Osteoarthritis and premature mortality: pathways for hand, hip, knee and foot osteoarthritis

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A thesis submitted for the degree of Master of Philosophy

October 2019

Keele University

DECLARATION

This thesis was untaken as part of an intercalated degree between the fourth and fifth year of an undergraduate medical degree (MBChB) at Keele University.

This thesis was part of a programme of study on osteoarthritis and premature mortality within the Versus Arthritis Primary Care Centre at Keele University. The study used data from a prospective cohort study, the North Staffordshire Osteoarthritis Project, that was conducted in the centre. The initial idea for this thesis was conceived by Dr Ross Wilkie, Dr Martin Thomas and Dr Milica Bucknall.

I was responsible for deriving the search strategy for the included systematic searches with guidance from Dr Martin Thomas and Dr Ross Wilkie.

The statistical analyses presented in this thesis were planned with support from Dr Milica Bucknall and Dr Ross Wilkie. I was responsible for conducting the statistical analysis and interpreting the results.

ABSTRACT

Purpose:

Evidence of an association between osteoarthritis (OA) and mortality is conflicting; differences in definitions and anatomical sites explain some of the discordance**.** The high frequency and increasing prevalence of OA highlights the need to understand its impact and potential association with premature mortality. The aims of this study were to: (i) examine the strength and direction of the association between different clinical case definitions of OA and premature mortality at different anatomical sites (hand, hip, knee and foot) (ii) identify the role of potentially modifiable factors on the pathway between OA at each site and premature mortality using mediation (path analysis) within a Cox proportional hazard model (survival analysis).

Methods:

A population-based prospective cohort study was conducted using data from the North Staffordshire Osteoarthritis Project (NorStOP), in which primary care medical record data was linked to self-report information collected by questionnaire in adults aged 50 years and over (n= 8066). Different case definitions of OA at each site were derived based on whether individuals had consulted in general practice for OA, self-reported pain in the hand, hip, knee or foot in the baseline questionnaire and indicated moderate to severe pain interference. A Cox proportional hazards analysis was performed to determine the total effect of each case definition of OA on mortality with adjustment for confounders (age, gender, education, occupation, non-steroidal anti-inflammatory drug use, ischaemic heart disease, self-reported cardiovascular disease, diabetes mellitus, smoking, chronic obstructive pulmonary disease and body

mass index). Within the Cox model, path analysis was used to decompose the total effects to assess the indirect and direct effects for potential mediators (walking frequency, depression, anxiety, insomnia, and social participation*).* Results are expressed as hazard ratios (HR); bootstrap resampling was used to generate 95% confidence intervals (95% CIs).

Results:

Mean age of participants was 65.2 (SD 9.8) years and 51.6% were female. 1515 (18.8%), 1323 (16.4%), 1774 (22.0%) and 1387 (17.2%) had disabling hand, hip, knee and foot OA respectively. Participants were followed up over 10 years during which time 1188 (14.7%) died. Disabling hand, knee and foot OA were significantly associated with premature mortality (adjusted HR 1.18 95% CI 1.02, 1.35; 1.16 95% CI1.02, 1.33; and 1.21 95% CI 1.05, 1.40 respectively); the increased HR for disabling hip OA was not significant (adjusted HR 1.06 95% CI 0.91, 1.23). Low walking frequency, depression, social participation were significant mediators of the relationship between premature mortality and OA ($p<0.05$). Taking knee OA to illustrate this, the indirect effects for low walking frequency, depression and social participation were 1.06 (95% CI 1.05, 1.09), 1.05 (95% CI 1.01, 1.08) and 1.09 (95% CI 1.05, 1.13) respectively.

Conclusions:

This novel approach to understanding pathways within a survival model indicates that potentially modifiable factors explain the link between hand, knee, hip and foot OA and premature mortality. Increasing walking, exercise and activity in general may also

reduce the impact of depression and improve social participation, and subsequent mortality.

ACKNOWLEDGEMENTS

Firstly, I am extremely grateful to Keele University School of Medicine for permission to complete this intercalated MPhil, and for granting me an intercalation bursary. There are numerous individuals I need to thank for their help, guidance and teaching this year, without whom this thesis would not have been completed.

Firstly, I would like to thank my supervisors Dr Martin Thomas, Dr Ross Wilkie and Dr Milica Bucknall. Their guidance and teaching goes far beyond the remit of what is presented in this thesis and will help me for many years to come.

Thank you to my fellow students in the research institute. Their technical guidance and motivating words have been extremely valuable at some of the more difficult parts of this year.

Thank you to my parents, Andrew and Jane, for being constantly supportive and having a never-ending belief in me. Thank you to my partner, James, for always encouraging me to be the best I can be. Thank you to my late grandfather, John Byrne, for being an inspiration to work hard.

Finally, thank you to all the patients I have encountered at medical school that have kept me asking ‘why’ and ‘how’ and ultimately inspired my interest in research.

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LIST OF ABBREVIATIONS

ACL	Anterior Cruciate Ligament
ACR	American College of Rheumatology
ADLs	Activities of Daily Living
AHPs	Allied Healthcare Practioners
AUSCAN	Australian/Canadian Hand Osteoarthritis Index
BMI	Body Mass Index
BML	Bone Marrow Lesion
BS	Bethany Seale
CI	Confidence Interval
CMC	Carpometacarpal Joint
COPD	Chronic Obstructive Pulmonary Disease
COX-2	Cyclo-oxygenase 2
CPRD	Clinical Practice Research Datalink
CRP	C Reactive Protein
CVD	Cardiovascular Disease
DALYs	Disability Adjusted Life Years
DDH	Developmental Dysplasia of the Hip
DE	Direct Effect
DIP	Distal Interphalangeal Joint
FAI	Femeroacetabular impingement
FIHOA	Functional Index for Hand OA
GHED	Global Health Exchange Data
GP	General Practice/Practioner

HADS	Hospital Anxiety and Depression Scale
HR	Hazard Ratio
HRCOL	Health Related Quality of Life
IADL	Instrumental Activities of Daily Living
ICD	International Classification of Diseases
ICF	International Classification of Functioning, Disability and Health
IE	Indirect Effect
IHD	Ischaemic Heart Disease
IL	Interleukin
Kg	Kilogram
M	Metre
MeSH	Medical Subject Headings
MOS	Medical Outcome Studies
MRI	Magnetic Resonance Imaging
MTP	Metatarsophalangeal joint
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NorStOP	North Staffordshire Osteoarthritis Project
NSAIDs	Non-Steroidal Anti-Inflammatory Drugs
OA	Osteoarthritis
OARSI	Osteoarthritis Research Society International
OKS	Oxford Knee Score
OR	Odds Ratio
PECO	Population, Exposure, Comparison and Outcome

PIP	Proximal interphalangeal joint
PRIMSA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RA	Rheumatoid Arthritis
REC	Research Ethics Committee
REM	Rapid Eye Movement
SF-36	Short Form 36
SMR	Standardised Mortality Ratio
SPSS	Statistical Package for the Social Sciences
TE	Total Effect
TNFα	Tumour necrosis factor α
UK	United Kingdom
USA	United States of America
WHO	World Health Organisation
WOMAC	Western Ontario and McMaster Universities Osteoarthritis Index
WOS	Wuchuan Osteoarthritis Study

RESEARCH OUTPUT FROM THIS THESIS

PRESENTATIONS

- Poster presentation and inclusion in the 'Presidents Picks' at the British Society of Rheumatology (01.05.19)
- Poster presentation at Research Institute of Primary Care and Health Science Postgraduate Symposium (16.05.19)
- Oral presentation at Royal College of General Practitioners Midland Faculty Research and Innovation Symposium (23.05.19)

1 INTRODUCTION

1.1 OSTEOARTHRITIS: THE BIG PICTURE

Osteoarthritis (OA) is the most common type of arthritis in the United Kingdom (UK) with 4% of adults aged 45 and over consulting for OA each year (Jordan et al., 2014). It most commonly affects peripheral joints including the knee, hip, hand and foot, and is characterised by pain on movement and morning stiffness (Arden and Nevitt, 2006). OA has a considerable impact on the quality of life of older adults and is the 11th highest cause of disability worldwide (Cross et al., 2014). Between 1990 and 2010, the rate of disability in the UK from OA rose by 16%, attributed to an ageing population (Murray et al., 2013). This has wide reaching effects on service provision and patient welfare. As well as impacting quality of life, OA has a significant impact on the economy. Oxford Economics (2010) estimated the direct cost of OA to the health service to be £5.2 billion. This considerable impact on the UK economy highlights the importance of OA and establishing effective management.

1.2 WHAT IS OSTEOARTHRITIS?

The traditional view that OA is a disease of 'wear and tear' of articular cartilage is now considered to be somewhat outdated. If OA was simply caused by wear of the articular cartilage within the joint, it would be expected most older members of the population would eventually get OA, whereas the prevalence lies around 50% (Porcheret et al., 2011). It has been suggested that terms like 'wear and repair' or 'wear, flare and repair' better describe the metabolically active process of developing OA (Porcheret et al., 2011). Problems with the joint include a contribution from the bone, menisci, muscles, synovial fluid and ligaments as well as the articular cartilage (Hunter, 2006).

There is increasing evidence and discussion that OA is a disease of the entire 'joint as an organ', rather than a specific part of the joint (Loeser et al., 2012). Furthermore, there is debate surrounding the contribution of systemic factors to the development OA. The combined involvement of all of these elements more accurately represent the aetiology of OA, as opposed to the more restricted view referring to cartilage wear only.

1.2.1 A synovial joint and osteoarthritis

Each of the joints this thesis looks to explore (hand, hip, knee and foot) are synovial joints. These will be expanded on individually later in sections 1.3.1, 1.3.2, 1.3.3 and 1.3.4. Although the ways in which the bones in each joint articulate are different, the core features of a synovial joint are essentially the same. A synovial joint arises at the end of two bones lined with articular cartilage. A fibrous capsule, continuous with the periosteum, lines the joint capsule. The inner layer of the fibrous capsule is the synovial membrane. The joint capsule is filled with synovial fluid (Drake et al., 2004). The following sections discuss key aspects of the OA pathology and process within a synovial joint.

1.2.1.1 Synovium

Despite OA not being classified as an inflammatory arthritis, synovial inflammation with immune cell invasion and cytokine secretion has been observed in osteoarthritic joints (de Lange-Brokaar et al., 2012). This inflammatory process has been implicated in the destruction of the joint, leading to OA. Synovitis, the inflammation of the synovium, has also been attributed to specific OA symptoms, including joint swelling, night pain and morning stiffness (Berenbaum, 2013). Inflammation has been observed

on the synovial membrane and in the synovial fluid. Increased amounts of mononuclear cells (macrophages, monocytes and activated B and T cells) have been found in the synovial fluid, along with associated synovial membrane hypertrophy, the formation of giant multinucleate cells and angiogenesis (Mathiessen and Conaghan, 2017). These changes indicate that OA is not simply an acute inflammatory process, but involves chronic inflammation leading to destruction of the joint. Furthermore, inflammatory changes to the synovium have been specifically found around areas of degenerative cartilage, highlighting the relationship between inflammation and the development of OA (de Lange-Brokaar et al., 2012). This is further evidence to support the proposition that simple 'wear and tear' does not fully explain the aetiology of OA. Orita et al. (2011) found increased pain in osteoarthritic joints were associated with increased levels of tumour necrosis factor α (TNF-α) within the synovium but could not explain why some patients with OA had higher cytokine levels in their joints than others. Despite the mechanism for inflammation being unknown, the knowledge that it contributes to OA impacts the management of the condition. Non-steroidal anti-inflammatory drugs (NSAIDs), like ibuprofen and naproxen, are the second line pharmacological treatment, following paracetamol, recommended by the National Institute for Health and Care Excellence (NICE) (NICE, 2014).

1.2.1.2 Bone and articular cartilage

Bone and cartilage changes have long been considered the primary pathological process in the development of OA (Berenbaum, 2013; Sharma et al., 2003). The expansion of subchondral bone, bone marrow lesions (BMLs) and the thinning of

articular cartilage have all been shown to be an important part of the progression of OA (Ding, Cicuttini and Jones, 2007; Felson et al., 2012).

BMLs are associated with changes in bone turnover and volume, as well as alterations to localised bone density. Subchondral bone in OA tends to be thicker but is less mineralised than bone without OA (Buckland-Wright, 2004). BMLs have been found to be associated with the position and weight-bearing compartment of a joint; a medial BML is more likely to be in a varus knee, whereas a lateral BML is more likely to be in a valgus knee (Felson et al., 2003, Felson, 2013). This supports the theory that load has an important role in the development of BMLs and therefore OA. BMLs have been implicated both in causing pain from OA, but also in causing the variable symptoms of OA, such as pain and morning stiffness (Hunter et al., 2013; Yusuf et al., 2011). Haugen et al. (2011) found an increase in hand tenderness associate with BMLs. This suggests that BMLs can form upon both load and weight-bearing and are important in the development of OA across all the joint sites examined within this thesis.

Subchondral bone, the bone distal to calcified cartilage, plays an important part in the development of OA (Li et al., 2013). Subchondral bone is dynamic; it alters depending on forces across the joint. Mechanical stress caused by changes in the load from injury, or as part of the pathological process of OA leads to changes in subchondral bone, leading to remodelling and expansion (Goldring, 2012). Subchondral bone deterioration and expansion is associated with also subchondral bone sclerosis, which is a key radiographic feature of OA. The turnover of subchondral bone is significantly increased in patients with OA and is predictive of disease progression (Dieppe et al., 1993), highlighting the important role that subchondral bone plays in OA.

Articular cartilage consists of chondrocytes and the extra-cellular matrix, including proteoglycans and a collagen network. Articular cartilage lines the joint space between the different bones. Failure of the chondrocytes to preserve the homeostasis of the extra-cellular matrix contributes to OA (Heijink et al., 2012). Although the initial trigger for this alteration to cartilage homeostasis is not known, it has been theorised that tissue injury leads to inflammation and the production of pro-inflammatory cytokine (Miller, Miller and Malfait, 2014). These cytokines then bind to chondrocytes causing them to release matrix metalloproteases which degrade the extra-cellular matrix of the articular cartilage tissue (Stannus et al., 2010).

1.2.1.3 Load and Weight-Bearing

Weight-bearing refers to how humans place their own body weight through joints; for example, upon standing weight is distributed across the lower limb joints and the lower back (Pierson, 2002). Load bearing refers to any joint that load can be passed across; this includes hand joints as well as lower limb joints (Shaaban et al., 2004). Both weight-bearing and load bearing have an important role to play in the development of OA. Repetitive joint load, either through occupation or sports, are associated with the development of OA (Arden and Nevitt, 2006; Spector et al., 1996; Vannini et al., 2016). For example, farming is strongly associated with hip OA with a hazard ratio (HR) of 1.63 after 1-5 years working as a farmer (Andersen et al., 2012). The suggested mechanisms of occupational groups developing OA surround excessive or repetitive joint loading. Mechanics, and load-bearing, have been attributed as one of the main predictors of OA progression (Felson, 2013). This is due to OA causing abnormal joint mechanics, such as valgus or varus malalignment at the knee, micro-

cracks and bone marrow lesions (Felson, 2013). These professions and modifications of load-based activity could represent target groups for preventative strategies for the development of OA.

1.2.2 Muscular strength

Muscular strength is important across a joint site; muscles both move the joint and provide stability upon joint motion and loading (Solomonow et al., 1987). The relationship between muscular strength and OA in the corresponding joint, particularly regarding quadriceps femoris and the knee, has been examined in depth (Kus and Yelden, 2019; Øiestad et al., 2015) Quadriceps femoris works to accommodate load and stabilise the knee joint. Reduced muscle strength and morphological differences were found in quadriceps femoris muscles of people with OA (Liikavainio et al., 2008; Serrão et al., 2015). In asymptomatic individuals with radiographic OA, atrophy of quadriceps femoris was more common when compared to control participants with no radiographic OA (Ikeda, Tsumura and Tonsu, 2005). Although significantly less literature has been published surrounding OA at other joints and muscle strength, there is evidence that muscle weakness and atrophy occurs at other osteoarthritic joints (Hurley, 1999). At the hip, significant weakness of both hip and knee extensors and flexors and hip adductors and abductors have been found in people with OA (Loureiro et al., 2018). Furthermore, atrophy of hip abductor muscles has also predicted the severity of hip OA (Loureiro, Mills and Barrett, 2013; Zacharias et al., 2018). Tevald et al. (2016) also explored the relationship between muscles around different joint sites and the development of OA; a reduction in hip abductor strength

was found in patients with knee OA, highlighting that muscular weakness in the whole limb can contribute to developing OA in a joint.

1.2.3 Systemic factors

It has been proposed that OA is not simply the consequence of increased or aberrant joint loading but is also caused by a complex network of systemic factors, such as inflammation, obesity and poor metabolic regulation (Cicuttini and Wluka, 2014). In a study looking to establish the relative contribution of mechanical stress compared to systemic factors in developing OA, in both weight-bearing (the knee) and non-weight-bearing joints (the hand), it was observed that mechanical stress was a more important risk factor in weight-bearing joints and systemic factors were more important in non-weight-bearing joints (Visser et al., 2015). This suggests that systemic factors do have a role to play in the pathogenesis of OA, but their contribution relative to excessive loading is unclear. Further discussion on obesity as a risk factor for OA can be found in 1.5.3.1.

1.3 OSTEOARTHRITIS AT THE HAND, HIP, KNEE AND FOOT

OA can occur at many different joints, but the most common anatomical locations affected by OA are the hand, hip knee and foot (Arden and Nevitt, 2006; Cushnaghan and Dippe, 1991). The unique function and anatomy of each joint site means that the aetiology and pathophysiology of OA at each location is slightly different.

1.3.1 The hand joints and osteoarthritis

The hand is a complex network of twenty-seven joints (Sharp et al., 1985). The three joints with the highest known prevalence per 100 of radiographic OA include the distal interphalangeal joint (DIP) at 35%, proximal interphalangeal joint (PIP) at 18% and

carpometacarpal joint (CMC) at 21% (Wilder, Barrett and Farina, 2006). Bouchard's and Heberden's nodes, found on the PIP joint and DIP respectively, are widely agreed to be related to osteophytes; small bony outgrowths on the joint margins (Alexander, 1999; Cicuttini et al., 1998). The role of excessive use, or overuse, of specific hand joints and an association with OA remains unclear (Alexander, 1999; Felson, 2004). There is some evidence that both DIP and CMC OA may, in part, be explained by overuse of the joint (Alexander, 1999; Jacobson et al., 2008). It has been proposed that overuse of the tendons leads to tendon inflammation, both causing adjacent joint inflammation and altered biomechanics of the joint, eventually leading to OA (Stäbler, Heuck and Reiser, 1997). In contrast, other studies point to risk factors such a genetics and postulate moving a malpositioned joint rather than overuse as a contributor (Felson, 2004; Leung, Rainsford and Kean, 2014). Among all joint sites examined within this thesis, a genetic susceptibility to OA is most pronounced at the hand (Spector and MacGreggor, 2004). Felson (2004) has described a 50% heritability for hand OA and twin studies have shown that up to 65% of hand OA is contributed to by genetic factors (Spector and MacGreggor, 2004). Identified susceptible genes have been located on chromosome 6 (Jakowlev et al., 2007). Hand OA is also common as a 'secondary' OA, particularly following rheumatoid arthritis (RA). RA is an autoimmune inflammatory condition that primarily affects joints. Although RA and OA have distinct pathophysiological mechanisms, the destruction around a joint from RA can then lead to OA in the same joint (Nuki, 1999).

1.3.2 The hip joint and osteoarthritis

The hip joint is a ball and socket joint comprising of the articulation between the head of the femur and the acetabulum of the pelvis. As well as undergoing processes described above, such as synovial inflammation, BML formation and reduce muscular strength, the development of hip OA is associated with several congenital and acquired malformations of the hip. Developmental dysplasia of the hip (DDH) is a congenital condition caused by a shallow acetabulum. It is associated with the premature (under 40) development of hip OA (Weinstein, 1987). Although this is not a common cause of hip OA it does highlight that abnormal morphology of the articulating surface can lead to the development of OA. Over the last 15 years there has been increased interest in the contribution of hip anatomy to the onset of OA (Murphy et al., 2016). Much of this surrounds the labrum, a semi-circular piece of fibrocartilage that lines the acetabulum like a cuff. Ganz et al. (2003, 2008) proposes that minor anatomical differences contribute to the development of hip OA. Ganz et al. also discusses the impact of femeroacetabular impingement (FAI), which leads to damage of the anterosuperior labrum. Following this new theory into the development of hip OA, researchers have presented evidence both supporting and rebutting this theory (Ahedi et al., 2017; Bardakos and Villar, 2009). Worldwide, radiological studies have identified labral damage following different types of FAI, that progress to OA (Nicholls et al., 2011; Tanzer and Noiseux, 2004). Furthermore, the prevalence of FAI has been estimated to be 10-15%, which correlates with the estimated prevalence of hip OA (Arthritis Research UK, 2013; Leunig and Ganz, 2005). Criticism of this theory surrounds the lack of clinical evidence for FAI induced hip OA, with limited large population-based cohort studies carried out assessing FAI as an

independent risk factor for OA over time (Sankar et al., 2013). Despite this, labral injury does appear important in the development of hip OA. Felson (2004) has also described a 50% heritability in some cases of hip OA, therefore indicating that the aetiology of OA is multifactorial with numerous potential different factors contributing to the disease process.

1.3.3 The knee joint and osteoarthritis

The knee joint is a modified hinge joint. It comprises of two joints; the articulation between the tibia and femur, and the articulation between the patella and the femur. Prevalence of symptomatic knee OA is estimated to be 13% of females over 60, and 10% of men over 60 (Heidari, 2011). Menisci are a feature of the knee joint not shared by the other joints examined in this thesis.

Post-traumatic OA, via meniscal damage, has a part to play in describing the aetiology of OA in the knee. Both traumatic meniscal tears, degenerative meniscal injury and surgical management of meniscal injury via a meniscectomy have been reported to contribute to the development of knee OA (Englund and Lohmander, 2004). It has also been observed that individuals with OA are more likely to have meniscal damage on imaging studies, perhaps showing that the relationship between meniscal damage and OA is not entirely linear (Englund et al., 2008).

There is growing evidence that injuries to the anterior cruciate ligament (ACL) can contribute to the development of OA (Paschos, 2017). In 65-75% of cases, traumatic ACL rupture and meniscus injury occur together (Slauterbeck et al., 2009). Following ACL or meniscal injury it is common to undergo surgery to repair the ligament. Although both surgical and conservative management can still lead to radiographic

knee OA 10 to 20 years following initial injury (Lohmander et al., 2007), a systematic review found a reduced rate of knee OA in those having operative management compared to non-operative management (Ajuied et al., 2014). This confirms the importance of joint mechanics in the development and progression of OA (Felson, 2013).

1.3.4 The foot joints and osteoarthritis

The foot is a complex network involving 33 joints (Oxford University Hospitals, 2019). The anatomy of the foot is split into forefoot, midfoot and hindfoot, with OA affecting joints in each area.

Roddy and Menz (2018) highlighted in a recent review that there remains a very limited number of studies investigating foot OA. Among adults aged 50 years and over, the population prevalence of symptomatic radiographic foot OA has been estimated as 7.8% in the metatarsophalangeal (MTP) joint, 6.8% in the 2nd cuneometatarsal joint and 5.8% in the talonavicular joint (Roddy et al., 2015). These joints, along with the 1st cuneometatarsal joint (prevalence 3.9%) and navicular first cuniform (prevalence 5.2%) represent the five foot joints that are easiest to identify radiographic OA changes on, and have therefore been included in an atlas for measuring foot OA changes on x-ray (Menz et al., 2007).

However, this may not actually represent all joints most affected by OA, as some joints are difficult to observe on plain radiograph (Menz et al., 2007). Therefore, it is likely that foot OA is under-identified in many joints of the foot. A systematic review from 2010 identified 27 publications relating to radiographic foot OA. By comparison, review articles covering the same time period found 176 studies for radiographic hand

OA and 190 studies for radiographic knee OA (Marshall et al., 2008; Trivedi et al., 2010).

Despite this, foot pain is common in mid-to-older ages (Thomas et al., 2011), with approximately one in six having radiographic OA combined with foot pain in the last month in a corresponding region (Roddy et al., 2015). Furthermore, of the foot joints studied the focus has predominantly been on the first MTP joint, with few studies investigating OA in the midfoot. In a Cochrane review, only one randomised controlled trial (RCT) investigating the management of MTP OA was found (Zammit et al., 2010). This perhaps shows that foot OA is less well studied and understood than OA in other joints. Combined with the difficulty in radiographically identifying OA in many of the foot joints, foot OA is difficult to research. Furthermore, classical OA theories from large joints like the hip or knee are harder to apply to a complex interplaying network of joints like the foot.

Numerous studies have looked at the association between foot posture and the development of first MTP OA, particularly looking at foot arches. One study found no link between foot arch height and the development of hallux rigidus (Zammit, Menz and Munteanu, 2009). However other studies have found that a flatter arch is associated with more severe radiographic OA at the first MTP joint (Menz et al., 2015). Furthermore, previous foot injury, obesity and other load bearing joint pain have been found to have to contribute to the development of foot OA (Thomas et al., 2015). It has been theorised that flatter arches leads to increased pressure across the midfoot, both causing increased pain and an alteration in the load across the joint, therefore

leading to OA (Lundgren et al., 2008). Like hip OA, this emphasises the important of joint positioning in the development of OA.

1.4 DEFINING OSTEOARTHRITIS

Given the multifactorial complexity of OA and its different aetiology, risk factors and clinical course across different joint sites, defining OA for both clinical and research purposes remains a challenge. For a cumulative and unified approach to OA research its definition is vital (Sharma, 2011). This has implications for the subsequent study of individuals and populations and cross-study comparison. The selected definition can impact on measures of frequency (incidence and prevalence) and the identification of cases recruited into research studies. This difficulty in defining OA is heightened by differences in OA between joint sites, as well as the differences in the progression, risk factors and prognosis of OA (Pereira et al., 2011). Perhaps the biggest contributor to the issue surrounding defining OA lies in the schism between the phenotype, clinical case definition and case definitions based in imaging.

1.4.1 Phenotypes

By definition, a phenotype is “the observable properties of an organism that are produced by the interaction of the genotype and the environment” (Driban et al., 2010). The heterogeneity of the disease process and variety of aetiologies of OA has led to the widely held idea that OA has numerous phenotypes (Felson, 2010). Within each joint affected by OA there are numerous different observable traits and therefore potentially different phenotypes. There are many different proposed phenotypes of OA, including but not limited to: generalised versus joint specific OA; secondary versus primary OA; radiographic versus painful OA; and comorbidity based

diagnosis (Bierma-Zeinstra and Verhagen, 2011; Felson, 2010; Marshall et al., 2013). For an OA phenotype to both be meaningful to clinical practice and research, phenotypes should also be identified based on disease management or prevention and clear aetiological evidence (Felson, 2010).

Two contrasting phenotypes are painful and non-painful OA (Felson, 2010). Collectively, previous literature demonstrates that radiographic OA and pain are often discordant (Bedson and Croft, 2008). This also highlights the relationship between diagnosis and phenotype; those who do not experience OA pain are less likely to consult and are therefore less likely to be diagnosed with OA. In accordance with NICE guidelines, in the UK OA can be clinically diagnosed without x-ray, and a phenotype of radiographic non-symptomatic OA would be seen infrequently in clinical practice (NICE, 2014)

1.4.2 Case definition

Case definition is an epidemiological set of criteria that determines whether an individual has the disease in question (Gregg, 2008). Various different case definitions are used across studies, including radiographic and clinical definitions, often making it difficult to compare studies directly.

1.4.3 Imaging based definitions

Radiological definitions for OA are all based on structural abnormalities within or surrounding the joint that can be identified through imaging. The most common radiographic definition for OA comes from the Kellgren and Lawrence grading system (Kellgren and Lawrence, 1957; Kohn, Sassoon and Fernando, 2016). The severity of OA on an x-ray is graded 0-4, with a score of more than 2 defining OA. This grading system

used five radiological characteristics to define and categorise OA; osteophytes, narrowing of joint space with associated subchondral sclerosis, pseudocysts, altered bone shapes (particularly of the femur) and periarticular ossicles (referring to the proximal and distal interphalangeal joints).

The simplicity of the Kellgren and Lawrence grading system means it has been widely used throughout literature and provides an easy comparison between the results of different studies. However, this grading system is not without limitations (Kohn, Sassoon and Fernando, 2016). Alterations to the definitions corresponding to each severity have changed since conception, particularly to class 2, the OA diagnostic level. This means that older studies do not necessarily have the same radiological classification for OA that more recent studies do. (Kellgren and Lawrence, 1963; Kohn, Sassoon and Fernando, 2016; Lawrence, 1977). Spector and Cooper (1993) also criticise Kellgren and Lawrence's emphasis on the osteophyte through its grading system, also highlighting that the original description of the grading system is not clear as to whether each numerical stage describes the progression of OA or not; this lead to misinterpretation of the grading system.

Although Kellgren and Lawrence provide the most widely used radiographic definition and grading system for OA, more recent alternative grading systems have also been proposed, and other imaging techniques are becoming more commonplace in OA research. The Osteoarthritis Research Society International (OARSI) atlas provides images of different joints and rates them as either absent/present or as normal and then with 1+, 2+ and 3+ of change (Altman and Gold, 2007; Altman et al., 1995).

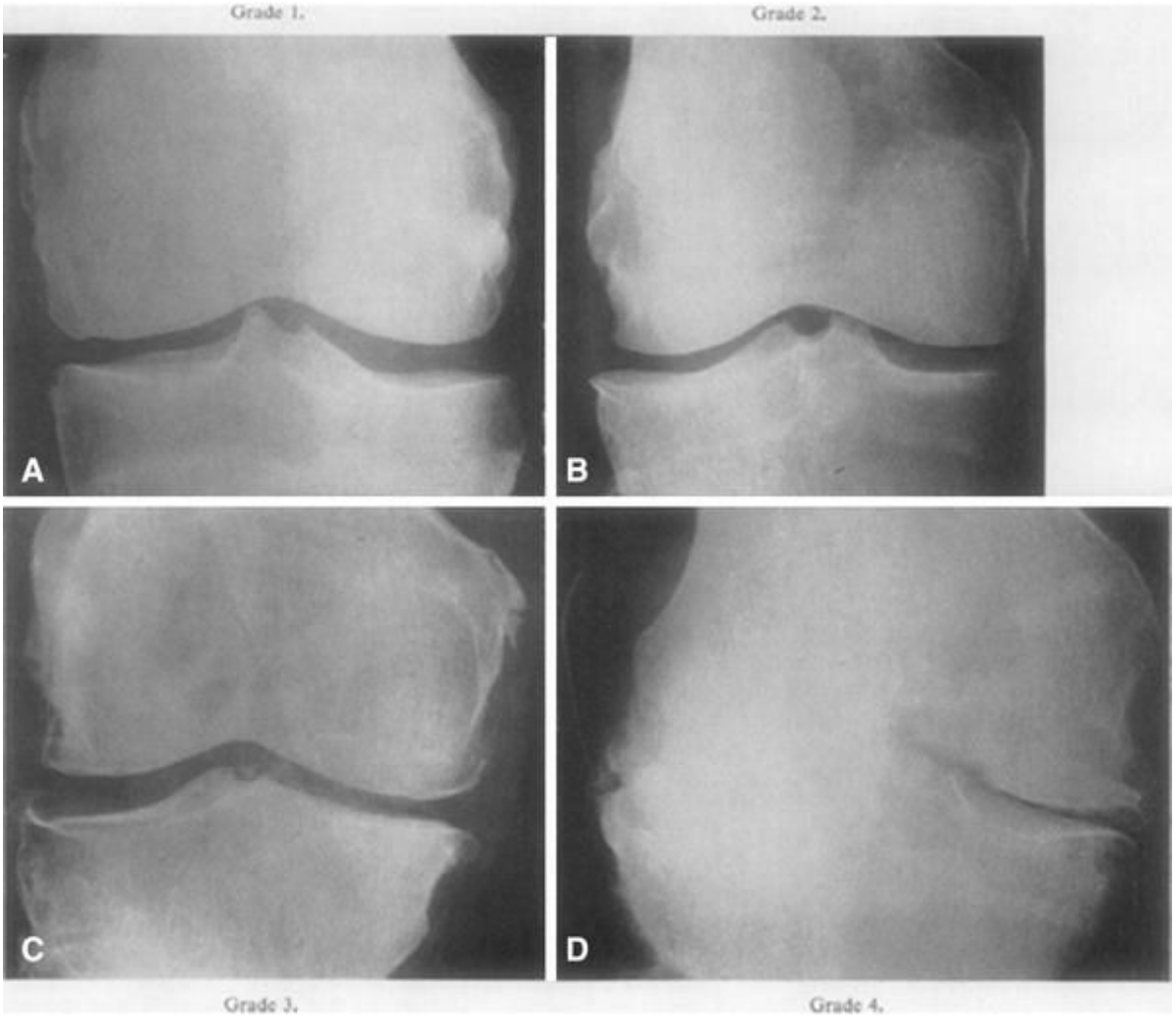


Figure 1.1: Anterior-posterior radiographs of the knee presented in the original Kellgren-Lawrence article

(A) Representative knee radiograph of KL classification Grade 1, which demonstrates doubtful narrowing of the joint space with possible osteophyte formation.

