The Influence of Multimorbidity on the Management of Patients with Hip Osteoarthritis

A dissertation submitted to the University of Oxford in partial fulfilment of the requirements for the degree of

Doctor of Philosophy in Musculoskeletal Sciences



Rory James Ferguson

Oriel College

2021

Abstract

Background & Aims

Osteoarthritis of the hip is a major cause of pain and disability worldwide. There is no successful disease modifying therapy, and treatment primarily consists of pain management with total hip replacement for advanced symptomatic disease. The success of total hip replacement may be evaluated through of a number of complementary outcomes, including the risks of complications, the need for further surgery, and the improvement in pain, function and quality of life.

Multimorbidity is associated with increased risks and reduced benefits of a range of elective surgical procedures. Evidence on the influence of multimorbidity on the outcomes of total hip replacement specifically, however, remains limited. Patients with hip osteoarthritis and concurrent multimorbidity, and their clinicians, must decide whether to proceed with total hip replacement without personalised information available to them on the likely risks and benefits of surgery. This lack of information may lead to worse health outcomes, with the uncertainty increasing decisional anxiety and regret. It is unknown how such patients are currently managed.

The aim of this thesis was to investigate the influence of multimorbidity on the rate of patients with hip osteoarthritis receiving total hip replacement and, in those patients receiving surgery, the influence of multimorbidity on the outcomes of surgery.

Methods & Results

Following a validation of diagnostic codes for hip osteoarthritis, a cohort study was performed using data from the Clinical Practice Research Datalink (CPRD) to investigate the influence of multimorbidity on whether patients with hip osteoarthritis and concurrent multimorbidity receive total hip replacement in the UK. Multimorbidity was measured in five different ways: (1) Charlson Comorbidity Index, (2) a count of chronic diseases, (3) a count of medications prescribed in the previous 12 months, (4) a count of contact episodes with primary care in the previous 12 months, and (5) the Electronic Frailty Index. Overall, patients with increased multimorbidity were one third to two thirds less likely to undergo surgery. With the same cohort, the influence of multimorbidity on the outcomes of total hip replacement recorded in the Hospital Episode Statistics Admitted Patient Care (HES APC) and Patient Reported Outcomes Measures (HES PROMs) databases was then investigated. Patients with multimorbidity were at a slightly increased risk of complications and hospital readmission, and had an increased length of stay, between 1-3 times greater than patients without multimorbidity. However, the difference in benefits of surgery by having multimorbidity, in terms of pain, function and quality of life, was less than the established minimum clinically important differences of the PROMs investigated.

Given weaknesses in data quality on revision and other reoperations in HES APC, a further cohort study using data from two arthroplasty registries (Geneva Arthroplasty Registry and Swedish Hip Arthroplasty Registry) was performed, with multimorbidity measured with the American Society of Anesthesiologists (ASA) Classification System. Patients with ASA class

III-IV had a three times higher risk of revision surgery and two times higher risk of other reoperation compared with ASA class I within three months of total hip replacement.

Comparisons between arthroplasty registries are performed to understand of variations in practice and outcomes. For comparisons of outcomes to be valid, controlling for the differences between the populations is required. In turn, the controlling relies on a consistent approach to the scoring of the variable in question. A study was performed that investigated the between-registry variation in multimorbidity in patients undergoing total hip replacement recorded in one regional (Kaiser Permanente, USA) and six national (Australia, Finland, Netherlands, New Zealand, Norway and Sweden) arthroplasty registries. Large variations in the distribution of ASA class were observed between the participating registries. The broad consistency in mortality rates by ASA class suggests there was consistency in assignment of ASA class in the different countries.

Conclusions

The increase in risks of total hip replacement for patients with multimorbidity appears to be modest and there is no clinically meaningful reduction in benefit. It is notable therefore that patients with multimorbidity are one third to two thirds less likely to undergo total hip replacement. It is possible that the substantial difference in the rate of total hip replacement by multimorbidity reflects previous inaccurate estimations of the risks and benefits of the surgery.

The variation in distribution of ASA class of patients undergoing total hip replacement in different countries, and the consistency in assignment of ASA class observed, underlines the importance of controlling for ASA class in future comparisons between arthroplasty registries.

Acknowledgements

A sincere thank you is offered to my supervisors, Professors Alan Silman and Siôn Glyn-Jones, and to Professor Afsie Sabokbar, the Departmental Director of Graduate Studies, for their support and guidance through all stages of my degree.

The central questions this thesis set out to answer were originally proposed by Professor Alan Silman as part of an NIHR Research for Patient Benefit grant application (PB-PG-0815-20024). I am therefore indebted to Professor Silman for sharing these ideas and the opportunity to work on the project with me. I would like to thank Professor Anne Lübbeke-Wolff for hosting me at the University of Geneva, Switzerland, and for her supervision during the resulting collaborative projects. In addition, thanks are due to Professor Ola Rolfson of the University of Gothenburg, Sweden, for supporting and facilitating collaborations with the wider International Society of Arthroplasty Registries community.

Each chapter included in this thesis is associated with a published paper. Through the process of publishing these papers, I have received the assistance of co-authors. The following statement contains details of the authorship of the work presented in this thesis:

Chapter 3: Extraction and processing of raw data from CPRD GOLD, and the linked HES APC and HES PROMs databases, was performed by Dr Antonella Delmestri, Lead Health Data Scientist at NDORMS, University of Oxford.
Chapter 6: I developed the protocol for the study in collaboration with Professor Alan Silman, Professor Anne Lübbeke and Professor Ola Rolfson. I performed the data analysis on data from the Geneva Arthroplasty Registry using SPSS Version 23 software (IBM Corp, Armonk, NY, USA). Analysis of data from the Sweden Hip Arthroplasty Registry was performed by local researchers Mr Daniel Odin and Mr Erik Bulow using R (R Foundation for Statistical Computing, Vienna, Austria), and results were sent to me. In order for consistency between the registries, the data analysis on data from the Geneva Arthroplasty Registry was re-run using R, performed by Dr Christophe Combescure, Statistician at the Geneva Arthroplasty Registry.
Chapter 7: I developed the protocol for the study in collaboration with Professor Alan Silman, Professor Anne Lübbeke, and Professor Ola Rolfson. I contacted each registry to invite them to participate and deliver the protocol. Local researchers at each collaborating registry performed patient level analysis on data from the registry. Aggregated data was then passed to Dr Christophe Combescure, who performed the meta-analysis of aggregated data using R.

I am very grateful to my parents for their support during the entire course of my DPhil studies, and in particular for their encouragement at the beginning of the journey. Finally, special thanks are due to my partner for her unwavering support through this journey. Her patience, understanding, enthusiasm and humour were greatly appreciated during the long write up process.

Contents

Chapter 1	**Introduction and Literature Review**		**1**
1.1	Current Clinical Challenges	1	
1.2	Scope of Thesis	5	
1.3	Hip Osteoarthritis	5	
1.4	Total Hip Replacement	7	
1.5	Pathway to Surgery in the UK	9	
1.6	Assessment of Outcomes of THR	11	
1.7	Factors Influencing Outcomes of THR	13	
1.8	Multimorbidity	13	
1.9	Influence of Multimorbidity on the Outcomes of THR	21	
1.10	Influence of Multimorbidity on the Likelihood of THR	32	
1.11	Conclusions	33	
1.12	Thesis Aim and Objectives	34	
Chapter 2	**Design of Thesis Studies**		**35**
2.1	Objective 1	35	
2.2	Objective 2	49	
2.3	Objective 3	56	
2.4	Structure of Thesis	58	
Chapter 3	**Validation of the Diagnosis of Hip Osteoarthritis in CPRD**		**60**
3.1	Abstract	60	
3.2	Introduction	62	
3.3	Methods	63	
3.4	Results	71	
3.5	Discussion	74	
Chapter 4	**Influence of Multimorbidity on the Likelihood of THR**		**80**
4.1	Abstract	80	
4.2	Introduction	82	
4.3	Methods	82	
4.4	Results	92	
4.5	Discussion	103	
Chapter 5	**Influence of Multimorbidity on the Outcomes of THR**		**117**
5.1	Abstract	117	

5.2	Introduction	119
5.3	Methods	119
5.4	Results	127
5.5	Discussion	144
Chapter 6	**Influence of ASA Class on Early Revision & Other Reoperations**	**167**
6.1	Abstract	167
6.2	Introduction	169
6.3	Methods	170
6.4	Results	175
6.5	Discussion	180
Chapter 7	**International Variation in Distribution of ASA Class in Patients undergoing THR and its Influence on Mortality**	**185**
7.1	Abstract	185
7.2	Introduction	187
7.3	Methods	188
7.4	Results	190
7.5	Discussion	194
Chapter 8	**Conclusions and Future Work**	**199**
References		**206**

Figures

Figure 1-1 Radiographs demonstrating hip anatomy and osteoarthritis 7

Figure 1-2 Total hip replacement with different designs and fixation 8

Figure 1-3 Prevalence of multimorbidity (defined as ≥2 chronic conditions) by age reported in studies from primary care settings (reproduced from Fortin et al., 2012[1]) 14

Figure 1-4 An illustration of the conceptual differences between comorbidity, multimorbidity, frailty, multimorbidity burden and patient's complexity (reproduced from Valderas et al., 2009[2]) 17

Figure 3-1 Questionnaire sent to GPs 67

Figure 3-2 Algorithms for diagnosis based on radiologic and clinical parameters 69

Figure 3-3 Identification of the cohort in CPRD 71

Figure 3-4 Box and whisker plot of the time in years between dates of patients with a different date of diagnosis between CPRD and GP patient record 74

Figure 4-1 Charlson Comorbidity Index prior to diagnosis 94

Figure 4-2 Count of chronic diseases prior to diagnosis 95

Figure 4-3 Count of different medications prescribed prior to diagnosis 96

Figure 4-4 Count of contacts with primary care prior to diagnosis 97

Figure 4-5 Electronic Frailty Index prior to diagnosis 97

Figure 4-6 CPRD cohort with adequate HES APC linkage 102

Figure 5-1 Flow diagram showing the selection of patients for inclusion 127

Figure 5-2 Distribution in length of stay in hospital 134

Figure 5-3 Flow diagram showing the inclusion process for revision surgeries 140

Figure 5-4 Cumulative incidence of revision in HES APC 140

Figure 5-5 Flow diagram showing the inclusion process for other reoperations 142

Figure 5-6 Cumulative incidence of other reoperations in HES APC 142

Figure 6-1 Cumulative incidence of Revision and Other Reoperations in GAR and SHAR by ASA class 177

