50.0)	1 (100.0)	2 (66.7)	90 (56.6)
Recent MSD pain	58 (60.4)	14 (56.0)	1 (33.3)	60 (69.8)	7 (70.0)	1 (100.0)	2 (66.7)	98 (61.6)
Hypertension	84 (87.5)	9 (36.0)	1 (33.3)	17 (19.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Primary care mental health problems	8 (8.3)	2 (8.0)	0 (0.0)	79 (91.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Diabetes	32 (33.3)	2 (8.0)	0 (0.0)	3 (3.5)	1 (10.0)	0 (0.0)	1 (33.3)	0 (0.0)
Asthma	0 (0.0)	24 (96.0)	0 (0.0)	9 (10.5)	1 (10.0)	0 (0.0)	0 (0.0)	0 (0.0)
Heart failure	10 (10.4)	0 (0.0)	0 (0.0)	5 (5.8)	9 (90.0)	0 (0.0)	0 (0.0)	0 (0.0)
Ischaemic heart disease	12 (12.5)	3 (12.0)	0 (0.0)	2 (2.3)	5 (50.0)	0 (0.0)	0 (0.0)	0 (0.0)
Sleep disorders	1 (1.0)	0 (0.0)	0 (0.0)	30 (34.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cerebrovascular accident	3 (3.1)	1 (4.0)	0 (0.0)	1 (1.2)	0 (0.0)	0 (0.0)	3 (100.0)	0 (0.0)
COPD	0 (0.0)	1 (4.0)	3 (100.0)	4 (4.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Peripheral atherosclerotic disease	4 (4.2)	0 (0.0)	0 (0.0)	3 (3.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Psychiatric care mental health problems	1 (1.0)	0 (0.0)	0 (0.0)	4 (4.7)	1 (10.0)	0 (0.0)	0 (0.0)	0 (0.0)
Epilepsy	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.1)	3 (30.0)	0 (0.0)	0 (0.0)	0 (0.0)
Arrythmias	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (10.0)	1 (100.0)	0 (0.0)	0 (0.0)
Structural heart disease	2 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Venous thrombus	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Appendix to Chapter 8

Appendix Table 77: A description of participants with MSDs for SOC-10 sub-major occupational categories, stratified by type of MSD

Demographic variable	Prevalence among participants with any MSDs, n (%)	Prevalence among participants with chronic MSDs, n (%)	Prevalence among participants with MSD pain, n (%)
Corporate managers and directors	14 (3.7)	9 (4.1)	8 (3.3)
Science, research, engineering, and technology professionals	6 (1.6)	5 (2.3)	4 (1.7)
Health professionals	20 (5.2)	10 (4.6)	16 (6.6)
Teaching and educational professionals	30 (7.8)	16 (7.3)	17 (7.1)
Business, media and public service professionals	15 (3.9)	11 (5.1)	9 (3.7)
Other managers and proprietors	11 (2.9)	4 (1.8)	8 (3.3)
Science, engineering, and technology associate professionals	7 (1.8)	5 (2.3)	4 (1.7)
Health and social care associate professionals	9 (2.4)	7 (3.2)	3 (1.2)
Protective service occupations	3 (0.8)	1 (0.5)	2 (0.8)
Culture, media, and sports occupations	0 (0.0)	0 (0.0)	0 (0.0)

Business and public service associate professionals	14 (3.7)	6 (2.8)	9 (3.7)
Skilled agricultural and related trades	8 (2.1)	4 (1.8)	5 (2.1)
Skilled metal, electrical and electronic trades	12 (3.1)	4 (1.8)	10 (4.2)
Skilled construction and building trades	7 (1.8)	3 (1.4)	6 (2.5)
Textiles, printing, and other skilled trades	11 (2.9)	6 (2.8)	6 (2.5)
Administrative occupations	45 (11.8)	26 (11.9)	28 (11.6)
Secretarial and related occupations	14 (3.7)	6 (2.8)	11 (4.6)
Caring personal service occupations	28 (7.3)	16 (7.3)	16 (6.6)
Leisure, travel and related personal service occupations	7 (1.8)	3 (1.4)	6 (2.5)
Sales occupations	35 (9.1)	25 (11.5)	19 (7.9)
Customer service occupations	7 (1.8)	3 (1.4)	5 (2.1)
Process, plant and machine operatives	13 (3.3)	9 (4.1)	6 (2.5)
Transport and mobile machine drivers and operatives	22 (5.7)	14 (6.4)	16 (6.6)
Elementary trade and related occupations	5 (1.3)	2 (0.9)	5 (2.1)
Elementary administration and service occupations	36 (9.4)	21 (9.6)	20 (8.3)

Appendix to Chapter 9

Appendix Table 78: Examining the preliminary main effects model for statistical interactions, including participants with any MSD.