(B) Representative knee radiograph Grade 2, which demonstrates possible narrowing of the joint space with definite osteophyte formation.

(C) Representative knee radiograph of Grade 3, which demonstrates definite narrowing of joint space, moderate osteophyte formation, some sclerosis, and possible deformity of bony ends.

(D) Representative knee radiograph of Grade 4, which demonstrates large osteophyte formation, severe narrowing of the joint space with marked sclerosis, and definite deformity of bone ends.

(Kellgren and Lawrence, 1957, reproduced with permission)

Radiographic rating using the Kellgren and Lawrence system has been found to be ineffective in grading foot OA. A radiographic foot atlas allowing grading to be more reliably scored by raters has been developed more recently (Menz et al., 2007). Magnetic resonance imaging (MRI) definitions of OA have been proposed (Hunter et al., 2011). Despite this, the time-consuming and expensive nature of MRI scans in comparison to plain radiographs explains their infrequent use in clinical practice (Dieppe, 2011).

In addition to the exposure to radiation on assessment, a negative aspect of choosing a radiographic diagnosis of OA is the inconsistent association between observed structural change and pain (Hannan, Felson and Pincus, 2000). A recent systematic review on knee OA reported that between 19-45% of asymptomatic adults aged 40 years had structural changes indicative of OA on MRI (Culvenor et al., 2018). Although this may demonstrate the early stages of OA, it is unlikely that patients would present to primary care in the absence of pain. Therefore, radiographic OA definitions have limited clinical relevance (Hunter and Bierma-Zeinstra, 2019).

1.4.4 Clinical definition

Although the radiological definition is well suited to research, the majority of OA in the UK can be diagnosed and defined clinically, as per NICE guidelines (2014). NICE (2014) defines OA as: activity-related joint pain, morning stiffness of less than 30 minutes and functional impairment. NICE also states that radiological investigations of the affected joint are not necessary if the clinician is confident with their clinical diagnosis but may be beneficial if looking for specific therapeutic targets or with atypical symptoms (Sakellariou et al., 2017). The majority of the NICE guidelines are not joint-specific,

and instead define OA using the same criteria regardless of where in the body the suspected OA is.

Another way of clinically defining OA via published classification criteria is the American College of Rheumatology (ACR). The ACR criteria do have joint-specific diagnosis, unlike the NICE criteria also have similar criteria for hand, hip, knee and foot OA. Their definition, as well as activity-related joint pain and functional impairment includes examination findings, including joint crepitus, radiographical findings and biochemical signs (Altman et al., 1986, 1990, 1991), unlike the NICE guidelines (NICE, 2014). ACR has received criticism, as it picks up signs of late disease rather than early disease, when the disease process is potentially modifiable (Peat et al., 2006).

1.4.5 Identifying cases of osteoarthritis in primary care

There has been an increase in adoption of electronic healthcare records in clinical practice. This in turn has led to opportunity to use the data from electronic databases for research purposes (Parkin, 2016). In the UK primary care system, consultations and con-morbidities are coded on healthcare records via Read codes (NHS Information Authority, 2000). Read codes are a thesaurus of over 110,000 clinical terms available to compare co-morbidities and demographics of patients with a variety of different conditions, including OA (NHS Digital, 2018).

Read code defined OA is a diagnosis made within primary care indicating doctor-diagnosed OA. However, this does not necessarily explain how the diagnosis was made, or what diagnostic criteria was used to reach that Read code. For example, the diagnosis of Read code OA could be radiographic, clinical or a combination thereof.

This definition is limited by clinician subjectivity, patient subjectivity and the diagnostic criteria used. Read codes therefore risk misclassification; this can limit the clarity in research studies due to heterogeneity between patients classified with the same code. This highlights some inherent subjective limitations in using Read codes for OA clinical research questions.

1.5 EPIDEMIOLOGY

1.5.1 Prevalence

Deriving prevalence estimates is important for quantifying the disease burden in a defined population (Szklo and Nieto, 2018). All cases of disease, new and old, are included in a prevalence estimate.

Prevalence estimates are a vital source of information that can compare a disease across different populations and inform the economic planning of healthcare systems (Harder, 2014). They also provide a baseline measure prior to interventions for disease (Spencer et al., 2012).

There are some challenges to measuring OA using prevalence. Different definitions of OA can lead to different prevalence estimates. For example, the Global Health Exchange Data (GHED; Institute for Health Metrics and Evaluation, 2017) estimated worldwide OA prevalence using a variety of case definitions in those aged over 55 to be 4.11%. Turkiewicz et al. (2014) estimated the prevalence of clinically defined OA in Skåne in those aged over 45 to be 26.6% and Muraki et al. (2009) estimated the prevalence of radiographic OA in those aged 60 and over in rural Japan to be between 47.0% and 70.2%. This variety in prevalence estimates shows the importance of clinical definitions for OA. Furthermore, it has been established that clinically defined OA has

a fluctuating time course; patients can be symptomatic on some days and asymptomatic on others with 'flares' of OA pain (Parry et al., 2018).

This can lead to problems when using clinically defined OA for point-prevalence

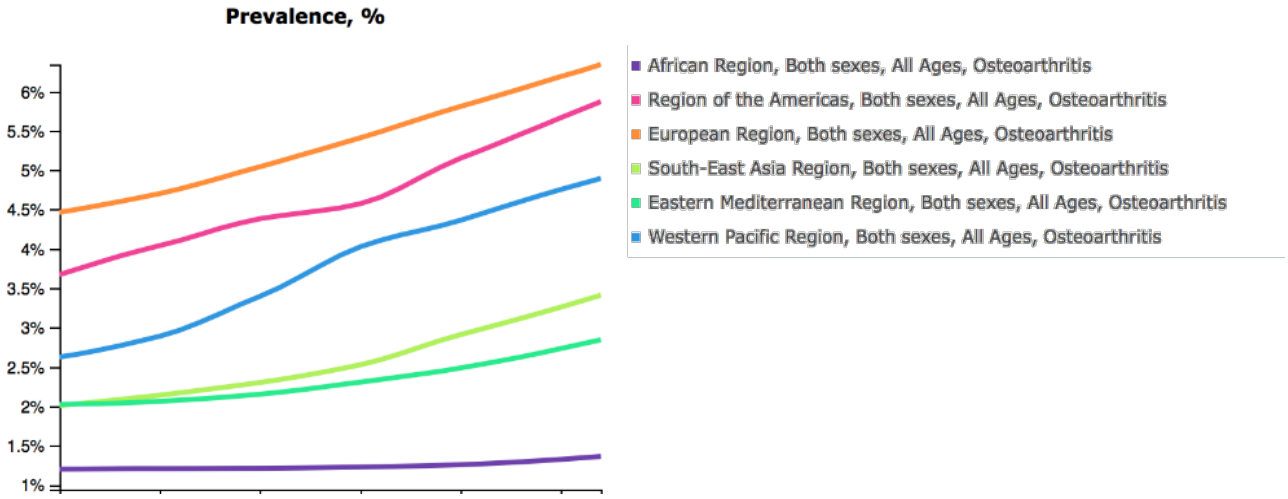


Figure 1.2- Osteoarthritis unadjusted prevalence by WHO region (Institute for Health Metrics and Evaluation, 2017)

estimates, particularly when using self-report data collection methods, as point-prevalence estimates do not consider the long-term effects of a chronic disease like OA and therefore the estimates may be inaccurate (Coggon, Rose and Barker, 2003).

As highlighted in Figure 1.2, the prevalence of OA is greater in high income continents including Europe, the Americas and the Western Pacific Region. In the GHED study (Institute for Health Metrics and Evaluation, 2017) data is collected using systematic data and literature searches by disease, meaning that many different case definitions of OA have been used in this database. Therefore, there are multiple explanations for the results from GHED. The increased prevalence in affluent areas could be due to higher research activity, and therefore there is more information to draw conclusions from. Furthermore, data collection and record keeping is likely to be better in more

affluent areas. This increased prevalence could also be explained by a reduced life expectancy in poorer countries, particularly those in Africa; as OA is associated with age, this could explain the reduced prevalence in these areas. The GHED is a good example of the positives and negatives of using prevalence estimates.

1.5.2 Incidence

The nature of OA as a disease process means that incidence can be difficult to define and quantify, and, like prevalence, varies depending on the case definition used and the anatomical areas investigated. A recent systematic review identified a significantly smaller number of papers addressing OA incidence in comparison to prevalence, in which only 8 of 72 papers presented data on incidence (Pereira et al., 2011). Furthermore incidence was defined and measured in different ways, making meta-analysis impossible (Pereira et al., 2011). As it is difficult to determine true onset of OA as a disease process and given its often gradual and progressive clinical course, incidence can be difficult to define (Chaisson et al., 1997). Radiographic definitions of OA tend to over-estimate incidence. Felson (1995) demonstrated that by changing the case definition between symptomatic and radiographic OA, the incidence appeared to double; in women 2% per year developed radiographic incident OA and 1% developed symptomatic incidence OA. In this study, incidence of radiographic OA was defined as a Kellgren and Lawrence score of less than two at baseline and a score of two or more at follow–up (Felson et al., 1995). Felson et al. (1995) defined symptomatic OA as reporting OA symptoms upon questioning. This highlights the discordance between radiographic and clinical OA definitions.

1.5.3 Risk factors

As discussed previously, there are many risk factors that have been implicated in the development of OA. A recent systematic review specifically looked at the risk factors for knee OA and found significant results for raised body mass index (BMI), female gender and previous knee injury, but not for smoking or concurrent hand OA (Silverwood et al., 2015). Risk factors can be viewed as modifiable and non-modifiable. This is important for the general management of OA. Modifiable risk factors represent targets to manage OA and slow down or potentially halt the disease progression. Local risk factors, including previous joint injury and malposition, have been discussed above.

1.5.3.1 Modifiable Systemic Risk Factors

Obesity has been shown to significantly contribute to the development and progression of OA (Zhang and Jordan, 2010). The World Health Organisation (WHO) described obesity as a main priority for healthcare worldwide, highlighting that the worldwide prevalence of obesity has risen from 21.5% in 1975 to 38.9% in 2016, with the highest prevalence areas being Europe and the Americas (WHO, 2018). The Chingford survey (Hart and Spector, 1994) showed that for every 2 units of BMI the risk of OA increased by 36%. More recent findings show every 5 kilograms (kg) of weight gain increasing the risk of OA by 36% (March and Bagga, 2004). This increase in the prevalence of obesity, combined with the ageing population, will ensure that the number of people with OA will continue to rise.

However, the mechanism by which obesity leads to OA is not clear. Obesity was associated with OA in the knee and CMC joints but not in PIP joints in the Chingford

study (Hart and Spector, 1993). In another study obesity was associated hand and knee OA but not hip OA (Grotle et al., 2008). Furthermore, the BMI of patients undergoing knee arthroplasty is higher than those undergoing hip arthroplasty for OA (Culliford et al., 2015), perhaps highlighting that obesity affects weight-bearing joints differently. Although it may seem logical that obesity would affect weight-bearing joints more, simple load theory does not explain the impact on the CMC joint, highlighting that obesity must contribute to the development of OA via a separate mechanism as well.

It has suggested a culmination of different mechanisms leading to the development of OA (Vincent et al., 2012). The low volume of muscle mass associated with obesity, mechanical forces and systemic inflammation have all been implicated in the development of OA. Systemic inflammation via hyperleptinaemia and a decrease in adiponectin leads to the widespread release of pro-inflammatory cytokines including TNF-α, interleukin (IL)6, IL-1ß and c-reactive protein (CRP) (Schrager et al., 2006). Increases in the systemic levels of each of these cytokines have been found to be predictive of the development of OA over time (Livshits et al., 2009; Sharif et al., 2000). It has therefore been suggested that weight loss is a core treatment of OA.

Low levels of physical activity have also been reported to contribute to development and progression of OA (Petrella, 2000). Most studies in this area look into the effect that exercise programmes have on reducing pain or radiographic progression of OA (Hunter and Eckstein, 2009).

1.5.3.2 Non-Modifiable Systemic Risk Factors

OA is a disease associated with increased age. NICE (2014) states that for a typical diagnosis of OA, the patient is aged over 45 years. Despite OA being associated with increased age, it is not an inevitable consequence of ageing. Incident rates for OA rise quickly after the age of 50 but begin to subside in the over 70s (Oliveria et al., 1995).

OA is more common in women, particularly those who are post-menopausal. Although the post-menopausal period for most women also corresponds to the over 50 increase in OA incidence, there is still a higher incidence than in men. Women also have a greater severity of OA than men, when calculated by standardised mean differences (Srikanth et al., 2005). MRI studies have shown women have a reduced volume of knee cartilage than men, perhaps explaining the increase in OA in this joint specifically, but this has not been shown in other joints. There has been conflicting evidence on the effects of oestrogen and OA, as well as the impact of oestrogen on pain receptors for OA (Cirillo et al., 2006; Nevitt et al., 2001). The precise reason why OA is more common in women has not been established.

1.6 MANAGEMENT OF OSTEOARTHRITIS

There are numerous options for managing OA including non-pharmacological, pharmacological and surgical approaches. The core treatments include weight loss, patient education and exercise, before escalation to more complex treatments including medications, intra-articular injections and joint surgery (Figure 1.3).

Exercise is central to OA management, involving both muscular conditioning and generalised aerobic exercise (Deyle et al., 2000; NICE 2014). It is very important to try to prolong the lifespan of the joint and halt or reduce the disease process, given the limitations of joint replacement surgery (NICE, 2014). Surgical limitations include: operative failure, the lifespan of the replaced joint outlasting the patient and risk of post-operative complications (National Health Service, 2016). Exercise and physical activity can also help combat some reversible local and systemic risk factors for OA, such as obesity and reduced muscle strength. Despite this, OA was the main reason for 99% of knee replacements and 90% of hip replacements with 112836 knee replacements and 105306 hip replacements performed in 2017 in the UK, an increase from the previous year (National Joint Registry, 2018).

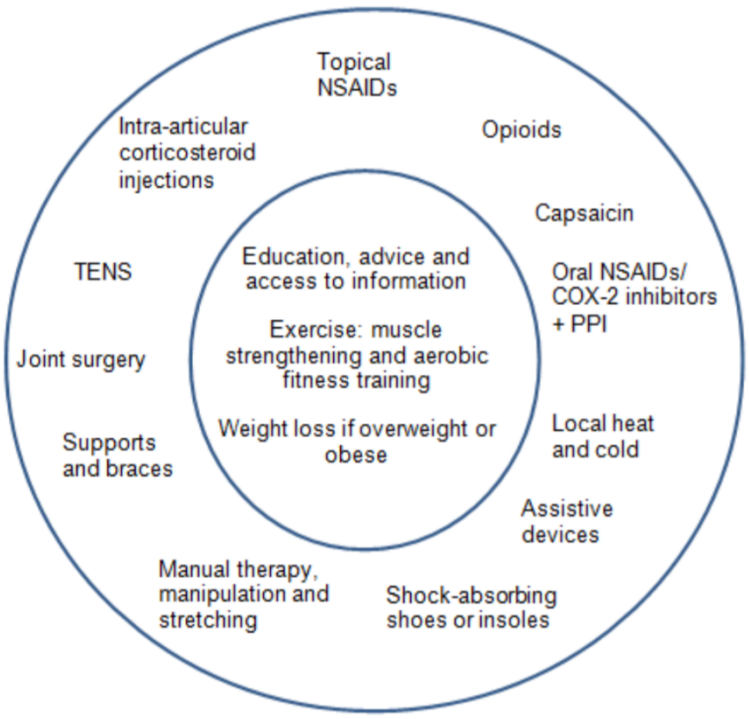


Figure 1.3- NICE (2014) recommended management of osteoarthritis (Figure used with permission)

The invasive nature of these procedures and the risk of requiring a revision surgery highlights the importance of first exhausting all other management options to preserve the original joint.

Education is paramount to ensure any interventions are effective and are well understood by the patient (Martin et al., 2005). The controversy surrounding NSAID prescription and their impact on the cardiovascular system illustrates the importance of high-quality approaches to the non-pharmacological management of OA (Bavry et al., 2011).

1.7 SUMMARY

OA is a joint condition which has a number of case definitions and phenotypes. The incidence and prevalence of OA is high for all definitions. No matter how OA is defined, it is important to look at its consequences and determinants. The impact of OA on individuals is important to them and will drive healthcare consultation and the need for interventions. Given that the population is ageing, there will be an increasing number of adults with OA which will escalate the burden on society and health resources. An understanding of the magnitude of impact of OA, and of what factors influence this, will enhance the development of potential strategies to reduce the burden of the condition. The following chapter makes the case for premature mortality being an important outcome measure for OA and examines the current 'state-of the-science' on the relationship between OA and mortality.

CHAPTER 2: MEASURING THE IMPACT OF OSTEOARTHRITIS

2.1 IMPACT OF OSTEOARTHRITIS

Identifying and measuring the extent of the impact of osteoarthritis (OA) is important to understand how it affects people and to drive interventions to reduce the burden on them and society; OA impacts on mental, physical and social health and quality of life.

2.1.1 Mental Health

The World Health Organisation (WHO) defines mental health as a state of well-being where individuals can cope with day-to-day stresses, work productively and contribute to their community (WHO, 2014). An increasing awareness of mental health problems, especially amongst older people, has led to increased focus on the association between chronic disease, like OA, and mental health problems (Moussavi et al., 2007). Results from a recent Korean study (n= 8271) highlighted an association between OA and impaired mental health, including depression, stress perception and suicidal ideation, (Jung et al., 2018). Depressive symptoms are associated with an increase in the severity of symptoms and radiographic changes of OA (Rathbun et al., 2017). A recent systematic review identified that 20% of adults with OA experienced anxiety and depression, however this study was unable to establish directional causality (Stubbs et al., 2016). The interplay between mental health conditions and OA can also reduce quality of life (Rosemann et al., 2007a). Pain levels fluctuate more in those with OA and mental health problems, suggesting that anxiety and depression alter pain threshold levels (Neogi et al., 2010). As chronic pain can lower mood and increase anxiety levels (Creamer and Hochberg, 1998; Hansen and Streltzer, 2005), the cycle of worsening mental health and increased OA symptoms continues.

There are multiple implications of having poor mental health in the context of OA. The core management options for OA (education, exercise and weight loss) require significant motivation to understand and engage with (Beebe et al., 2010; Robson et al., 2013). Patients with depression struggle to take part in physical exercise, therefore reducing their muscle strength and increasing the risk of their OA progressing (Rosemann, Laux and Kuehlien, 2007b).

2.1.2 Physical Health

OA is an important cause of functional limitation in older adults and impacts on daily activities, such as walking and climbing stairs (Guccione et al., 1994; Murray et al., 2010). Although physical activity is part of the core management of OA, only 30% of primary care clinicians regularly recommend exercise for OA (Maserejian et al., 2014). Walking is an important basic skill and can be assessed in a variety of ways in sedentary adults. Methods of assessment includes direct methods, such as diaries or accelerometry, or indirect methods, such as self-report questionnaires (Tudor-Locke and Myers, 2001). When using accelerometry, individuals with hip and knee OA have been found to have significantly reduced step counts, in comparison to age-matched controls (Winter et al., 2010). Whilst using step counts measured by accelerometry is an accepted objective method to gauge the amount of steps taken per minute, hour and day, it is expensive to implement in large population-based studies. The association between OA and reduced walking frequency has also been observed using self-report methods of data collection (King et al., 2018). There has been criticisms surrounding self-report methods for walking frequency, stating that these approaches often fail to measure routine or light activity or fail to measure the lower end of

sedentary activity (Mâsse et al., 1998; Tudor-Locke and Myers, 2001). Despite this, self-report questionnaires represent a more efficient mode of data collection for use in large population-based studies. Questionnaires designed for OA, including the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) for hip and knee OA and the Oxford Knee Score (OKS) for knee OA attempt measure low levels of activity (Bellamy et al., 1988; Dawson et al., 1998). The relationship between OA and walking frequency appears to be bidirectional; that is, those who walk less are more at risk of developing OA, and those with OA have a reduced walking frequency (King et al., 2018; Leong and Sun, 2014).

Stair climbing is also an important measure for establishing the physical impact of OA. Stair climbing is more physically demanding than walking and requires a good degree of lower limb range-of-motion and muscle strength (Nadeau et al., 2003; Riener et al., 2002; Rowe et al., 2000). An inability to climb stairs can have a significant impact on patients, and lead to difficulties with self-care, and may require patients to modify their house, or move house, to live comfortably. In a sample of participants with clinically defined OA, those with mild to moderate pain had a better ability to climb stairs than those in more severe pain (Whitchelo, McClelland and Webster, 2014). Both reduced walking frequency and stair climbing are a consequence of lower limb OA, however hand OA can also have significant effect on physical function. Hand OA can lead to deficits in fine motor skills, including opening tins or doors, buttoning a shirt and fastening jewellery (Kjeken et al., 2005). Specific self-report measurement tools help quantify the activity restriction caused by hand OA, including the

Australian/Canadian Hand OA Index (AUSCAN) function subscale and the Functional Index for Hand OA (FIHOA) (Bellamy et al., 2002; Dreiser et al., 1995).

2.1.2.1 Pain and physical limitation

Pain caused by OA often leads to physical limitation (Neogi, 2013), and the optimal approach to adequate analgesia is at the centre of current debate. NICE (2014) guidelines suggest the use of NSAIDs (non steroidal anti-inflammatory drugs; topical and oral), cyclo-oxygenase 2 (COX-2) inhibitors, paracetamol and, if this does not work, opioids. There is increasing evidence that gabapentinoid neuromodulating agents (gabapentin or pregabalin) have some effect in OA, with promising results in animal models (Vonsy, Ghandehari and Dickenson, 2009). An increase in gabapentinoid neuromodulating agent prescriptions over the last 10 years has been attributed to OA (Appleyard et al., 2019).

Optimal analgesia is integral to OA management. As well as making day-to-day activities more comfortable, controlling pain increases the likelihood that patients will exercise and adhere to physiotherapy, thus helping to manage the condition (Alami et al., 2011).

2.1.3 Social Health

WHO highlighted the importance and impact of social health by including social participation in the International Classification of Functioning, Disability, and Health (ICF; WHO, 2002). In the ICF, social health was defined as the involvement in meaningful activities that fulfil aspects of an individual's identity, and roles in family and community life (WHO, 2002). The effects of OA and co-morbidities associated with OA, including reduced mobility, chronic pain and mental health problems, restrict

individuals' participation within society (Wilkie et al., 2007a). There are few measures that assess social participation; the Keele Assessment of Participation (KAP) reflects the ICF measures of social health to quantify social participation (Wilkie et al., 2005). Social participation was significantly restricted if an individual with OA was unable to mobilise outside of the home (Wilkie et al., 2007b). This reduced mobilisation was not just a result of joint pain, but also a result of comorbidities and environmental barriers, like public transport or devices to assist walking (Wilkie et al., 2007b). Reduced mobilisation means that people are unable to go to work, do their own shopping or take part in social activities. Furthermore, individuals with disabling OA (OA with pain interference) were more likely to retire prematurely than those with non-disabling OA, thus reducing their social participation (Wilkie et al., 2014).

2.1.4 Quality of Life

Quality of life is defined as "the extent to which [a] life is comfortable and satisfying" (Collins English Dictionary, 2019). Health related quality of life (HRQOL) encompasses any aspect of life that relates to physical or mental health (Centres for Disease Control and Prevention, 2018). There are numerous important reasons for measuring HRQOL. In chronic diseases such as OA, cancers or chronic respiratory conditions, HRQOL became a key target in managing disease outcomes, as these conditions cannot be 'cured'. HRQOL quantifies the burden of disease and helps measure the effect of interventions on participants lives (Centres for Disease Control and Prevention, 2018). Furthermore, HRQOL is an important and individualised measurement method for patients. A commonly used method of measuring HRQOL is the Short Form-36 (SF-36; Ware, 1993). The SF-36 allows participants to define their levels of health; for example

in the question “In general, would you say your health is: excellent; very good; good; fair; poor”. There is no definition of the word health, allowing the participant to define this themselves. This therefore presents HRQOL, as a target for disease intervention and for patient satisfaction. Symptomatic knee OA has been significantly associated with poor HRQOL in older adults (Alkan et al., 2014, Kawano et al., 2015). Furthermore, Takegami et al. (2017) highlighted the relationship between the radiographic progression of OA and reduced HRQOL. This association between OA and reduced HRQOL is also observed in clinical definitions of OA (Hoogeboom et al., 2013). This affirms the importance of good management to reduce OA progression to improve HRQOL. A study examining health-related quality of life among OA participants, via a quality of wellbeing scale, found that patients with OA had a significantly lower quality of wellbeing score compared to community dwelling adults without OA (Groessl, Kaplan and Cronan, 2003). Furthermore, those with OA had a comparable score to participants with depression or advanced cancer (Groessl, Kaplan and Cronan, 2003).

2.1.4.1 Activities of Daily Living

OA also impacts on activities of daily living (ADLs) and instrumental activities of daily living (IADLs). ADLs include basic activities such as personal care and self-feeding that are essential for day-to-day survival (Lawton and Brody, 1969). IADLS also include cooking, shopping and are essential for independent living in the community (Williams, 2011). Reduced independence with ADLs is detrimental to HRQOL (Lyu and Wolinsky, 2017). A study of 10000 patients found that over 80% of those with clinically defined OA were six times more likely to report limitations with ADLs compared with

those without OA (Fautrel et al., 2005). The physical, psychological and economic impact of this is wide reaching. An inability to perform basic activities, like ADLs, leaves an individual requiring extra care, either from family members or from outside agencies.

2.1.4.2 Insomnia

Insomnia has significant implications for patients; reduced sleep is associated with reduced productivity, work absenteeism and increased rates of healthcare utilisation (Léger et al., 2002; Léger et al., 2006; Roth and Ancoli-Israel, 1999). Insomnia is both a physical and psychological complication of OA and significantly affects HRQOL (Kyle, Morgan and Espie, 2010). Previous studies have found that up to 81% of those with OA struggle to maintain their sleep (Wilcox et al., 2000). Spira et al. (2015) highlighted the abnormal circadian rest and activity rhythms in those with OA and insomnia, and postulated that dysregulated circadian rhythm could eventually lead to premature mortality, via increases in leptin and ghrelin leading to cardiovascular disease (Paudel et al., 2011; Taheri et al., 2004). Multiple studies have investigated the relationship between reduced sleep and pain perception. Reduced sleep, particularly Rapid Eye Movement (REM) sleep, has been shown to increase pain perception (Lautenbacher, Kundermann and Krieg, 2006; Roehrs et al., 2006). Finan, Goodin and Smith, (2014) reported that pain simultaneously reduces sleep and increases stress, therefore causing a cycle of poor sleep leading to increased pain. Studies have investigated the effect of insomnia on pro-inflammatory cytokines in OA patients, to establish the mechanism of insomnia related hyperalgesia. However, no significant evidence of a

relationship between knee OA, insomnia and cytokine levels, such as interleukin (IL)6 and IL10, was seen (Quartana et al., 2015).

2.1.5 Mortality

A full appreciation of the natural history of OA is vital to identify factors to improve OA management. Although there is a growing body of literature on the natural course of the condition, less is known about the direct link between OA and mortality. OA is now recognised as a serious condition and is associated with other comorbidities, such as cardiovascular disease (CVD) and diabetes, which are associated with premature mortality (Cleveland and Callahan, 2017; Osteoarthritis Research Society International, 2016). Previous studies have attributed the increased mortality rate in those with OA to concomitant risk factors (Cleveland and Callahan, 2017). However, more recent studies implicate OA itself as the cause of premature mortality, independent of these risk factors (Watson et al., 2003). OA affects a large proportion of the population in the UK, and this is likely to increase as the population ages (Murray et al., 2013). Despite this, there are no large scale public health initiatives for OA. If those with OA have a higher level of mortality than those without OA, the importance of a national approach to combatting OA will be justified. Identifying and addressing modifiable factors will reduce mortality as a result of OA (Juni, Reichenbach and Dieppe, 2006; Nüesch et al., 2011).

Previous studies looking at the association between OA and premature mortality have investigated both all-cause and cause-specific mortality, with conflicting results. Some studies appear to show no clear relationship between OA and all-cause mortality, whereas other find an association between all-cause mortality and OA (Nüesch et al.,

2011; Xing et al., 2016). Investigating the relationship between OA and cause-specific mortality provides evidence towards potential mechanisms for the relationship between OA and premature mortality. Like all-cause mortality, there is no unity in evidence reporting an association between cause-specific mortality and OA (Hawker et al., 2014; Haugen et al., 2015).

There are a number of studies evaluating the association between premature mortality and OA. To identify all previous literature examining OA and premature mortality, two systematic literature searches were untaken.

2.2 AIMS AND OBJECTIVES OF SYSTEMATIC LITERATURE SEARCHES

Due to the publication of more recent studies examining the association between OA and premature mortality, previous systematic reviews in this area were deemed no longer comprehensive. Consequently, up-to-date systematic searches and narrative synthesis were undertaken.

2.1.1 Aims

To synthesise information in published literature and determine the direction of the association between OA and mortality.

2.1.2 Objectives

1. To identify published systematic reviews of the association between OA and premature mortality (Search 1).
2. To identify original studies that have examined the association between OA and premature mortality, published following the search strategy end dates of the systematic reviews identified in Search 1 (Search 2).

3. To narratively synthesise the information from both searches and determine the strength and direction of association between OA and mortality.

2.3 WHY PERFORM SYSTEMATIC LITERATURE SEARCHES?

A systematic search, when designed properly, should identify all relevant literature on a research question and allows synthesis of all empirical evidence via explicit and systematic methods to reduce bias (Antman et al., 1992; Oxman and Guyatt, 1993). Therefore, a systematic search provides a thorough way of identifying and analysing current literature on the associations between OA and premature mortality, and summarising this data via a meta-analysis. Large amounts of data can be amalgamated succinctly within one document, providing an efficient way of summarising information. Combining data from primary studies via meta-analysis may provide a more precise estimate of the relationship between OA and premature mortality than any one study (Pogue and Yusuf, 1998). Furthermore, systematic searches help to identify gaps in current knowledge; if no gaps are found this highlights that further work may not be necessary (Garg, Hackman and Tonelli, 2008). However, there are limitations in performing systematic searches. The data found in a systematic search is only as reliable as its constituent studies and the rigor with which the search was conducted. Moreover, meta-analysis of studies with high heterogeneity in design and quality may lead inaccurate estimates of the true relationship between OA and premature mortality (Lau, Ioannidis and Schmid, 1998). In these circumstances, narrative synthesis is useful to interpret the data (Cochrane Collaboration, 2011). Systematic searches also do not account for publication bias (Garg, Hackman and Tonelli, 2008).

2.4 METHODS FOR THE SYSTEMATIC LITERATURE SEARCHES

A protocol was first developed to identify all systematic reviews examining the association between OA and mortality, and then for individual studies published more recently. These systematic searches were performed in line with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Liberati et al., 2009).

Two systematic searches were performed. Search 1 aimed to identify existing systematic reviews in peer-reviewed journals, whereas Search 2 aimed to identify original peer-reviewed articles published more recently than those included in the systematic reviews from Search 1. Both searches involved four stages:

Stage 1: Formulation of search strategy and identification of studies.

Stage 2: Screening of titles against eligibility criteria.

Stage 3: Reviewing potential eligibility of abstracts identified in Stage 2.

Stage 4: Reviewing potential eligibility of full-text articles identified in Stage 3.

2.4.1 Search Strategy

In stage 1 a comprehensive search strategy was conducted by one researcher (BS). The search strategy used text terms for osteoarthritis (osteoarthritis/, osteoarthr*, OA, arthrit* and joint pain), mortality (mortality/, mortalit*, premature mortality, death) and in search 1 study type (systematic review, systematic, review). Subject headings (i.e. medical subject headings [MeSH]) were also used. A full list of search terms for search 1 can be found in Appendix 1. A full list of search terms for search 2 can be

found in Appendix 2. One notable exclusion in search terms in search 2 is study type, as this search was not specifically looking for systematic reviews.

2.4.2 Information Sources

Two sources of information were used to find relevant articles. Firstly, both searches used OVID SP interface (OVID Technologies Inc, 2019). This includes over 100 different databases, including MEDLINE and EMBASE. Databases were searched as part of Search 1 between database inception to 13th November 2018. For Search 2, databases were searched from 1st January 2015 to 18th December 2018. This start date was selected following the completion of the first search and represents the search end date of the most recent systematic review identified on OA and mortality. Secondly, a hand search of the reference lists of all included studies was also completed.