Figure 7-1 Distribution of age (years) in registries, by ASA class 192

Tables

Table 1-1 Summary table of types of multimorbidity scores 18
Table 1-2 Summary of studies investigating multimorbidity & revision surgery 25
Table 1-3 Summary of studies investigating multimorbidity and PROMs 25
Table 1-4 Summary of studies investigating multimorbidity & complications 27
Table 3-1 Read Codes for Hip Osteoarthritis 64
Table 3-2 Demographic characteristics of patients in the entire CPRD cohort, and of responders and non-responders to GP validation questionnaire 72
Table 3-3 Overlap of Cases, by Radiological & Clinical Parameters 73
Table 4-1 Scoring of the Charlson Comorbidity Index 85
Table 4-2 Diseases included in the Count of Chronic Diseases 86
Table 4-3 Deficits included in the Electronic Frailty Index 87
Table 4-4 Cross-tabulation for agreement between CPRD vs. HES APC 92
Table 4-5 Demographic details of the CPRD cohort 93
Table 4-6 Distribution of categories of multimorbidity prior to diagnosis of hip osteoarthritis, by each measure 98
Table 4-7 Rate of undergoing THR by multimorbidity measure 101
Table 4-8 Cross-tabulation of total hip replacements during follow-up according to CPRD versus HES APC 102
Table 4-9 Demographics of CPRD cohort and subset with HES APC linkage 103
Table 5-1 Demographic details of CPRD cohort with THR recorded in HES APC 128
Table 5-2 Distribution of categories of multimorbidity prior to primary total hip replacement, by each measure 129
Table 5-3 Serious complications within 90 days 130
Table 5-4 Risk of any serious complication in 90 days by multimorbidity 131
Table 5-5 Risk of hospital readmission within 90 days by multimorbidity 133
Table 5-6 Length of stay in hospital by multimorbidity 135
Table 5-7 Oxford Hip Score by multimorbidity 136
Table 5-8 EQ-5D score by multimorbidity 138
Table 5-9 Rate of revision surgery by multimorbidity measure 141
Table 5-10 Rate of other reoperation by multimorbidity measure 143
Table 5-11 Comparison of rate of serious complications 151
Table 6-1 Categories of the ASA Physical Status Classification System 172
Table 6-2 Preoperative Patient Characteristics by ASA Class 175
Table 6-3 Cumulative incidence of revision and other reoperation by Class of ASA Classification System 176

Table 6-4 Associations between ASA Class & Risk of Revision Surgery 178
Table 6-5 Associations between ASA Class & Risk of Other Reoperations 179
Table 6-6 Indications for Revision & Other Reoperations in 3m by ASA grade 180
Table 7-1 Patient Demographics by Arthroplasty Registry 191
Table 7-2 Distribution of ASA Class by Arthroplasty Registry 192
Table 7-3 One-year mortality by Registry & combined across Registries 193
Table 7-4 Meta-analysis of unadjusted and age- and sex-adjusted hazard ratios for the association between ASA classes and one-year mortality 193

Chapter 1: Introduction and Literature Review

1.1 Current Clinical Challenges

Osteoarthritis of the hip is a major cause of pain and disability worldwide. It is common, affecting an estimated 9% of men and 14% of women over 50 years of age in the UK.[3] There is no successful disease modifying therapy, and treatment primarily consists of pain management with total hip replacement for advanced symptomatic disease.[4]

Total hip replacement is undertaken to relieve pain, restore function and improve quality of life. The number of total hip replacements performed annually has increased considerably in the past two decades, rising from 71,000 in 2009 to 101,000 in 2019 in the UK, according to the National Joint Registry for England, Wales, Northern Ireland and the Isle of Man (NJR).[5]

Full evaluation of the degree of success of total hip replacement should include consideration of a number of complementary outcomes. These include the safety of the procedure, assessed with the specific outcomes of peri- and post-operative complications and mortality[6,7]; the need for further surgery, assessed with the specific outcomes of rate of revision surgery and of other reoperations to the prosthetic hip[5,8]; and the improvement in pain, function and quality of life for patients, assessed with the specific outcomes of patient reported outcome measures (PROMs).[9,10]

The procedure is highly successful. Less than 6% of patients suffer a major post-operative complication and less than 1% die within 90 days of surgery.[11–15] Overall, 89% of patients do not undergo revision surgery within 15 years, and 58% of patients do not within 25 years.[16] Over 90% of patients report being satisfied with the outcome and having a favourable reduction in pain within 5 years of surgery.[9,17]

However, despite advances in care and improvements in safety, an important minority of patients continue to receive a less than optimal outcome after primary total hip replacement. A number of patient factors have been identified that place patients at a higher risk of a poor outcome, including advanced age, male sex, certain ethnic backgrounds, and obesity.[18,19]

With elective primary total hip replacement being a preference-sensitive procedure[20], making the decision to proceed with surgery should be a shared process by the patient and clinician.[21] The decision should be informed by careful consideration and weighing up of the short- and long-term risks and benefits of surgery. Accurate, evidence-based predictions of the outcomes of total hip replacement, personalised to each patient, would therefore be invaluable in supporting the process.

Consideration of the risks and benefits of surgery is of particular significance in elderly patients. The threshold for undergoing total hip replacement in this population is becoming less restrictive because of improvements in peri-operative care and increased societal expectations of maintained health and physical function at older age.[5] Advancing age, though, is associated with poorer overall health status and an accumulation of long-term health disorders, with 60% of the elderly population suffering from multimorbidity, a term that indicates the presence of two or more chronic health disorders.[22,23] Indeed, patients with osteoarthritis are more likely to suffer with other chronic health disorders than those without osteoarthritis.[24,25]

Multimorbidity is a growing global health concern. Patients with multimorbidity have poorer health outcomes, in terms of hospital admissions, quality of life and mortality.[26] However, a report by the Academy of Medical Sciences, UK, into multimorbidity in 2018 concluded that evidence and understanding about the impact of multimorbidity on health outcomes is inadequate.[27] Recent studies have demonstrated that across a variety of elective surgical procedures, multimorbidity is associated with reduced benefits of surgery and increased risks of post-operative complications.[28–34] Evidence on the influence of multimorbidity on the outcomes of total hip replacement specifically, however, remains limited.

This is a major limitation to the information that is available to patients with multimorbidity and their clinicians when deciding whether to proceed with total hip replacement. This lack of information may lead to worse health outcomes, with the uncertainty increasing decisional anxiety and regret.[35,36] An answer to the question of what influence does multimorbidity have on the outcomes of the procedure is therefore a pressing research priority.

There is concern amongst the orthopaedic community in the UK that patients with hip osteoarthritis and concurrent multimorbidity are not being managed appropriately as a result of this lack of evidence. Appropriate healthcare is defined here, using the original RAND corporation definition, as interventions performed where the "expected health benefits exceeded the expected negative consequences by a sufficiently wide margin that the procedure was worth doing".[37] There are a number of potential scenarios by which inappropriate healthcare management may occur. First, patients at high risk of a complication may undergo total hip replacement but would have chosen not to if accurate, personalised evidence were available. Second, patients may choose or be advised to not undergo surgery due to ill-informed excessive concerns about the risk of a complication. Third, patients likely to have only a small benefit in pain, function or quality of life may undergo surgery but would have chosen not to if such information were available in advance. Fourth, patients may choose or be advised not to undergo surgery due to incorrect expectations that they would likely not benefit substantially in terms of pain, function or quality of life.

Furthermore, if patients with hip osteoarthritis and concurrent multimorbidity are missing out on total hip replacement due to inappropriate care, this has the secondary implication that their healthcare management is not fair relative to patients with hip osteoarthritis without multimorbidity. Fair healthcare is defined here in line with the constitution of the National Health Service (NHS) in the UK, which states that all patients should be able to access (i.e. be offered and receive) the same quality care based on clinical need, irrespective of personal circumstances.[38,39] However, evidence suggests there is variation in the rate of provision of total hip replacement relative to the rate of need in the UK.[40,41] Certain patients groups may more likely be to undergo surgery than others, despite no difference in clinical need. Patient factors identified as contributing to this inequity in access include age, sex, ethnicity, socio-economic deprivation and geographical location. Multimorbidity may also be a contributory factor, however, its role has not yet been investigated. It is acknowledged too there are clear associations between multimorbidity and these other patient factors, in particular age and socio-economic deprivation.[22,42] At present, there is no information on how patients with hip osteoarthritis and concurrent multimorbidity are currently being managed compared with patients without

multimorbidity. An answer to the question of what influence does multimorbidity have on the likelihood of a patient undergoing total hip replacement is therefore a pressing research priority.

1.2 Scope of Thesis

This thesis is concerned with the issue of multimorbidity in the management of patients with hip osteoarthritis. The global aim is to investigate the influence of multimorbidity on whether such patients go on to have total hip replacement and, in those patients that do, the influence of multimorbidity on the outcomes of surgery. It starts with a literature review of current understanding and practice in the fields of hip replacement, of assessment of surgery outcomes, and of multimorbidity.

1.3 Hip Osteoarthritis

Hip osteoarthritis refers to a clinical syndrome of joint pain, accompanied by varying degrees of joint stiffness, functional limitation and reduced quality of life.[43] It is characterised pathologically by degradation and loss of articular cartilage at the joint interface, remodelling of subchondral bone and associated inflammation. Pain results from the stimulation of periarticular nociceptors in response to tissue injury and inflammation, and increased pain sensitisation through neuropathic pain mechanisms and structural nerve changes.[44]

Disease aetiology is multifactorial. Articular cartilage is mechanosensitive, and evidence has demonstrated that hostile biomechanics precipitate enzymatic and biochemical changes within the hip joint that lead to cartilage degradation.[45] Biomechanical factors include joint anatomy[46,47], leg length inequality[48,49], sporting activity[50,51], and joint injury.[52] However, despite these strong associations, most individuals with abnormal joint biomechanics do not develop osteoarthritis.[47] Susceptibility to hip osteoarthritis is also partly determined by systemic factors, including age, sex[53], obesity[52,54] and genetics.[55]

Estimates of the prevalence of hip osteoarthritis vary widely. A systematic review in 2011 reported the prevalence in individual studies depended on the definition of osteoarthritis used, and the age, gender and countries of origin of the study population.[56] The Global Burden of Disease 2010 study estimated the age-standardised prevalence of hip osteoarthritis at 0.85%, based on 40 studies from 19 countries.[57]