		Effect estimates in the preliminary main effects model	Adjusted for interaction term	RERI coefficient (additive scale)	Interaction (multiplication scale)
	Any MSD	1.86 (1.35 to 2.56)	1.87 (1.33 to 2.64)	2.03 (-2.25 to 6.31)	0.97 (0.41 to 2.29)

Primary care level MHP	Primary level MHP	3.49 (2.26 to 5.40)	3.54 (1.98 to 6.31)		
Hypertension	Any MSD	1.86 (1.35 to 2.56)	1.72 (1.24 to 2.40)	1.54 (-0.40 to 3.49)	2.02 (0.89 to 4.62)
	hypertension	1.58 (1.07 to 2.32)	1.30 (0.83 to 2.02)		
Heart failure	Any MSD	1.86 (1.35 to 2.56)	1.85 (1.34 to 2.56)	5.29 (-9.15 to 19.72)	1.25 (0.27 to 5.72)
	Heart failure	5.02 (2.14 to 11.77)	4.67 (1.77 to 12.35)		
Asthma	Any MSD	1.86 (1.35 to 2.56)	1.75 (1.25 to 2.44)	4.02 (-2.21 to 10.26)	2.24 (0.68 to 7.35)
	Asthma	2.18 (1.24 to 3.82)	1.64 (0.82 to 3.29)		
CVA	Any MSD	1.86 (1.35 to 2.56)	1.87 (1.36 to 2.58)	0.16 (-13.26 to 13.57)	0.66 (0.05 to 9.32)
	CVA	3.88 (1.17 to 12.94)	4.33 (1.05 to 17.78)		
Epilepsy	Any MSD	1.86 (1.35 to 2.56)	1.84 (1.34 to 2.54)	NE	NE
	Epilepsy	5.74 (1.02 to 32.45)	4.25 (0.66 to 27.39)		
Diabetes	Any MSD	1.86 (1.35 to 2.56)	1.99 (1.43 to 2.78)	-1.40 (-4.34 to 1.55)	0.43 (0.14 to 1.33)
	Diabetes	1.93 (1.06 to 3.52)	2.84 (1.27 to 6.39)		

Appendix Table 79: Examining the preliminary main effects model for statistical interactions, including participants with chronic MSDs.

		Effect estimates in the preliminary main effects model	Adjusted for interaction term	RERI coefficient (additive scale)	Interaction (multiplication scale)
Primary care level MHP	Chronic MSD	1.69 (1.19 to 2.41)	1.93 (1.31 to 2.84)	-1.87 (-5.31 to 1.57)	0.41 (0.16 to 1.05)
	Primary care MHP	3.58 (2.32 to 5.54)	4.50 (2.70 to 7.51)		
Hypertension	Chronic MSD	1.69 (1.19 to 2.41)	1.47 (0.98 to 2.19)	2.09 (-0.67 to 4.84)	1.94 (0.81 to 4.68)

	Hypertension	1.66 (1.13 to 2.42)	1.38 (0.88 to 2.16)		
Heart failure	Chronic MSD	1.69 (1.19 to 2.41)	1.73 (1.20 to 2.49)	-1.05 (-9.78 to 7.68)	0.54 (0.09 to 3.41)
	Heart failure	4.50 (1.94 to 10.45)	5.08 (2.01 to 12.85)		
Asthma	Chronic MSD	1.69 (1.19 to 2.41)	1.62 (1.12 to 2.35)	2.21 (-3.23 to 7.64)	1.71 (0.42 to 7.00)
	Asthma	1.80 (1.02 to 3.20)	1.60 (0.83 to 3.07)		
CVA	Chronic MSD	1.69 (1.19 to 2.41)	1.72 (1.21 to 2.46)	-4.84 (-13.45 to 3.77)	0.15 (0.01 to 2.86)
	CVA	4.12 (1.23 to 13.77)	5.60 (1.42 to 22.10)		
Diabetes	Chronic MSD	1.69 (1.19 to 2.41)	1.95 (1.33 to 2.86)	-2.53 (-5.13 to 0.07)	**0.24 (0.07 to 0.82)**
	Diabetes	2.01 (1.10 to 3.67)	3.01 (1.48 to 6.13)		

Appendix Table 80: Examining the preliminary main effects model for statistical interactions, including participants with recent musculoskeletal pain

		Effect estimates in the preliminary main effects model	Adjusted for interaction term	RERI coefficient (additive scale)	Interaction (multiplication scale)
Primary care level MHP	MSD pain	2.14 (1.48 to 3.09)	1.93 (1.30 to 2.86)	7.13 (-2.04 to 16.30)	1.97 (0.74 to 5.24)
	Primary care MHP	3.41 (2.24 to 5.20)	2.89 (1.79 to 4.66)		
Hypertension	MSD pain	2.14 (1.48 to 3.09)	2.21 (1.45 to 3.37)	0.32 (-1.88 to 2.52)	0.88 (0.38 to 2.04)
	Hypertension	1.56 (1.07 to 2.28)	1.61 (1.04 to 2.49)		
Heart failure	MSD pain	2.14 (1.48 to 3.09)	3.42 (2.24 to 5.22)	7.72 (-12.40 to 27.84)	1.68 (0.30 to 9.54)

	Heart failure	3.82 (1.78 to 8.10)	3.49 (1.56 to 7.80)		
CVA	MSD pain	2.14 (1.48 to 3.09)	2.12 (1.47 to 3.06)	NE	NE
	CVA	3.93 (1.13 to 13.63)	2.95 (0.79 to 11.00)		
Epilepsy	MSD pain	2.14 (1.48 to 3.09)	2.14 (1.48 to 3.09)	NE	NE
	Epilepsy	5.92 (1.06 to 33.17)	5.73 (1.00 to 32.66)		
Diabetes	MSD pain	2.14 (1.48 to 3.09)	2.22 (1.52 to 3.25)	-0.63 (-4.29 to 3.03)	0.56 (0.15 to 2.14)
	Diabetes	2.04 (1.14 to 3.63)	2.32 (1.20 to 4.50)		