Citations identified following both searches were exported into RefWorks ProQuest (RefWorks, 2009). RefWorks stored these citations and identified duplicated articles prior to the title and abstract screening.

2.4.3 Eligibility Criteria

The inclusion criteria for both systematic searches were a clear focus on the investigation of OA and mortality.

Search 1 inclusion criteria:

- Systematic review
- Examination of the relationship between OA and mortality
- Published at any time
- Written in any language

Search 2 inclusion criteria:

- Examined the relationship between OA and mortality
- Published from January 2015 to December 2018 (time of the last search identified in Search 1 to when this search was completed)
- Written in any language

Search 1 exclusion criteria

- Non-systematic review papers

Search 2 exclusion criteria

- Systematic review papers

Both searches followed the PECO (population, exposure, comparison and outcome) framework (Huang, Lin and Demner-Fushman, 2006). The PECO for this review was:

Population: *Adults (18+ years)*

Exposure: *osteoarthritis*

Comparison: *no osteoarthritis*

Outcome: *mortality*

2.4.4 Identification of literature

Stage 2 involved the screening of titles against the eligibility criteria. Titles that met criteria or potentially met the criteria were taken forwards to Stage 3: reviewing the abstracts for eligibility. Literature that met the criteria were retained for Stage 4 which was to review full-text articles. Any articles that could not be definitively included or excluded based on the eligibility criteria were always retained in the next stage of review.

2.4.5 Data Extraction

Following the identification of relevant articles in Stage 4, data extraction commenced. All data extraction for both systematic searches was performed independently by the thesis author. Extracted information included the following; lead author name, publication year, country and continent in which the study was based, study population and type of study (clinical or community based), mean age of population, percentage female in population, main findings, case definition of OA used, anatomical site of OA, and confounders adjusted for. Following Search 1, all included studies identified by each systematic review were obtained and subjected to the same data extraction process. A narrative synthesis was then performed.

2.4.6 Narrative synthesis

Due to heterogeneity between study design, population sample, setting and reported measures, a narrative synthesis approach was used to analyse the data from the systematic searches, as meta-analysis would have been difficult (Popay et al., 2006). Tabulation was used to allow easy comparison between studies in multiple different domains, including results, case definition and anatomical location (Jones, 2004). 'Vote-counting' (i.e. counting how many studies found a certain outcome) was also used to establish, in summary, the direction of the relationship between OA and premature mortality (Ragin, 2014).

2.5 RESULTS

2.5.1 Search 1: Identification of reviews

The systematic search identified 1623 papers. One additional paper was identified from hand searching references and 1611 were excluded during the review as they did

not meet the inclusion criteria during title and abstract screening. Papers were excluded at this stage if they were clearly not a systematic review, did not focus on mortality or did not focus on OA. The full texts of 13 articles were screened and a further 10 of these were excluded. This is illustrated in Figure 2.1. Three systematic reviews met the inclusion criteria (Hochberg et al. 2008; Veronese et al. 2016; Xing et al. 2016), with their extracted data presented in Table 2.1.

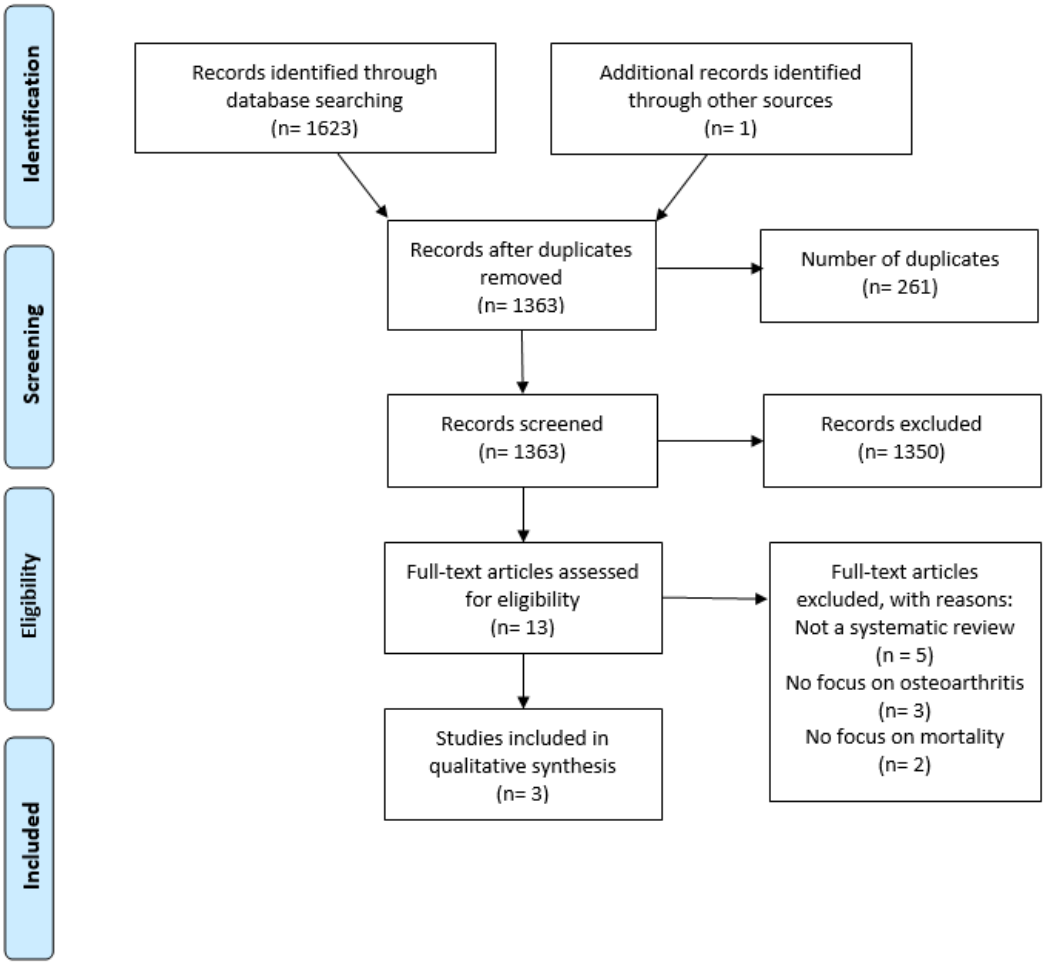


Figure 2.1- PRISMA flow chat for the results of search strategy 1 (Liberati et al., 2009).

Table 2.1- Systematic reviews of OA and mortality and their included studies.

Systematic Search ID	Study ID	Geography	Population	Age (mean)	Sex (% female)	Anatomical Site	Case Definition of Osteoarthritis	Reference Group	Results	Confounders
Hochberg, (2008)	Monson and Hall (1976)	United States, North America	Hospital based cohort (n= not reported)	Not reported	72.6	Not reported	Clinician diagnosed	USA population expected vs observed	SMR for all-cause mortality 111	Not reported
	Lawrence et al. (1989)	United States, North America	Community based NHANES I and NHEFS cohorts (n= 6912)	Not reported	67.5	Knee	Radiographic (Kellgren and Lawrence grades 2-4)	No OA on x-ray mortality vs observed	Women RR 1.45 p=0.02 Men RR 1.2 p=0.22	Age, duration of follow up
	Cerhan et al. (1995)	United Kingdom, Europe	Radium dial-painting works (n= 320)	57.1	100	Hands, feet, cervical spine, lumbar spine, pelvis, and knees	Radiographic (Kellgren and Lawrence grades 2-4)	No OA on x-ray	HR 1.45 (95% CI 1.12, 1.87)	Age, diabetes, smoking, alcohol use, and BMI
	Haara et al. (2003, 2004)	Finland, Europe	Population register (n= 8000)	Not reported	54.5	Hand	Radiographic (Kellgren and Lawrence grades 2-4)	No OA on x-ray	Females: RR: 1.23 95% CI 1.01 to 1.51 Men: RR 0.89, 95% CI 0.68 to 1.16	Age, education, physical stress at work, BMI, and smoking

Table 2.1- Continued…

Systematic Search ID	Study ID	Geography	Population	Age (mean)	Sex (% female)	Anatomical Site	Case Definition of Osteoarthritis	Reference Group	Results	Confounders
	Watson et al. (2003)	United Kingdom, Europe	GRPD (n= 2370000)	M: 54.5 F: 57.2	62.3	Not reported	Clinical diagnosis	No arthritis vs arthritis	SIR per 1000 patient-years: male 19.5, female 15.9	Age and gender
	Kumar et al. (2007)	United Kingdom, Europe	Clinical cohort (n= 1113)	Not reported	Not reported	Knee and hip	Clinical diagnosis	RA siblings	RR of IHD-mortality 1.96 95% CI 1.21, 3.25	Age
Veronese et al. (2016)	Barbour et al. (2015)	United States, North America	From Study of Osteo-porotic Fractures, community based (n= 9704)	No baseline XR= 73.6 Baseline XR= 71.4	100	Hip	Radiographic (Kellgren and Lawrence grades 2-4)	No RHOA on x-ray	RHOA associated with mortality: HR 1.14 95% CI 1.05, 1.24	Age, current smoking, health status, history of diabetes, stroke, chronic obstructive pulmonary disease, osteoporosis, oestrogen use, calcium use, BMI, fracture history

Table 2.1- Continued…

Systematic Search ID	Study ID	Geography	Population	Age (mean)	Sex (% female)	Anatomical Site	Case Definition of Osteoarthritis	Reference Group	Results	Confounders
	Castano Betancourt et al. (2013) *conference abstract*	The Nether-lands, North America	Rotterdam Study I and II, community based cohort (n= 9150)	-	100	Hip or knee	Radiographic (definition not given)	No OA on x-ray	HR: 1.19, 95% CI: 1.06, 1.33	Diabetes, dementia, analgesic use, difficulties in functional activities and walking disability
	Cacciatore et al. (2014)	Italy, North America	Osservatorio Geriatrico Regione Campania, community based cohort (n= 1780)	73.8	57.5	Hand, knee, hip and spine	Clinical and radiological (definition not given)	No clinical or radiological OA	HR 1.28, 95% CI 0.99, 1.39	Age, female sex, BMI, WC, heart rate, pulse blood pressure, Charlson co-morbidity index, number of drugs, NSAIDs, corticosteroids and GDS.

Table 2.1- Continued…

Systematic Search ID	Study ID	Geography	Population	Age (mean)	Sex (% female)	Anatomical Site	Case Definition of Osteoarthritis	Reference Group	Results	Confounders
	Haugen et al. (2015)	United States, North America	Framingham Heart Study, community based cohort (n= 1348)	62.2	53.8	Hand	Radiographic OA and self-reported pain the in same joint (Kellgren and Lawrence grades 2-4)	No clinical or radiological OA	Radiographic: HR 0.82 95% CI 0.63, 1.07 Clinical: HR 0.79 95% CI 0.57, 1.10	Age, sex, cohort, BMI, total cholesterol: HDL ratio, current lipid lowering treatment, increased blood pressure, current antihypertensive treatment, elevated fasting or non-fasting blood glucose, current antidiabetic treatment (oral or insulin), current use of NSAIDs, daily use of aspirin, current/ previous smoking, alcohol use

Table 2.1- Continued…

Systematic Search ID	Study ID	Geography	Population	Age (mean)	Sex (% female)	Anatomical Site	Case Definition of Osteoarthritis	Reference Group	Results	Confounders
	Kluzek et al. (2015)	United Kingdom, Europe	Chingford Cohort Study, community based cohort (n= 1003)	No OA or pain= 55.2 OA only= 58.7 Pain only= 56.4 Symptom-atic OA= 59.6	100	Hand and knee	Clinical diagnosis and radiographic (Kellgren and Lawrence grades 2-4)	Compared with no radiographic or clinical OA, radiographic OA only and clinical OA only.	Pain positive, radiographic positive All-cause mortality HR = 1.97 (95% CI 1.23 to 3.17)	Age, body mass index, typical cardiovascular risk factors, occupation, past physical activity, existing CVD disease, glucose levels and medication use.
	Liu et al. (2015)	Combined in this review, constituent studies included in Xing et al. (2016) review below								
	Veronese et al. (2016)	Italy, Europe	Progetto Veneto Anziani (PRO.V.A. study), community based cohort (n= 2927)	OA group= 77.5 Non-OA group= 74.6	OA group= 66.4 Non-OA group= 48.2	Hand, hip and knee	Clinical diagnosis and radiographic (definition not given)	No clinical or radiographic OA	HR 0.95 (95% CI: 0.77, 1.15)	Age, gender, BMI, education, alcohol, monthly income, physical activity, CVD, fractures, COPD, orthostatic hypotension, hypertension, DM, frailty, cancer, number of medications, smoking, ADLs, MMSE, GDS, GNRI

Table 2.1- Continued…

Systematic Search ID	Study ID	Geography	Population	Age (mean)	Sex (% female)	Anatomical Site	Case Definition of Osteoarthritis	Reference Group	Results	Confounders
Xing et al. (2016)	Liu et al. (2015a)	The Nether-lands, Europe	Genetics ARthrosis and Prog-ression (GARP), compares siblings (n= 384)	60	82	Hand, hip, knee or spine	Clinical diagnosis	No clinical OA. For all-cause mortality expected 34 and observed 16.	SMR 0.54, (95% CI 0.37, 0.79)	Age and sex
	Barbour et al. (2015)	Included in Veronese et al. (2016) above								
	Liu et al. (2015b)	China, Asia	Wunchan Osteo-arthritis Study, community based cohort (n= 1025)	-	-	Knee	Clinical diagnosis and radiographic (Kellgren and Lawrence grades 2-4)	Compared with no radiographic or clinical OA, radiographic OA only and clinical OA only.	All-cause mortality for SxOA 1.9 (95 % CI 1.0, 3.5) All-cause mortality for radiographic OA 1.2) 95% CI 0.7,1.9)	Baseline age, sex, BMI, income level, education, levels of occupational physical activity and comorbidities.
	Liu et al. (2015c)	The Nether-lands, Europe	Osteo-arthritis Care Clinic Study, clinical cohort (n= 460)	61	88	Hand, hip, knee or spine	Clinical diagnosis	No clinical OA. For all-cause mortality expected and observed	SMR 0.45 (95% CI 0.25, 0.82)	Age and sex (combined with GARP cohort)

Table 2.1- Continued…

Systematic Search ID	Study ID	Geography	Population	Age (mean)	Sex (% female)	Anatomical Site	Case Definition of Osteoarthritis	Reference Group	Results	Confounders
	Cacciatore et al. (2014)	Included in Veronese et al. (2016) above								
	Haugen et al. (2015)	Included in Veronese et al. (2016) above								
	Haara et al. (2003)	Included in Hochburg (2008) above								
	Nüesch et al. (2011)	United Kingdom, Europe	Somerset and Avon Survey of Health, community based cohort study (n= 1163)	-	56.7	Hip or knee	Clinical diagnosis and radiographic (Kellgren and Lawrence grades 1-4)	Compared to general population	SMR 1.55 (95% CI 1.41, 1.70)	Age and gender
	Tsuboi et al. (2011)	Japan, Asia	Hokkaido town, community based cohort study (n= 789)	No OA: 67.5 OA: 65.5	58.3	Knee	Clinical features	No clinical OA	OR death after 10 years 2.31 (95% CI 1.41, 3.80)	Age, gender, BMI, and lifestyle

Table 2.1- Continued…

Systematic Search ID	Study ID	Geography	Population	Age (mean)	Sex (% female)	Anatomical Site	Case Definition of Osteoarthritis	Reference Group	Results	Confounders
	Holbrook et al. (1990)	United States, North America	Rancho Bernardo, California, community based cohort study (n= 519)	-	54.9	Hand, hip, knee or spine	Clinical features	No self-reported arthritis	HR 0.82 (95% CI 0.69, 0.98)	Age
	Veronese et al., (2016)	Included in Veronese et al. (2016) above								

Abbreviations: SMR = standardised mortality ratio, SIR = standard incident ratio, CI = confidence intervals, HR = hazard ratio, SxOA = symptomatic osteoarthritis, CVD = cardiovascular disease, COPD = chronic obstructive pulmonary disease, DM = diabetes mellitus, ADLs = activities of daily living, MMSE = mini mental state exam, BMI = body mass index, IHD = ischaemic heart disease, RHOA = right hip osteoarthritis, HDL = high density lipoprotein, GDS = geriatric depression scale, NSAIDs = non-steroidal anti-inflammatory drugs, RA= rheumatoid arthritis, USA= United States of America, GNRI = geriatric nutrition risk index, RR = relative risk.

2.5.1.1 Study Characteristics from Search 1

The three systematic reviews found in Search 1 identified 24 different papers that have examined the association between OA and mortality (Table 2.1). Each study reports on data from different study cohorts. The three systematic reviews did not identify the same studies. Four studies were included in both the Xing et al. (2016) review (of eleven studies) and Veronese et al. (2016) review (of seven studies); only one study was included in both the Xing et al. (2016) review and the Hochberg, (2008) review (of six studies). Veronese et al. (2016) combined two cohorts led by Liu et al. (2015a,c), however these were reported individually in Xing et al. (2016) review. The Liu et al. (2015a,c) studies are two cohorts presented in one paper, and were examined individually, as in the Xing et al. (2016) systematic review. Haara et al. (2003, 2004) had one cohort described across two papers, and therefore was only included once, as in the Hochberg (2008) systematic review. Most studies were from community-based cohort studies (n=15), with fewer studies from clinical cohorts (n=3).

Four studies identified female only cohorts (Barbour et al., 2015; Castano Betancourt et al., 2013; Cerhan et al., 1995; Kluzek et al., 2015), with all other studies identifying a larger number of female participants. All of the studies were based in developed countries: United States of America (USA) (n=5), UK (n=5), the Netherlands (n=3), Italy (n=2), Japan (n=1), China (n=1) and Finland (n=1). All studies that stated a mean participant age reported a mean age over 50 years.

2.5.2 Search 2

2.5.2.1 Study Selection Process for Search 2

The search identified 10,323 papers. No additional papers were identified from hand searching references. 10,033 were excluded during the review as they did not meet the inclusion criteria during title and abstract screening. Papers were excluded at this stage if they were the incorrect study design, did not focus on mortality, did not focus on OA or were published prior to January 2015. This is illustrated in Figure 2.2. The full texts of 19 articles underwent screening; 15 of these were excluded. A total of three papers were included (Cleveland et al., 2019; Mendy et al., 2018; Turkiewicz et al., 2016), with their extracted data presented in Table 2.2.

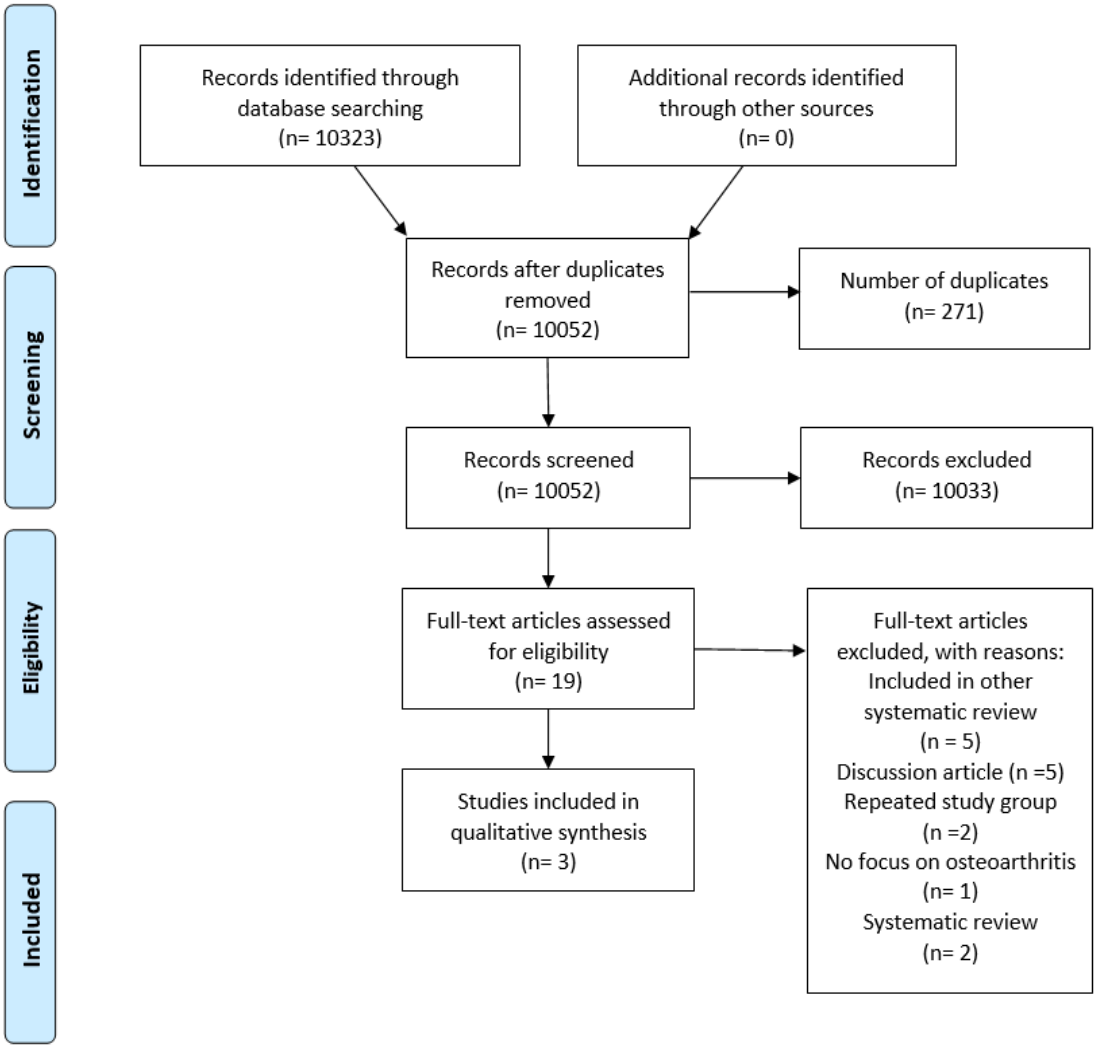


Figure 2.2- PRISMA flow chat for the results of search strategy 1 (Liberati et al., 2009).

Table 2.2- Studies included in Search 2

Study ID	Geography	Population	Age (mean)	Sex (% female)	Anatomical Site	Case Definition of Osteoarthritis	Reference Population	Results	Confounders
Mendy et al. 2018	United States, North America	Community based cohort study National Health and Nutrition Examination Surveys 1 and 2 (n= 51938)	-	66.7	Knee	Radiographic and self-reported joint pain (Kellgren and Lawrence grades 2-4)	For radiographic OA, no radiographic OA (67.0 vs 56.0). For self-reported joint pain, no self-reported joint pain (40.9 vs 13.9).	HR for all-cause mortality in self-reported OA vs no OA 0.95 (95% CI 0.87, 1.05) HR for all-cause mortality in radiographic OA vs no OA 1.06 (95% CI 0.99, 1.14)	Age, gender, race/ethnicity, BMI, smoking, physical activity, poverty income ratio, DM, hypertension and history of myocardial infarction or stroke

Table 2.2- Continued…

Study ID	Geography	Population	Age (mean)	Sex (% female)	Anatomical Site	Case Definition of Osteoarthritis	Reference Population	Results	Confounders
Turkiewicz et al. 2016	Sweden, Europe	Skåne region, mandatory register. Community based cohort study (n= 524136)	63.3	53	Knee and hip	Consulted for knee/hip OA	No consultation for hip or knee OA.	Hip OA Male HR 0.90 (95% CI 0.87, 0.94) Female HR 0.90 (95% CI 0.86, 0.93) Overall HR 0.90 (95% CI 0.87, 0.92) Knee OA Male HR 0.89 (95% CI 0.86, 0.92) Female HR 0.85 (95% CI 0.83, 0.87) Overall HR 0.87 (95% CI 0.87, 0.92)	Sex, income, highest level of achieved education, marital status, residential area, and year of first health-care visit, IHD, cerebrovascular disease, DM, cancer, COPD

Table 2.2- Continued…

Study ID	Geography	Population	Age (mean)	Sex (% female)	Anatomical Site	Case Definition of Osteoarthritis	Reference Population	Results	Confounders
Cleveland et al. 2019	United States, North America	Community based cohort study, Johnston County Osteoarthritis Project (n= 4182)	61	63.2	Knee	Radiographic and clinical examination	Clinical OA is compared to those without clinical OA. Radiographic OA is compared to those without radiographic OA.	HR radiographic OA all-cause mortality 0.99 (95% CI 0.90, 1.09) HR clinical OA all-cause mortality 1.13 (95% CI 1.01, 1.26) HR severe radiographic OA all-cause mortality 0.96 (95% CI 0.86, 1.08)	Enrolment wave, age, sex, race, education, knee injury, cancer, NSAIDs, hypertension, smoking, liver disease, alcohol use, depression, physical activity, BMI, DM, CVD

Abbreviations: CI = confidence intervals, HR = hazard ratio, OA = osteoarthritis, BMI= body mass index, DM = diabetes mellitus, CVD = cardiovascular disease, NSAIDs= non-steroidal anti-inflammatory drugs, COPD = chronic obstructive pulmonary disease.

2.5.2.2 Study characteristics from Search 2

The search returned the original studies examining the association between OA and premature mortality from January 2015 to the search date. One study used a more recent dataset from a cohort found in Search 1 (Lawrence et al., 1989; Mendy et al., 2018). The study settings were heterogeneous, with studies set in different locations across the world. The three studies from Search 2 all included a higher percentage of females. Studies were conducted in the USA (n=2) and Sweden (n=1). All studies were community-based cohort studies, with similar mean ages. As with Search 1, all studies included more female participants.

2.5.3 Narrative synthesis: 'vote-counting' the direction of the association between OA and premature mortality

Different methods for quantifying association were used in the studies. The direction and strength of the association between OA and mortality significant varied between studies. Of the 21 studies, there was a significant association between OA and premature mortality (hazard ratio [HR] or standardised mortality ratio [SMR] greater than 1 with the lower bound confidence interval [CI] above 1) in nine studies (Barbour et al., 2015, Castano Betancourt et al., 2013; Cerhan et al., 1995; Haara et al., 2003, 2004; Kluzek et al., 2015; Kumar et al., 2007; Liu et al., 2015b; et Nüesch al., 2011; Tsuboi et al., 2011). Four of these studies were female only cohorts or only found significant results in a sex stratified analysis for female participants (Barbour et al., 2015; Castano Betancourt et al., 2013; Haara et al., 2003; Kluzek et al., 2015,). Eight of these studies examined the association between OA and all-cause mortality, however Kumar et al. (2007) only explored the association of OA with ischaemic heart disease (IHD) specific mortality. Five studies found statistically insignificant results (HR or SMR

greater or lesser than 1 with confidence intervals that included unity) (Cacciatore et al., 2014; Cleveland et al., 2019; Haugen et al., 2015; Mendy et al., 2018; Veronese et al., 2016). Four studies found OA was protective against premature mortality (HR or SMR less than 1 and upper bound confidence intervals below 1) (Holbrook et al., 1990; Liu et al., 2015a; Liu et al., 2015c; Turkiewicz et al., 2016). Three studies could not be interpreted due to a lack of quantitative estimates (Lawrence et al., 1989; Monson and Hall, 1976; Watson et al., 2003).

2.5.4 Narrative synthesis: exploration of potential sources of heterogeneity

The high heterogeneity between studies can be explained by the different population characteristics, OA case definitions, anatomical location, approach to analysis and potential confounders included.

2.5.4.1 Population Characteristics

Age

The mean age of the populations included were all over 50, however a range of ages were reported. The lowest sample mean being 54.5 years (Watson et al., 2003), the highest 77.5 years (Veronese et al., 2016).

Sex

All studies included a higher percentage of females, and four studies had female only cohorts (Barbour et al., 2015; Castano Betancourt et al., 2013; Cerhan et al., 1995; Kluzek et al., 2015). However, most studies adjusted for age and sex via multivariate analysis, thus minimising the effects these factors had.

Geographical location

All of the studies were based in high income countries: USA (n=7), UK (n=5), Netherlands (n=3), Italy (n=2), Japan (n=1), China (n=1), Finland (n=1) and Sweden (n=1). The majority of studies were conducted in western countries. The results from these studies may therefore not be generalisable to eastern regions or less affluent countries.

Clinical cohort vs community cohort

A combination of community-based cohort studies and clinical cohorts were found in Search 1 and Search 2, further adding to the heterogeneity. The clinical cohort studies included in this systematic search are susceptible to selection bias. Participants under clinician care for OA are more likely to have other co-morbidities in comparison to the general population or sibling controls. The settings of community-based studies were varied, including country based (Watson et al., 2003) via CPRD, region based (Cleveland et al., 2019; Lui et al., 2015b; Nüesch et al., 2011; Turkiewicz et al., 2016) and town based (Tsuboi et al., 2011) approaches. This increased the heterogeneity between studies.

2.5.4.2 OA Case Definitions

A variety of case definitions of OA were employed across the studies identified in both Searches 1 and 2. Broadly these are radiographic OA (n= 5), clinical OA (n= 8) and a combination of radiological and clinical OA (n= 8). Some studies presented individual results for radiographic and clinical case definitions within the same cohort, therefore ten studies examined radiographic case definitions (Barbour et al., 2015, Castano

Betancourt et al., 2013; Cerhan et al., 1995; Cleveland et al., 2008; Haara et al., 2003, 2004; Haugen et al., 2015; Lawrence et al., 1989; Liu et al., 2015b; Mendy et al., 2018; Monson and Hall, 1979), eleven studies examined clinical case definitions (Cleveland et al., 2008; Haugen et al., 2015; Holbrook et al., 1990; Kumar et al., 2007; Liu et al., 2015a; Liu et al., 2015b; Liu et al., 2015c; Mendy et al., 2018; Turkiewicz et al., 2016; Tsuboi et al., 2011; Watson et al., 2003) and four studies examined combined clinical and radiographic case definitions that could not be separated (Cacciatore et al., 2014; Kluzek et al., 2015; Nüesch et al., 2011; Veronese et al., 2016). Following the removal of studies that were unable to be interpreted due to a lack of quantitative estimates (Lawrence et al., 1989; Monson and Hall, 1976; Watson et al., 2003), four studies found a significant association between radiographic OA definitions and mortality (Barbour et al., 2015, Castano Betancourt et al., 2013; Cerhan et al., 1995; Haara et al., 2003, 2004), and four studies found a significant association between clinical OA case definitions and mortality (Cleveland et al., 2008; Liu et al., 2015b; Kumar et al., 2007; Tsuboi et al., 2011). One study using a combined case definition found a significant association between OA and mortality (Nüesch et al., 2011). Statistically insignificant results were found in three studies investigating radiological case definitions (Cleveland et al., 2008; Liu et al., 2015b; Mendy et al., 2018), one study investigating clinical case definitions (Mendy et al., 2018) and three studies using a combined case definition (Cacciatore et al., 2014; Kluzek et al., 2015; Veronese et al., 2016). Results suggesting OA was protective against premature mortality was found in one study with a radiographic case definition (Haugen et al., 2015), and five studies with a clinical case definition (Haugen et al., 2015; Holbrook et al., 1990; Liu et al., 2015a; Liu et al.,

2015c; Turkiewicz et al., 2016). No studies found a protective relationship between OA and premature mortality in combined case definitions.

The biggest contributor to heterogeneity between the included studies was the differences in OA definition used. Within each of these broad categories OA is defined differently. For example, in the mixed definition some studies produced an analysis for both radiographic and clinical OA definitions, whereas others created a case definition based upon radiographic and clinical parameters combined. For example, although most radiological case definitions applied Kellgren and Lawrence (1957) grading, one study did not (Veronese et al., 2016). Both Mendy et al. (2018) and Cleveland et al. (2019) adopted the Kellgren and Lawrence (1957) grading system for radiographic OA, however Cleveland et al. (2019) used sub-categories (≥2 as OA diagnosis, ≥3 as severe diagnosis), and Mendy et al. (2018) did not use the severe sub-category. This makes these studies difficult to compare.

Requiring participants to have radiographic assessment necessitates certain level of functional activity, and therefore risks excluding participants with reduced functional ability. This potentially introduces bias, increasing heterogeneity within results. As discussed in 1.4.4, a symptomatic or clinical case definition is almost entirely dependent on the diagnostician and therefore has high variability between cases, making comparison difficult.

2.5.4.3 Anatomical sites

A variety of different joint sites were investigated across all eighteen studies. Joint sites investigated include: knee (n= 16), hip (n= 11), hand (n= 9) and foot (n=1). Some

other joints sites beyond this thesis were also discussed, for example, different parts of the spine (n= 5). Two studies did not specify joint site.

2.5.4.4 Analysis

Most papers used either HRs or SMRs as an outcome measure.