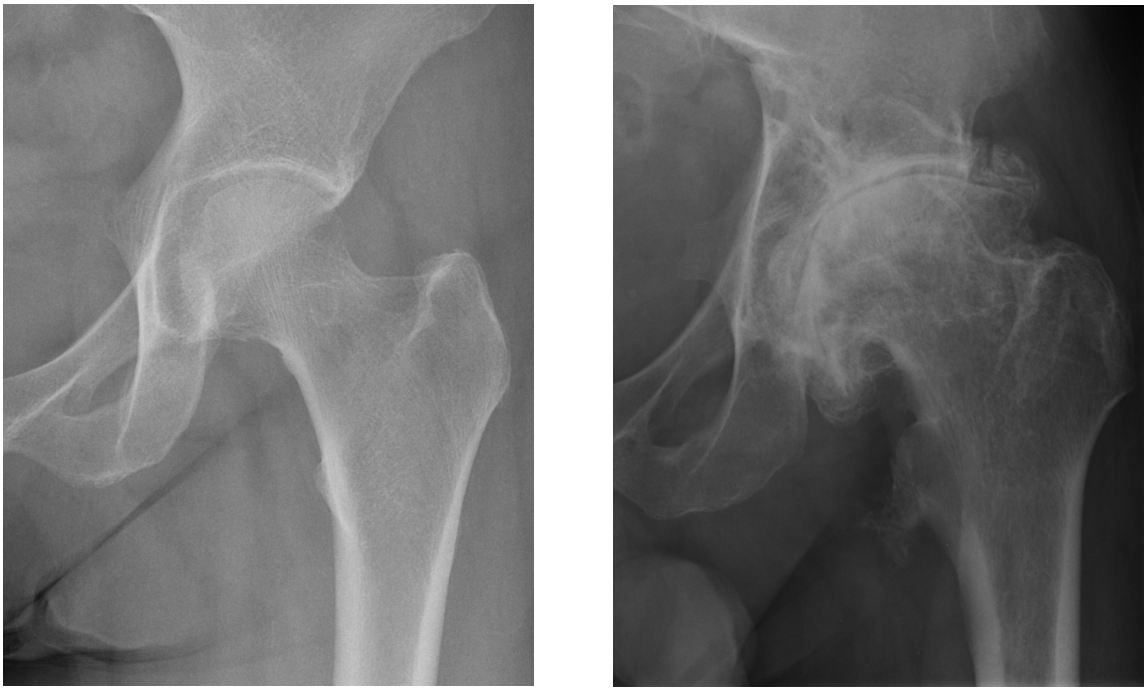
A Swedish study using primary care registry data reported a prevalence of 5.8% in individuals aged ≥45 years[58], while a German study using health insurance claims data reported a prevalence of 6.2% in individuals aged ≥60 years.[59] Data from the English Longitudinal Study of Ageing estimated a prevalence of 9% in men and 14% in women aged ≥50 years.[3] The incidence of the disease increases sharply with age, reaching a peak around the age of 70 years. Spanish and English primary care registry data both estimated an incidence rate of 6 per 1000 person-years for individuals aged >75 years.[53,60]

Hip osteoarthritis has characteristic appearances on imaging. Plain film radiography may demonstrate osteophyte formation, narrowing of the joint space width, sclerosis of subchondral bone and development of subchondral cysts (Figure 1-1). MRI has advantages over radiography; it allows assessment of the joint in three-dimensions, and is more sensitive in detecting early structural changes.[61] However, the National Institute for Health and Care Excellence (NICE) advises that osteoarthritis may be diagnosed clinically, from patient symptoms, without the need for confirmatory imaging.[43] Similarly, the American College of Rheumatology criteria for the diagnosis of hip osteoarthritis do not require imaging.[62] These guidelines are in part due to evidence that plain film radiographs, and even MRI, only show moderate associations between structural signs of osteoarthritis and the presence of pain.[63,64]

Treatment guidelines include non-pharmacological methods, pharmacological agents, and surgery.[65] Non-pharmacological methods shown to alleviate symptoms include education, exercise, weight loss if overweight and walking aids. Recommended pharmacological agents include paracetamol and NSAIDs, intra-articular corticosteroids, and neuropathic pain agents. Other agents under investigation as potential disease modifying agents, including hyaluronans, glucosamine, and chondroitin, have not shown any effect of sufficient clinical relevance.[44] For individuals with severe symptoms, joint replacement surgery is a highly effective intervention that improves pain, function and quality of life.

Figure 1-1 – Radiographs demonstrating hip anatomy and osteoarthritis

Anteroposterior radiographs of a normal hip (left) and a hip with severe osteoarthritis (right)



1.4 Total Hip Replacement

Total hip replacement is a procedure in which a patient's diseased femoral head and acetabular cup are removed, under anaesthesia, and replaced by a prosthetic construct. The development of the procedure is viewed as one of the major achievements in surgical innovation in the 20th century CE. The first surgical attempts to treat the arthritic hip were made over 100 years ago, initially by interposing tissue or synthetic material at the painful articulating joint interface. The results of such procedures were poor: even in the minority of patients that received an improvement in symptoms, the benefits were not long-lasting.[66]

The first recognisable total hip replacement was performed by Philip Wiles in London in 1938, building on work by Marius Smith-Petersen in Boston and Jean and Robert Judet in Paris. The prosthetic joint consisted of a stainless steel femoral head and acetabular cup, fixed in position with screws and bolts.[67,68] John Charnley in Wrightington in the 1950s pioneered two further design innovations that substantially improved long-term function: the insertion of a polyethylene liner into the prosthetic acetabular cup to create a low friction bearing interface, and the use of acrylic cement to fix prostheses

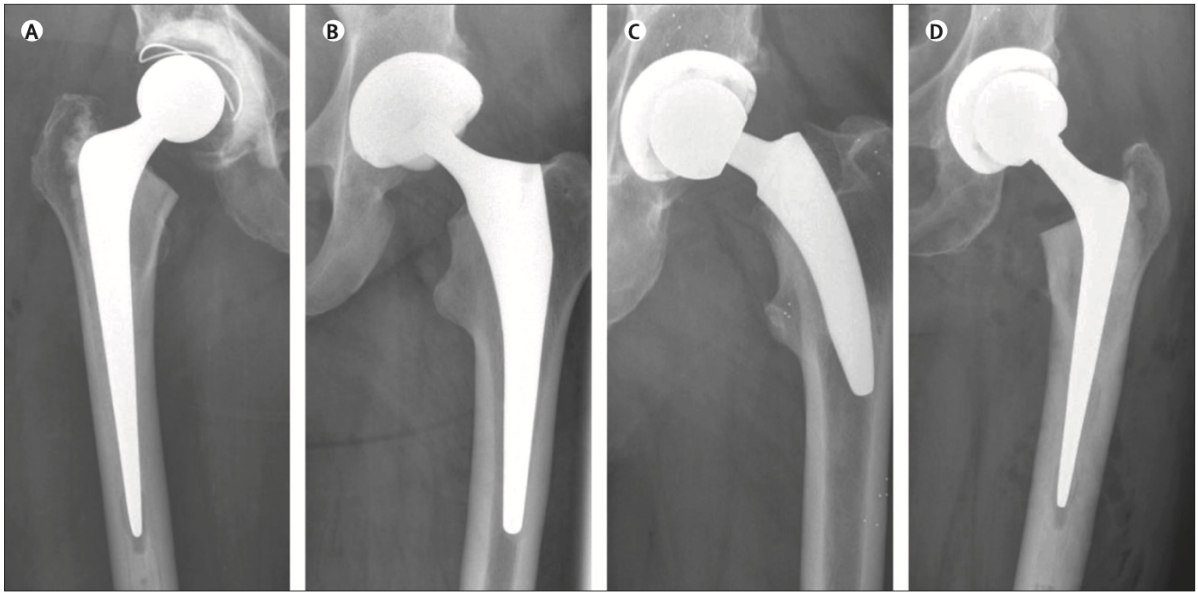
to bone.[69,70] Charnley's design led to a substantial improvement in outcomes, with over 75% of patients free of revision surgery at 25-year follow up.[71,72]

Since then, incremental improvements in the field of hip replacement have continued and are continuing. Advances have been made in implant design, implant materials, fixation methods, surgical technique, and perioperative medical care. Research efforts focus on three key goals: extending implant lifespan, improving functional outcomes, and reducing complications.

The modern construct consists of (1) a stem, which is fixed in the native proximal femur, (2) a ball, which is attached to the stem, (3) a cup, which is fixed in the native pelvis, and (4) a liner, which is fitted into the cup and articulates with the ball to form the bearing interface (Figure 1-2).[5] In some constructs the stem and ball may comprise a single unit and the cup may not require a liner, instead articulating directly with the ball. Many different brands of implant are available for use; in the UK in 2011, 142 different brands of stem and 119 different brands of cup were used.[73]

Figure 1-2 – Total hip replacement with different designs and fixation

Postoperative radiographs of cemented total hip replacement (A); cementless total hip replacement (B), with conventional length femoral stem; cementless total hip replacement, with short length femoral stem (C); and hybrid total hip replacement (D).



Today, stem and cup implants may be fixed in position either with or without cement. In the UK in 2019, 26% of hip replacements were cemented, 35% were uncemented, 35% were hybrid (cemented stem, uncemented cup), and 2% were reverse hybrid (uncemented stem, cemented cup).[5]

The bearing interface is the critical part of the prosthetic hip, through which substantial forces are transmitted. The ideal bearing interface is chemically inert in vivo, has a low wear rate, produces non-immunogenic wear debris, and is sufficiently tough to resist fracture. In the UK in 2019, implants with metal-on-polyethylene bearings were used in 52% of procedures, those with ceramic-on-polyethylene bearings in 38% of procedures, and those with ceramic-on-ceramic bearings in 6% of procedures.[5]

Of the 101,000 primary total hip replacements performed in the UK in 2019, the indication for 90% was hip osteoarthritis.[5] The remaining procedures were performed for fractured neck of femur (5%), avascular necrosis (2%), dysplasia (2%), and inflammatory arthritis (1%).

1.5 Pathway to Surgery in the UK

The NHS in the UK is a taxpayer funded healthcare service that provides comprehensive services to all UK residents. NHS services are free of charge, except in limited circumstances sanctioned by government. Although a separate NHS system exists in each of the four nations of the UK, accountable to the relevant government, the four systems are essentially equivalent.[74] Access to non-emergency NHS services is via primary care practitioners, known as general practitioners (GPs). The pathway to access healthcare management for hip osteoarthritis therefore begins with a patient making an appointment with their GP in response to symptoms caused by hip osteoarthritis.

NICE has published a guideline for GPs (and other relevant healthcare professionals) working within the NHS and their patients on the assessment and management of osteoarthritis in adults.[43] Once the diagnosis of hip osteoarthritis has been made, a holistic patient assessment is advised, with a focus on the effect of osteoarthritis on the patient's function, quality of life, occupation, mood, relationships and leisure activities. The guidance recommends that a management plan should be agreed with the patient, based on the principles of shared decision making, after a discussion of the risks and benefits of

treatment options that takes into account patient comorbidities. The management plan should first involve offering core (non-surgical) treatment options, including education about the disease, exercise, weight loss and pharmaceutical analgesics.

Once core treatment options have been offered, referral to secondary care for joint surgery may be considered. The guidance recommends that referrals should be considered in patients who experience symptoms that have a substantial impact on their quality of life and are refractory to non-surgical treatment. The threshold for referral should be based on the discussion with the patient and not on any scoring tool. Referral should be made before there is prolonged functional limitation and severe pain, and patient specific factors (including age, sex, smoking, obesity, and comorbidities) should not be barriers to referral. Importantly, when discussing whether a patient wishes to be referred, information on the benefits and risks of surgery and potential consequences of not having surgery should be provided. An assessment of a patient's multimorbidity and its likely influence on the benefits and risks of surgery should therefore be a key factor in this discussion.

Once referred, a patient will be reviewed in clinic in secondary care by an orthopaedic surgeon, with a further assessment and discussion held. The NICE guideline on primary hip replacement advises that the decision to offer surgery should be made via a shared patient-clinician decision, following a discussion of the potential benefits and risks of total hip replacement and the alternative management options.[75] Importantly when counselling patients, clinicians should explain the potential benefits and risks with regards to the different domains in which the outcome of total hip replacement can be assessed. (These different domains are discussed below in section 1.6.) Following such a consultation, if the decision is made to proceed with total hip replacement, the patient can finally be added to the waiting list for surgery.