2.5.4.5 Confounding

Most papers included some adjustment for confounding, however a minority did not adjust for any confounders. One paper had no adjustment (Monson and Hall, 1976). Two papers adjusted for age only (Holbrook et al., 1990; Kumar et al., 2007). All other studies included at least age and sex as confounders. Many papers included numerous adjustments for lifestyle factors, but these were difficult to compare across studies. For example, when adjusting for body mass index (BMI), it was not clear whether BMI was used as a categorical or continuous variable in each analysis. This also makes the studies difficult to compare and therefore heterogeneous.

2.6 DISCUSSION

The studies identified from both searches report conflicting evidence of the relationship between OA and premature mortality. It is unclear if there is a case definition (radiographic or clinical definition) of OA where there is a positive association between OA and mortality and whether this is dependent on anatomical area. Some studies discuss potential reasons for why there may be stronger associations, although they have not examined these potential mechanisms (discussed below).

Each study applied a slightly different case definition, preventing straightforward comparison. Some studies used both clinical and radiological case definitions allowing comparison between definitions within the study, providing an insight into the effect of OA definition on the relationship between OA and mortality. Kluzek et al. (2015) reported the effect of having clinically defined OA, combined with no radiologically defined OA, had a significant association with CVD specific mortality (adjusted HR 2.93 95% CI 1.47, 5.85). However, when using both a joint pain and radiographic OA case definition with CVD specific mortality there is a HR of 1.97 (95% CI 1.23 to 3.17). This highlights that joint pain itself seems to be the best predictor of OA related mortality opposed to a radiological definition. This was further supported by Cleveland et al. (2019), who observed an adjusted HR for radiographic OA and mortality to be 0.99 (95% CI 0.90, 1.09). However, when applying their symptomatic OA case definition, having pain, aching or stiffness in the knee joint on most days, this estimate became significant 1.13 (95% CI 1.01, 1.26). The presence of heterogeneity between studies using clinical case definitions was much higher; although some studies using radiographic definitions used slightly different Kellgren and Lawrence criteria, or unspecified radiological criteria, these are likely to be more comparable to clinical diagnosis. In the UK, radiographic case definition is used less frequently in clinical practice than clinical case definitions, in accordance with the NICE guidelines (NICE, 2014). This supports further investigation into the association between clinical case definitions and premature mortality.

2.6.1 Anatomical area

Of the nine studies that look at hand OA, three found that it was protective against premature mortality, three found a significant association between hand OA and premature mortality and three found non-significant results. These studies included different case definitions of hand OA, including clinical, radiographic and a combination of clinical and radiographic. Some of these studies only looked at hand OA (n= 2), whereas others looked at hand OA in combination with OA at other joint sites. The heterogeneous nature of the studies gives conflicting evidence about the direction of the association between hand OA and premature mortality.

Like hand OA, heterogeneity presents conflicting evidence about the relationship between knee OA and premature mortality. This was the most frequently investigated joint site (n= 16). Overall, three studies found that knee OA was protective against premature mortality, eight found a significant association between OA and premature mortality and five studies found non-significant results. Some studies included knee only subgroup analysis, or knee only cohorts and others combined knee OA with other joint sites during survival analysis. This makes the results of the studies difficult to pool and interpret. This conflicting evidence means no clear conclusions can be drawn about the direction of the association between knee OA and premature mortality.

Hip OA also presents conflicting results. Of the eleven studies looking at hip OA, three studies found hip OA was protective of premature mortality, five found a significant association between hip OA and premature mortality and three found an had a non-significant association between OA and premature mortality. One study included description of the 'pelvis' (Cerhan et al., 1995). It is not clear whether this referred to

the hip joint or to other joints formed by the pelvic bones, like the sacroiliac joint. The heterogeneity between studies makes it very difficult to ascertain the direction of the relationship between hip OA and premature mortality.

As discussed in 1.3.4 there seems to be limited research surrounding foot OA, which is supported by this systematic review. Only one study (Cerhan et al., 1995) looked at foot OA. This study found a significant association between OA and premature mortality but used a radiographic OA case definition. Furthermore, Cerhan et al., (1995) grouped each anatomical area together for a survival analysis. This highlights the lack of research into foot OA despite both its prevalence and clinical significance.

2.6.2 All cause and cause-specific mortality

The majority of papers do not specify cause of death, making it difficult to infer the mechanism of premature mortality. Mendy et al. (2018) found a significant association between both CVD and diabetes related mortality and knee OA, suggesting that OA leads to premature mortality by affecting these disease pathways. In the discussion of these studies, pathways were proposed explaining the association between OA and premature mortality. Nüesch et al. (2011) explored the relationship between CVD, walking distance and diabetes with OA, postulating that walking distance and diabetes both mediated the relationship between OA and CVD; reduced walking distance impacted cardiovascular health leading to CVD. Other studies have found links between the severity of OA and serious CVD events (Hawker et al., 2014). It has been suggested that the link between lower limb OA and CVD based mortality is simply based upon an inability to exercise. This does not explain how some studies found a significant link between symptomatic hand OA and cardiovascular events (Haugen et

al., 2015), given that hand OA does not impact mobility. Furthermore, Veronese et al. (2016) suggested that hand OA was a moderator in their systematic review. Although this relationship between OA and exercise ability seems feasible in lower limb OA, the association with hand OA is more difficult to ascertain.

2.6.3 Confounders and potential mechanisms

The earliest systematic review (Hochberg, 2008) implicated CVD and gastroenterological pathology resulting from NSAID use as the reason for increased mortality in those with OA. Included studies adjusted for these measures as confounders: four papers specifically adjust for NSAID use, with two papers adjusting for any medication use, eight papers adjust for CVD and ten papers adjust for lifestyle factors such as smoking, alcohol use and BMI. The wide array of confounders used, with different measures and different definitions makes comparability between studies difficult and also makes pooled estimates from meta-analysis difficult to interpret. The proposed mechanism of OA contributing to CVD which then causes premature mortality provides little explanation of how OA may actually contribute to developing CVD, however more recent papers provide a mechanism for OA leading to premature mortality. The most recent papers found in Search 2 (Turkiewicz et al., 2016; Cleveland et al., 2019; Mendy et al., 2018) suggest that the association between OA and premature mortality can be explained by the impact that OA has one physical activity, as discussed in section 2.1.2. As OA is a disease that can significantly impact physical activity, it seems logical that this may be a contributing factor as to why OA is associated with premature mortality. Only two papers adjusted for physical activity as a confounder, which highlights that effect of reduced physical activity in those with OA

has influenced the data found in these systematic searches. No studies adjusted for mental or social health parameters, and little consideration has been given as to how these may impact premature mortality as a result of OA.

2.7 STRENGTHS AND LIMITATIONS

The strength of this study is the systematic approach taken to searching for eligible articles. Both Search 1 and Search 2 involved a systematic method with a search criteria adapted from previous studies (Veronese et al., 2016, Xing et al., 2016) to identify relevant papers and systematic reviews. Conducting two separate searches, one for systematic reviews and one for primary studies, provided an efficient method for identifying relevant papers.

The main limitation of these systematic searches was that the search and data extraction was performed by one reviewer, although strict search methods were adhered to. Only involving one reviewer increased the risk of bias being introduced into the screening process, and also meant there was no formal opportunity for the discussion of more borderline studies. There was also no formal quality assessment of the papers included.

The searches included over 100 databases, including MEDLINE and EMBASE, ensuring a wide array of databases were examined. However, it does remains possible that some journals may have not been included in these databases. A hand search of the reference sections of included papers was completed to minimise this risk and ensure the inclusion of all relevant papers.

The efficiency of this method relies on the assumption that the included systematic reviews included all papers prior to 2015. The three systematic reviews included did not find and include the same studies. In particular the Veronese et al. (2016) and Xing et al. (2016) review were conducted within a year of each other but did not include all of the same studies. This is due to a difference in the search terms, databases searched and inclusion criteria. The search strategy for the systematic searches in this chapter included more search terms than these reviews used, increasing the yield of the searches ensuring no papers were missed (Veronese et al., 2016; Xing et al., 2016).

2.8 SUMMARY AND IMPLICATIONS FOR FURTHER RESEARCH

The principal finding from these systematic searches was that there is considerable heterogeneity across previous research that has examined whether there is an association between OA and premature mortality. Multiple definitions of OA have been used across previous studies. Overall, clinically diagnosed OA was more strongly associated with premature mortality than radiographic OA only. This suggests that if there is a relationship between OA and mortality it occurs due to factors that drive clinical diagnoses. However, within this there are multiple different clinical definitions of OA and further investigation of the most efficient approach to case definition selection would appear worthwhile and important.

Further research is therefore required to identify which definitions of OA are associated with mortality. None of these studies were able to directly compare different clinical case definitions within a single cohort, therefore the clinical case definition with the strongest association between OA and premature mortality is unclear. Looking at different case definitions within a defined cohort could provide an

opportunity to establish whether there is an association between OA and premature mortality and also to identify whether this is confined to one particular case definition.

None of the included studies examined in this chapter specifically looked at what explains the relationship between OA and mortality. Although many studies proposed ideas of pathways linking OA and premature mortality, none of the studies examined this empirically. This indicates a potential gap in the evidence base. Some of the included confounders may actually be mediators of the association between OA and premature mortality. Limited discussion of mediators was included in some studies included in the systematic reviews, however this was not consistently addressed throughout (Nüesch et al., 2011; Veronese et al., 2016). As discussed in 2.1.5 a suggested cause-specific mortality measure is CVD. Hochberg, (2008) specifically looked at CVD-specific mortality and included four of the six papers in the systematic review with causes of death data in this narrative synthesis. This found that those with OA were more likely to die of CVD than any other cause. Examining the pathways between OA and premature mortality provides an opportunity to examine not only the association between OA and premature mortality, but also why this association may occur.

3 CHAPTER 3: AIMS AND OBJECTIVES, STUDY DESIGN AND THESIS STRUCTURE

3.1 INTRODUCTION

The strength and direction of the association between osteoarthritis (OA) and mortality is unclear. Previous studies (identified in Chapter 2) reported different strengths and directions of the association between OA and premature mortality. A key reason for this was heterogeneity between studies. The variety of case definitions applied in previous studies prevents a clear understanding of whether there is an association between OA and premature mortality, and why, if there is an association, it exists. Identifying which case definitions of OA are associated with premature mortality will help determine those at an increased risk of premature death. Identifying why this association between OA and premature mortality exists will help influence interventions that could reduce premature death as a result of OA. Examining the association of different case definitions of OA with premature mortality within one dataset will remove the difference between studies to help clarify the direction of association. In addition, the reason for why adults with OA have higher risk of premature mortality is unclear. Recent developments in methodology now allow examination of mediation of associations within survival analyses and present the opportunity to explore reasons for this increased risk. This thesis now presents empirical work exploring the associations between different case definitions and premature mortality, before examining why these associations may occur, through mediation analysis. These studies will help to identify who and what to target to reduce premature mortality in adults with OA.

3.2 AIMS AND OBJECTIVES

The aims of the work described in this thesis are to determine the association between OA and premature mortality and to identify factors that mediate this relationship. The specific objectives are:

Objective 1: To examine the strength and direction of association between different clinical case definitions of OA and premature mortality at different anatomical sites (hand, hip, knee and foot).

i. To identify which case definitions of OA have the strongest association with premature mortality.
ii. To compare these case definitions across different anatomical sites to establish the impact of anatomical location of OA on premature mortality.

Objectives 2: To identify factors that mediate the association between OA and premature mortality at different anatomical sites (hand, hip, knee and foot).

i. To determine factors, amenable to primary care, that mediate the relationship between OA and premature mortality.
ii. To identify which factors mediate the relationship between OA and premature mortality across different anatomical sites.

3.3 STUDY DESIGN

This thesis utilises pre-existing data from a UK-based prospective cohort study; the North Staffordshire Osteoarthritis Project (NorStOP). This thesis describes two analyses.

The first analysis was performed to establish whether there is a relationship between OA and premature mortality, using different clinical case definitions of OA. This was performed across different anatomical sites, providing a comparison of mortality by case definition and site of OA.

The second analysis looked to identify factors that mediated the association between mortality and different case definitions of OA at different anatomical sites. Results from this may provide insights that could influence how patients with OA and other long-term conditions are managed.

3.4 THESIS STRUCTURE

An outline of the following four chapters is described below:

Chapter 4: The methods of original data collection for NorStOP are described. Analyses using different clinical case definitions within NorStOP and their relationships with premature mortality are examined. Case definitions included OA consulters, symptomatic OA and disabling OA. Each case definition was applied to different anatomical sites, including the hand, hip, knee and foot.

Chapter 5: This chapter describes the analysis of mediation of the association between an OA case definition, identified in Chapter 4, and premature mortality. Proposed mediators of this relationship are amenable to primary care and include reduce walking frequency, depression, anxiety, insomnia and reduced social participation.

Chapter 6: The main findings from this thesis are highlighted and discussed with reference to existing literature. Strengths and limitations of the thesis are identified

and discussed. The implications for clinical practice and future research are considered.

4 CHAPTER 4: IS THERE AN ASSOCIATION BETWEEN OSTEOARTHRITIS AND PREMATURE MORTALITY?

4.1 INTRODUCTION

The systematic searches described in Chapter 2 identified an inconsistent relationship between osteoarthritis (OA) and premature mortality due to heterogeneity between studies. The systematic searches also identified that a variety of case definitions for OA were used across the different studies, with clinical definitions appearing to have a stronger relationship with mortality than radiographic case definitions. This chapter describes analyses that examine whether the relationship between OA with mortality is dependent on the case definition of OA, with the aim of identifying which case definitions have the strongest relationship. The analysis uses data from one dataset, the North Staffordshire Osteoarthritis Project (NorStOP), which removes differences in the magnitude of association due to study sample characteristics.

4.2 AIMS AND OBJECTIVES

4.2.1 Aims

The chapter aims to examine the strength and direction of association between different clinical case definitions of OA and premature mortality at different anatomical sites (hand, hip, knee and foot).

4.2.2 Objectives

i. To outline the relevant aspects of NorStOP for the subsequent analyses.

ii. To identify different case definitions within the NorStOP cohort.

iii. To identify which case definition of OA (OA consulter, self-reported joint pain, symptomatic OA or disabling OA) has the strongest association with premature mortality.

iv. To establish confounders of the relationship between OA and mortality.

v. To establish if the impact of OA on premature mortality is dependent on anatomical location.

4.3 STUDY DESIGN OF THE NORTH STAFFORSHIRE OSTEOARTHRITIS PROJECT

NorStOP is a longitudinal population-based cohort study of adults aged 50 or over. The aim of NorStOP was to examine the natural history of OA and joint pain specifically of the hand, knee, hip and foot. Data from two cohorts of NorStOP (NorStOP 1 and NorStOP 2) were used in the analyses described in this thesis. Baseline data of each cohort was collected at different time points; NorStOP 1 was collected in April 2002 and NorStOP 2 was collected from between July/August 2002 to July/August 2003.

4.3.1 Ethical Approval

Ethical approval for NorStOP was granted from the North Staffordshire Local Research Ethics Committee (REC reference numbers 1351, 1430 and 05/Q2604/20) (Thomas et al., 2004a).

4.3.2 Population and sampling frame

During the development of NorStOP in 2001, North Staffordshire had four Primary Care Trusts, with an estimated combined population of 460,000 (Office for National Statistics, 2001). Six practices from the North Staffordshire General Practice Research Network were recruited for the study; three practices for NorStOP 1 and three for NorStOP 2. These were a mix of rural and urban practices. In mid-2017, the UK

population was estimated to be 66,040,200 people, with 58,437,363 people registered with a general practitioner (GP) (88.5%) (NHS Digital, 2017; Office for National Statistics, 2017), making the registers a good sampling frame for identifying representative samples of the local population.

4.3.3 Data from the 'Health Survey'

The 'Health Survey' questionnaire was a self-complete postal questionnaire sent to all eligible participants. This initial questionnaire contained 3 sections:

A. General Health (including physical function, mental health, social isolation, access to materials, good and services, demographic characteristics, occupational characteristics, anthropometric characteristics, lifestyle characteristics and cognition)
B. Both generalised and joint-specific pain with medications used to manage this pain (via a manikin diagram and joint-specific questions)
C. Study consent

A more detailed description of questions included can be found in Appendix 3.

4.3.4 Method of Administration

In the two NorStOP cohorts, 20,293 adults were included in the original sampling frame (Figure 4.1) These were all adults aged 50 and over who were registered with one of the six general practices included in the study. Before mailing, the sampling frame was checked by the general practitioners from the practice for exclusions; patients were excluded if they were unable to complete the questionnaire due to

illness, had severe learning disabilities, had severe psychological disorders, or if they had previously declined taking part in research projects (n=79).

In stage 1, those eligible (n=20214) were mailed a 'Health Survey' questionnaire. Following this, in stage 2, those responding to the stage 1 'Health Survey' who both gave permission to be re-contacted and indicated they had hand, hip, knee or foot pain or a problem with their hands in the last 12 months were mailed a 'Regional Pain Survey', which had a more detailed assessment of the specific regional sites. Data from the 'Regional Pain Survey' questionnaire was not used in the analyses within this thesis. Questionnaires were accompanied by a letter from the GP practice and a study information leaflet; reminder postcards were sent to those that had not responded after two weeks and at four weeks a repeat questionnaire was sent.

In accordance with the Data Protection Act, Keele Primary Care Research Centre followed data security standards and guidelines. Personally identifiable information was only held to undertake mailing and was removed from databases as soon as possible.

4.3.5 Questionnaire Processing

On receipt of completed questionnaires, sex and date of birth were compared with surgery records, to ensure responses were from invited participants. Afterwards, questionnaires were put in secure storage. Data was entered using Teleform™, an automatic data entry system. This method of data entry has high levels of data accuracy and was used to reduce potential information bias (Jinks, Jordan, and Croft,

2003). To check the accuracy of scanned data, one in five paper copies of the questionnaire were checked against the exported data.

4.3.6 Data Cleaning

Data was exported from the Teleform™ system and exported to iBM's Statistical Package for the Social Sciences (SPSS). Data was then checked for anomalies, particularly in hand written responses, such as date of birth, sex, height, weight and age the participant left school. If birth or sex data were missing, information from the mailing list was used. Unrealistic values for height, weight and age of leaving school were marked as missing. Complete data cleaning processes followed the Keele University Data Cleaning Standard Operating Procedures.

4.4 PARTICIPANT FLOW

After GP exclusions, 20,214 adults over 50 were mailed a questionnaire in NorStOP 1 and 2. During the mailing procedure a further 396 were excluded (due to death, GP screening, departure from GP practice or unknown addresses), therefore leaving an eligible baseline population of 19,818. Of these 13,986 (adjusted response 70.6%) responded at baseline. From these respondents, 3554 did not give consent for their primary care medical records to be accessed, leaving 10,432 participants. A further 2366 participants had incomplete data for, mortality, mediators or covariates, leaving 8066 for the analyses (Figure 4.1).

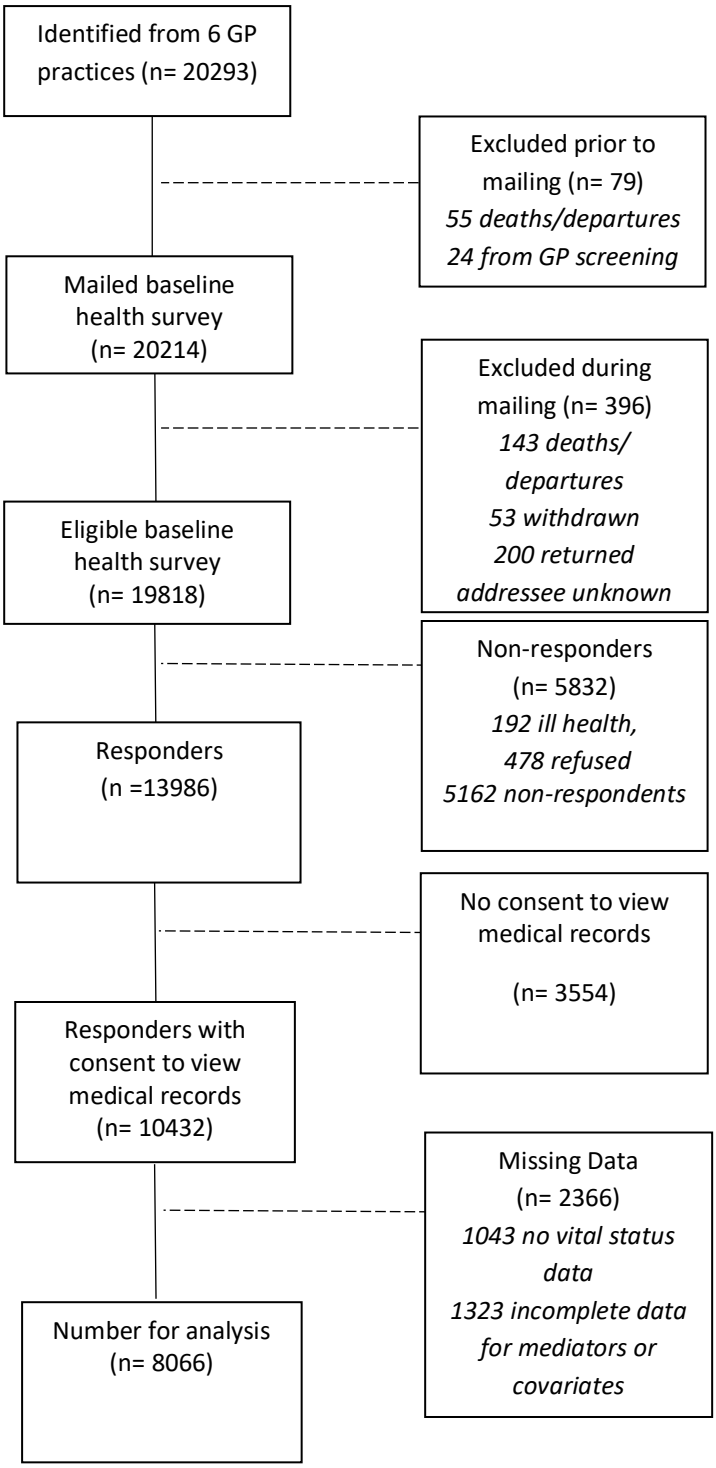


Figure 4.1-Flowchart of baseline response to NorStOP

4.5 SELECTION BIAS

4.5.1 Non-response bias

A number of those contacted did not complete the initial baseline survey (n= 5832). Three reasons were cited for this; ill health (n= 192), refusal (n= 478) and non-response (n= 5162). It is possible that these reasons for non-response may be due to OA; for example, the ill health may represent disabling OA or comorbidities associated with OA. Furthermore, the non-response group could represent some individuals that were physically unable to send any response to the survey due to their OA. Conversely, those with joint pain may be more likely to respond to the survey due to an interest in the outcomes, therefore over-estimating the prevalence of joint pain within the population. A number of participants also did not consent to having their primary care medical records reviewed as part of the study. This could represent participants that were worried about having certain co-morbidities (such as mental health problems) viewed negatively by the research team. These potential sources of selection bias could potentially affect the representativeness of the population sample (Szklo and Nieto, 2018).

Non-response or non-consent to medical record review or the 'Health Survey' could also reflect participants failing to understand the question due to poor literacy skills. The survey was aimed at a reading age of 9 to overcome this problem. As this thesis only uses the baseline data from NorStOP, missing data from attrition does not affect the study. Overall selection bias may affect both the internal and external validity of this study. The internal validity may be compromised as the sample for analysis may not represent the proposed study population (i.e. adults aged 50 years and over living

in North Staffordshire). Similarly, this may affect generalisability to wider populations (for example the West Midlands or England) or to other locations.

4.5.2 Missing data

Missing data refers to the absence of information or missing values for a variable (Kang, 2013). There are various reasons why missing data can occur, including random error, researcher error and participant error. There was missing data for 2366 participants who had consented to medical record review but did not provide complete data for covariates and mediators, or where vital status was unobtainable, and were therefore excluded from the full analysis.

The characteristics of those with missing data may be different to those included in the analyses, which would indicate potential selection bias. The mean age and proportion of females and those who went onto further education were different in those with complete data to those worth missing data ($p<0.05$) (Table 4.1). Those with complete data were younger (65.16 years cf 69.57 years), more likely to have gone into further education (12.37% cf 9.55%) and less likely to be female (51.64% cf 61.35%).

Table 4.1- Sex, age and education characteristics between those with complete data and missing data at baseline

	Complete data (n=8066)	Consent but missing data (n= 2366)	P value
Sex (F)	51.64%	61.35%	<0.001
Age (mean)	65.16	69.57	<0.001
Further education	12.37%	9.55%	<0.001

4.6 DEFINITIONS OF OA IDENTIFIABLE IN THE NORTH STAFFORDSHIRE OSTEOARTHRITIS PROJECT

4.6.1 Operationalising OA; identifying case definitions

As highlighted in Chapter 2, there are different case definitions of OA. The combination of medical record data and self-report data offers the opportunity to define OA in a number of ways; this involves combinations of information based on clinician diagnosis of OA (via the primary care medical record) and self-reported information on where joint pain occurs or pain interference, as well as other morbidities. Definitions are described below and organised with reference to:

1. OA diagnosis in the participant's primary care record: 'OA Consulter'.
2. Self-reported joint pain.
3. Self-reported joint pain and OA diagnosis in the participant's primary care record: 'Symptomatic OA'.
4. Self-reported pain interference and self-reported joint pain and OA diagnosis in the participant's primary care medical record: 'Disabling OA'.

Each of these were then further defined by anatomical area (Table 4.2).

4.6.2 OA consulters

General practitioners in the study used the Read system to code all reasons for clinical encounters in primary care consultations (NHS Information Authority, 2000). The Read codes cross-map to International Classification for Diseases (ICD) 9/10. Morbidity data (i.e. symptoms and diseases) in this system are grouped into 19 Read chapters. Data on these diagnostic groups were aggregated starting in 2000, continuing through the time of the follow-up questionnaire in 2008. Individuals were defined as having OA if

they had at least one consultation during this period primarily for OA and allied disorders based on Read codes (N05 category) for primary care consultations (NHS Information, 2000). The code N05 for OA is an umbrella code encompassing over 100 specific codes, including those for OA at specific joint sites and OA secondary to other diseases. As OA is a longstanding, gradually progressive chronic condition, it was assumed that a clinician-established diagnosis at any point during the study period implied that OA was likely present to at least to some degree during the entire period of observation.

4.6.3 Self-reported joint pain

Self-reported joint pain was defined by participants indicating in the 'Health Survey' questionnaire that they experienced pain in the hand, hip, knee and/or foot for one day or more during the past year.

4.6.4 Symptomatic OA

Symptomatic OA combined information on consultation and self-report as outlined above. Symptomatic OA was defined as consultation for OA (as identified in the medical records) and self-reported joint pain. This lead to seven definitions: symptomatic hand OA, symptomatic knee OA, symptomatic hip OA and symptomatic foot OA, combinations of joint pains lead to symptomatic upper limb OA only, symptomatic lower limb OA only and symptomatic upper and lower limb OA

4.6.5 Disabling OA

Disabling OA was defined by consultation to primary care for OA, self-report of joint pain and self-report of pain interference. Pain interference was measured using a

using a single item from the Medical Outcomes Study Short Form-12 (Ware et al. 1996): “During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework?)”. This question has five responses, which were dichotomised for the purpose of this analysis: (i) Pain interference- ‘Moderately’, ‘Quite a bit’ or ‘Extremely’ and (ii) No pain interference- ‘Not at all’ or ‘A little bit’. This lead to eight definitions: disabling OA at any site, disabling hand OA, disabling knee OA, disabling hip OA and disabling foot OA, combinations of joint pains lead to disabling upper limb OA only, disabling lower limb OA only and disabling upper and lower limb OA.

Table 4.2- Summary of case definitions used within the NorStOP cohort

Osteoarthritis case definition		Osteoarthritis in the primary care medical records	Joint pain reported on 'Health Survey'	Pain interference reported on 'Health Survey'	Anatomical Area				
					Any	Hand	Knee	Hip	Foot
OA Consulters		x			x				
Self-reported hand pain			x			x			
Self-reported knee pain			x				x		
Self-reported hip pain			x					x	
Self-reported foot pain			x						x
Symptomatic hand OA		x	x			x			
Symptomatic knee OA		x	x				x		
Symptomatic hip OA		x	x					x	
Symptomatic foot OA		x	x						x
Disabling OA		x	x	x	x				
Disabling hand OA		x	x	x		x			
Disabling knee OA		x	x	x			x		
Disabling hip OA		x	x	x				x	
Disabling foot OA		x	x	x					x
Number of anatomical areas affected by disabling OA	1	x	x	x	x				
	2	x	x	x	x				
	3	x	x	x	x				
	4	x	x	x	x				
Symptomatic lower limb OA		x	x				x	x	x

Table 4.2- Continued…

Osteoarthritis case definition		Osteoarthritis in the primary care medical records	Joint pain reported on 'Health Survey'	Pain interference reported on 'Health Survey'	Anatomical Area				
					Any	Hand	Knee	Hip	Foot
Disabling lower limb OA		x	x	x			x	x	x
Symptomatic upper limb OA		x	x			x			
Disabling upper limb OA		x	x	x		x			
Symptomatic upper and lower limb OA		x	x			x	x	x	x
Disabling upper and lower limb OA		x	x	x		x	x	x	x
Number of anatomical areas with symptomatic OA	1	x	x		x				
	2	x	x		x				
	3	x	x		x				
	4	x	x		x				
Number of anatomical areas with disabling OA	1	x	x	x	x				
	2	x	x	x	x				
	3	x	x	x	x				
	4	x	x	x	x				

4.6.6 Mortality Ascertainment

Vital status of participants was collated from two different sources. Mortality was obtained from the Exeter patient registration system - a database of all patients registered with a GP in England and Wales (NHS Digital, 2018). Date of death is recorded by this system. Those whose mortality was unclear in 2012 were excluded from the dataset. Days in study was calculated from response to the questionnaire until date of death or census date (01/10/2012).

4.6.7 Measurement of and rationale for proposed confounders

A confounder is associated with both the exposure and the outcome, but is not on the causal pathway (Szklo and Nieto, 2018). In this case a confounder is associated with both OA and premature mortality and is not on the causal pathway. Without adjustment the results may be misleading. Comorbidities, socio-demographic and lifestyle factors associated with OA and premature mortality were included as confounders

4.6.7.1 Age

As discussed in 1.5.3.2, age has a strong association with OA (Oliveria et al., 1995). Furthermore, mortality increases with age (Office for National Statistics, 2017). Table 4.3 on page 95 demonstrates that participants with disabling OA tend to be older than participants within the rest of NorStOP. Data pertaining to age was self-reported via the 'Health Survey' and checked against medical records. Age will be included in the model as a confounder.

4.6.7.2 Sex

OA is more common in females, as discussed in 1.5.3.2. Table 4.3 on page 95 shows that a higher proportion of females are in the pain interference case definitions in comparison to the rest of the NorStOP cohort. Sex was self-reported via the 'Health Survey' and checked against medical records.

4.6.7.3 Socioeconomic Status

Education and occupation were surrogate markers of socioeconomic class (Galobardes et al., 2006). Socioeconomic status is associated with OA for lots of different reasons, including access to healthcare, links with other comorbidities, mental health problems and poor quality of life (Knight et al., 2011; Reyes et al., 2015). Socioeconomic status is also associated with other confounders listed here including body mass index (BMI) and smoking (Hiscock et al., 2012; Morgenstern, Sargent and Hanewinkel, 2009). Furthermore, low socioeconomic status is associated with premature mortality (Jensen et al., 2017). Data relating to this is self-reported via the 'Health Survey'. Low education level was defined as those with a school education only. The Health Survey included questions "How old were you when you left school?" and "Did you go on from school to full-time education or university? Yes; No- If yes, what age did you finish full-time education?" A low socioeconomic class classified as those with a manual occupation. The Health Survey asked "What is your current employment status? Employed; not working due to ill-health or disability; retired; unemployed/seeking work; housewife; other" to ascertain working status. Short answer questions were then asked to classify work "If working, what is your job title?" and "If not working, or retired what was your last job?" These were then compared to

the Standard Occupational Classification framework to identify the proportion of respondents with a manual occupation (Office of National Statistics, 2002). As socioeconomic status is not on the causal pathway, both occupation and education will be adjusted for as binary confounders.

4.6.7.4 Non-steroidal anti-inflammatory drug (NSAID) use

As discussed in 2.1.2.1, there is a reduction in the prescriptions of NSAIDs for joint pain. This is due to their associations with renal and gastrointestinal problems alongside emerging evidence suggesting that they contribute to cardiovascular disease (CVD; Bavry et al., 2011; Trelle et al., 2011). Data on the prescription of NSAIDs was taken from the participants' medical records. Medical record data categorised participants into one of three groups: no NSAID prescriptions, those with less than 10 NSAID prescriptions and those with 10 or more NSAID prescriptions. NSAIDs will be included as a categorical confounder.

4.6.7.5 Ischaemic heart disease (IHD) and self-reported CVD

As discussed in 2.1.5, CVD is associated with OA. The systematic searches in Chapter 2 highlighted that some papers considered cardiovascular specific mortality, with physical activity implicated as a potential mechanism (Cleveland et al., 2019; Turkiewicz et al., 2016; Mendy et al., 2018). Studies have found that the relationship between OA and CVD is not entirely clear. A recent systematic review discussed that OA is a risk factor for CVD (Wang et al., 2016). However, other studies found a non-directional association between OA and CVD (Rahman et al., 2013). Furthermore, CVD is associated with premature mortality (Ordunez et al., 2015). Two measures of CVD were included as potential confounders. IHD refers to a diagnostic code for IHD on the

medical records, whereas self-reported CVD refers to participants indicating they had one or more cardiovascular diseases on the 'Health Survey'. Given the unclear relationship between OA and CVD, it has been included as a binary confounder, with one medically defined and one self-reported measure.

4.6.7.6 Diabetes mellitus

OA is frequently a co-morbid condition with diabetes mellitus (Louati et al., 2015). Diabetes mellitus is also associated with premature mortality (Roglic and Unwin, 2010). This association is attributed to their shared risk factors, such as raised BMI and CVD. Diabetes mellitus refers to those indicating that they had any type of diabetes mellitus on the 'Health Survey'. It will be included as a binary confounder.

4.6.7.7 Smoking

Smoking is an important surrogate marker of socioeconomic status and contributes to the development of other diseases (Hiscock et al., 2012). Participants were asked on the 'Health Survey' to indicate whether they had never smoked, previously smoked or currently smoked. This was dichotomised to 'never and previous' and 'current'. There has been limited evidence suggesting that smoking is protective against radiographic OA, but overall it appears to be a contributor to other risk factors (Felson and Zhang, 2015).

4.6.7.8 Chronic Obstructive Pulmonary Disease (COPD)

COPD, commonly caused by smoking, is an important disease that is associated with both OA and mortality (Manino, 2002; Wshah et al., 2018). COPD was defined as self-reported chest problems and/or cough with spit on the healthy survey and was dichotomised. COPD was included in the analysis as a binary confounder.

4.6.7.9 Body Mass Index (BMI)

Participants were asked to provide a height and weight in the 'Health Survey', from which BMI was calculated and classified as follows; BMI of <20kg/m^2 was classed as underweight; 20-24.9kg/m^2 as normal; 25-29.9kg/m^2 as overweight and over 30kg/m^2 as obese (Erens, Primatesta and Prior, 2001 As discussed in 1.5.3.1 increased BMI has an association with both OA and mortality (Bhaskaran et al., 2018, Zheng and Chen, 2015). A low BMI is also associated with OA and mortality (Ghosh et al., 2017). In this analysis BMI was classed as a confounder and used as a continuous variable.

4.7 DATA ANALYSIS

4.7.1 Descriptive statistics

The characteristics of individuals were summarised using frequencies and percentages, with means and standard deviations (SDs) used for continuous variables. Descriptive statistics were performed for each case definition. The data from this can be found in Table 4.3.

4.7.2 Survival analysis

Survival analysis is the analysis of times from a defined time origin (in this study defined as participant study entry) until occurrence of event of interest (in this study mortality). Survival data tend to follow a non-symmetrical distribution and usually a substantial proportion of survival times are censored (Kleinbaum, 1998; Hosmer Jr, Lemeshow and May, 2008). Censored observations are those which have not been fully observed, and the most commonly encountered form of censoring is right censoring. An observation is right censored if at the time of analysis the exact value of

survival time is unknown. This may occur if an individual is lost to follow-up or is still alive at the end of the study where mortality is the outcome. In this study, right censoring refers to participants that were alive on 01/10/12 (the census date).

4.7.2.1 Cox proportional hazard models

The Cox proportional hazard regression model (Cox, 1972)describes the relationship between time to event and covariates (represented by the hazard function h(t)). Both numerical and categorical predictor variables can be used, individually or simultaneously, giving rise to univariable and multivariable models respectively. Survival times may be characterised in terms of various functions, including hazard and survival functions. The general equation for a Cox hazard function is:

$$h(t) = h_0(t) \times exp(b_1x_1 + b_2x_2 + \ldots + b_px_p)$$

where t= time, h_0 (t) >0 is the baseline hazard, x_1, x_2…are time-invariant predictor variables with the coefficients b1, b2,…measuring their effect; by its definition, a hazard function represents instantaneous event rate.

A hazard ratio (HR) is a measure of the effect of a predictor variable on time to event of interest (death in this study). A hazard ratio of 1 implies no difference between categories of the exposure on survival; a hazard ratio greater than 1 shows an increase in the hazard for the exposed group compared to unexposed and a hazard ratio of less than 1 shows a reduction in the hazard for the exposed compared to the unexposed groups.

A Cox Model was used to assess the association, in terms of HRs and corresponding 95% confidence intervals (CIs), between each case definition of OA and mortality. First

of all, univariate analyses were performed to assess the unadjusted association between each OA definition and OA. Then multivariable analysis was performed, whereby the association between each definition and mortality was adjusted for confounders simultaneously.

Cox model is proportional is because the hazard ratio for two individuals with covariates (x and x*) is exp([x-x*]b), which is constant over time. The assumption of proportionality needs testing throughout, which was done via Schoenfeld residuals (Schoenfeld and Herrman, 1982). A p value of more than 0.05 confirms the proportionality (i.e. the hazards for participants are the same across time).

The independence of outcomes (in this case deaths) between each participant is also an assumption of the Cox proportional hazards model. The Kaplan Meier method was used to create Kaplan Meier curves, as 'events' (in this case, death) are assumed to be independent of each other (Kaplan and Meier, 1958).

Table 4.3- The characteristics of each case sample and the whole sample for each case definition of OA

		NorStOP Cohort	OA Consulters	Self-reported joint pain				Symptomatic OA				Disabling OA			
				Hand	Hip	Knee	Foot	Hand	Hip	Knee	Foot	Hand	Hip	Knee	Foot
Number of participants (%)		8066 (100%)	4653 (57.69%)	3559 (44.12%)	2720 (33.72%)	4271 (52.95%)	3099 (38.42%)	2376 (29.46%)	1902 (23.58%)	2866 (35.53%)	2105 (26.10%)	1515 (18.78%)	1323 (16.4%)	1774 (21.99%)	1387 (17.20%)
Age (standard deviation)		65.16 (9.76)	65.55 (9.62)	65.51 (9.75)	66.01 (9.57)	65.58 (9.81)	65.97 (9.83)	65.69 (9.66)	66.33 (9.48)	65.79 (9.65)	66.09 (9.64)	66.99 (9.83)	67.14 (9.71)	67.24 (9.82)	67.09 (9.78)
Sex (% female)		4165 (51.64%)	2032 (43.67%)	1459 (40.99%)	1128 (41.47%)	1931 (45.21%)	1323 (42.69%)	891 (37.50%)	738 (38.80%)	1189 (41.49%)	829 (39.38%)	950 (62.71%)	813 (61.45%)	1039 (58.57%)	841 (60.63%)
Self-reported manual occupation		4381 (54.31%)	2562 (55.06%)	1902 (53.44%)	1539 (41.47%)	2410 (56.43%)	1769 (57.08%)	1360 (57.24%)	1078 (56.68%)	1624 (56.66%)	1224 (58.15%)	907 (59.87%)	801 (60.54%)	1067 (60.15%)	828 (59.70%)
Self-reported school education only		7068 (87.63%)	4108 (88.29%)	3159 (88.76%)	2425 (89.15%)	3806 (89.11%)	2767 (89.29%)	2117 (89.10%)	1700 (89.38%)	2562 (89.39%)	1892 (89.88%)	1387 (91.55%)	1212 (91.61%)	1627 (91.71%)	1275 (91.93%)
NSAIDs prescribed on primary care medical records	**None**	5019 (62.22%)	2233 (47.99%)	1999 (56.17%)	1463 (53.79%)	2426 (56.80%)	1746 (56.34%)	1081 (45.50%)	846 (44.48%)	1306 (45.57%)	968 (45.99%)	683 (45.08%)	584 (44.14%)	800 (45.10%)	628 (45.28%)
	< 10	2293 (28.43%)	1773 (38.10%)	1081 (30.37%)	847 (31.14%)	1288 (30.16%)	948 (30.59%)	888 (37.37%)	702 (36.91%)	1075 (37.51%)	789 (37.48%)	519 (34.26%)	467 (35.30%)	603 (33.99%)	485 (34.97%)
	> 10	754 (9.45%)	647 (13.91%)	479 (13.46%)	410 (15.07%)	557 (13.04%)	405 (13.07%)	402 (16.92%)	354 (18.61%)	485 (16.92%)	348 (16.53%)	313 (20.66%)	272 (20.56%)	371 (20.91%)	274 (19.75%)
Ischaemic heart disease on the primary care medical records		707 (8.76%)	504 (10.83%)	339 (9.53%)	290 (10.66%)	419 (9.81%)	313 (10.10%)	265 (11.15%)	236 (12.41%)	330 (11.51%)	243 (11.54%)	192 (12.67%)	184 (13.91%)	244 (13.75%)	184 (13.27%)
Self-reported cardiovascular disease		3385 (41.97%)	2056 (44.19%)	1599 (44.93%)	1245 (45.77%)	1954 (45.75%)	1465 (47.27%)	1103 (46.42%)	890 (46.79%)	1343 (46.86%)	1022 (48.55%)	800 (52.81%)	699 (52.83%)	953 (53.72%)	757 (54.58%)
Self-reported diabetes mellitus		470 (5.82%)	325 (6.98%)	226 (6.35%)	181 (6.65%)	297 (6.95%)	240 (7.74%)	177 (7.45%)	140 (7.36%)	227 (7.92%)	183 (8.69%)	127 (8.38%)	114 (8.62%)	162 (9.13%)	139 (10.02%)

Table4.3- Continued

		NorStOP Cohort	OA Consulters	Self-reported joint pain				Symptomatic OA				Disabling OA			
				Hand	Hip	Knee	Foot	Hand	Hip	Knee	Foot	Hand	Hip	Knee	Foot
Self-reported smoking		1237 (15.34%)	633 (13.60%)	516 (14.50%)	412 (15.15%)	625 (14.63%)	468 (15.10%)	304 (12.79%	268 (14.09%)	367 (12.81%)	278 (13.21%)	211 (13.93%)	201 (15.19%)	234 (13.19%)	197 (14.20%)
Chronic Obstructive Pulmonary Disease		354 (4.39%)	234 (5.03%)	176 (4.95%)	134 (4.93%)	185 (4.33%)	163 (5.26%)	128 (5.39%)	111 (5.84%)	140 (4.88%)	97 (4.61%)	97 (6.40%)	87 (6.58%)	108 (6.09%)	97 (6.99%)
Body Mass Index	20-24.9 kg/m^2	2836 (35.16%)	1454 (31.25%)	1163 (32.68%)	816 (30.00%)	1278 (29.92%)	962 (31.04%)	704 (29.63%)	518 (27.23%)	792 (27.63%)	591 (28.08%)	402 (26.53%)	322 (24.34%)	431 (24.30%)	348 (25.09%)
	<20kg/m^2	306 (3.94%)	157 (3.37%)	120 (3.37%)	86 (3.16%)	123 (2.88%)	102 (3.29%)	70 (2.95%)	63 (3.31%)	65 (2.27%)	62 (2.95%)	52 (3.43%)	48 (3.63%)	49 (2.76%)	44 (3.17%)
	25-29.9 kg/m^2	3380 (41.90%)	2009 (43.18%)	1509 (42.40%)	1179 (43.35%)	1835 (42.96%)	1300 (41.95%)	1044 (43.94%)	835 (43.90%)	1248 (43.55%)	897 (42.61%)	638 (42.11%)	566 (42.78%)	751 (42.33%)	589 (42.47%)
	>30kg/m^2	1544 (19.14%)	1033 (22.20%)	767 (21.55%)	639 (23.49%)	1035 (24.23%)	735 (23.72%)	558 (23.48%)	486 (25.55%)	761 (26.55%)	555 (26.37%)	423 (27.92%)	387 (29.2%)	543 (30.61%)	406 (29.27%)

Abbreviations: North Staffordshire Osteoarthritis Project (NorStOP), Osteoarthritis (OA), NSAIDs (non-steroidal anti-inflammatory drugs), kilogram (kg), metre (m)

4.8 RESULTS

4.8.1 Description of population

In total, 8066 participants were included in the analysis from NorStOP 1 and 2. The mean age was 65.2 years and 51.6% of the population were female. At follow up, 1188 (17.2%) had died. 12.4% of participants completed further education and 54.3% were classified as having manual occupations. Table 4.3 presents the characteristics of participants within each OA group. Some participants belonged to more than one OA group. There are more females within the disabling OA group than in the other OA case definitions. Participants with disabling OA were more likely to have a lower level of education, more likely to be overweight or obese and more likely to have a manual occupation than participants without disabling OA.

4.8.2 Assumption testing

The hazard ratios were proportional across time for all of the OA definitions except two; the p-values from the Schoenfeld test for OA Consulters was <0.01 and symptomatic lower limb OA was <0.01. All other case definitions had p-values of >0.05, showing proportionality.

Figure 4.2 is a Kaplan Meier curve for the case definition OA Consulters. Kaplan Meier curves for each of the other definitions of OA can be found in Appendix 4. This Kaplan Meier curve illustrates the difference between the mortality rates in the OA consulters and the non-OA consulters. This graph shows that non-OA consulters (blue line) have a faster rate of mortality than the OA consulters (red line).

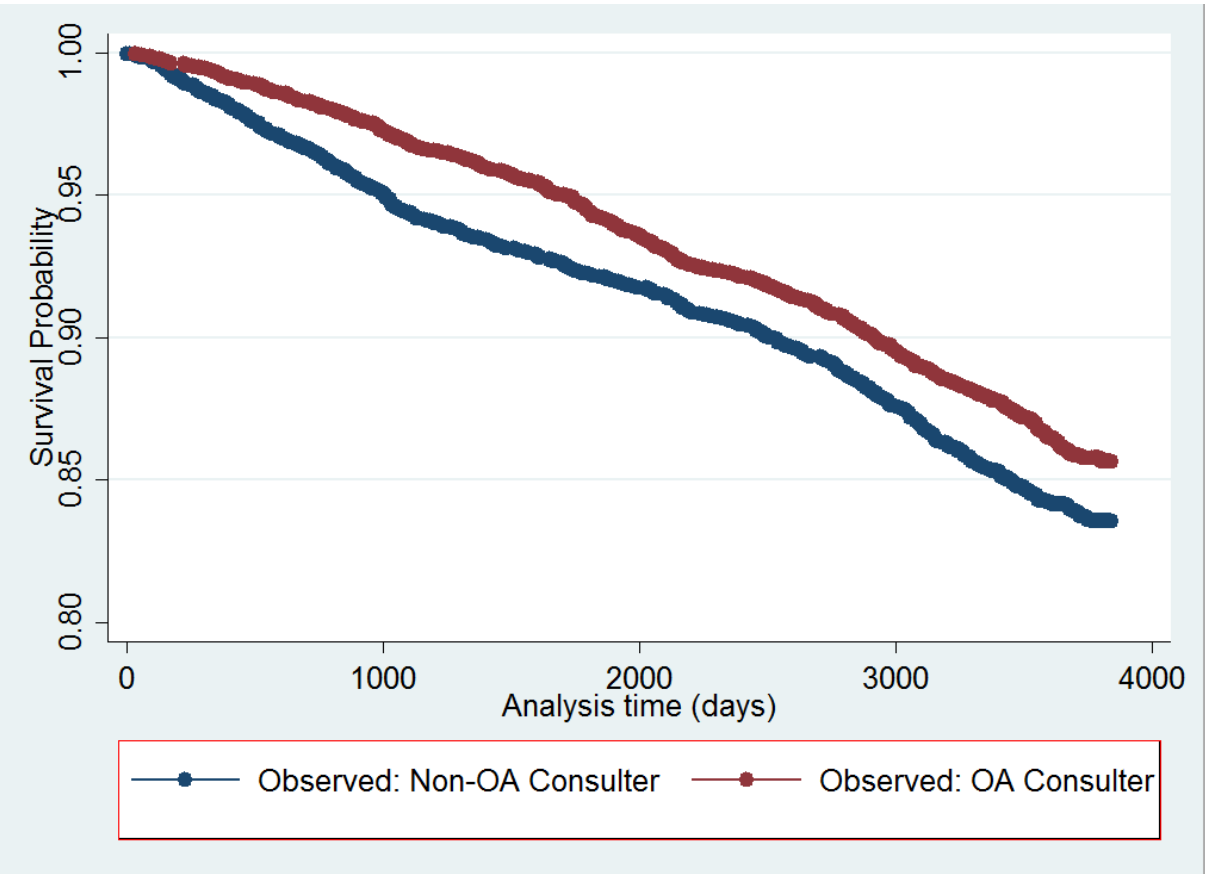


Figure 4.2- Kaplan Meier plot of survival in those who have consulted for osteoarthritis and those who have not

Table 4.4- Adjusted and unadjusted hazard ratios with confidence intervals for different clinical case definitions of OA and their effect on premature mortality

		N=	Unadjusted HR	Adjusted* HR
OA Consulters		4653	0.84 (0.75, 0.94)	0.84 (0.74, 0.94)
Self-reported hand pain		3559	0.99 (0.88, 1.11)	1.03 (0.92, 1.16)
Self-reported knee pain		3689	1.00 (0.90, 1.11)	1.03 (0.92, 1.15)
Self-reported hip pain		2720	1.02 (0.91, 1.15)	0.99 (0.87, 1.12)
Self-reported foot pain		3099	1.10 (0.98, 1.24)	1.04 (0.93, 1.17)
Symptomatic hand OA		2376	0.92 (0.81, 1.05)	0.98 (0.86, 1.11)
Symptomatic knee OA		2866	0.91 (0.80, 1.02)	0.92 (0.81, 1.04)
Symptomatic hip OA		1902	0.97 (0.84, 1.10)	0.94 (0.82, 1.08)
Symptomatic foot OA		2105	1.02 (0.90, 1.16)	1.01 (0.88, 1.15)
Disabling OA		2396	1.38 (1.27, 1.55)	1.23 (1.08, 1.39)
Disabling hand OA		1515	1.24 (1.08, 1.43)	1.18 (1.02, 1.35)
Disabling knee OA		1774	1.28 (1.13, 1.46)	1.16 (1.02, 1.33)
Disabling hip OA		1323	1.16 (1.00, 1.35)	1.06 (0.91, 1.23)
Disabling foot OA		1387	1.32 (1.15, 1.52)	1.21 (1.05, 1.40)
Number of anatomical areas affected by disabling OA	**1**	375	1.52 (1.20, 1.92)	1.29 (1.02, 1.64)
	2	545	1.35 (1.10, 1.67)	1.16 (0.94, 1.44)
	3	658	1.46 (1.21, 1.76)	1.30 (1.07, 1.57)
	4	600	1.08 (0.87, 1.35)	1.05 (0.84, 1.32)
Symptomatic lower limb OA		3746	0.93 (0.83, 1.04)	0.93 (0.82, 1.05)
Disabling lower limb OA		2185	1.36 (1.20, 1.53)	1.21 (1.07, 1.38)
Symptomatic upper limb OA		231	0.75 (0.51, 1.10)	0.88 (0.60, 1.30)
Disabling upper limb OA		71	1.51 (0.89, 2.56)	1.29 (0.76, 2.19)

Table 4.4- Continued…

		N=	Unadjusted HR	Adjusted* HR
Symptomatic upper and lower limb OA		2145	0.91 (0.80, 1.05)	0.95 (0.82, 1.09)
Disabling upper and lower limb OA		1444	1.29 (1.13, 1.50)	1.21 (1.04, 1.41)
Number of anatomical areas with symptomatic OA	**1**	2961	0.94 (0.79, 1.13)	0.97 (0.81, 1.67)
	2	2433	1.02 (0.85, 1.23)	1.02 (0.84, 1.22)
	3	1462	1.00 (0.81, 1.22)	1.00 (0.82, 1.23)
	4	141	0.94 (0.59, 1.50)	1.01 (0.63, 1.61)
Number of anatomical areas with disabling OA	**1**	399	1.49 (1.18, 1.88)	1.26 (1.00, 1.59)
	2	571	1.43 (1.17, 1.75)	1.23 (1.00, 1.51)
	3	686	1.49 (1.24, 1.79)	1.33 (1.10, 1.61)
	4	600	1.09 (0.88, 1.36)	1.06 (0.85, 1.33)

Adjusted for: age, gender, education, occupation, non-steroidal anti-inflammatory drugs, ischaemic heart disease on medical records, self-reported cardiovascular disease, diabetes, smoking, chronic obstructive pulmonary disease and body mass index

4.8.3 OA Consulters

Consultation for OA had a significant protective association with mortality (adjusted HR 0.84 95% CI 0.74, 0.94) (Table 4.4).

4.8.4 Symptomatic OA

Fewer participants were included in this analysis compared with OA consulters, representing the difference between those diagnosed with OA and those reporting symptoms of OA. In this definition, none of the joints investigated showed a significant association with premature mortality in the adjusted analysis (hand adjusted HR 0.98 95% CI 0.86, 1.11; knee adjusted HR 0.92 95% CI 0.81, 1.04; hip adjusted HR 0.94 95% CI 0.82, 1.08; foot adjusted HR 1.01 95% CI 0.88, 1.15) (Table 4.4). Symptomatic OA was not associated with premature mortality in number of anatomical areas including, upper limb, lower limb and upper and lower limb OA.

4.8.5 Disabling OA

Overall, disabling OA and premature mortality had a significant association (adjusted HR 1.23 95% CI 1.08, 1.39). On an individual joint basis, most of the anatomical areas investigated had a significant association with premature mortality (hand adjusted HR 1.18 95% CI 1.02, 1.35; knee adjusted HR 1.16 95% CI 1.02, 1.35; foot adjusted HR 1.21 95% CI 1.05, 1.40). Hip OA did not have a significant association with premature mortality (hip adjusted HR 1.06 95% CI 0.91, 1.23).

There was no trend with increasing number of joints and disabling OA. There was a significant association for one joint and three joints with disabling OA and premature mortality, however having two or four joints with disabling OA were not significantly associated with premature mortality (one joint adjusted HR 1.29 95% CI 1.02, 1.64;

two joints adjusted HR 1.16 95% CI 0.94, 1.44; three joints adjusted HR 1.30 95% CI 1.07, 1.57; four joints adjusted HR 1.05 95% CI 0.84, 1.32).

When categorising by limb, there was a significant association with premature mortality and lower limb disabling OA with but not with upper limb disabling OA with (lower limb adjusted HR 1.21 95% CI 1.07, 1.38; upper limb adjusted HR 1.29 95% CI 0.76, 2.19). When looking at disabling OA across both regions (both upper and lower limb) the adjusted analysis also shows a significant association with premature mortality (adjusted HR 1.21 95% CI 1.04, 1.41).

4.9 DISCUSSION

The aim of this study was to examine the strength and direction of association between different clinical case definitions of OA and premature mortality at different anatomical sites. It identified that simply consulting for OA or having symptomatic OA does not predict mortality. However, disabling OA characterised by having pain interference, in addition to consultation to primary care for OA and self-report of joint pain, does predict premature mortality across all anatomical locations, except for the hip joint.

4.9.1 OA Consulters

Consultation for OA was protective of premature mortality (adjusted HR 0.84 95% CI 0.74, 0.94). This could be explained because patients under the care of a GP are likely to have other health checks, and therefore co-morbidities treated. For example, a patient attending primary care who is diagnosed with OA should be initially managed using patient education and weight loss advice, if necessary (NICE, 2014). This may then impact other co-morbidities from developing or worsening, such as CVD or

diabetes mellitus, therefore reducing premature mortality. Those diagnosed with OA in primary care are likely to be a heterogeneous group. OA documentation on medical records relies on the clinician's diagnosis, which may not link with criteria or be correct. Furthermore, this measurement does not provide information about the severity of the patient's symptoms.

4.9.2 Self-report of joint pain

OA defined by self-report of joint pain was measured by indication in the NorStOP 'Health Survey' that they had more than one day of pain in the last year in either the hand, knee, hip or foot. None of the analyses revealed a significant association with premature mortality using this case definition. As with the first definition, a consequence of this definition is the lack of information about the severity of the symptoms experienced by the patient. Another limitation of this case definition is the reliance on self-report alone without affirmation from primary care medical record data.

4.9.3 Symptomatic OA

Symptomatic OA was defined as OA on the primary care medical record and more than one day of pain in the last year in either the hand, knee, hip or foot. The analyses did not show a significant association between symptomatic OA and premature mortality at any anatomical location. The definition does not take into account the severity of the OA or symptomology of the participant. This definition also has a risk of misclassification, discussed below.

4.9.4 Disabling OA

Self-report of pain interference was included in the disabling OA case definition. This was defined by OA diagnosis on the primary care medical records plus self-reported joint pain and self-reported pain interference. All definitions with these criteria were positively and significantly associated with mortality although the association with hip pain was not significant (adjusted HR 1.06 95% CI 0.91, 1.23). It is not clear why disabling hip OA does not have a significant association with premature mortality. Other studies have found a significant association between clinical hip OA and premature mortality (Nüesch et al., 2011). Disabling OA also showed a significant association with premature mortality when one or three anatomical areas were involved, the lower limb was involved, and the lower and upper limb were both involved. The disabling lower limb OA group reported combined hip, knee and foot OA within the case definition to show a significant association with premature mortality. In the disabling upper limb OA group, the participants reporting pain in any other joint were removed. Compared to the disabling hand OA group, which included those reporting joint pain in other anatomical areas, the number of participants with hand pain alone was 76 compared with 1515 with hand pain plus pain at other joint sites; the sample of those with disabling hand OA alone is very small. Disabling hand OA alone showed a non-significant but positive association with premature mortality (adjusted HR 1.29 95% CI 0.76, 2.19). The small numbers included in this analysis meant the power of the analysis was low, and although the result are not statistically significant they do indicate an association between disabling hand OA alone and premature mortality. The papers identified in the systematic review in Chapter 2 reported contrasting findings for the relationship between hand OA and premature

mortality. Some papers reported no association between hand OA and premature mortality, as found in this study (Veronese et al., 2015). In contrast, other papers reported an association between hand OA and premature mortality, however it was unclear if those with hand pain in these studies also had pain in other joints (Haara et al., 2003, 2004, Haugen et al., 2015).

4.9.5 Limitations

As briefly discussed above, there are limitations to the use of medical records to identify OA. Firstly, OA coding in medical records relies on the diagnostic accuracy of the primary care clinician and therefore includes a risk of misclassification. Up to 8% of read codes have been found to be misclassified (Kang et al., 2015). Additionally, OA is under-reported on medical records, which further risks the misclassification of participants (Yu, Jordan and Peat, 2018). The case definition of symptomatic OA encompasses any pain felt within that joint for more than a day over the last year, and therefore includes a full spectrum of pain felt within the joint, from transient joint pain to pain every day. This therefore means that participants with minimal symptoms, or OA in a joint area not covered by NorStOP, could have been included in this group, further risking information bias. The NorStOP questionnaire also risks recall bias; participants may not remember episodes of joint pain and therefore not respond to this question. Finally, the disabling OA case definition also risks misclassification. The questions about the location of joint pain and pain interference were not linked; this potentially means that reported pain interference did not refer to pain felt in that joint in particular or pain attributed to OA. However, using pain interference within the

disabling OA case definition establishes the symptomology of the participant, decreasing the chances of misclassification of participants.

4.10 SUMMARY

This study has identified that the association between OA with mortality is dependent on the case definition. Overall, the strongest positive associations with premature mortality were with case definitions of OA that combined pain interference, self-reported joint pain and OA consultation coded in the primary care medical records. This case definition had a significant association with premature mortality across most joint sites. Using disabling OA as a case definition is the best approach to identify more severe OA and its impact on daily life.

Whilst this chapter has identified that disabling OA is associated with premature mortality, it has not identified what causes, or mediates, this association. Identifying pathways offers the potential to better target ways to reduce premature mortality for the large number of people with disabling OA.

5 CHAPTER 5: MEDIATION ANALYSIS AND RESULTS

5.1 INTRODUCTION

Osteoarthritis (OA) with pain interference (disabling OA) is associated with premature mortality. However, why this association, or that of other definitions of OA, occurs has not been previously explored. The studies identified in the systematic searches included confounders but did not explore the mechanism by which OA was associated with premature mortality. Examining mediators of the association between OA and mortality has not been previously conducted within a survival analysis setting. This chapter describes such analyses using a novel approach to mediation within survival analysis to identify factors that mediate the relationship between pain interfering OA and premature mortality. These factors present targets to reduce premature mortality in the large number of people in the community with pain interfering OA.

5.2 AIMS AND OBJECTIVES

5.2.1 Aims

The overall aim of this chapter was to identify factors that mediate the relationship between OA and premature mortality.

5.2.2 Objectives

1. To test the hypotheses that the association between premature mortality and OA is mediated by low walking frequency, depression, anxiety, insomnia and low social participation.
2. To identify if the mediators of the association between disabling OA and mortality differ by anatomical location (hand, hip, knee and foot).

5.3 MEASUREMENT AND RATIONALE OF PROPOSED MEDIATORS

Following the study in Chapter 4, disabling OA was used as a case definition for OA in this chapter. In chapter 4, different case definitions, including OA consulter and symptomatic OA were analysed for their association with premature mortality. Disabling OA was the only case definition to have a significant association with premature mortality. The case definitions of OA used in this analysis were all significantly and positively associated with mortality (Table 5.1).

Table 5.1- Case definitions of OA included in the mediation analysis

Case definition	Description
Disabling osteoarthritis (n= 2396)	Osteoarthritis coded on the primary care medical record, any self-reported joint pain and self-reported pain interference.
Disabling hand osteoarthritis (n= 1515)	Osteoarthritis coded on the primary care medical record, self-reported hand pain and self-reported pain interference.
Disabling knee osteoarthritis (n= 1774)	Osteoarthritis coded on the primary care medical record, self-reported knee pain and self-reported pain interference.
Disabling hip osteoarthritis (n= 1323)	Osteoarthritis coded on the primary care medical record, self-reported hip pain and self-reported pain interference.
Disabling foot osteoarthritis (n= 1323)	Osteoarthritis coded on the primary care medical record, self-reported foot pain and self-reported pain interference.
Disabling lower limb osteoarthritis (n= 2185)	Osteoarthritis coded on the primary care medical record, self-reported knee, hip or foot pain and self-reported pain interference.

The hypothesis investigated in this study was that OA leads to a decrease in walking frequency, depression, anxiety, insomnia and reduced social participation, and then that these lead to premature mortality. Each mediator proposed was amenable to primary care intervention. The reasoning behind each mediator and the measurement of each mediator is discussed below. A summary of confounders and mediators can be found in Table 5.2 on page 113. Within the statistical software used, all mediators were required to be binary.

5.3.1 Walking frequency

Walking frequency is a marker of physical activity, a core treatment for OA (NICE, 2014). Walking frequency may also represent motivation to perform activities (Farholm and Sørensen, 2016). As discussed in 2.1.2 there is an association between exercise and fewer symptoms of OA. OA predicts a reduction in walking frequency (Palazzo et al., 2016). Furthermore, reduced physical activity is associated with premature mortality (Lee et al., 2018). The proposed mediation pathway is therefore: disabling OA leads to reduced walking frequency, both from pain on movement and reduced motivation which then leads to premature mortality. Walking frequency was measured in the health survey questionnaire. Participants were asked the frequency (not the ability) they walked 10 continuous minutes per week. Response categories were: daily, every other day, twice a week, once a week or less, and not at all. This data was categorised *a priori* to less than once per week (infrequent) and a minimum of once a week or more (frequent).

5.3.2 Depression

OA can lead to, or aggravate, depression (Sharma et al., 2016). OA, and the chronic pain associated with it, leads to low mood (Hansen and Streltzer, 2005). The association between depression and OA is discussed in 2.1.1. Depression is associated with premature mortality (Gilman et al., 2017). The Hospital Anxiety and Depression Scale (HADS) was used to measure depression. For the depression subscale scores can range from 0 to 21. Score of less than or equal to 7 indicated no depression; scores 8-10 indicated possible depression and scores of 11-21 indicated probable depression. The categories of 'possible' and 'probable' were combined to give non-cases (scoring 0-7) as reference group and cases (scoring 8 or more; Zigmond and Snaith, 1983). The proposed mediation pathway is that disabling OA causes to depression and therefore premature mortality.

5.3.3 Anxiety

OA can both cause and exacerbate anxiety (Sharma et al., 2016). As discussed in 2.1.1 anxiety is associated with OA. Anxiety is associated with premature mortality (Meier et al., 2016). HADS was used to measure anxiety. For the anxiety subscale scores can range from 0 to 21. Score of less than or equal to 7 indicated no anxiety; scores 8-10 indicated possible depression and scores of 11-21 indicated probable anxiety. The categories of 'possible' and 'probable' were combined to give non-cases (scoring 0-7) as reference group and cases (scoring 8 or more; Zigmond and Snaith, 1983). The proposed mediation pathway is that disabling OA leads to anxiety which then leads to premature mortality.