In certain areas of the country, there is an additional step in the pathway: referrals from GPs for orthopaedic specialist care are directed to intermediate musculoskeletal assessment centres where patients are reviewed by physiotherapists or GPs with a specialist interest in musculoskeletal conditions.[76] Introduced in 2006 under the NHS Elective Care Transformation Programme with the aim of reducing inappropriate referrals and waiting times for specialist care, the centres triage referrals to

determine which patients would benefit from further non-surgical management and which patients need review by an orthopaedic surgeon.

A minority of patients in the UK access healthcare that is not funded by the NHS. The pathway for such patients may bypass primary care as patients may arrange review directly by an orthopaedic specialist, however, the NICE guideline on shared decision making before hip replacement surgery remains applicable.

1.6 Assessment of Outcomes of Total Hip Replacement

The outcomes of total hip replacement are determined in several different ways, and full evaluation of the degree of success of surgery should include consideration of the different domains.

Historically, the primary focus has been on how long the implant lasts for, measured with the outcome of time to revision hip replacement.[18] Revision surgery is defined as any surgery that involved the addition, removal or exchange of one or more components of the prosthetic hip. The procedure is only indicated when the original implant has 'failed' and serious adverse symptoms, including pain or fracture, have occurred or are predicted. Implant survivorship may be analysed in different ways, including Kaplan-Meier survival analysis, cumulative revision rates, and lifetime risk of revision.[77] In addition, in recent years there has been increased acknowledgement that any further surgery required to the prosthetic hip represents a negative outcome for patients. Surgeons and researchers therefore may also study 'other reoperations' after hip replacement. 'Other reoperations' are defined as any surgery to the prosthetic hip that did not involve the addition, removal or replacement of any components of the prosthetic hip.

However, the limitation of using of further operations (either revision surgery or other reoperations) as an outcome measure is that patients can have complications, pain, or poor function without having further surgery. A patient may not undergo revision surgery despite a 'failed' implant because either the patient or surgeon is unwilling to proceed with surgery. There are many reasons this may occur, including concerns that patient age or comorbidities would make surgery high risk. Illustrating the

limitation of using further operations as an outcome measure, a systematic review in 2012 found that an unfavourable pain outcome was reported in 9% or more of patients at between 3 months and 5 years of follow up, whereas the 5-year revision rate reported by the UK NJR in the same year was 2.7% (95% confidence interval [CI] 2.7, 2.8).[5,17]

Reducing hip pain and improving function are the aims of primary total hip replacement, and therefore questionnaires on the pain and function experienced by patients are used in addition to implant survival analysis. Such questionnaires are referred to as Patient-Reported Outcomes Measures (PROMs). A number of PROMs focussed on hip pain and function have been validated and are in common use, including the Oxford Hip Score, the Harris Hip Score, and the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC).[78–80] The limitation of such scores is that they do not provide information about whether any change in pain or function is viewed as a success by the patient. PROMs focussed on health-related quality of life and satisfaction are therefore used alongside functions scores to provide further insights, including the EuroQol five-dimensional score (EQ-5D).[81] The PROMs working group of the International Society of Arthroplasty Registries recommended in 2016 that outcome evaluation must consider both the amount of change in PROMs score (pre-operative to post-operative) and the absolute level of PROMs score at a specific time after surgery.[82]

Assessment of the safety of the procedure is another essential domain. It should constitute analysis of the rates of peri- and post-operative complications, and death. In the literature, there is a variability in the time window included to assess for adverse events. Some studies have only included adverse events that occurred intra-operatively.[83,84] The limitation of this approach is that it fails it measure adverse events that occurred post-operatively as a result of the surgery. Some studies include adverse events that occurred a long time post-operatively, beyond one year.[85,86] The limitation of this approach is that adverse events that occurred that were unrelated to the surgery would be included, potentially masking the true complication rate of surgery. The majority of recent studies have selected complications within either 30 days or 90 days as the inclusion period.[87,88]

In many countries, registries have been created to collect uniform data on patients undergoing total hip replacement and follow patients up over time. The benefit of registries is that large cohorts with defined

data points are available for study, although the limitation is only observational research on outcomes is possible. The first hip replacement registry was created in Sweden over 40 years ago and now 24 such registries exist in Europe alone.[89] Originally registries only studied the outcome of revision surgery, however in recent years, many registries have begun recording the outcomes of PROMs and post-operative complications. Such registries have facilitated the comparisons of outcomes between patients in different countries to further understanding of variations in practice.

1.7 Factors Influencing Outcomes of Total Hip Replacement

The outcomes of total hip replacement are influenced by patient, implant, surgeon, operation, and hospital factors. Patient factors that have been identified as influencing the outcomes of the operation include age, sex, ethnicity, socio-economic status, emotional wellbeing, and multimorbidity.[5,90–95] Implant factors include prosthesis bearing interface materials, femoral stem length, femoral head size and prosthesis fixation method.[16,18] Surgeon factors include level of training and annual volume of procedures performed.[96,97] Operation factors include anaesthetic type, surgical approach, and use of computer-assisted surgery systems.[5,18,98] Hospital factors include post-operative VTE prophylaxis management, infection control management and annual volume of procedures performed at the hospital site.[18,99]

The focus of this thesis is the influence of multimorbidity, alternatively termed comorbidities or other health problems, on the outcomes of total hip replacement. The current evidence on the influence of multimorbidity is detailed in section 1.9, following a discussion on the definitions and methods of scoring multimorbidity in section 1.8.

1.8 Multimorbidity

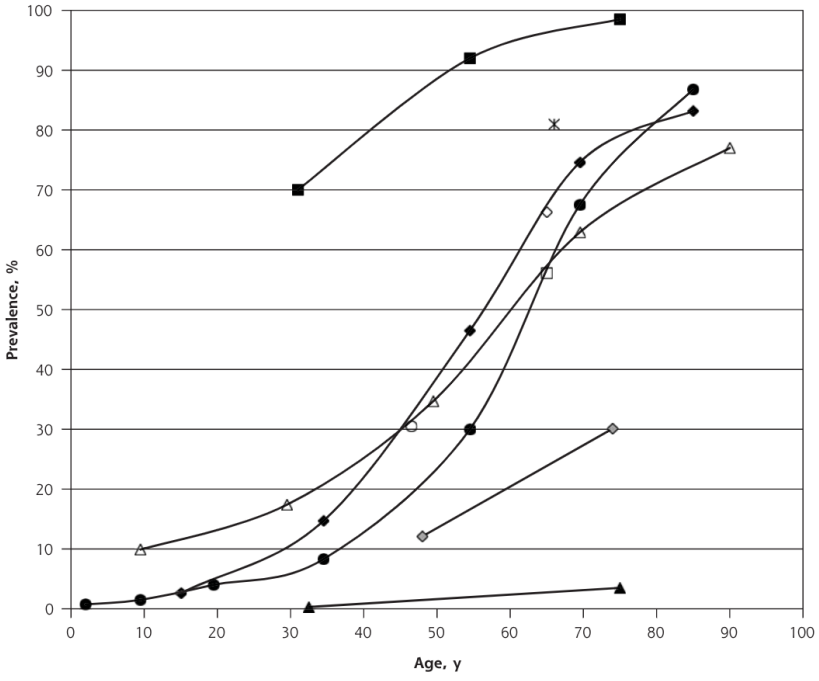
Multimorbidity is the term used to describe the co-occurrence of more than one chronic health disorder in an individual. NICE defines multimorbidity as the presence of two or more long-term health

conditions, which can include (1) defined physical and mental health conditions such as diabetes or schizophrenia, (2) ongoing conditions such as learning disability, (3) symptom complexes such as frailty or chronic pain, (4) sensory impairment such as sight or hearing loss, and (5) alcohol and substance misuse.[100]

1.8.1 Epidemiology of multimorbidity

Multimorbidity is common. In high-income countries such as the UK, the prevalence of multimorbidity is estimated at 20% by the age of 40 years.[1] Prevalence increases with age, reaching 40-60% by 60 years and 60-80% by 80 years of age, according to a systematic review that included studies from the UK, Australia, Canada, the Netherlands, Germany, Sweden and the USA, with methods including review of electronic medical records, review of pharmacy claims databases, and questionnaires sent to randomly selected individuals (Figure 1-3).[1]

Figure 1-3 – Prevalence of multimorbidity (defined as ≥2 chronic conditions) by age reported in studies from primary care settings (reproduced from Fortin et al., 2012[1])



The recorded rates of multimorbidity have increased over time, due to factors including ageing populations in many countries worldwide, unhealthy diet and lifestyle habits, longer survival with long-term health conditions due to improved medical care, increased diagnosis due to more sensitive diagnostic procedures, and improved recording of conditions in medical records.[101] Patients with hip

osteoarthritis are more likely to have multimorbidity than the wider population.[24] Indeed, a case control study of patients using UK primary care data found that patients with osteoarthritis had an approximately 50-70% increased rate of multimorbidity.[25]

1.8.2 Influence of multimorbidity on health status

The effects of multimorbidity are substantial and wide reaching. The management of each health disorder is more complex. Patients with multimorbidity are prescribed an increased number of medications, which leads to a higher rate of drug-drug interactions and poorer medication adherence.[102,103] Surgical interventions in patients with multimorbidity may have a lesser benefit and carry a greater risk of complications.[28–34] For example, a patient with hip osteoarthritis and co-existing chronic obstructive pulmonary disease may have a reduced improvement in health-related quality of life following hip replacement because of limitations on mobility due to respiratory symptoms. Similarly, the same hypothetical patient may have an increased risk of respiratory complication such as hypoxia or pneumonia following general anaesthetic.

Disease treatment guidelines are often designed around a single condition and do not pay attention to the management of co-existing conditions.[104,105] This is in part because patients with multimorbidity are frequently excluded from randomised clinical trials. The result is that healthcare professionals are forced to make challenging management decisions with limited directly relevant guidance. Other difficulties faced by healthcare professionals managing patients with multimorbidity include: being required to manage co-existing conditions outside their area of specialty, having inadequate time to manage all conditions fully, and having difficulty accessing input from other professions due to fragmented healthcare services and limited communication.[106]

Multimorbidity is associated with a faster decline in physical function. Several longitudinal studies have shown that adults with multimorbidity deteriorate more over time in terms of walking speed, grip strength, unintentional weight loss and self-reported exhaustion than equivalent adults without multimorbidity.[101,107–111] Similarly, observational studies have found that multimorbidity is associated with cognitive dysfunction and accelerated cognitive decline.[112–114] In addition, a systematic review

found patients with multimorbidity consistently report worse quality of life, psychological distress and rates of depression.[115] One narrative review concluded that "the impact of multimorbidity on individuals' health profiles surpasses the impact we would expect from the summed effect of single conditions".[101]

Multimorbidity is therefore an important public health issue. However, a policy report published by the UK Academy of Medical Sciences in 2018 into multimorbidity concluded that there remained significant knowledge gaps in the impact of multimorbidity on health outcomes, and advised multimorbidity should be a priority for global health research.[27]

1.8.3 Multimorbidity and associated terminology

A key factor holding back research has been the lack of agreed terminology and definitions in the field of multimorbidity. This is in part because there are a number of overlapping concepts, including comorbidity, multimorbidity, multimorbidity burden, frailty, and patient complexity. The history and the current usage of these concepts and terms is discussed below.