5.3.4 Insomnia

Insomnia and reduced sleep, discussed in 2.1.4.2, are associated with both OA and premature mortality (Allen et al., 2008; Cappuccio et al., 2010). This was assessed in the 'Health Survey'. Participants were asked whether they awoke feeling unrefreshed. Response options were not at all, some nights and most nights. This was then dichotomised into refreshed (not at all/some nights) and unrefreshed (most nights; Hayward, Jordan and Croft, 2012). The proposed mediation pathway is the pain interference from OA leads to insomnia with in turn leads to premature mortality.

5.3.5 Social participation

Social participation was included as a mediator in the analysis. Participation restriction can be defined as difficulties in life situations like working or shopping and is reduced in those with OA (Wilkie, Peat, Thomas and Croft, 2007). Low social participation is association with premature mortality (Dalgard and Håheim, 1998). Social participation was measured using the Keele Assessment of Participation. The scores from this range from 0 to 11. This was dichotomised into no restriction (score = 0) and restriction (score > 0). The proposed mediation pathway for this is that OA with pain interference leads to reduced social participation and premature mortality.

5.3.6 Confounders

The same confounders were adjusted for in both this study and the study in Chapter 4 (described 4.6.7). These were age, gender, education, occupation, non-steroidal anti-inflammatory drug use (NSAID), ischaemic heart disease (IHD), self-reported cardiovascular disease (CVD), diabetes mellitus, smoking, chronic obstructive pulmonary disease (COPD) and body mass index (BMI). The analysis required that

confounders were either binary or continuous. NSAID prescriptions were used as a categorical variable in Chapter 4; this was dichotomised into any previous NSAID prescription and no NSAID prescription on the primary care medical records. Age and BMI were used as continuous variables. As the other covariates were already binary, these were not changed.

Table 5.2- Summary of the exposures, outcomes, mediators and confounders used in the analyses

Concept	Exposure	Outcome	Mediator	Confounder
Osteoarthritis	x			
Mortality		x		
Age				x
Sex				x
Socioeconomic status				x
Non-steroidal anti-inflammatory drugs				x
Cardiovascular disease*				x
Chronic obstructive pulmonary disease				x
Diabetes mellitus				x
Body mass index				x
Smoking				x
Walking frequency			x	
Depression			x	
Anxiety			x	
Insomnia			x	
Social participation			x	

* including both self-reported cardiovascular disease and ischaemic heart disease on the primary care medical record

5.4 METHODS

5.4.1 Mediation Analysis

Mediation analysis aims to explain an association between an independent and dependent variable by the inclusion of a third variable, a mediator (Mackinnon, Fairchild and Fritz, 2007). A mediator is a factor that is both associated with the exposure and the outcome and is proposed be on the causal pathway (Mackinnon, Fairchild and Fritz, 2007). This contrasts with a confounder; a variable that is related to both the exposure and outcome but is not on the causal pathway. Figure 5.1 shows a simple mediation model.

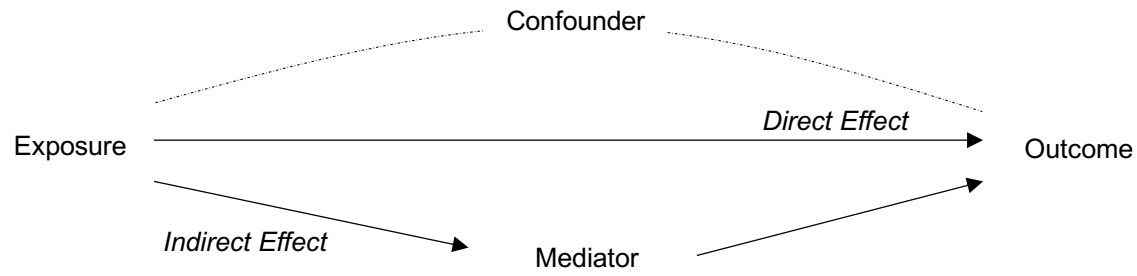


Figure 5.1- A simple mediation model, showing the relationship between exposure and outcome going via the mediator

Mediation analysis sets out to test whether a change in the exposure causes a change in the mediating variable, which in turn causes a change in the outcome (Hayes, 2013). An example of this is in Figure 5.2.

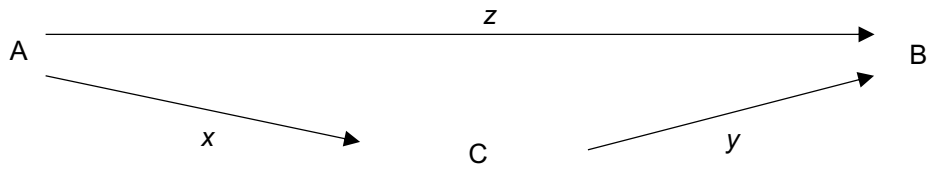


Figure 5.2- A simple mediation model, where A= the exposure, B= the outcome, C= the mediator, x= the effect of the exposure on the mediator, y= the effect of the mediator on the outcome, xy= indirect effect, z= direct effect and xy+z= total effect

The mediation model presented in Figure 5.2 shows an association between A and B mediated by C. In this example C at least partially explains the association between A and B. The association between A and B could be partly explained by the direct pathway, z, and the indirect pathway xy. However, the whole association between A and B could be explained by the pathways xy, showing 'complete mediation'; the whole of the association between A and B is via the mediator, C (Hayes, 2013).

5.4.2 Exposure variables

The different case definitions of OA used in this analysis from NorStOP are described in Table 5.2. These case definitions were chosen following an analysis in Chapter 4, showing the case definitions of disabling OA to have a significant association with premature mortality.

The analyses in the chapter empirically examine hypothesised pathways from OA to mortality. Previous literature and clinical reasoning helps to design potential mediation pathways, which occurs via the indirect pathway. Baron and Kenny (1986) discuss that the strongest evidence of mediation occurring is when only the indirect

pathway remains statistically significant, and the direct pathway shows no effect; this is “full mediation”. A reduction in the direct effect and significant indirect effect would be termed “partial mediation”.

Baron and Kenny (1986) assert that the basic approach to their mediation analysis is that there is a significant association between the exposure and the outcome before decomposing into the direct and indirect effects. In other words, Baron and Kenny (1986) maintain the importance of a significant total effect for a mediation analysis to be performed. However, Zhao, Lynch and Chen (2010) suggest that there is no need for a significant total effect for mediation analysis to be performed; a total effect can be decomposed into its direct and indirect constituents regardless of the significance of that initial figure, as mediation has potentially still occurred. As insignificant total effects were found for one anatomical site in chapter 4 (disabling hip OA; adjusted hazard ratio [HR] 1.06 95% confidence interval [CI] 0.91, 1.23), this thesis will still decompose the effects to establish whether mediation has occurred or not.

5.4.3 Mediation analysis within survival analysis; Using Cox proportional hazard models for mediation analysis

A mediation model within survival analysis has been proposed (Lange and Hansen, 2012). This is based on a counterfactual framework and therefore models the total, direct and indirect of the exposure on the outcome.

5.4.3.1 Counterfactual framework

The counterfactual framework both considers the effect of an exposure on a participant and also what would have happened if this participant did not have this exposure (Robins and Greenland, 1992). Therefore, the framework replicates the

analysis to firstly include the exposure as it occurred with a participant with its original value and then to take the counterfactual, or opposite, value. Weights are calculated via logistic regression of a binary mediator on the exposure and baseline confounders via this equation:

$$W_i^c = \frac{P(M = M_i \,|A = A_i^*, C = C_i)}{P(M = M_i \,|A = A_i, C = C_i)}$$

Where A is the exposure of interest, M is the mediator and C is the baseline confounders. Within this example, * represents the counterfactual values. If the assumptions of Cox proportional hazard models are met, this model will give hazard ratios representing direct and indirect effects; the product of this is the total effects. This approach was used by Rochon et al., (2014) and has been used by Smith et al., (2018) within NorStOP. Mediation analysis was performed using the technique described by Rochon et al., (2014). Data cleaning for the mediation analysis was performed within Stata. The mediation analysis was performed in survival package of the statistical software R (Therneau and Lumley, 2015). Bootstrapping was then used to calculate standard error and confidence intervals.

5.4.3.2 *Bootstrapping*

Bootstrapping is a method of resampling that determines the accuracy of a result by calculating confidence intervals (Preacher and Hayes, 2008a). Bootstrapping estimates the indirect effect by taking a new sample from the original sample and repeating the analysis a specified number of times; in these analyses, this was repeated 100 times. Following the repeated analysis, values' indirect effects were sorted from low to high

in order to calculate standard error of the indirect effects, and therefore confidence intervals (Preacher and Hayes, 2008b).

5.5 ANALYSIS

Firstly, associations between the predictor exposure (OA) and each mediating variable was examined using logistic regression to explain the direction of any mediating effect (i.e. a positive association (odds ratio greater than 1) between OA and low walking frequency means the HR (above 1) of the indirect effect refers to an increased risk of mortality as a result of OA and lower levels of walking frequency). All associations between OA and potential mediators are presented as odds ratios (OR) with 95% CIs. All analyses were adjusted for potential confounders (as per Cox modelling described in chapter 4: age, gender, education, occupation, NSAID use, IHD, self-reported CVD, diabetes mellitus, smoking, COPD and BMI).

Results of the mediation analyses are presented as HR for the direct, indirect and total effects with associated 95% CIs. Mediation was indicated by the presence of a statistically significant indirect effect. This can occur whether the total effects are statistically significant, or not (Zhao, Lynch and Chen, 2010). In a case of full mediation, the direct effect then attenuates (becomes non-significant), indicating the full effect of the association between the exposure and outcome is via the indirect pathway and therefore the mediator.

5.6 RESULTS OF MEDIATION ANALYSIS

Table 5.3- Pathways between 'general disabling osteoarthritis' and premature mortality via listed mediators (n=8066)

Mediator	Association between general osteoarthritis and potential mediator Adjusted OR (95%CI)	Pathway	Adjusted HR (95%CI)
Walking frequency		Direct	1.07 (0.95, 1.24)
Frequent walker	Reference	Indirect	**1.08 (1.05, 1.10)**
Non-frequent walker	**2.33 (2.10, 2.59)**	Total	1.16 (1.01, 1.32)
Depression		Direct	1.11 (0.93, 1.30)
No depression	Reference	Indirect	**1.05 (1.01, 1.08)**
Depression	**3.28 (2.90, 3.70)**	Total	1.16 (1.00, 1.33)
Anxiety		Direct	1.16 (1.01, 1.32)
No Anxiety	Reference	Indirect	1.00 (0.98, 1.03)
Anxiety	**2.62 (2.35, 2.91)**	Total	1.16 (1.00, 1.32)
Insomnia		Direct	1.17 (1.03, 1.32)
No insomnia	Reference	Indirect	1.01 (0.98, 1.04)
Insomnia	**2.82 (2.47, 3.21)**	Total	1.17 (1.03, 1.32)
Social Participation		Direct	1.06 (0.95, 1.19)
Social Participation	Reference	Indirect	**1.10 (1.06, 1.13)**
No social participation	**3.32 (2.97, 3.90)**	Total	1.17 (1.05, 1.32)

All models adjusted for age, gender, education, occupation, non-steroidal anti-inflammatory drug use, ischaemic heart disease, self-reported cardiovascular disease, diabetes mellitus, smoking, chronic obstructive pulmonary disease and body mass index.
Significant indirect effects are highlighted in **bold.**
OR = Odds ratio, HR = Hazard ratio, CI = Confidence Intervals

Table 5.4- Pathways between 'disabling hand osteoarthritis' and premature mortality via listed mediators (n=8066)

Mediator	Association between hand osteoarthritis and potential mediator Adjusted OR (95%CI)	Pathway	Adjusted HR (95%CI)
Walking frequency		Direct	1.07 (0.91, 1.24)
Frequent walker	Reference	Indirect	**1.06 (1.03, 1.09)**
Non-frequent walker	**2.19 (1.94, 2.47)**	Total	1.13 (0.98, 1.32)
Depression		Direct	1.10 (0.93, 1.30)
No depression	Reference	Indirect	**1.05 (1.02, 1.08)**
Depression	**3.05 (2.67, 3.48)**	Total	1.16 (0.98, 1.36)
Anxiety		Direct	1.14 (0.97, 1.36)
No Anxiety	Reference	Indirect	1.00 (0.97, 1.04)
Anxiety	**2.82 (2.50, 3.18)**	Total	1.14 (0.99, 1.34)
Insomnia		Direct	1.14 (0.99, 1.32)
No insomnia	Reference	Indirect	1.01 (0.99, 1.04)
Insomnia	**2.87 (2.50, 3.29)**	Total	1.16 (1.00, 1.35)
Social Participation		Direct	1.06 (0.91, 1.11)
Social Participation	Reference	Indirect	**1.09 (1.06, 1.12)**
No social participation	**3.08 (2.71, 3.51)**	Total	1.16 (1.00, 1.32)

All models adjusted for age, gender, education, occupation, non-steroidal anti-inflammatory drug use, ischaemic heart disease, self-reported cardiovascular disease, diabetes mellitus, smoking, chronic obstructive pulmonary disease and body mass index.
Significant indirect effects are highlighted in **bold.**
OR = Odds ratio, HR = Hazard ratio, CI = Confidence Intervals

Table 5.5- Pathways between 'disabling knee osteoarthritis' and premature mortality via listed mediators (n=8066)

Mediator	Association between knee osteoarthritis and potential mediator Adjusted OR (95%CI)	Pathway	Adjusted HR (95%CI)
Walking frequency		Direct	1.05 (0.91, 1.18)
Frequent walker	Reference	Indirect	**1.06 (1.05, 1.09)**
Non-frequent walker	**2.31 (2.06, 2.60)**	Total	1.12 (0.98, 1.26)
Depression		Direct	1.08 (0.95, 1.23)
No depression	Reference	Indirect	**1.05 (1.01, 1.08)**
Depression	**3.00 (2.64, 3.41)**	Total	1.13 (1.00, 1.32)
Anxiety		Direct	1.12 (0.99, 1.28)
No Anxiety	Reference	Indirect	1.00 (0.98, 1.03)
Anxiety	**2.48 (2.21, 2.79)**	Total	1.12 (0.98, 1.29)
Insomnia		Direct	1.12 (0.98, 1.25)
No insomnia	Reference	Indirect	1.01 (0.98, 1.03)
Insomnia	**2.75 (2.40, 3.15)**	Total	1.13 (0.97, 1.27)
Social Participation		Direct	1.04 (0.90, 1.17)
Social Participation	Reference	Indirect	**1.09 (1.05, 1.13)**
No social participation	**3.06 (2.71, 3.46)**	Total	1.03 (0.98, 1.26)

All models adjusted for age, gender, education, occupation, non-steroidal anti-inflammatory drug use, ischaemic heart disease, self-reported cardiovascular disease, diabetes mellitus, smoking, chronic obstructive pulmonary disease and body mass index.
Significant indirect effects are highlighted in **bold**.
OR = Odds ratio, HR = Hazard ratio, CI = Confidence Intervals

Table 5.6- Pathways between 'disabling hip osteoarthritis' and premature mortality via listed mediators (n=8066)

Mediator	Association between hip osteoarthritis and potential mediator Adjusted OR (95%CI)	Pathway	Adjusted HR (95%CI)
Walking frequency		Direct	0.97 (0.85, 1.08)
Frequent walker	Reference	Indirect	**1.06 (1.04, 1.09)**
Non-frequent walker	**2.25 (1.97, 2.56)**	Total	1.03 (0.89, 1.16)
Depression		Direct	1.00 (0.86, 1.14)
No depression	Reference	Indirect	**1.05 (1.02, 1.07)**
Depression	**2.80 (2.44, 3.20)**	Total	1.05 (0.90, 1.20)
Anxiety		Direct	1.03 (0.89, 1.24)
No Anxiety	Reference	Indirect	1.01 (0.99, 1.03)
Anxiety	**2.46 (2.17, 2.79)**	Total	1.04 (0.89, 1.23)
Insomnia		Direct	1.04 (0.86, 1.20)
No insomnia	Reference	Indirect	1.01 (0.99, 1.04)
Insomnia	**2.80 (2.42, 3.22)**	Total	1.05 (0.88, 1.21)
Social Participation		Direct	0.94 (0.81, 1.10)
Social Participation	Reference	Indirect	**1.10 (1.06, 1.12)**
No social participation	3.25 (2.83, 3.73)	Total	1.04 (0.88, 1.22)

All models adjusted for age, gender, education, occupation, non-steroidal anti-inflammatory drug use, ischaemic heart disease, self-reported cardiovascular disease, diabetes mellitus, smoking, chronic obstructive pulmonary disease and body mass index.
Significant indirect effects are highlighted in **bold.**
OR = Odds ratio, HR = Hazard ratio, CI = Confidence Intervals

Table 5.7- Pathways between 'disabling foot osteoarthritis' and premature mortality via listed mediators (n=8066)

Mediator	Association between foot osteoarthritis and potential mediator Adjusted OR (95%CI)	Pathway	Adjusted HR (95%CI)
Walking frequency		Direct	1.12 (0.99, 1.08)
Frequent walker	Reference	Indirect	**1.06 (1.04, 1.09)**
Non-frequent walker	**2.27 (2.00, 2.58)**	Total	1.19 (1.04, 1.37)
Depression		Direct	1.14 (0.98, 1.32)
No depression	Reference	Indirect	**1.05 (1.01, 1.09)**
Depression	**3.29 (2.87, 3.76)**	Total	1.20 (1.04, 1.35)
Anxiety		Direct	1.19 (1.03, 1.37)
No Anxiety	Reference	Indirect	1.00 (0.97, 1.03)
Anxiety	**2.75 (2.42, 3.11)**	Total	1.19 (1.04, 1.36)
Insomnia		Direct	1.19 (1.06, 1.33)
No insomnia	Reference	Indirect	1.00 (0.98, 1.03)
Insomnia	**2.74 (2.38, 3.16)**	Total	1.19 (1.07, 1.35)
Social Participation		Direct	1.11 (0.93, 1.29)
Social participation	Reference	Indirect	**1.09 (1.06, 1.13)**
No social participation	**3.27 (2.86, 3.74)**	Total	1.21 (1.00, 1.40)

All models adjusted for age, gender, education, occupation, non-steroidal anti-inflammatory drug use, ischaemic heart disease, self-reported cardiovascular disease, diabetes mellitus, smoking, chronic obstructive pulmonary disease and body mass index.
Significant indirect effects are highlighted in **bold.**
OR = Odds ratio, HR = Hazard ratio, CI = Confidence Intervals

Table 5.8- Pathways between 'disabling lower limb osteoarthritis' and premature mortality via listed mediators (n= 8066)

	Association between lower limb osteoarthritis		

Mediator	and potential mediator Adjusted OR (95%CI)	Pathway	Adjusted HR (95%CI)
Walking frequency		Direct	1.10 (0.97, 1.27)
Frequent walker	Reference	Indirect	**1.07 (1.04, 1.09)**
Non-frequent walker	**2.33 (2.09, 2.59)**	Total	1.17 (1.02, 1.36)
Depression		Direct	1.13 (0.97, 1.28)
No depression	Reference	Indirect	**1.04 (1.01, 1.08)**
Depression	**3.22 (2.84, 3.64)**	Total	1.18 (1.02, 1.34)
Anxiety		Direct	1.17 (1.06, 1.34)
No Anxiety	Reference	Indirect	1.00 (0.97, 1.02)
Anxiety	**2.61 (2.34, 2.31)**	Total	1.17 (1.06, 1.34)
Insomnia		Direct	1.18 (1.05, 1.35)
No insomnia	Reference	Indirect	1.00 (0.98, 1.03)
Insomnia	**2.76 (2.42, 3.15)**	Total	1.18 (1.06, 1.34)
Social Participation		Direct	1.07 (0.92, 1.20)
Social Participation	Reference	Indirect	**1.10 (1.07, 1.14)**
No social participation	**3.36 (3.00, 3.77)**	Total	1.07 (1.02, 1.30)

All models adjusted for age, gender, education, occupation, non-steroidal anti-inflammatory drug use, ischaemic heart disease, self-reported cardiovascular disease, diabetes mellitus, smoking, chronic obstructive pulmonary disease and body mass index.
Significant indirect effects are highlighted in **bold**.
OR = Odds ratio, HR = Hazard ratio, CI = Confidence Intervals

This analysis identified three factors that mediated the relationship between OA and premature mortality for all case definitions of OA: walking frequency, depression and social participation. For each of these mediators in each case definition the direct effects (DE) attenuated (became non-significant). The reduction in the DE shows that the effect of OA on premature mortality has decreased once taking account of the mediator. Anxiety and insomnia did not mediate the relationship between premature mortality and any case definition of OA.

5.6.1 Walking frequency

Walking frequency was a significant mediator of the association between each case definition of OA and premature mortality; the indirect effects (IE) for disabling general OA was 1.08 (95% CI 1.05, 1.10;) with DE attenuating to 1.07 (95% CI 0.95, 1.24); disabling hand OA 1.06 (95% CI 1.03, 1.09) with DE attenuating to 1.07 (95% CI 0.91, 1.24); disabling knee OA 1.06 (1.05, 1.09) with DE attenuating to 1.05 (95% CI 0.91, 1.18); disabling hip OA 1.06 (1.04, 1.09) with DE attenuating to 0.97 (95% CI 0.85, 1.08); disabling foot OA 1.06 (1.04, 1.09) with DE attenuating to 1.12 (95% CI 0.99, 1.08) and disabling lower limb OA 1.07 (1.04, 1.09) with DE attenuating to 1.10 (95% CI 0.97, 1.27). Each anatomical area has a relatively similar IE and a similar reduction in DE.

5.6.2 Depression

Each included case definition showed depression to be a significant mediator between OA and premature mortality. This is demonstrated by statistically significant IE with attenuation of the DE (general OA IE 1.05 95% CI 1.01, 1.08, DE 1.11 95% CI 0.93, 1.30; hand OA IE 1.05 95% CI 1.02, 1.08, DE 1.10 95% CI 0.93, 1.30; knee OA IE 1.05 95% CI

1.01, 1.08, DE 1.08 95% CI 0.95, 1.23; hip OA IE 1.05 95% CI 1.02, 1.07, DE 1.00 95% CI 0.86, 1.14; foot OA IE 1.05 1.01, 1.09, DE 1.14 95% CI 0.98, 1.32; lower limb OA IE 1.04 95% CI 1.01, 1.08, DE. Each anatomical area has a relatively similar IE and a similar reduction in DE, however this was less marked than in the walking frequency analysis.

5.6.3 Anxiety

None of the included case definitions showed anxiety to be a significant mediator between OA and premature mortality. There was a non-significant IE at each anatomical site and a low effect on DE; in some cases the DE remained statistically significant showing that anxiety was not a mediator: (general OA IE 1.00 95% CI 0.98, 1.03, DE 1.16 95% CI 1.01, 1.32; hand OA IE 1.00 95% CI 0.97, 1.04, DE 1.14 95% CI 0.97, 1.36; knee OA IE 1.00 95% CI 0.98, 1.03, DE 1.12 95% CI 0.99, 1.28; hip OA IE 1.01 95% CI 0.99, 1.03, DE 1.03 95% CI 0.89, 1.24; foot OA IE 1.00 95% CI 0.97, 1.03, DE 1.19 1.03, 1.37; lower limb OA IE 1.00 95% CI 0.97, 1.02, DE 1.17 95% CI 1.06, 1.34).

5.6.4 Insomnia

None of the included case definitions showed insomnia to be a significant mediator between OA and premature mortality. There was a non-significant IE at each anatomical site and a low effect on DE: (general OA IE 1.01 95% CI 0.98, 1.04, DE 1.17 95% CI 1.03, 1.32; hand OA IE 1.01 95% CI 0.99, 1.04, DE 1.14 95% CI 0.99, 1.32; knee OA IE 1.01 95% CI 0.98, 1.03, DE 1.12 95% CI 0.98, 1.25; hip OA IE 1.01 95% CI 0.99, 1.04, DE 1.04 95% CI 0.86, 1.20; foot OA IE 1.00 95% CI 0.98, 1.03, DE 1.19 95% CI 1.06, 1.33; lower limb OA IE 1.00 95% CI 0.98, 1.03, DE 1.18 95% CI 1.05, 1.35). Although each anatomical area had relatively similar IEs, the DEs varied across anatomical location with some DEs showing no attenuation and remaining statistically significant.

5.6.5 Social participation

Each included case definition showed walking frequency to be a significant mediator between OA and premature mortality. This is demonstrated by statistically significant indirect effects (IE) with attenuation of DEs (general OA IE 1.10 95% CI 1.06, 1.13, DE 1.06 95% CI 0.95, 1.19; hand OA IE 1.09 95% CI 1.06, 1.12, DE 1.06 95% CI 0.91, 1.11; knee OA IE 1.09 95% CI 1.05, 1.13, DE 1.04 95% CI 0.90, 1.17; hip OA IE 1.10 95% CI 1.06, 1.12, DE 0.94 95% CI 0.81, 1.10; foot OA IE 1.09 95% CI 1.06, 1.13, DE 1.11 95% CI 0.93, 1.29; lower limb OA IE 1.10 95% CI 1.07, 1.14, DE 1.07 95% CI 0.92, 1.20). For four anatomical areas (hand, knee, hip and foot OA) the total effects (TE) were not statistically significant (hand TE 1.16 95% CI 1.00, 1.32; knee TE 1.03 95% CI 0.98, 1.26; hip TE 1.04 95% CI 0.88, 1.22; foot 1.21 95% CI 1.00, 1.40). Overall, the low social participation had the largest effect size, indicated by the highest IE and the lowest DE.

5.7 DISCUSSION

The analyses showed walking frequency, depression and social participation mediated the relationship between OA and premature mortality. Anxiety and insomnia were not a significant mediator with premature mortality at any joint site.

5.7.1 Walking frequency

A pathway from OA to premature mortality via walking frequency, and perhaps physical activity in general, was well supported; it was a mediator for the association between OA and premature mortality at all anatomical areas investigated. This is consistent with previous literature examining reduced activity in those with OA (Dunlop et al., 2011) and associations between low physical activity and premature mortality (Lee et al., 2018). As walking frequency is a surrogate marker of physical

activity, it presents a potential target for reducing OA related mortality. The low walking frequency was classified in this study as 5-10 minutes of walking less than once a week; this is particularly low. This analysis suggests that increasing this low amount of walking would reduce premature mortality as a result of OA, which is more attainable to those with restricted mobility than completing the a certain amount of steps per day. It has been previously suggested that small amounts of frequent walking is associated with lower mortality (Simonsick et al., 2005). This presents a target for reducing mortality from OA that is both simple and attainable to patients.

5.7.2 Depression

Each case definition was associated with depression. Each analysis found a significant association between OA and depression. Although the different between the IE and DE was less marked than in the low walking frequency or low social participation analysis (i.e. the IE was lower and the DE was higher) the IE was found to be significant across all anatomical location with attenuation of the DE. This shows that depression was a significant mediator of the relationship between OA and premature mortality. HADS was a screening tool, rather than a diagnostic tool for depression. Although it has been widely validated, it does not represent the diagnostic threshold for depression, and therefore there is risk of misclassification. Depression also represents a potential way of modifying the relationship between OA and premature mortality. Identifying depressive symptoms and managing them could help reduce mortality as a result of OA. Management options for depression include psychological and pharmacological therapy, with some evidence that physical activity can alleviate depressive symptoms (Cooney et al., 2013; NICE, 2009)

5.7.3 Social participation

Each case definition was associated with low social participation. Low social participation was the strongest mediator (i.e. the point estimate for the indirect effect was highest for social participation) in the association between OA and premature mortality, defined by the highest hazard ratios of the IE and lowest DE. Both general OA and lower limb OA also found a significant total effect with attenuation of the direct effect, showing the strength of this association. Social participation appears to be a surrogate marker of other mediators included in this analysis. However, it is a key target and could be the mechanism for maintaining physical activity, maintaining a sense of purpose and positive mood, which has further positive effects on health. Social participation is reduced in those with mental health problems, such as depression, and in those with a reduced capability of physical activity. Interventions focussed on increasing walking frequency, reducing depression symptom and facilitating social activities may help reduce mortality as a result of OA.

5.7.4 Comparison with current literature

There have been no other published studies that have investigated mediation with a survival model focusing on the association between OA and premature mortality. Other studies have examined mediation within a survival analysis. Smith et al., (2018) reported that the association between pain and mortality was mediated by lifestyle, health, social and psychological factors, however this study did not examine links with OA. Previous studies have used Cox proportional hazards regression analysis. One study found mortality was significantly associated with walking disability, supported by the results from this study (Hawker et al., 2014). Another study did not find a

significant relationship between OA and premature mortality, but did find that those with OA had an increased risk of IHD and heart failure in comparison to those without OA (Turkiewicz et al., 2016). This was suggested to be caused by a "modifiable intermediate factor" like physical activity, which would further support finding from this study (Turkiewicz et al., 2016). Therefore, this study represents the first to use mediation analysis within a Cox proportional hazards models to investigate the association between clinically defined OA and premature mortality.

5.8 LIMITATIONS

Successful application of the statistical technique in R to examine mediation within a survival model required all mediators to be dichotomous variables. This is a potential limitation as dichotomising variables may result in a loss of richness in the data set, particularly for continuous variables (Royston, Altman and Sauerbrei, 2006). There may be some misclassification for all variables in the study, which may occur due to the approach to dichotomising each variable.

Mediation analysis assumes that the exposure, in this case OA, should be measured prior to mediators (Kline, 2015). Therefore, a limitation of this study is that both the exposure and mediators were measured at the same time, at baseline. Furthermore, as OA Read codes were identified from the participant's primary care medical records at any point across the duration of NorStOP 1 and 2, formal clinician diagnosed OA may have been established after collection of the mediators. However, as OA is a longstanding, chronic condition, with a long period of development, OA on the primary care medical record at any point across the study period implied that OA was likely present at least to some degree during the entire duration of NorStOP 1 and 2.

It has been suggested that the bootstrapping to calculate confidence intervals should involve 1000 replications (Efron and Tibshirani, 1986), however due to time constraints this was not performed. Using 1000 replications could have made the confidence intervals smaller, providing more accurate results. It is unlikely that this would have made a significant different to the results shown above; most of the confidence intervals of the IE were narrow.

The use of self-report measures in this study may be a limitation, as discussed in 4.9.5. There is risk of information bias within responses. For example, a participant declaring that they walked daily for over 10 minutes could represent someone who simply walks from room to room of their house across the day, totally 10 minutes overall due to misunderstanding the question. However, some of the included mediators, including depression, anxiety and insomnia, are best measured via self-report (Uher et al., 2012).

Each case definition included participants used in another case definition, as those with OA are likely to have more than one site affected (NICE, 2014). For example, if a participant has reported hand and knee pain, they will be included in both the hand and knee OA group. However, if a participant has reported knee and hip pain, whilst they will be included separately in the knee and hip analysis, they will only be included once in the lower limb analysis. The number of participants that reported an individual joint pain, opposed to pain at multiple sites, was very small. Using these smaller numbers would result in a diminishing of the analysis' power.

Given that the number of participants with specifically hand OA and OA at no other anatomical site is very small (n=71), it does not have the power that other anatomical

locations do. Although the results looking at the association between disabling hand OA alone and premature mortality were non-significant (adjusted HR 1.29 95% CI 0.76, 2.19), there is still an association present. This, therefore, suggests that low walking frequency, depression and low social participation are mediators of the relationship between OA and premature mortality at hand joints alone.

5.9 SUMMARY

This study has identified factors that explain the link between OA and premature mortality; these represent targets for reducing this risk. This study has shown that low walking frequency, depression and low social participation represent targets within primary care to reduce the risk of mortality. Chapter 6 will outline the implications of these findings on clinical practice and future research.

6 CHAPTER 6: DISCUSSION

6.1 INTRODUCTION

This thesis aimed to determine if there was an association between osteoarthritis (OA) and premature mortality and to identify factors that mediate this relationship. Chapter 4 examined the strength and direction of the association between different case definitions and premature mortality. Chapter 5 then examined if a number of mediator variables (factors amenable to management in primary care) explained the relationship between OA and premature mortality. This chapter discusses these findings in the context of previous literature and outlines implications for clinical practice and future research.