The scientific study of the significance of coexisting medical conditions on overall healthcare outcomes began over 50 years ago, with the term comorbidities proposed to describe the phenomenon.[116] Initially, the focus was on investigating the influence of individual comorbid diseases, such as diabetes, on healthcare outcomes. However, researchers acknowledged that this approach limited the generalisability of the results and did not fully account for patients' other comorbidities. Studying the influence of all comorbidities together has therefore become common.

As understanding grew, the terminology developed: in 1996 comorbidity was more precisely defined as the coexistence of other conditions alongside an index condition that is the specific focus of attention. A new term, multimorbidity, was proposed to refer to the coexistence of several conditions where none are considered an index condition that is the specific focus of attention.[117]

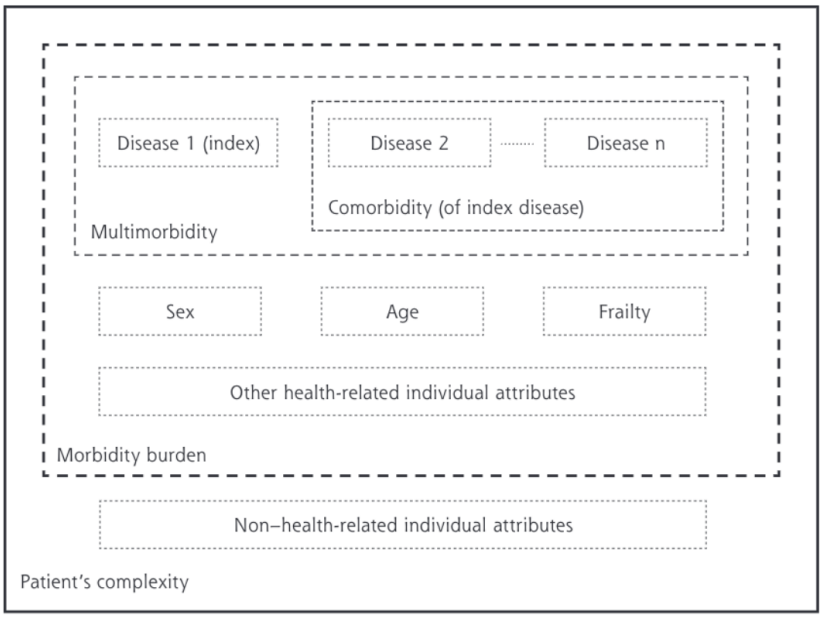
The presence or absence of multimorbidity may be recorded as a simple binary outcome. However, it is acknowledged that this is of limited clinical value, and that the clinically important issue is the magnitude of the impact of multimorbidity on an individual's overall health status, a concept that has

been termed the multimorbidity burden. Researchers and clinicians have therefore aimed to develop methods to stratify or score the severity of the multimorbidity burden.

Frailty is a related but distinct concept to multimorbidity. Frailty is defined as a state of increased vulnerability to poor resolution of homeostasis after a stressor event, which increases the risk of adverse health outcomes.[118] There are two leading models in how to assess for and score frailty. The phenotype model, proposed by Fried et al, scores frailty by assessing patient performance in five variables: un-intentional weight loss, self-reported exhaustion, low energy expenditure, slow gait speed, and weak grip strength.[110] The cumulative deficit model, proposed by Rockwood et al, scores frailty by the number of physiological deficits present in a patient.[119] Deficits include symptoms, signs, abnormal laboratory values, disease states and functional impairments.

There is substantial overlap between multimorbidity and frailty. Most older individuals with frailty have multimorbidity, estimated at 72% prevalence in a recent meta-analysis, whereas the majority of individuals with multimorbidity are not phenotypically frail, estimated at 16% prevalence.[111] It has been proposed that the accumulation of long-term health conditions can lead to the development of frailty, and that frailty can be considered as a method of identifying older individuals with multimorbidity who are especially vulnerable to adverse health outcomes.[120]

Figure 1-4 – An illustration of the conceptual differences between comorbidity, multimorbidity, frailty, multimorbidity burden and patient's complexity (reproduced from Valderas et al., 2009[2])



Finally, an emerging conceptualisation is that of patient complexity. This construct acknowledges that the multimorbidity burden is influenced by health-related characteristics, and also by socioeconomic, cultural, environmental, and patient behaviour characteristics.[2] Capturing a patient's complexity within a score, however, is very difficult, with researchers recommending comprehensive, multi-dimensional assessment of patients to understand it.[121] Scoring a patient's complexity is not possible from routinely collected electronic health records at present. Figure 1-4 illustrates the conceptual differences between the terms described.

1.8.4 Multimorbidity scores

Researchers have developed scores to measure the severity of multimorbidity, or, more correctly, the multimorbidity burden. The major types of scores are shown in Table 1-1, along with examples of commonly used scores.

Table 1-1 – Summary table of types of multimorbidity scores

Type of score	*Example of scores*
Simple count of coexisting diseases	Count of chronic diseases Elixhauser Comorbidity Index (original)[122]
Count of coexisting diseases, with weighting by disease type	Charlson Comorbidity Index[123] Elixhauser Comorbidity Index (van Walraven modified score)[124] USA National Cancer Institute Comorbidity Index[125]
Count of coexisting disease, with weighting by disease severity AND/OR weighting by functional limitation	Index of Co-Existent Disease[34] Cumulative Illness Rating Scale[126] Modified Frailty Index[127] Electronic Frailty Index[128]
Direct subjective assessment of overall health status and multimorbidity burden	ASA Classification System[129]
Surrogate measures of multimorbidity burden	Number of medications prescribed Frequency of hospital admissions or visits to GP

The first widely used score of the severity of comorbidity or multimorbidity burden calculated from a medical history was published by Charlson et al in 1987, validated in predicting risk of death from comorbid disease in a cohort of 685 breast cancer patients.[123] The score is based on the presence or absence of 19 diseases, with each disease assigned a weighting. Since it was modified by Deyo et al in

1992 to fit the International Classification of Diseases (ICD-9) diagnosis and procedure codes, enabling calculation from electronic health records, the Charlson Comorbidity Index has become the most widely used score of multimorbidity, cited over 8,000 times.[130,131] Many similar scores based on the Charlson Comorbidity Index have been developed for specific patient cohorts, such as the USA National Cancer Institute Comorbidity Index, for use in patients with cancer.[125]

The second most widely used score is the Elixhauser Comorbidity Index, published in 1998.[122] The developers reviewed comorbidity data from 1,779,000 hospital admissions in California, with the aim of creating a score with an increased ability to predict mortality than the Charlson Comorbidity Index. Initially 30 comorbidities (or disease groups) were included, with no weighting; however, subsequent modifications to the Elixhauser Comorbidity Index, such as that by van Walraven et al, have replaced disease weighting.[124] Comparisons with the Charlson Comorbidity Index have found the Elixhauser Comorbidity Index to be superior at predicting mortality in certain patient groups.[132,133]

The limitation of such disease count-based scores is that they are unable to measure and account for whether each disease is in a mild or severe state in each patient. As a result, this limits how accurately the scores reflect a patient's true multimorbidity burden and overall health status. Researchers have sought to improve multimorbidity scores by adding stratification for disease severity and measures of functional ability. The Index of Co-Existent Diseases, published in 1993, includes scoring of disease severity and functional impairment and has been validated in predicting functional status one year after hospitalisation and predicting mortality in end-stage renal failure patients.[34]

Challenges in classifying comorbid diseases as mild or severe remain. There may be a lack of consensus on what constitutes a disease being in a mild or severe state, and it may not be possible to determine whether a disease is in a mild or severe state from routinely collected electronic health records. As a result, in recent years scores have been developed that include objective measures of functional ability or impairment as a method of stratifying multimorbidity burden. Of note, some such scores were developed as measures of frailty, modelled on the cumulative deficit model, but, as discussed, since frailty may be viewed as a contributory factor to the overall multimorbidity burden, the scores are treated here as scores of multimorbidity burden.

The original Frailty Index developed by Rockwood et al, using data from the Canadian Study of Health and Ageing, encompassed 70 different deficits, including certain disease states, symptoms and functional impairments. However, the high number of variables in the Frailty Index limited its usage in clinical and research practice. In 2013, a simplified 'Modified Frailty Index' was developed. This score mapped 70 deficits from the Canadian Study of Health and Ageing onto 11 deficits, including the presence of diseases and functional impairments, recorded in the USA American College of Surgeons National Surgical Quality Improvement Program.[127] The score has been validated in predicting morbidity and mortality and is now frequently used in the USA. In 2016, a method of measuring frailty using UK primary care electronic health records was developed by Clegg et al.[128] The Electronic Frailty Index is based on the cumulative deficit model of frailty and calculated based on the presence or absence of 36 disease groups and functional impairments. It has been validated in predicting mortality, hospitalisation, and nursing home admission.

Another method of scoring multimorbidity burden is to require the clinician looking after the patient to review all the available information and examine the patient, then make a subjective judgement and classify the patient into a particular category. One such score is the American Society of Anesthesiologists' (ASA) Physical Status Classification System, first developed in 1963, which contains six categories from normal health to brain dead.[129,134] The purpose of the ASA Classification System is stated as "to assess and communicate a patient's pre-anaesthesia medical comorbidities, [in order to aid] predicting perioperative risks". As it requires the attending clinician to advise on the score, the ASA Classification System therefore cannot be derived from routinely collected electronic health records. A similar score is the Clinical Frailty Scale, also developed by Rockwood et al using data from the Canadian Study of Health and Ageing.[119] An attending clinician classifies patients into one of seven categories, from very fit to severely frail, defined as completely dependent on others for activities of daily living.

The use of surrogate markers of ill health to measure multimorbidity burden has also been validated. For example, a count of medications prescribed to patients may be a good proxy measure of multimorbidity burden, and has been validated in predicting hospitalisation and mortality.[135,136] A

limitation of this method of measuring multimorbidity burden is that some chronic diseases may require management with multiple medications (for example, hypertension), while other chronic diseases (with an equally severe impact on overall health) may only require management with a single medication (for example, rheumatoid arthritis), and so the unweighted count of medications prescribed may not reflect the true multimorbidity burden.

Similarly, counts of hospital attendances or other measures of healthcare usage have been proposed as proxy measures for severity of multimorbidity burden, although the limitation of these measures is that they are influenced by patient personality and behaviour.[137] For example, two patients with equivalent multimorbidity burden may visit their GPs with different frequencies, if one of them was lonely and isolated, and so sought the support of contact with the GP.

In summary, many different methods have been developed to measure multimorbidity burden, and the related concepts of comorbidity, frailty, and patient's complexity, with a view to predicting healthcare outcomes. A recent systematic review found 35 different multimorbidity indices.[136] There is no consensus on which score is 'best' at predicting outcomes. Rather, there is an appreciation that each score will have different relative strengths and weaknesses depending on the patient cohort or outcome under investigation. For example, the ASA classification system may be the score strongest at predicting perioperative risks, while the Electronic Frailty Index may be strongest at predicting all-cause mortality. In the context of total hip replacement outcomes, it is possible that one score will be best at predicting one type of outcome, while other multimorbidity scores will be best at predicting other types of outcomes.

1.9 Influence of Multimorbidity on the Outcomes of Total Hip Replacement

The range of ways in which multimorbidity may be measured and the range of domains in which the outcome of THR may be assessed make analysing the association between multimorbidity and outcome complex. Here, the current evidence on the association is considered.

1.9.1 Revision surgery

A literature search on PubMed and Google Scholar for studies published in English between 1945 and 2021 investigating the association between a multimorbidity or frailty score and all-cause revision surgery was performed (Medical Subject Headings of multimorbidity OR comorbidity OR frailty AND hip replacement AND revision). Six relevant studies were identified (Table 1-2).[138–143] All six studies used a count of coexisting diseases, with weighting by disease type (five used the Charlson Comorbidity Index, one used the Elixhauser Comorbidity Index). No studies investigating a score with weighting by disease severity or functional limitation, or a surrogate measure of multimorbidity were identified. All studies used well-recognised databases of routinely collected patient data, covered wide regional or national areas, described specific inclusion criteria, and had a had a large cohort size (>10,000 patients). All used appropriate survival methodology in the analysis and adjusted for relevant confounders, minimising the risk of bias. Only one study included data on THRs performed after 2006 and no study included UK patients. The period of included revisions varied between one and 12 years. All studies analysed the multimorbidity score as a categorical variable, with the highest category of patients varying between a score of >1 to >4. Across four of the six studies, increased multimorbidity was associated with an increased rate of revision, with the reported hazard ratios varying between 1.1 and 2.8. However, two studies did not find any significant association. A limitation of these studies is that they only assessed multimorbidity using the Charlson and Elixhauser Comorbidity Indices. These scores are only relevant to patients with diseases included in the scores, and do not account for whether the diagnosed diseases are mild or severe, nor the overall impact on a patient's health status.

Annual reports from joint replacement registries are a further source of data on revision surgery after hip replacement. A literature search of annual reports from joint replacement registries that are members of the International Society of Arthroplasty Registries identified two reports that investigated the association between a multimorbidity score and all-cause revision surgery. Both reports used the ASA Classification System. The New Zealand Joint Registry reported an adjusted hazard ratio of 1.4 (95% CI 1.0, 2.0) when comparing revision rates of patients with ASA class III-IV versus I within two years postoperatively.[144] The Dutch Arthroplasty Register reported graphically that patients with ASA class

III-IV have approximately double the rate of revision of patients with ASA class I within two years postoperatively, although beyond eight years postoperatively the rate of revision in patients with ASA class I is higher.[145] These data suggest a similar effect of multimorbidity on rate of revision within two years to the papers using the Charlson and Elixhauser Comorbidity Indices.

The limitation in using ASA Classification System data as the source of information on patient multimorbidity is that the score is based on a subjective assessment. Studies of anaesthetists have demonstrated only fair inter-observer consistency in the score.[146,147] Furthermore, it is possible that due to different practices in different countries, the ASA Classification System may be scored differently in different countries. To date, there has been no study investigating whether patients undergoing hip replacement in different countries differ by ASA Classification System score, or whether the ASA Classification System is scored in a consistent manner in different countries. Comparing patient outcomes between joint replacement registries in different countries requires controlling for the differences between the populations in different countries, and the uncertainty regarding the scoring of the ASA Classification System is therefore a limitation on such comparisons.

Many studies have investigated the association between individual comorbid diseases and all-cause revision surgery, rather than using a multimorbidity score. A literature search on PubMed for such studies identified 16 studies, with 12 included in a systematic review.[148–152] A systematic review in 2018 by Podmore et al investigated the influence of 11 comorbid diseases on the rate of revision surgery after hip or knee replacement, with the impact of each disease analysed separately.[152] Revision surgery was generally more likely in patients with a comorbid disease, with the meta-analysis finding an odds ratio of between 1.0 (95%CI 0.7, 1.4) for neurological disease and 2.0 (95%CI 1.1, 3.3) for liver disease. This information is helpful to some extent for patients with a particular disease when considering whether to proceed with hip replacement; however, the information does not stratify patients further to determine the different in risk between patients with mild multimorbidity and those with severe multimorbidity burden.

In summary, existing evidence suggests a mild association, with an increase in revision rate in patients with increased multimorbidity. Data from joint replacement registries suggest the effect is largest within

the first two years post-operatively. However, the available evidence is conflicting and limited in how multimorbidity has been measured.

1.9.2 Other reoperations

A literature search on PubMed and Google Scholar for studies published in English between 1945 and 2021 investigating the association between a multimorbidity or frailty score and the rate of other reoperations after hip replacement was performed (Medical Subject Headings of multimorbidity OR comorbidity OR frailty AND hip replacement AND reoperation). No relevant studies were identified. This reflects the fact that other reoperations have only recently been acknowledged to be an important outcome measure.

Table 1-2 – Summary table of studies investigating the association between multimorbidity and revision surgery after total hip replacement

Study	Country, coverage	TJA years	Cohort size, operation type	Multimorbidity measure	Outcome	Effect size
Arias-De La Torre (2020)[138]	Spain, regional	2005-16	17,923 THR	Elixhauser Comorbidity Index	Revision within 5y	Hazard ratio 1.3 (95%CI 1.0, 1.7) for score >2 vs 0
Johnsen (2006)[139]	Denmark, national	1995-02	36,984 THR	Charlson Comorbidity Index	Revision between 6m and 8y	Hazard ratio 2.8 (95%CI 2.4, 3.4) for score >2 vs 0
Katz (2012)[140]	USA, regional	1995-96	51,347 THR	Charlson Comorbidity Index	Revision within 12y	Hazard ratio 1.0 (95%CI 0.9, 1.1) for score >1 vs 0
Losina (2004)[141]	USA, regional	1995-96	57,488 THR	Charlson Comorbidity Index	Revision within 4y	Hazard ratio 0.9 (95%CI 0.7, 1.0) for score <2 vs ≥2
Ong (2010)[142]	USA, regional	1997-06	35,746 THR	Charlson Comorbidity Index	Revision within 5y	Hazard ratio 1.7 (95%CI 1.3, 2.2) for score >4 vs 0
Paterson (2010)[143]	Canada, national	2000-04	20,290 THR	Charlson Comorbidity Index	Revision within 1y	Odds ratio 1.1 (95%CI 0.5, 2.4) for score >1 vs 0

Table 1-3 – Summary table of studies investigating the association between multimorbidity and patient-reported outcomes measures after total hip replacement, including pain, function and quality of life

Study	Country, coverage	TJA years	Cohort size, operation type	Multimorbidity measure	Outcome	Effect size
Judge (2013)[153]	UK, regional	1999-02	1431 THR	Count of chronic diseases	Oxford Hip Score at 5y	Coefficient -0.90 (95%CI -1.27, -0.54; P <0.001) for continuous variable
Loth (2017)[154]	UK, single centre	2014	251 THR	Charlson Comorbidity Index	(i) Oxford Hip Score at 1y (ii) Short Form-12 at 1y	(i) Outcome 5.1 points lower (P <0.01) for count ≥1 vs 0 (ii) 7.2 points lower (P 0.08) for count ≥1 vs 0
Mannion (2020)[155]	Switzerland, single centre	2010-16	1,584 THR	(1) Charlson Comorbidity Index (2) ASA Classification System	Oxford Hip Score at 1y	(1) Coefficient -0.74 (P <0.01) for continuous variable (2) -0.80 (P 0.01) for continuous variable

Zhang (2018)[156]	Canada, regional	2009-15	3,374 THR	Count of chronic diseases	Oxford Hip Score at 1y	Outcome 2.4 points lower (P <0.01) for count ≥1 vs 0
Dowsey (2014)[157]	Australia, single centre	2006-09	835 THR	Charlson Comorbidity Index	Harris Hip Score (i) pain outcome and (ii) function outcome at 1y	(i) Coefficient -0.34 (P 0.03) for continuous variable (ii) -0.85 (P <0.001) for continuous variable
Hawker (2013)[158]	Canada, regional	1998-13	2,411 THR & TKR	Count of chronic diseases	WOMAC change ≥ the minimum important difference	Relative risk 0.88 (P 0.01) for continuous variable
Nilsdotter (2003)[159]	Sweden, single centre	1995-98	211 THR	Count of chronic diseases	WOMAC outcome at 3y	Odds ratio 1.48 (P 0.38)
Stevens (2012)[160]	Netherlands, regional	2005-07	653 THR	Count of chronic diseases	WOMAC outcome at 1y	Outcome 14.5 points lower (P 0.01) for count >2 vs 0
Quintana (2009)[161]	Spain, regional	1999-00	590 THR	Charlson Comorbidity Index	(i) WOMAC pain domain change at 6m (ii) SF-36 physical functioning domain change at 6m	(i) Coefficient 0.33 (P 0.93) for score >2 vs 0 (ii) -9.2 (P 0.12) for score >2 vs 0
Peter (2015)[162]	Netherlands, regional	2011	281 THR	Count of chronic diseases	(i) HOOS pain subscale (ii) HOOS physical functioning subscale (iii) Short Form-36 Questionnaire	(i) Coefficient -15.9 (P <0.01) for count ≥5 vs 0 (ii) -22.1 (P <0.01) for count ≥5 vs 0 (iii) -7.1 (P <0.01) for count ≥5 vs 0
Imamura (1998)[163]	UK & Japan, regional	1992-93	517 THR	Index of Co-Existent Diseases	Instrumental Activities of Daily Living Score change at 1y	Outcome 8 points lower (P value 0.04) for count ≥3 vs 1 in UK; no difference in Japan
Glassou (2018)[164]	Denmark, single centre	2008-13	1,582 THR	Charlson Comorbidity Index	EQ-5D index change at 1y	Coefficient -0.05 (P >0.05) for count >2 vs 0
Gordon (2013)[165]	Sweden & Denmark, national	2006-08	15,192 THR	Charlson Comorbidity Index	EQ-5D index at 1y	Coefficient -0.09 (P <0.01) for count >2 vs 0
Greene (2015)[166]	Sweden, national	2002-07	22,263 THR	(1) Charlson Comorbidity Index	EQ-5D index at 1y	(1) Coefficient -0.02 (P <0.01) for continuous variable

				(2) Elixhauser Comorbidity Index		(2) -0.01 (P <0.01) for continuous variable

Table 1-4 – Summary table of studies investigating the association between multimorbidity and complications after total hip replacement