6.2 SUMMARY OF RESULTS

This thesis presents the results of analyses, using data from a large population-based cohort study, that has examined whether there is, and the reasons for, an association between OA and premature mortality. Two systematic searches identified systematic reviews and recent studies that examined the association between OA and premature mortality. The heterogeneity between these studies prevented pooling of estimates. It is difficult to draw a clear conclusion on whether there was an association between OA and mortality, however there was a sense that if such an association existed it may be dependent on case definition. The North Staffordshire Osteoarthritis Project (NorStOP) dataset presented an opportunity to examine whether a positive association was dependent on case definition (described in chapter 4). There was a positive association between OA and premature mortality in those with disabling OA. Disabling OA was defined as primary care medical record data indicating consultation for OA, self-

reported of joint pain and self-reported of pain interference. Mediation analyses (described in chapter 5) identified that the association between disabling OA and premature mortality was mediated through walking frequency, depression and social participation.

6.3 COMPARISON WITH EXISTING LITERATURE

OA is a heterogeneous condition, which can be defined and researched using a variety of different case definitions (Pereira et al., 2011). The systematic searches in Chapter 2 identified studies using both radiographic and clinical case definitions of OA. Most studies used a clinical definition or a combination of clinical and radiologic definitions. The systematic searches highlighted papers comparing two different case definitions and their associations with premature mortality. Although this was between radiographic and clinical case definitions in the systematic searches, the NorStOP cohort provided the opportunity to investigate the relationship of different case definitions with premature mortality. Case definitions investigated were: (i) OA diagnosis in medical records (OA consulter), (ii) self-reported joint pain (iii) OA in medical records and specific joint pain (symptomatic OA), and (iv) OA in the medical records and specific joint pain with pain interference (disabling OA). Disabling OA was found to have significant associations with premature mortality across multiple joint site, including the hand, knee, foot and lower limb combined. None of the studies included in the systematic review specifically looked at OA with pain interference, however Smith et al. (2018) found that pain interference was associated with premature mortality, whereas the report of pain or having widespread pain was not, affirming the importance of pain interference in the OA case definition.

It is not clear why hip disabling OA was not significantly associated in comparison to the other joint sites. The number of participants with hip OA was smaller than the other groups but would have been large enough to maintain statistical power. Furthermore, the point estimate for disabling hip OA was lower indicating that the difference in mortality between those with and without disabling hip OA was smaller than for other joints. The systematic searches in Chapter 2 found a total of 11 papers investigating the association between hip OA and mortality, with 8 studies finding a significant association between hip OA and premature mortality. However, the majority of these papers used a radiographic case definition. Most papers investigating clinically defined hip OA found a non-significant association with hip OA, as was found in Chapter 4 of this thesis.

As discussed in 4.9, there was a non-significant association between disabling hand OA alone (i.e. in people that did not have hip, knee or foot pain) and premature mortality, however the sample size was small. This is contradictory to findings from Veronese et al. (2016), hypothesising that hand OA is a moderator in the relationship between OA and premature mortality. Furthermore, studies looking specifically at hand OA in the systematic search found an association with premature mortality, but OA at other joint sites were not considered in the analysis or adjusted for (Harra et al., 2003, 2004; Haugen et al., 2015). **Overall, this highlights that the case definition of disabling OA is important regardless of anatomical site.**

Chapter 5 focused on mediation of 'disabling OA' at different anatomical sites. Walking frequency, depression and social participation were significant mediators across the anatomical sites investigated. This is the first study exploring mediation of the

association between OA and mortality within a Cox proportional hazards model, and one of a few studies that have examined mediation within a survival analysis.

Other studies have reported that they have examined whether walking frequency is a mediator of the association between OA and premature mortality. The Wuchuan Osteoarthritis Study (WOS), a study identified from the systematic searches, examined whether walking frequency was a mediator of the relationship between OA and premature mortality in secondary analysis of the cohort (Liu et al., 2017). However, the analysis of mediation in the WOS used regression modelling rather than a survival model as used in this thesis. The sample size in the WOS study was small (n= 1025), and fewer participants had died at the time of this analysis (n= 99). This led to an imprecise estimate of indirect effect 1.92 (95% CI 0.86, 4.26). The study described in this thesis had a much larger overall sample size (n= 8066), with each case definition including more participants than in the WOS study. More participants had died over the follow up period within NorStOP, increasing the precision of indirect effects in comparison to WOS. Physical function and physical activity have also been examined as mediators of the association between OA and premature mortality; again, this was examined using regression modelling; where indirect effects were not estimated (Barbour et al., 2015). Physical function was found to be a 'partial mediator' of the association between OA and all-cause mortality, whereas physical activity was not found to be a significant mediator (physical function adjusted hazard ratio [HR] 1.06 95% confidence interval [CI] 1.02, 1.10; physical activity adjusted HR 1.01 95% CI 0.97, 1.05). The WOS also examined if non-steroidal anti-inflammatory drugs (NSAIDs) were a potential mediator of the association between OA and premature mortality; in this

study NSAIDs were included as a confounder. In the WOS, NSAIDs were associated with both OA and premature mortality but some studies have implicated NSAIDs in mortality from CVDs in those with OA (Atiquzzaman et al., 2018; Bavry et al., 2011; Trelle et al., 2011). Both Barbour et al. (2015) and Liu et al. (2017) found that NSAID use was not a significant mediator of the relationship between OA and premature mortality. Liu et al. (2017) included very small numbers in their analysis (63 participants with 15 deaths), leading to insufficient power for calculations. Barbour et al. (2015) had a much larger population included in the mediation analysis (n= 7889) and still found NSAIDs to be an insignificant mediator. In the study described in this thesis, NSAIDs were used as a confounder and adjusted for in the multivariate analysis. Moreover, the use of drugs, like NSAIDs, as a mediator could be seen as inappropriate: NSAIDs may be best included as an effect modifier. An effect modifier is when the magnitude of the effect of the exposure on the outcome differs depending on the level of a third variable (Szklo and Nieto, 2018). If the relationship between OA and premature mortality was significantly different in those taking NSAIDs compared to those not taking NSAIDs, it could be considered an effect modifier. These studies did not discuss this, and effect modification was not investigated in this thesis. Although NSAIDs were included as a categorical covariate in Chapter 4, they were dichotomised into yes and no for the sake of the mediation analysis in Chapter 5. The dichotomisation of the data loses information about the amount of NSAID prescriptions a participant has had but was necessary for the analysis. Based on the previous studies, including NSAIDs as a confounder seemed to be justified: NSAIDs have not been found to mediate the relationship between OA and premature mortality in other prospective cohort studies.

Depression was also found to be a significant mediator between all anatomical definitions of disabling OA and premature mortality. Although no other study has examined depression as a mediator, the importance of comorbid depression and OA on the association with mortality has been previously investigated. In comparison to OA alone, comorbid depression and OA increased the risk of mortality with an age adjusted mortality rate of 3.03% (95% CI 2.18, 3.88; Lee et al., 2007). Lee et al. (2007) did not examine the pathways between OA and premature mortality via depression. Smith and colleagues (2018) reported that depression was a significant mediator of the association between 'troubling pain' and premature mortality in the English Longitudinal Study of Ageing, although this is not specifically OA related pain, it supports the findings from the study in this thesis.

Low social participation was found to be a significant mediator of the association between OA with pain interference and premature mortality. No previous studies have examined OA and premature mortality mediated by low social participation. A previous study has examined both activity limitation and depression as mediators in the relationship between OA physical symptoms and social participation (Machado, Gignac and Badley, 2008). Reduced walking frequency and low mood can reduce both ability and motivation to take part in society (Ball et al., 2007; Sharma et al., 2003) and both reduced walking frequency and depression are associated with OA, as discussed in 5.3.1 and 5.3.2. The Cox proportional hazard modelling used in this thesis could not account for more than one step mediation, and therefore the hypothesis that reduced social participation from OA is itself caused by depression and reduced walking frequency could not be tested.

Overall, the low walking frequency, depression and low social participation were significant mediators of the association between OA and premature mortality, regardless of anatomical site.

6.4 STRENGTHS AND LIMITATIONS

Each of the constituent studies included in this thesis have a variety of strengths and limitations. The main strengths and limitations have been discussed in the corresponding chapter to each study. However, some common strengths and limitations are discussed below.

6.4.1 The NorStOP cohort

NorStOP is an established cohort, with a census date seven years prior to the analysis in this thesis. The main strengths of NorStOP include that it has collected data on a wide array of self-reported factors which have been combined with both primary care medical record data and mortality data from the Office for National Statistics. NorStOP provides the opportunity to investigate lots of different health outcomes in older adults and their potential socio-demographic and behavioural determinants. However, data analysis of an existing cohort is not optimal for answering research questions in comparison to a cohort designed to specifically answer the research question. A limitation of this work was that the diagnosis of OA was not always established prior the measurement of the mediator; the predictor variable should be measured prior to the mediator (Kline, 2015). In a cohort designed specifically for a mediation analysis, this would be an essential part of the protocol, but it was not in NorStOP. However, as OA is a longstanding, gradually progressive chronic condition, it was assumed that a

clinician-established diagnosis at any point during the study period implied that OA was likely present at least to some degree during the entire period of observation.

There were also be confounders of the association of OA and mortality that have not been included in this study. Other medication other than NSAIDs may confound the relationship between OA and premature mortality. Using a combination of self-report disease and diseases on the primary care medical records could help validate the self-report methods used. An example of this is the use of self-reported cardiovascular disease (CVD) and ischaemic heart disease (IHD) from the primary care medical records used in this study. The data was not available to confirm other diagnoses in other covariates in this way. Medication records could also support confounder ascertainment; in medications prescribed for a specific disease, such as anti-hyperglycaemic drugs in diabetes, this would confirm the disease following self-report.

Information on cause of death was not available on this study. Other studies have examined the link between OA and cause-specific mortality (e.g. mortality due to CVD) or attributed the mortality from OA to CVD (Hochberg, 2008; Turkiewicz, Kiadaliri and Englund, 2019). As discussed below, only one step mediation is possible using the mediation technique used in this study; finding cause-specific mortality within NorStOP may help illuminate the pathway from the proposed mediators to mortality. However, the reduced cost and efficiency of using an existing cohort, especially for the purpose of this thesis, means that the limitations are outweighed by the strengths of the NorStOP cohort. In addition, a key strength of this study is the identification that walking frequency is a key mediator which may also reduce the incidence and progression of other comorbidities such as cardiovascular disease and the subsequent

mortality; this indicates the need to focus on key modifiable targets and not only the morbidity.

The age and sex distribution within the NorStOP population were found to be similar to both the North Staffordshire area and England and Wales in 2001 (Office for National Statistics, 2001; Thomas et al., 2004b). Furthermore, the general health of the NorStOP cohort was similar to another cohort from the same time period in a different part of the UK (Pettit et al., 2001). However, this data may not be representative of international populations. Moreover, in the 17 years since NorStOP began collecting data, the population of the UK has changed dramatically. Between 2001 and 2017 the population of the UK had increased by approximately 12.2%; the largest increase in the population in this time period was in the over 65 group, with the total percentage of the population over 65 increasing from 16% to 18.2% (Office for National Statistics, 2001, 2017). As this study included age as a covariate, the effects of this are likely to be small. Between 2001 and 2011 the percentage of people identifying as 'White British' in the UK population had reduced from 85.6% to 80.5% (Office for National Statistics, 2001, 2011). Data closer to the present day is not available, however it is predicted that this reduction in the 'White British' population will continue at the next census date in 2021 (Wohland et al., 2010). This therefore makes the population of NorStOP different to current and future population of the UK. These results may therefore not be generalisable to the present day. However, there is no evidence that association between OA and premature mortality is different by ethnicity, therefore this is also unlikely to have an effect of the results presented in this thesis.

6.4.2 Mediation analysis

This study identified factors that mediated the association between OA and premature mortality. This novel analysis allows insight into the relationship between OA and premature mortality. As alluded to in Section 6.3, this method of mediation analysis, using Cox proportional hazard models, only allows for a one step mediation process. However, a single mediator is unlikely to be the only mediator on a specific pathway between OA and premature mortality. For example, OA leads to reduced walking frequency which could then cause depression, reduce social participation or worsen an existing co-morbidity which then leads to premature mortality. The proposed pathways for mediation analysis are based on theoretical events over time in a sequence that is conceivable. For example, the suggested pathway is that OA leads to reduced walking frequency which in turn leads to premature mortality. However, the converse relationship between OA and walking frequency is also true; that reduced walking frequency leads to OA (Leong and Sun, 2014). It is difficult to test models of relationships that involve feedback loops (Streiner, 2005). The models have therefore been overly simplified for the analysis, highlighting a further limitation of this study.

The individual study of mediators gives no information about the influence of mediators on each other and is therefore a limitation of this study. Other studies have proposed that premature mortality as a result of OA is a caused by CVD (Hochberg, 2008; Turkiewicz, Kiadaliri and Englund, 2019). To test this would require a two-step mediation pathway, which is currently not possible (discussed below).

6.5 IMPLICATIONS FOR CLINICAL PRACTICE AND RESEARCH

6.5.1 Implications for practice

The high prevalence of OA and the ageing UK population means that the increased risk of mortality affects a large and increasing number of people over the coming years. Chapter 1 highlighted the import risk factors in the aetiology of OA. One of the most effective ways of reducing mortality from OA is therefore to minimise the progression of OA in the first place. Increasing physical activity and losing weight can help reduce the onset and progression of OA; there are therefore both primary and secondary prevention strategies (Cooper et al., 2001; Leong and Sun, 2014). Chapter 4 showed that simply having OA on the medical record or reporting joint pain was not significantly associated with premature mortality; only disabling OA was. As listed in the most recent National Institute for Health and Care Excellence (NICE) guidelines providing patient education about weight-loss, exercise and managing co-morbidities reduces the progression of OA and helps to manage OA symptoms (NICE, 2014). The studies in this thesis have found the impact of OA causes premature mortality. The sequalae of disabling OA (reduced walking frequency, depression and low social participation) cause premature mortality. This is an important consideration in primary care settings; both reducing the progression and impact of OA is key to reducing premature mortality. Patients presenting with OA should be flagged up and monitored accordingly to reduce the risk of death from OA.

Each of the mediators included were chosen as they are amenable to primary care, where the vast majority of OA is managed (Dziedzic et al., 2009). The findings from this thesis indicate that interventions targeting physical activity, particularly frequent

walking, are important in reducing premature mortality as a result of OA. Although patients may worry that physical exercise can exacerbate their OA pain, the opposite is true. A Cochrane review found that physical activity can be as effective as NSAIDs in reducing pain from OA (Fransen et al., 2015). Furthermore, low or moderate intensity exercise, including walking, have been found to reduce the symptoms of OA (Bosomworth, 2009). Public Health England currently recommends that GPs are familiar with local physical activity schemes such as 'Walking for Health', which provides 1800 guided walking groups across England designed for older adults (Public Health England, 2018). Walking group interventions would also increase social participation, and therefore simultaneously target two of the mediators found in this study.

Despite physical activity being a key intervention in the management of OA, qualitative research has shown that GPs felt that giving specific advice on physical activity was outside of their expertise and remit (Din et al., 2015). Within the UK there are some physical activity programmes for clinicians to refer patients to, but often these are on a local scale or disease specific, such as for cardiac rehabilitation (Bethell, Lewin and Dalal, 2009; Murphy et al., 2012). Outside of the UK, guidance from the Swedish National Institute of Public Health provides a comprehensive guide for primary care clinicians to advise patients on physical activity for various diseases (Swedish National Institute of Public Health, 2010). This guide focuses on multiple different diseases, including OA. For OA it recommends different levels of physical activity from walking to dancing dependent on the patient's co-morbidities. No such

guide currently exists in the UK; this may partly explain why GPs struggle to give advice on physical activity.

There is an increased focused on the role of Allied Health Professionals (AHPs) within primary care, through schemes such as First Contact Practitioners (Chartered Society of Physiotherapy, 2019). This scheme aims for patients with musculoskeletal (MSK) problems, to see a physiotherapist in primary care rather than a GP. The scheme aims to include self-management advice, social prescribing, and information about physical activity and fitness for work (Chartered Society of Physiotherapy, 2019). This scheme currently is designed for acute problems, but there is scope to develop this service into chronic diseases, like OA, in the future. Physiotherapy both reduces pain and improves function in patients with OA and is therefore an important intervention on the pathway between OA and premature mortality (Page, Hinman and Bennell, 2011).

Previous studies have examined exercise referral schemes that aim to increase physical activity in adults. However, a narrative review showed that exercise referral schemes had a small effect on increasing physical activity in sedentary adults, due to poor compliance and high dropout rates (Nguyen et al., 2016). The mortality data included in this thesis may provide some patients with motivation to comply with physical activity; in a review of communicating risk information, 'loss framed' information (such as giving a mortality risk) was found to be more effective than 'gain framed' information (such as saying exercise will reduce joint pain) in changing a patient's behaviour (Edwards et al., 2001). Furthermore, the mediators found in this study give patients a target to reduce their risk of mortality.

The study in this thesis has also highlighted the importance of assessing mental health in patients with OA. Depression in those with OA is associated with more severe joint pain (Lin, 2008). Therefore, interventions to stop the progression of OA are also likely to reduce low mood as a result of OA. Depression is usually managed via psychological and pharmacological therapy, with some evidence that physical activity can alleviate depressive symptoms (Cooney et al., 2013; NICE, 2009). Identifying and managing low mood in patient with OA is a key factor in reducing premature mortality as a result of OA.

Increasing social participation is a key factor in reducing mortality from OA. Barrier to social participation include difficulty moving and low mood, and therefore interventions to reduce depression and increase physical activity may be effective in increasing social participation. Social prescribing (linking patients from primary care to community services) may be key to improving social participation (Bickerdike et al., 2017). There are lots of different community schemes available, including exercise based schemes, arts based schemes and education based schemes, that could provide opportunities for older adults to both become more involved in their community and to reduce their risk of mortality as a result of OA (Thompson, Camic and Chatterjee, 2015).

6.5.2 Areas for future research

As discussed above, one limitation of this study is that the time line between exposure, mediator and outcome may not have occurred as hypothesised. For example, this study hypothesises that OA leads to reduced walking frequency which leads to premature mortality. However, reduced walking frequency may have led to

OA in the first place (Leong and Sun, 2014). One potential future research area would be a prospective cohort study, designed to identify mediators after the onset of OA with participant follow-up until death. This would be a very time consuming and expensive study; it would require recruiting participants prior to developing the symptoms of OA at a young age and following them up repeatedly over 30-40 years until their death with repeated questionnaires. This study does not seem feasible due to the large sample size that would be required, the cost and attrition bias. Another option would be to use the Clinical Practice Research Datalink (CPRD) to establish the date of OA diagnosis and a group without OA diagnosis. The database could then be examined for potential mediators diagnosed after that date, and mortality ascertained. This would be a faster and cheaper way of conducting a large study with a representative sample of the UK population. However, different case definitions of OA would not be available using this method nor would clear measurement of mediators (e.g. social participation or how often per week people walk for five to ten minutes or more). Given a key finding from this study is that it is 'OA with pain interference' that is associated with premature mortality, at present there is no clear method for identifying pain interference in CPRD. The findings suggest that a combination of patient reported data and medical record data enhances the understanding of the impact of OA.

Development of the technique of performing mediation analysis within a Cox proportional hazard model would be valuable. It would be useful to examine a two-step mediation process (discussed above). The two step mediation pathways in this

case may be that OA leads to reduced walking frequency, which in turn causes CVD and then premature mortality.

Finally, the significant mediators found in this study present a target to tailor an intervention. A study designed to increase walking frequency could recruit those identified as having OA with pain interference from primary care into a physical activity group. A personalised activity programme could be delivered to ensure participants increase their physical activity within their personal abilities. These participants could then be followed up until death to assess mortality in comparison to those without the intervention. As discussed above, studies with physical activity interventions tend to have high dropout rates.

6.6 CONCLUDING MESSAGES

OA is the most common joint condition and the number of adults with the condition is expected to increase in the future due to an ageing population and an increase in the prevalence of risk factors. It is now considered to be a serious disease and there is increasing interest in its links with mortality. **This study identified that OA is associated with mortality when it is disabling.** It also identified that **anatomical site does not impact on mortality**; whether OA is disabling or not is the key**.** Targets for **reducing mortality for people with disabling OA are increasing walking frequency and social participation and reducing depression.**

APPENDIX 1: SEARCH CRITERIA FOR SYSTEMATIC SEARCH 1

1. Osteoarthritis/
2. Osteoarthr*.kw,ab,ti
3. OA.kw,ti,ab
4. Arthrit*.ti,ab
5. Joint pain.ti,ab
6. 1 OR 2 OR 3 OR 4 OR 5
7. Mortality/
8. Mortalit*.kw,ti,ab
9. Premature mortality.ti,ab
10. Death.ti,ab
11. 7 OR 8 OR 9 OR 10
12. Systematic review.kw,ti,ab
13. Systematic.ti,ab
14. Review.ti,ab
15. 12 OR 13 OR 14
16. 6 AND 11 AND 15

APPENDIX 2: SEARCH CRITERIA FOR SYSTEMATIC SEARC

1. Osteoarthritis/
2. Osteoarthr*.kw,ab,ti
3. OA.kw,ti,ab
4. Arthrit*.ti,ab
5. Joint pain.ti,ab
6. 1 OR 2 OR 3 OR 4 OR 5
7. Mortality/
8. Mortalit*.kw,ti,ab
9. Premature mortality.ti,ab
10. Death.ti,ab
11. 7 OR 8 OR 9 OR 10
12. 6 AND 11

APPENDIX 3: COMPONENTS OF 'HEALTH SURVEY' QUESTIONNAIRE

Concept	Measurement Method	Details
Perceived general health	12 Item Short-Form Health Survey (SF-12) (Ware et al., 1996)	Physical and mental component summary scores
Anxiety and depression	Hospital anxiety and depression scale (HADs) (Zigmond and Snaith, 1983)	Anxiety and depression sub-scales
Demographic characteristics	Date of birth, gender	-
	Marital status	Single, married, divorced, widowed, cohabiting
	Living arrangements	Alone, not alone
	Ethnic origin	White, afro caribbean, chinese, asian, african, other

APPENDIX 3: CONTINUED…

Concept	Measurement Method	Details
Occupational Characteristics	Current employment status	Employed, not working due to ill health, seeking employment, retired, housewife, other
	Current or recent job title	-
	Socio-economic classification	Using Standard Occupational Classification (Office of National Statistics, 2002)
	Educational attainment	
Anthropometric characteristics	Self-reported weight	-
	Self-reported height	-

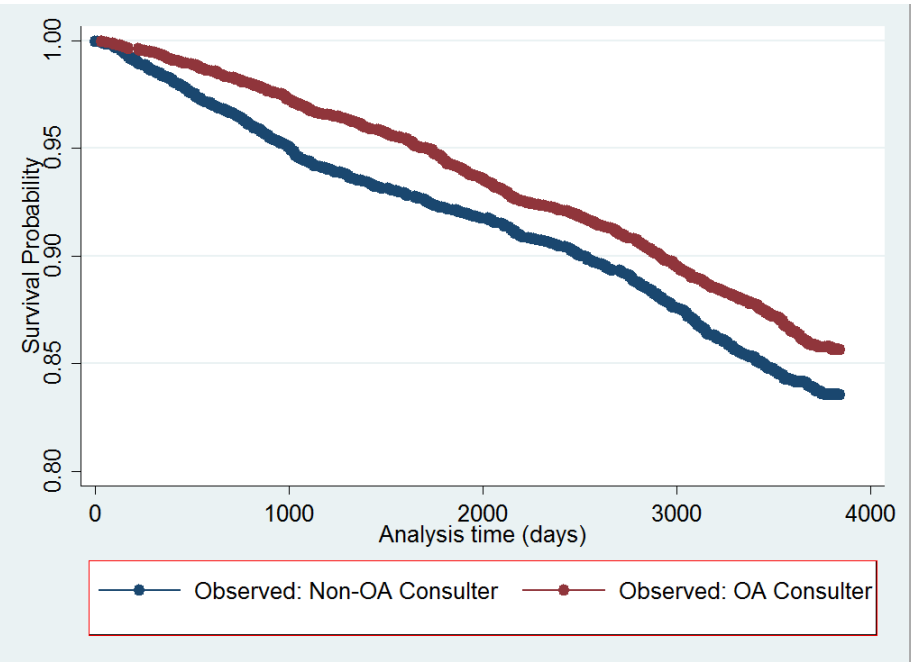
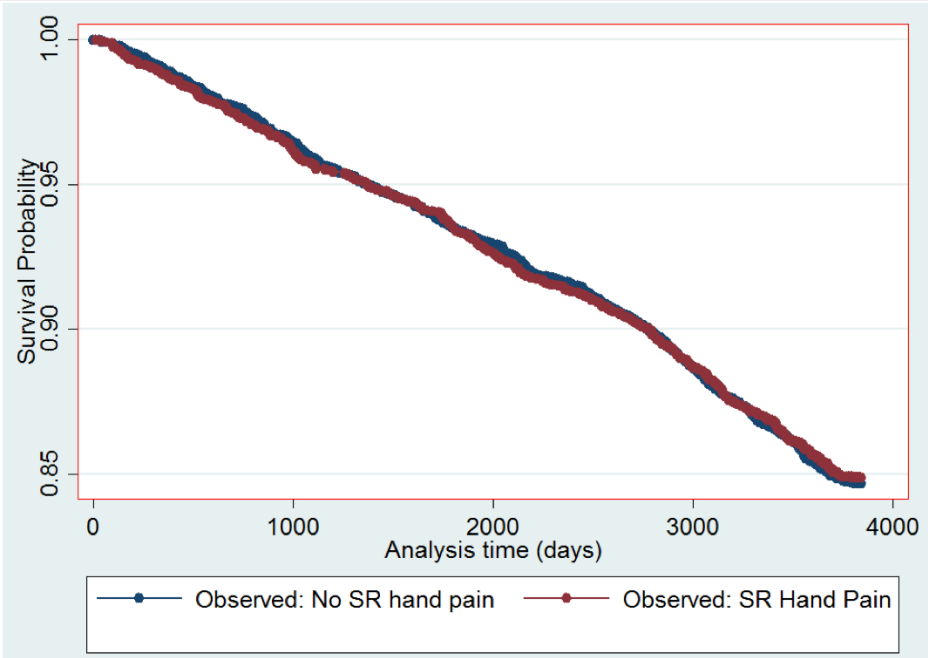
APPENDIX 3: CONTINUED…

Concept	Measurement Method	Details
Lifestyle characteristics	Alcohol intake	Daily, weekly, monthly, annually, never
	Smoking status	Current, previous, never
	Income adequacy	Strain, need to be careful, can manage, comfortably, well off
Comorbidities	Self-reported chest problems, heart problems, deafness, eyesight, raised blood pressure and diabetes	-
Symptoms	Falls, memory difficulties, cough with spit, breathless when walking, dizziness, weakness in arms/legs	In the last 3 months
Cognition	Functional Limitations Profile (FLP) (Bergner et al. 1981)	Alertness subscale form

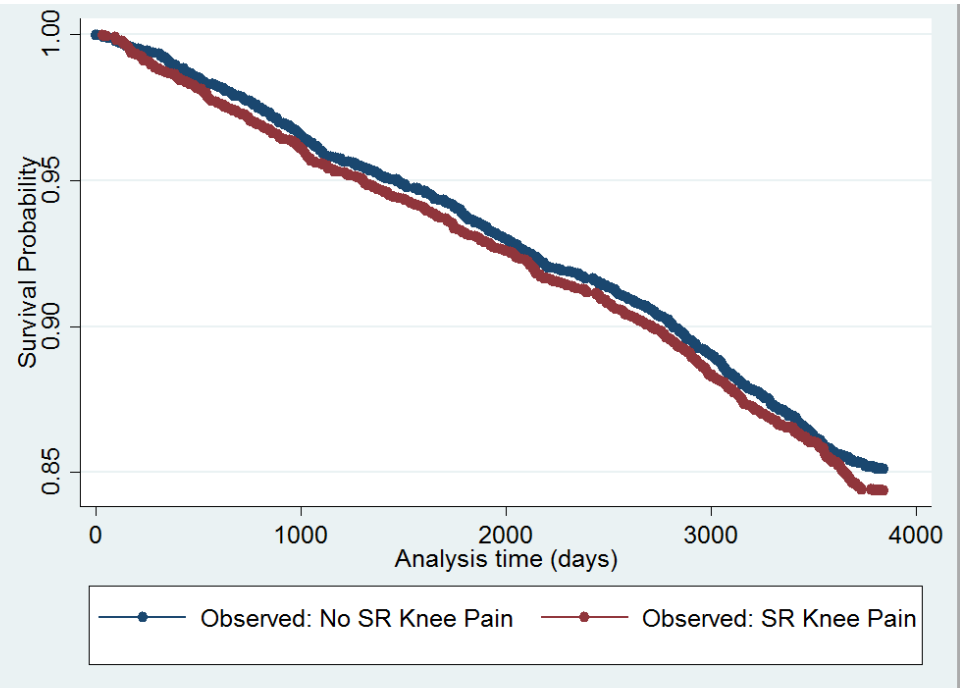
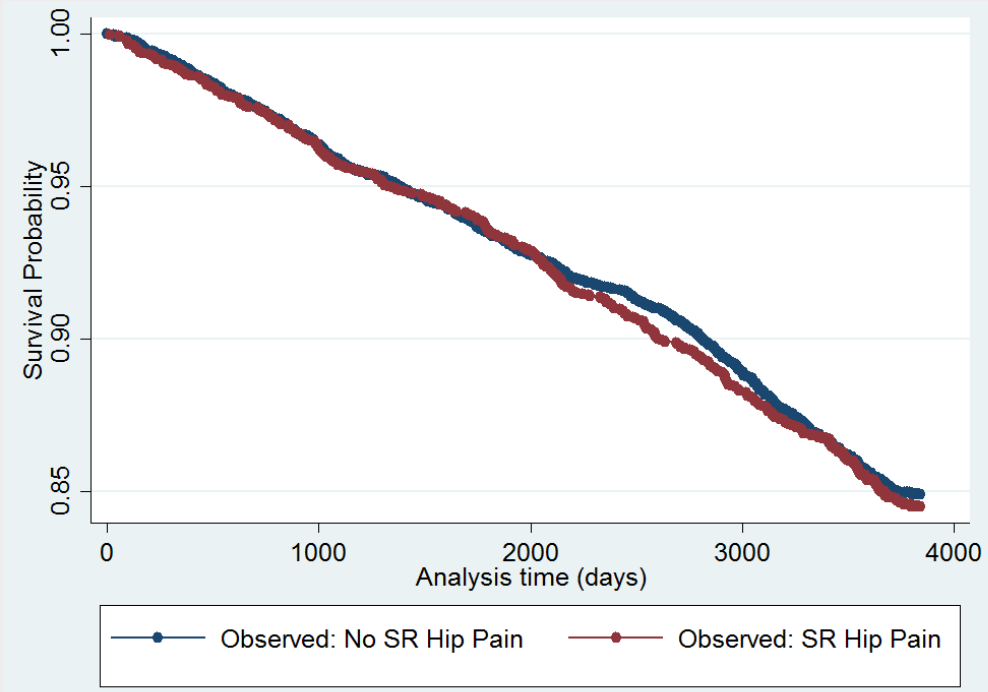
APPENDIX 3: CONTINUED…

Concept	Measurement Method	Details
Sleep Problems	Four Items Self Report Scale (Jenkins et al. 1988)	-
Bodily pain	Self-completed manikin	"In the past 4 weeks have you had pain that has lasted for one day or longer in any part of your body?"
	Specific site questions	"Have you had any problems in your hands or pain in your hands/knees/hips/feet in the last year?
Medication use	Painkillers, creams, natural medicines	Usage in past 4 weeks – daily, most days, some days, few days, no days
Physical function	MOS Short Form-36 (Ware and Sherbourne, 1992)	-
Consent	For both further contact and to check GP records	-