Study	Country, coverage	TJA years	Cohort size, operation type	Multimorbidity measure	Outcome	Effect size
Boniello (2017)[167]	USA, regional	2011-14	66,839 THR	ASA Classification System	Post-operative complications within 30d	Odds ratio 2.1 (95%CI 1.9, 2.4) for score >3 vs 1
Imamura (1998)[163]	UK & Japan, regional	1992-93	517 THR	Index of Co-Existent Diseases	Serious post-operative complications before hospital discharge	Odds ratio 2.56 (95%CI 1.00, 6.56) for count ≥3 vs 1 in UK; no difference in Japan
Mannion (2020)[155]	Switzerland, single centre	2010-16	1,584 THR	(1) Charlson Comorbidity Index (2) ASA Classification System	Post-operative complications within 30d	(1) Coefficient 0.21 (P 0.01) for continuous variable (2) 0.56 (P <0.001) for continuous variable
Singh (2011)[168]	USA, regional	1994-08	1,195 THR	(1) Charlson Comorbidity Index (2) ASA Classification System	Post-operative (i) cardiac and (ii) thromboembolic complications within 90d	(1) (i) Odds ratio 1.2 (95%CI 1.0, 1.4), and (ii) 1.0 (95%CI 0.9, 1.2) for continuous variable (2) (i) Odds ratio 6.1 (95%CI 1.6, 22.8), and (ii) 0.5 (95%CI 0.3, 1.0) for score ≥3 vs ≤2
SooHoo (2010)[19]	USA, regional	1995-05	138,399 THR	Charlson Comorbidity Index	Post-operative complications within 90d	Odds ratio 1.21 (95%CI 1.18, 1.24; P <0.001) for continuous variable
Paterson (2010)[143]	Canada, national	2000-04	20,290 THR	Charlson Comorbidity Index	(i) Surgical complication during admission (ii) Death within 90d	(i) Odds ratio 1.56 (95%CI 1.16, 2.11), and (ii) 3.82 (95%CI 2.07, 7.05) for score >1 vs 0
Rasouli (2014)[169]	USA, single centre	2010-12	6,111 THR	Charlson Comorbidity Index	Post-operative joint infection	Odds ratio 2.3 (95%CI 1.3, 3.9) for score ≥2 vs 0

Mahomed (2003)[87]	USA, regional	1995-96	61,568 THR	Charlson Comorbidity Index	Death	Odds ratio 1.7 (95%CI 1.5, 2.1) for continuous variable
Bellamy (2017)[170]	USA, regional	2005-14	51,582 THR	Modified Frailty Index (11-factor)	Post-operative complications	Odds ratio 3.6 (95%CI 1.6, 8.1),
Dharmasukrit (2021)[171]	USA, regional	2011-17	130,022 THR	Modified Frailty Index (5-factor)	(i) Length of stay in hospital (ii) Hospital readmission within 30d	(i) Odds ratio 1.05 (95%CI 1.04, 1.05) (ii) 1.26 (95%CI 1.21, 1.32)
Shin (2016)[172]	USA, regional	2005-12	14,583 THR	Modified Frailty Index (11-factor)	Post-operative complications (Clavien Dindo IV only)	Odds ratio 5.1 (95%CI 1.4, 18.9) for score >0.45 vs ≤0.45
Traven (2019)[173]	USA, regional	2005-16	140,158 THR	Modified Frailty Index (5-factor)	Post-operative complications within 30d	Odds ratio 1.25 (95%CI 1.21, 1.30) for continuous variable

1.9.3 Patient reported outcomes, including pain, function and quality of life

A literature search on PubMed and Google Scholar for studies published in English between 1945 and 2021investigating the association between a multimorbidity or frailty score and pain, function and quality of life after hip replacement was performed (Medical Subject Headings of multimorbidity OR comorbidity OR frailty AND hip replacement AND pain OR function OR walking OR quality of life). Eleven relevant studies were identified regarding pain or function (Table 1-3). Six studies used a simple count of coexisting diseases, and four studies used a count of coexisting diseases, with weighting by disease type (Charlson Comorbidity Index). One study used a count of coexisting diseases, with weighting by disease severity and functional impairment (Index of Co-Existent Diseases).[34] One study in addition studied the ASA Classification System. No studies investigating a surrogate multimorbidity score were identified. In terms of outcome, four studies used the Oxford Hip Score, one study used the Harris Hip Score, four studies used the Western Ontario and Mc-Master Universities OA Index (WOMAC), one study used the Hip disability Osteoarthritis Outcome Score (HOOS), and one study used the Instrumental Activities of Daily Living Score. The studies varied in scope, from single centre studies of 200 patients to regional studies of 3,000 patients. The lack of studies with national coverage likely reflects the administrative barriers to collecting PROM questionnaires nationally.

Nine of the 11 studies reported a significant association between increased multimorbidity and poorer pain or function outcome. However, only one of the studies using the Oxford Hip Score reported a difference larger than the minimal clinically significant difference of 5 points.[154,174] In addition, the only study that used change in function as the outcome, rather than post-operative function, reported no significant difference by multimorbidity.

A limitation of these studies is that multimorbidity was generally only measured with the Charlson Comorbidity Index or a count of co-existing chronic diseases. The study that investigated the Charlson Comorbidity Index and the ASA Classification System reported similar coefficients.[155] A limitation of this study is that it was a single centre, limiting the external validity. In addition, patients were from Switzerland and there has been no study investigating whether the ASA Classification System is scored in a similar manner in Switzerland to in the UK, reducing validity to UK patients. The study that

investigated the Index of Co-Existent Diseases reported conflicting results between small patient cohorts in the UK and Japan.[163]

Three studies were identified regarding quality of life (Table 1-3). All three studies used a count of coexisting diseases, with weighting by disease type (three used the Charlson Comorbidity Index, and one also used the Elixhauser Comorbidity Index). No studies investigating a score with weighting by disease severity or functional limitation, or a surrogate measure of multimorbidity were identified. In terms of outcome, all three studies used the EuroQol 5-dimension (EQ-5D) score. One study was single centre and found no association. However, two studies from Scandinavia were national in coverage and found that increased multimorbidity was associated with a lower quality of life outcome. However, the difference in EQ-5D index was smaller was smaller than the minimum clinically important difference of the score.[175]

Regarding studies that investigated the association between individual comorbid diseases (rather than a multimorbidity score) and pain, function or quality of life after hip replacement, the systematic review by Podmore et al identified 15 studies covering 11 comorbid diseases.[152] In the pain outcome, patients with comorbid disease had a slightly worse outcome but in none of the diseases studied was the difference statistically significant. In the function outcome, patients with depression, heart disease or stroke had slightly worse function after surgery than patients with no comorbid diseases (odds ratio between 1.24 and 1.69), while for the other diseases there was no difference. In the quality of life outcome, there was no consistent pattern. The authors note that of the 15 studies included, all were single-centre studies with a relatively small cohort of fewer than 2000 patients.

In summary, existing evidence suggests that there is no clinically important difference in pain, function or quality of life after hip replacement between patients with and without multimorbidity. However, the evidence is conflicting, only a limited range of multimorbidity measures have been investigated, and there have been no large, multi-centre studies of patients in the UK, which limits the relevance of the findings to UK patients.

1.9.4 Complications

A literature search on PubMed and Google Scholar for studies published in English between 1945 and 2021 investigating the association between a multimorbidity or frailty score and complications after hip replacement was performed (Medical Subject Headings of multimorbidity OR comorbidity OR frailty AND hip replacement AND complication OR death OR infection OR risk OR length of stay OR readmission). identified 12 studies (Table 1-4).

Six studies used a count of coexisting diseases, with weighting by disease type (Charlson Comorbidity Index). Five studies used a count of coexisting diseases, with weighting by disease severity or functional limitation (one used the Index of Co-Existent Diseases, and four used the Modified Frailty Index). Three studies used the ASA Classification System. No studies investigating a surrogate measure of multimorbidity were identified.

In terms of outcome, most studies investigated a range of surgical and medical complications within the early post-operative period. Two studies investigated mortality, and one study investigated length of hospital stay and readmission within 30 days of surgery. All were cohort studies, with all but three including >5,000 patients.

All studies reported an increased risk of complications with increased multimorbidity. The studies using Charlson Comorbidity Index a range in odds ratio from 1.2 to 2.3, with similar results for the ASA Classification System. The four studies using the Modified Frailty Index reported odds ratios for medical complications of 1.25 and 5.1. The study reporting an odds ratio of 5.1 focussed only on life-threatening complications and analysed Modified Frailty Index as a dichotomised variable with a threshold of >0.45, which represents only 0.2% of the entire cohort.[172] All four studies of Modified Frailty Index derived data from the American College of Surgeons National Surgical Quality Improvement Program database, which covers approximately 500 hospitals in the USA.

The systematic review by Podmore et al identified 60 studies that investigated the influence of comorbid diseases and short-term complications of surgery, including perioperative adverse events, and post-operative venous thromboembolism, surgical site infection, and death. Of the 11 diseases studied

separately, nearly all studies reported a small but statistically significant increase in risk of complication when a comorbid disease was present, with the pooled odds ratios between 1.03 and 3.55.[152]

In summary, the available evidence consistently shows that patients with multimorbidity have a mildly increased risk of a complication after primary THR. However, there is variation in the size of the association reported by different studies, reflecting the heterogeneity of complications investigated, time periods included, populations studied, and methods of analysis. Furthermore, there are no studies of scores with weighting by disease severity or functional limitation that included UK patients.

1.10 Influence of Multimorbidity on the Likelihood of Total Hip Replacement

A literature search on PubMed and Google Scholar for studies published in English between 1945 and 2021 investigating the association between a multimorbidity or frailty score and the likelihood of patients with hip osteoarthritis undergoing THR was performed (Medical Subject Headings of multimorbidity OR comorbidity OR frailty AND hip replacement AND access OR likelihood OR receive). No quantitative studies were identified.

One recent large study in the UK, of 640,000 patients that underwent total hip or knee replacement, investigated whether there was an association between the presence of comorbid diseases and the severity of pre-operative joint problems, measured with the Oxford Hip and Knee Scores.[176] The results showed that compared to patients without comorbidities, patients with chronic diseases reported more severe joint problems, including pain and function. The differences were clinically significant for patients with four or more comorbidities. The authors proposed their findings suggested that patients with chronic diseases have hip or knee replacement later in the course of their joint disease, likely as a result of delays in access to surgery.

In addition, two relevant qualitative studies were identified. One study in the USA from 1996 reported that some orthopaedic surgeons believed the presence of comorbidities should sway the decision towards not to proceeding with total hip replacement, as there was a lower likelihood of an excellent outcome.[177] The other study in the UK from 2018 reported that while a sample of 20 orthopaedic

surgeons, GPs and physiotherapists did not see the presence of comorbidities as a barrier to being referred or selected for joint replacement, the authors identified that the different professional groups disagreed on their responsibilities regarding the management of patients with comorbidities.[178] The authors suggested this disagreement may create an implicit barrier at the overall pathway-level such that patients with comorbidities get 'lost' to the system and miss out on total hip replacement, despite no formal decision that total hip replacement would not appropriate.

In summary, there is no direct evidence on influence of multimorbidity on the likelihood of patients with hip osteoarthritis undergoing THR. However, evidence does suggest patients with multimorbidity are likely to either face delays or barriers in their pathway to surgery.

1.11 Conclusions

Thousands of patients are diagnosed with hip osteoarthritis each year in the UK. A high proportion of them have multimorbidity, reflecting the wider population of the same age. Many different approaches to measuring the severity of multimorbidity burden have been developed. Making the decision to proceed with total hip replacement requires a careful evaluation of the expected benefits and risks of surgery. The evidence on how multimorbidity influences the expected benefits of total hip replacement and the risks of post-operative complications that is available to patients and clinicians is limited. Much of the evidence is based on simple counts of coexisting diseases that may only be weak tools are measuring multimorbidity burden. At present it is unclear which methods of scoring multimorbidity are best in each context. In order to provide future patients with accurate, evidence-based predictions of the outcomes of total hip replacement, research priorities should be to investigate the influence of multimorbidity, taking a broad approach to measuring multimorbidity, in the different outcomes of total hip replacement.