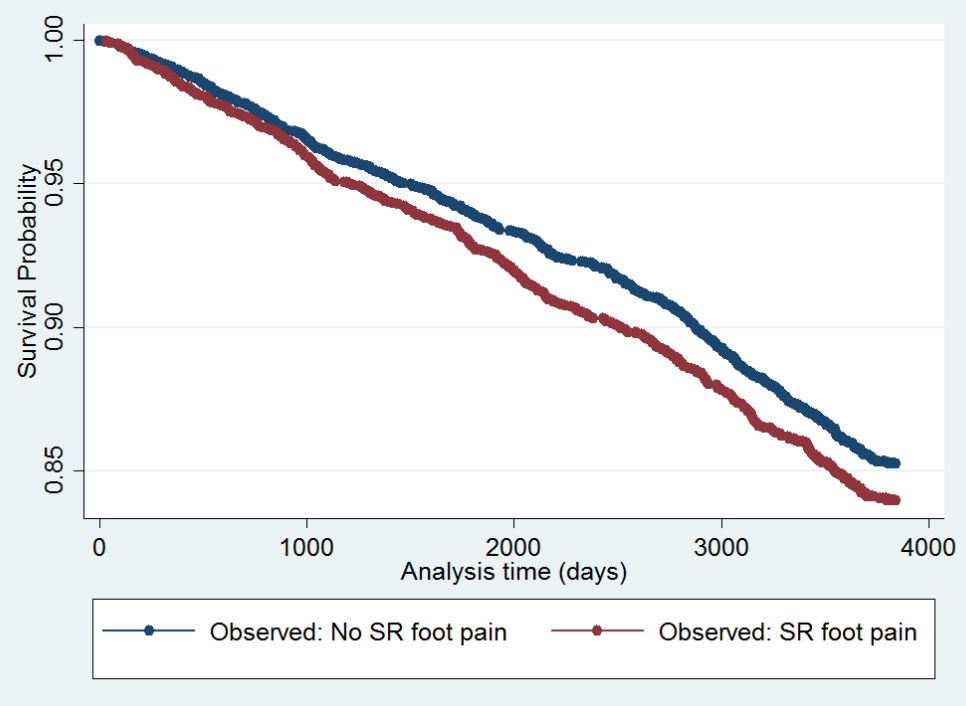
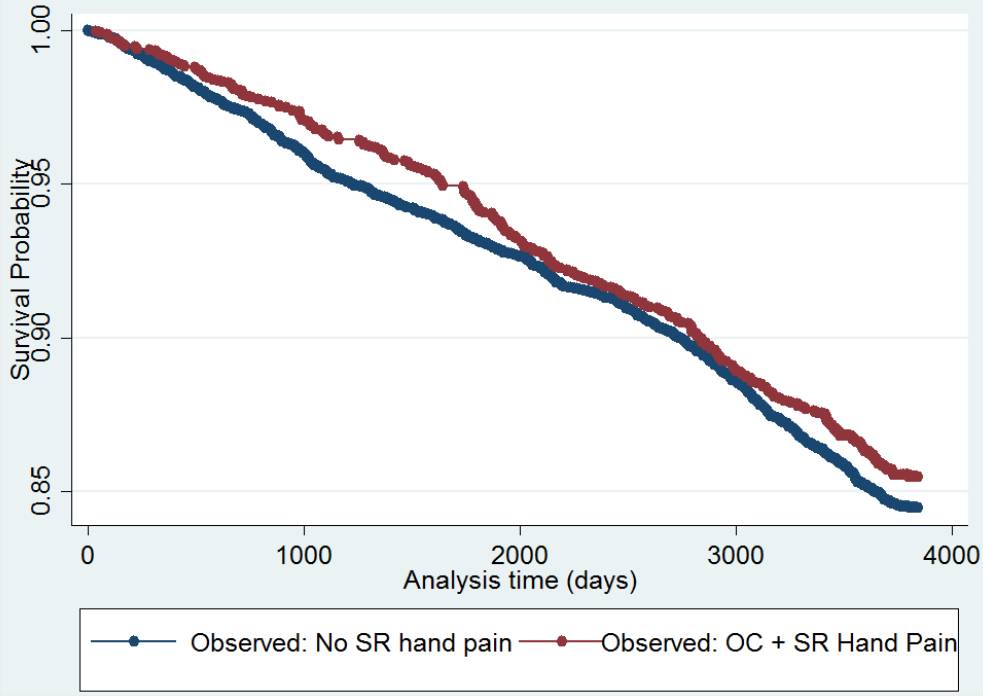
APPENDIX 4: KAPLAN MEIER CURVES FOR EACH OSTEOARTHRITS CASE DEFINITION

Definition	Kaplan Meier Curve
OA Consulter	
Self-reported hand pain	

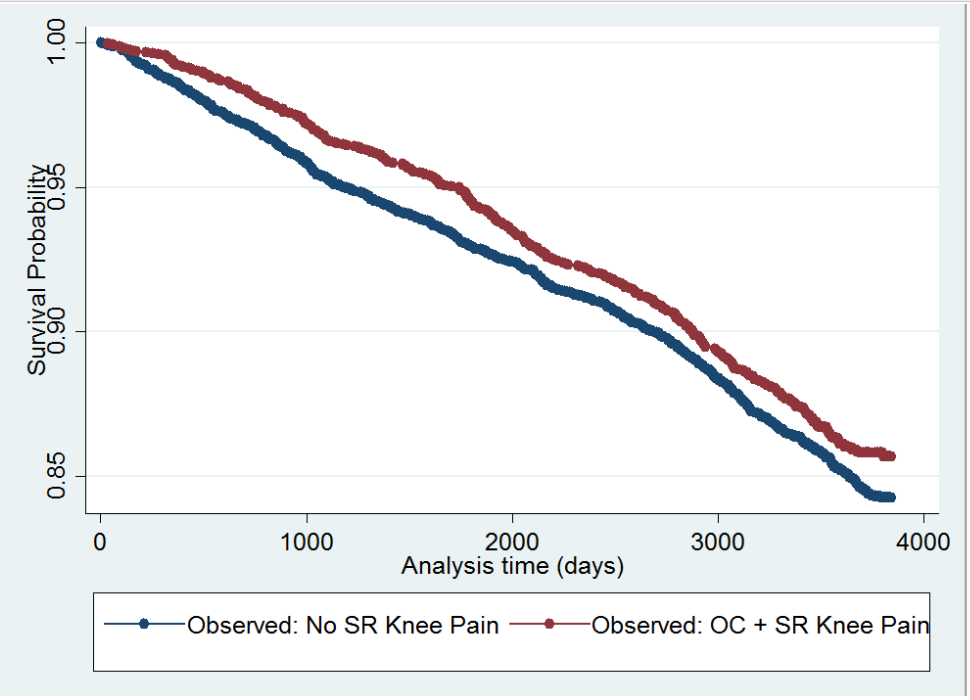
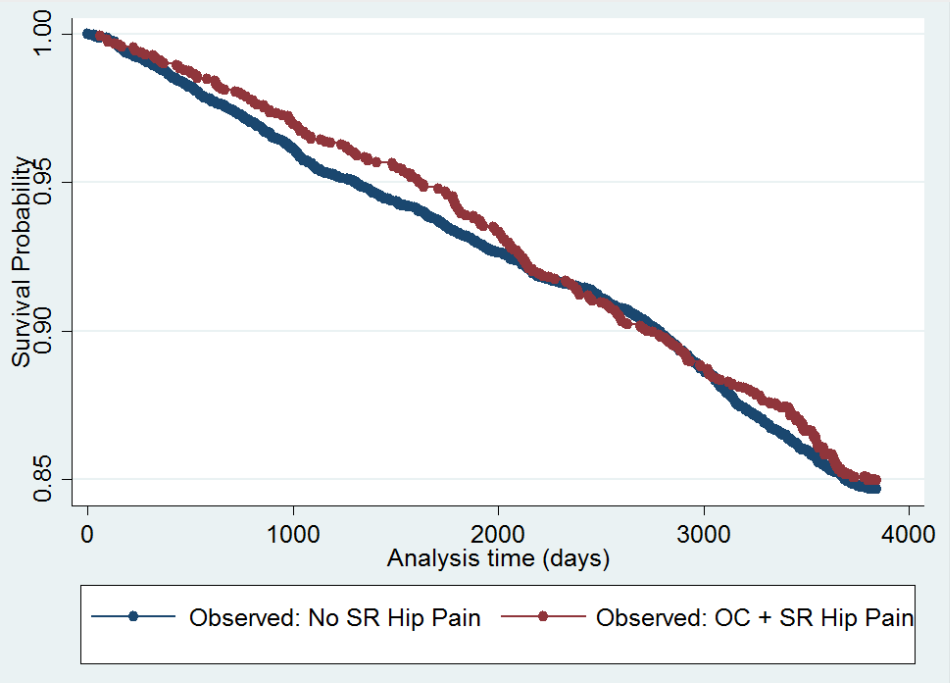
APPENDIX 4: CONTINUED…

Definition	Kaplan Meier Curve
Self-reported knee pain	
Self-reported hip pain	

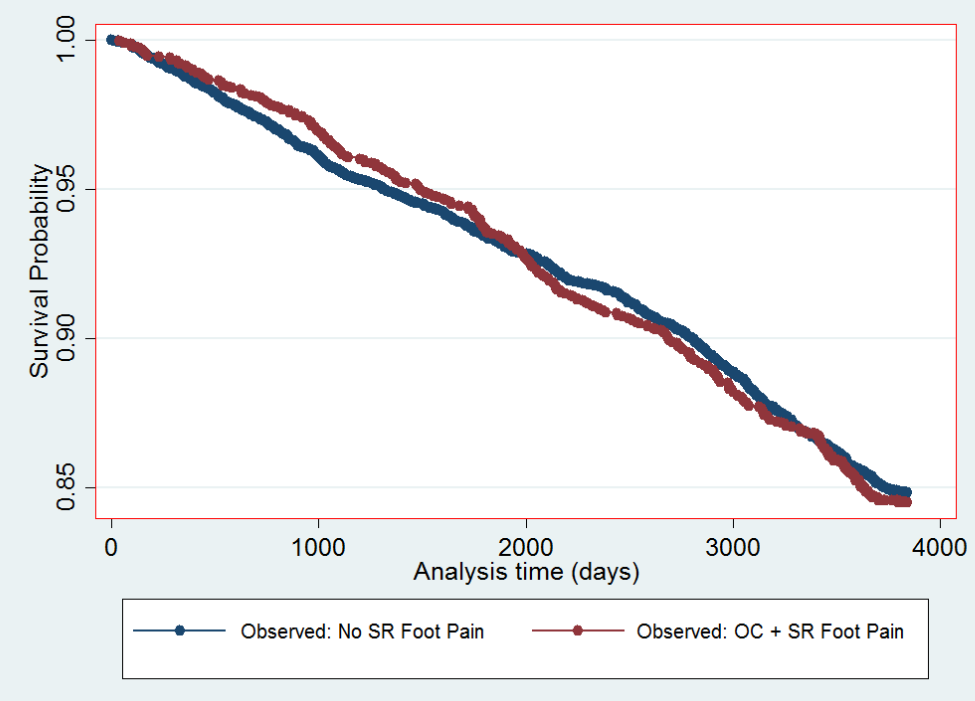
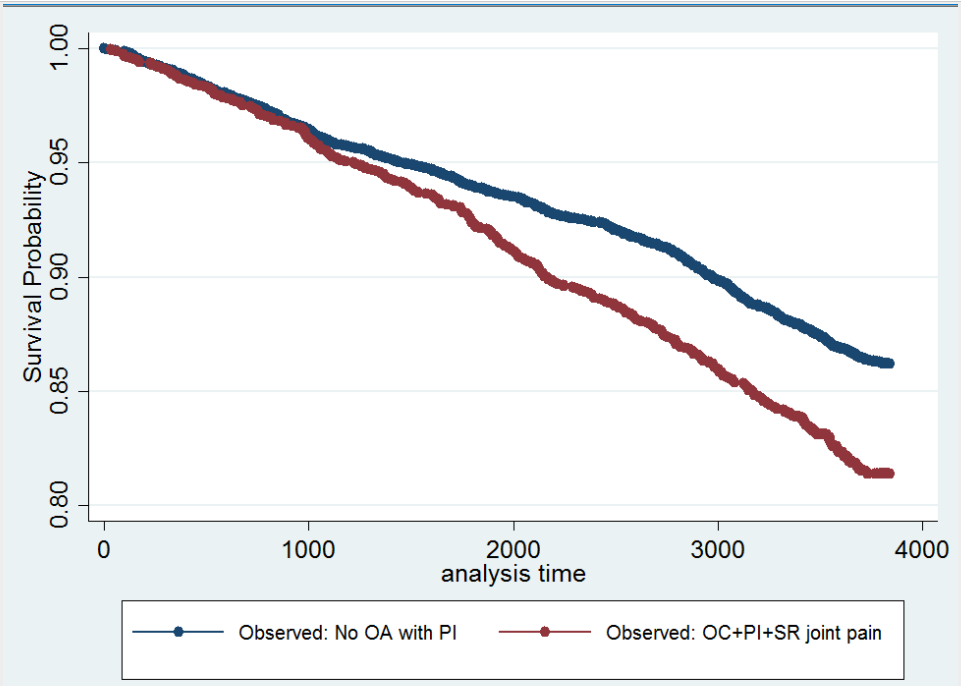
APPENDIX 4: CONTINUED…

Definition	Kaplan Meier Curve
Self-reported foot pain	
Symptomatic hand OA	

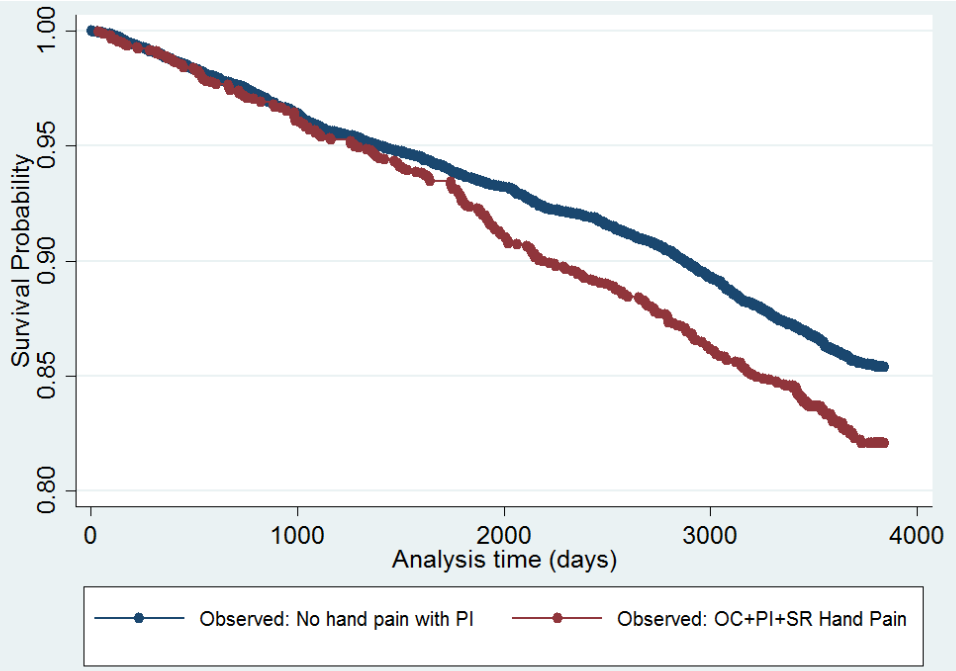
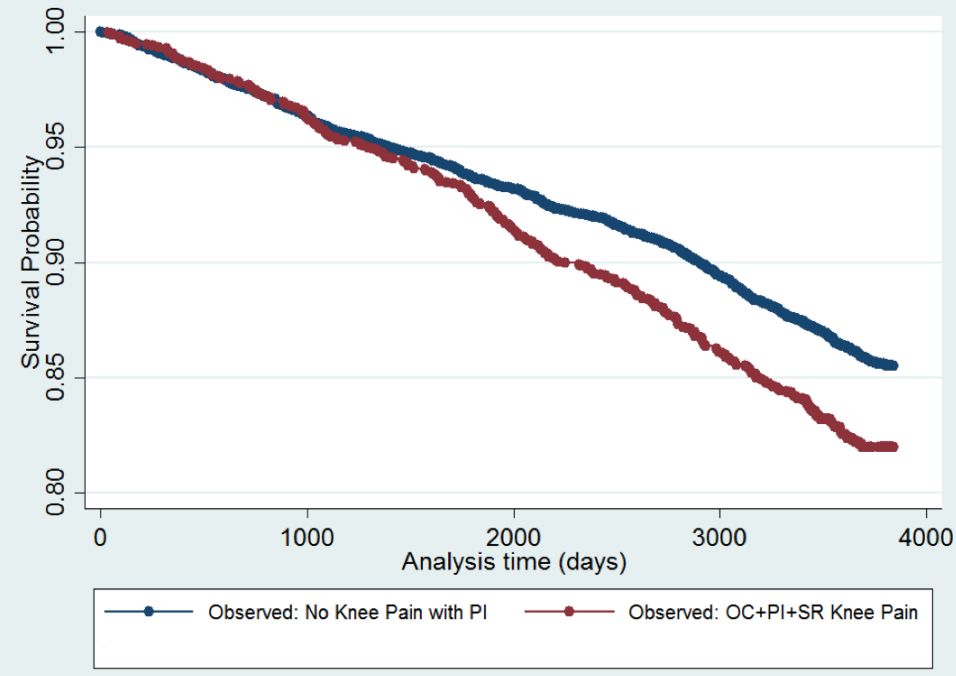
APPENDIX 4: CONTINUED…

Definition	Kaplan Meier Curve
Symptomatic knee OA	
Symptomatic hip OA	

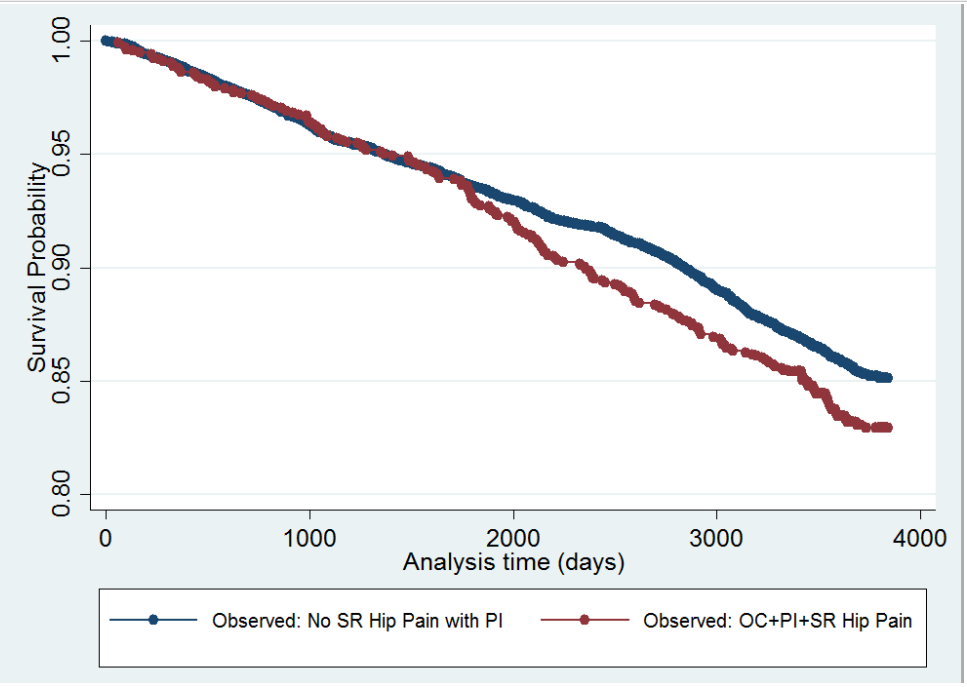
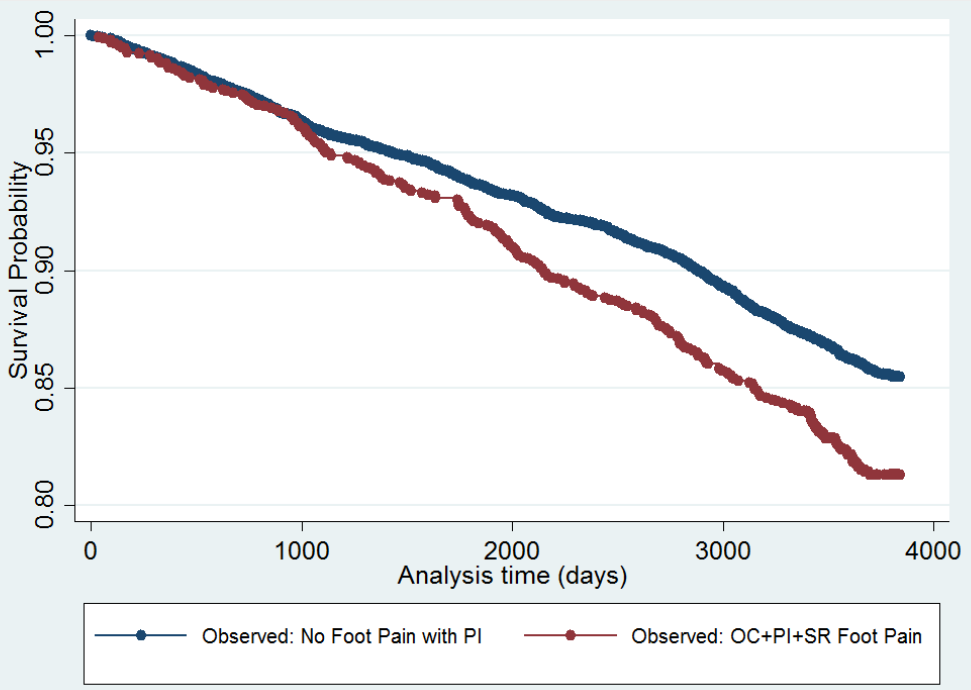
APPENDIX 4: CONTINUED…

Definition	Kaplan Meier Curve
Symptomatic foot OA	
Disabling OA	

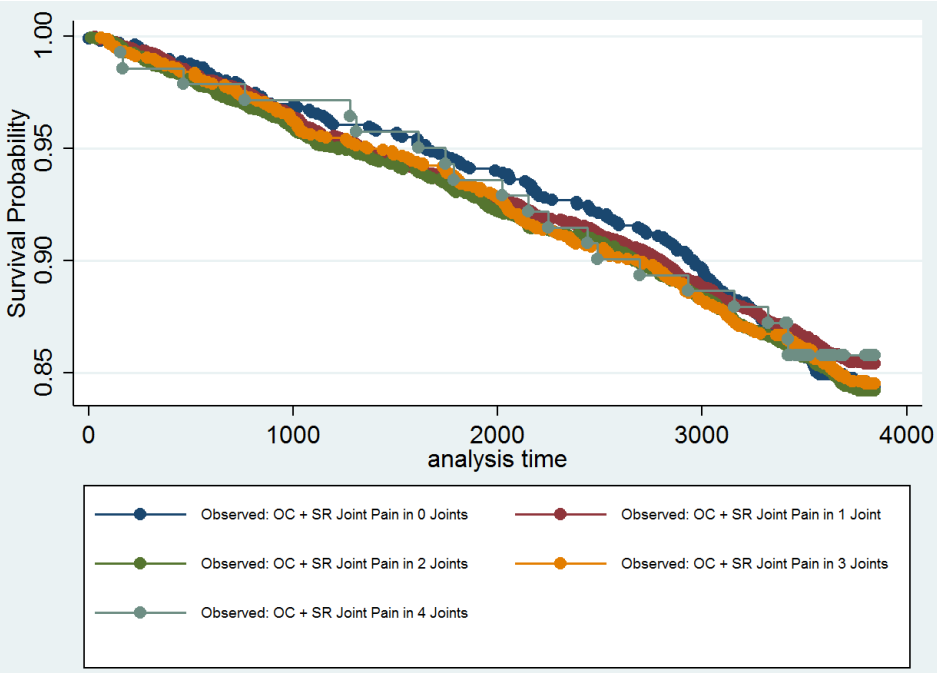
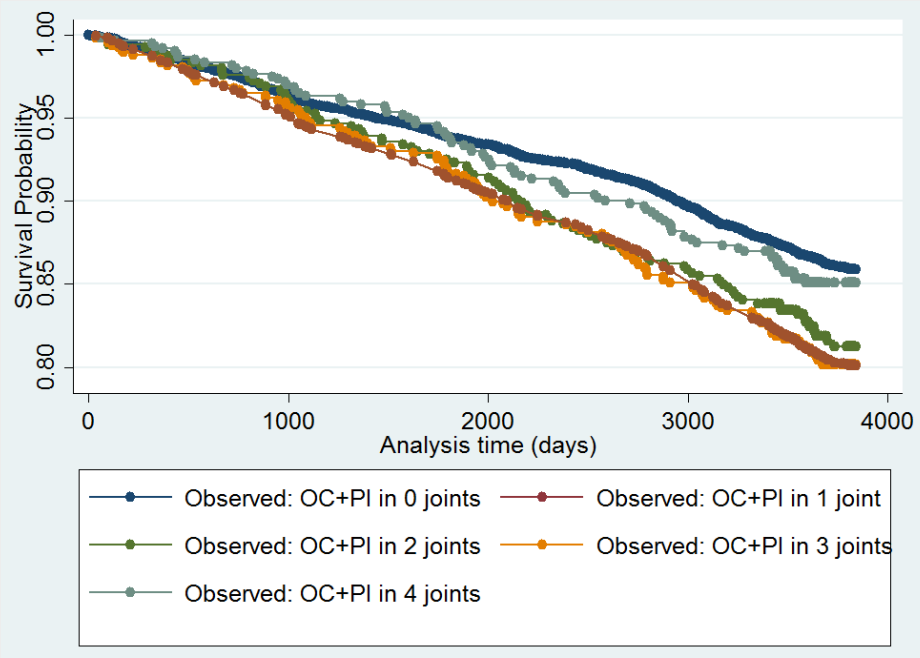
APPENDIX 4: CONTINUED…

Definition	Kaplan Meier Curve
Disabling Hand OA	
Disabling Knee OA	

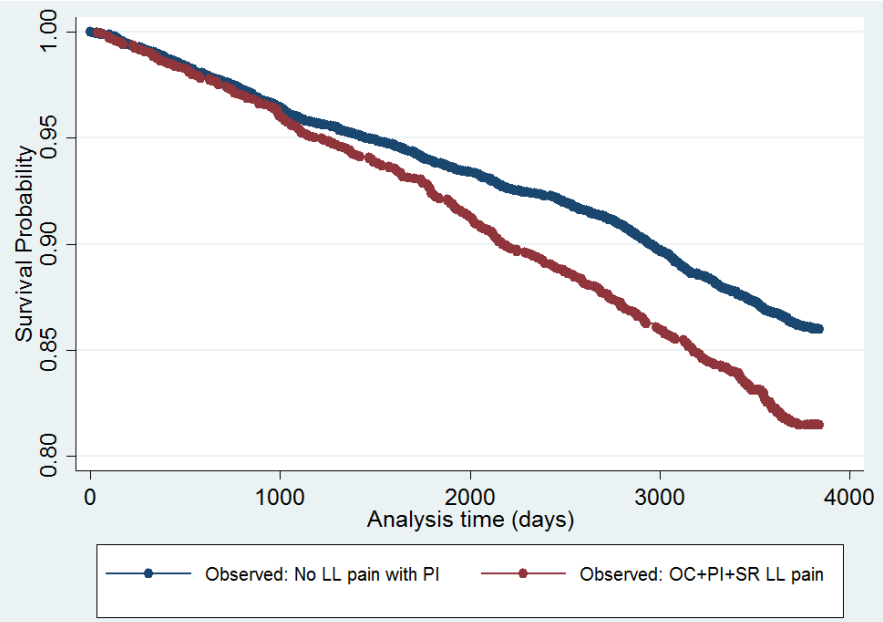
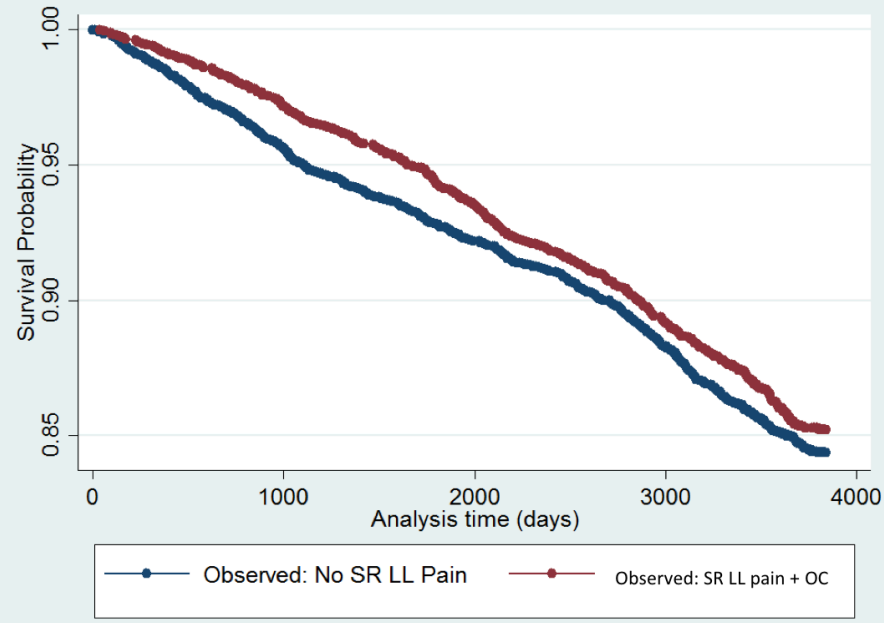
APPENDIX 4: CONTINUED…

Definition	Kaplan Meier Curve
Disabling Hip OA	
Disabling Foot OA	

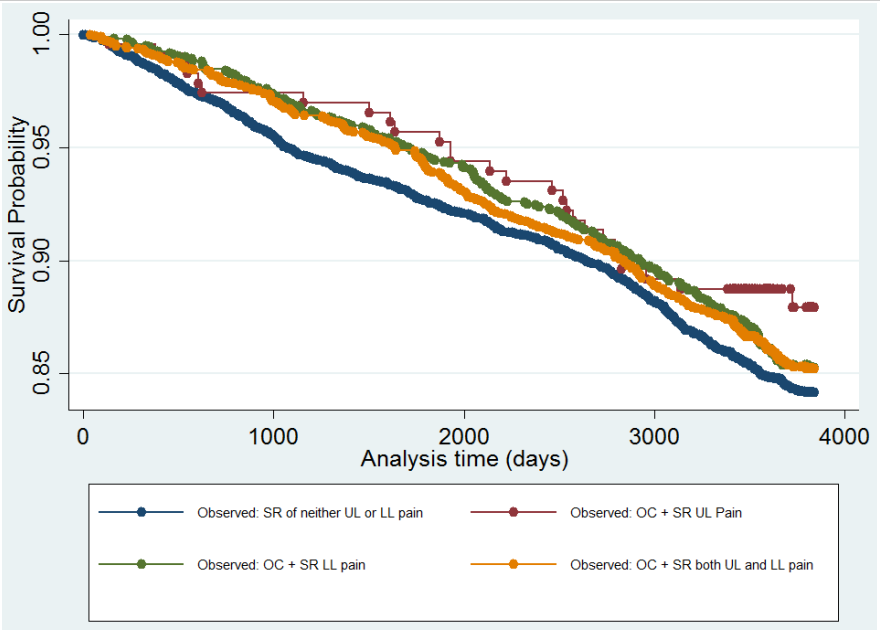
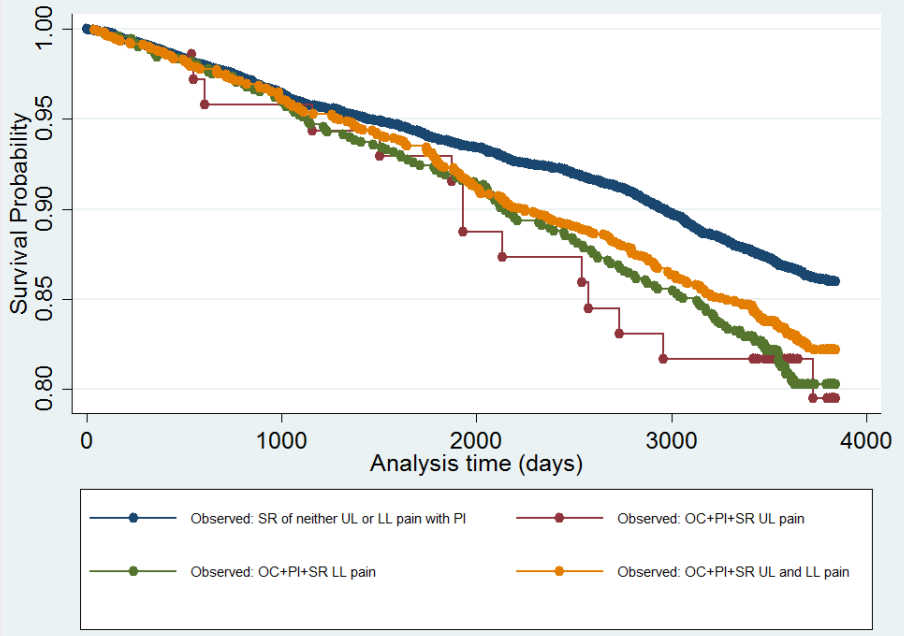
APPENDIX 4: CONTINUED…

Definition	Kaplan Meier Curve
Number of anatomical areas affected by symptomatic OA	
Number of anatomical areas affected by disabling OA	

APPENDIX 4: CONTINUED…

Definition	Kaplan Meier Curve
Disabling lower limb OA	
Symptomatic lower limb OA	

APPENDIX 4: CONTINUED…

Definition	Kaplan Meier Curve
Symptomatic upper limb OA, lower limb OA and combined upper and lower limb OA	
Disabling Symptomatic upper limb OA, lower limb OA and combined upper and lower limb OA	

Abbreviations: OA (Osteoarthritis) SR (self-reported), OC (OA Consulter), PI (pain interference), UL (upper limb), LL (lower limb)

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