Concerns remain that patients with hip osteoarthritis and concurrent multimorbidity are not being managed appropriately or fairly in comparison to patients without multimorbidity, as a result of the

limited information available on multimorbidity outcomes. Evidence is lacking on whether patients with multimorbidity are as likely to undergo hip replacement.

Comparisons between patients undergoing hip replacement recorded in registries in different countries are performed to further improve understanding of variations in practice and outcomes. Such comparisons should account and adjust for differences between patient populations. The degree of variation in multimorbidity between patients undergoing hip replacement in different countries is currently unknown, as is whether multimorbidity, assessed using the ASA Classification System, is scored in a consistent manner in different countries.

1.12 Thesis Aim and Objectives

The global aim of this thesis is to investigate the influence of multimorbidity on whether patients with hip osteoarthritis go on to have total hip replacement and, in those patients that do, the influence of multimorbidity on the outcomes of surgery.

The objectives of this thesis are:

1. To establish the influence of multimorbidity on the likelihood of patients with hip osteoarthritis undergoing primary total hip replacement.
2. To establish the influence of multimorbidity on the outcomes of primary total hip replacement, including:
    i. the rate of revision surgery and other reoperations,
    ii. the rate of complications, and
    iii. the patient-reported outcomes of pain, function, and quality of life.
3. To determine the variation in multimorbidity of patients undergoing primary total hip replacement in different countries.

Chapter 2: Design of Thesis Studies

This Chapter considers the design options for the studies that will address the objectives of the thesis. The structure of the thesis is then laid out.

2.1 Objective 1 – To establish the influence of multimorbidity on the likelihood of patients with hip osteoarthritis undergoing primary total hip replacement

There are a number of steps and issues to consider in the design of the study to address this objective. These include:

- Setting of the primary outcomes
- Identification of the cohort
- Source of electronic medical records
- Choice of primary care database
- Verification of the diagnostic codes
- Source of information on multimorbidity
- Source of information on study outcomes

2.1.1 Setting of the primary outcomes

Chapter 1 of the thesis describes the healthcare pathway in the UK that a patient with hip osteoarthritis, a diagnosis that is typically made in primary care, follows in order to receive hip replacement. The key steps in accessing hip replacement are (i) the decision in primary care to refer the patient to orthopaedic secondary care for consideration of hip replacement and (ii) the decision in secondary care to proceed with hip replacement. The primary outcomes of this study therefore will be (i) whether or not patients are referred from primary care to orthopaedic secondary care, (ii) and whether or not patients undergo

hip replacement. The time period from diagnosis of hip osteoarthritis to the outcome in question will be investigated.

2.1.2 Identification of the cohort

The cohort will be comprised of patients diagnosed with hip osteoarthritis. One method to identify a cohort for the study would be to identify and recruit eligible participants in secondary care, either patients that are seen in orthopaedic secondary care or patients that undergo hip replacement. The drawback of this method, however, is that patients with hip osteoarthritis who are not referred or do not undergo hip replacement would not be identified. An alternative method would be to identify and recruit participants at the time of diagnosis of hip osteoarthritis. This method would permit study of which patients are referred and undergo hip replacement and therefore will be used.

How to obtain data on which patients are diagnosed with hip osteoarthritis in primary care is the next consideration. One method would be a prospective cohort study. In such a study, GPs would notify the investigators on making a new diagnosis of hip osteoarthritis and patients would then be followed longitudinally. The advantage of such a design is that all variables could be defined in advance of recruitment and vigilant data collection would ensure a high degree of data completeness. However, the data collection process in prospective cohort studies is expensive and recruitment and follow up take a long time. For example, a prospective multicentre cohort study of symptomatic and radiographic predictors of hip joint replacement in new attenders in primary care with hip pain took four years to recruit 195 patients.[179] Here, recruited patients would need to be followed up for many years to determine if they were referred or underwent hip replacement. As a result, a prospective cohort study is not feasible within the time and financial resources available to the thesis.

The only viable method is a retrospective cohort study, using data that has already been recorded as part of routine clinical care. ‘Routinely collected patient information’ refers to the information that is stored in patients’ longitudinal medical records as part of routine clinic care and contains details on symptoms, investigations, diagnoses and treatments. In the UK all medical records in primary care are

fully computerised and stored electronically.[180] This study will use electronic medical records from primary care as the data source to identify eligible patients for inclusion in the study cohort, based on the diagnosis of hip osteoarthritis.

2.1.3 Source of electronic medical records

There are a number of potential ways of obtaining electronic medical records from primary care to derive the cohort for this study. One method would be to obtain records directly from a single GP practice. However, this method has three drawbacks. First, the cohort size derived from this method would likely not be sufficiently large for the study to be adequately powered. Secondly, for the results of the study to be relevant to patients across the UK, the cohort should be representative of the UK patient population. Deriving the cohort from a single GP practice might not yield a sufficiently diverse and representative patient cohort, because the populations of patients can vary significantly between GP practices by factors of age, ethnicity and deprivation. Thirdly, the management of patients by GPs may differ between GP practices, and so using data from a single practice could yield biased results.

Instead, to ensure adequate statistical power, maximise external validity and minimise bias, electronic medical records should be sought from many GP practices across the UK. It is possible to analyse electronic medical records from different GP practices because all GP practices in the NHS between 1985 and 2018 recorded information using the same hierarchical clinical coding system, known as Read codes. (Since April 2018, GP practices have been changing in a phased manner to a new coding system, known as SNOWMED CT.[181] To remove the possibility of incorrect data analysis from using data from more than one coding system, this thesis will only use Read code data from prior to April 2018.)

To obtain the electronic medical records from different GP practices directly would require applying to each GP practice individually for access to their records. Applying to many GP practices separately would be expensive and take significant time. Electronic medical records obtained in this way could also have the drawback that records may be structured differently if obtained from GP practices using different clinical computing systems. Different clinical computing systems exist because GP practices

are permitted to choose a clinical computing system from commercial providers. In 2011, seven clinical computer systems were consistently active in England, all with varying interfaces, in total holding 99% of the market share. EMIS systems were active in 54.7% of practices, followed by Vision V.3 in 18.1%, and SystmOne in 17.8%, with the remaining 9.4% held by Synergy, Practice Manager, Premiere and EMIS Web.[180] Obtaining electronic medical records by applying to GP practices directly is therefore not feasible for this study.

Fortunately, there is an alternative: it is possible to obtain the electronic medical records from different GP practices from one centralised source. Over the last thirty years, public health policy makers and researchers have become increasingly aware of the value of electronic medical records to improve clinical care through observational healthcare research. To facilitate such research, a number of databases have been created by policy makers and researchers that contain anonymised electronic medical records of NHS patients, with data submitted to the databases by many GP practices across the UK. Data is generally uploaded to the databases by participating practices from the primary care electronic medical records of patients registered with the practice on a monthly basis. All patients registered with the participating practices are included unless they have individually opted out. This study will therefore obtain electronic medical records via applying to such a primary care database in order to identify the study cohort.

2.1.4 Choice of primary care database

The four largest primary care databases in terms of numbers of patient records are QResearch, ResearchOne, The Health Improvement Network (THIN) and Clinical Practice Research Datalink (CPRD). All cover in excess of 400 GP practices and 10 million patients across the UK.

In 2017, the largest database was QResearch.[180] It collects data from approximately 1500 practices using EMIS systems, which has excellent geographical coverage across the UK. ResearchOne collects data from approximately 420 practices using SystmOne systems, which has good coverage in many areas but lacks coverage in the North West, London and the South East. Despite their strengths, these two

databases have significant barriers in access to data. This has resulted in a substantially lower publication output than from the other two major databases: as of July 2017, PubMed listed 32 published papers linked to QResearch from the previous five years and two linked to ResearchOne, whereas there were 303 published papers linked to THIN from the previous five years and 886 linked to CPRD.[180]

THIN was established in 2003 as a collaboration between the company that owned Vision (In Practice Systems) and Quintiles IMS. It collects data from approximately 560 practices using Vision systems, containing the records of 11 million patients. The Vision system is used in practices nationwide, although has relatively few practices in London and the North East.

CPRD was established in 1987 and is a not-for-profit research service funded by the NHS National Institute for Health Research (NIHR) and the Medicines and Healthcare products Regulatory Agency (MHRA). It is now owned by the UK Department of Health. Similar to THIN, CPRD collects data from GP practices using Vision systems, with approximately 718 in total. The nomenclature of CPRD has evolved over time: it was originally termed the General Practice Research Database (GPRD) until 2012 when it was renamed CPRD. It is now termed CPRD GOLD, to differentiate it from a recently launched 'sister' database CPRD Aurum that collects data from GP practices using EMIS Web software. Henceforth in this thesis, use of the term CPRD refers to CPRD GOLD. CPRD contains the records of 17 million patients, of which 4.4 million are active, covering approximately 7% of the UK population.[182] Importantly, CPRD patients are broadly representative of the UK population in terms of age, sex, ethnicity and body mass index distribution.[183] Some practices submit data to both THIN and CPRD, and overlap of THIN and CPRD practices is estimated at 60%.[184]

A major advantage of THIN and CPRD databases is that data can be linked to other databases, if GP practices have consented to participate in the linkage scheme. In CPRD approximately 58% of GP practices have consented to the linkage scheme, meaning that over half the patients registered in CPRD are eligible to have their records linked to additional datasets.[183] Established linkages include to the Hospital Episode Statistics Admitted Patient Care database for data on NHS-funded hospital inpatient episodes, the Office for National Statistics for data on mortality, and to the Index of Multiple Deprivation for data on socioeconomic status. Together, these factors suggest that both THIN and

CPRD would be an appropriate source of electronic medical records. Access to data stored in CPRD was available to this study.

Whether the quality and completeness of the CPRD data is sufficiently high to permit legitimate conclusions from research using CPRD data is the next consideration. Since CPRD contains data that GPs have entered into electronic medical records, the CPRD data quality depends on the accuracy of coding by GPs.

Diseases may be recorded in CPRD data using Read codes for specific diseases. Validation studies of CPRD data have investigated the Read codes for specific diseases. These have shown high positive predictive value of many diseases and, where evaluated, incidences of diseases to be similar to those in other UK data sources. In 2010 a systematic review found that 183 different diagnoses had been investigated, and since 2010 many further validation studies have been performed.[185,186] Overall, the systematic review found that estimates of validity were high, with a median proportion of cases with a confirmed diagnosis of 89%.

However, there are limitations of the validation studies of CPRD data. Firstly, the authors of the systematic review noted that reporting of validation studies was often too poor to permit a clear interpretation. Secondly, the vast majority of validation studies reported the positive predictive value of Read codes for a disease, but no other measures of validity, such as sensitivity, specificity and negative predictive value. The reason that usually only the positive predictive value is investigated is that the other measures require additional sampling of cases in CPRD without the Read codes of interest. The large number of cases in CPRD makes investigating false negatives a daunting task, and indeed researchers often only have access to the records of patients with a Read code for the disease under investigation, meaning sensitivity, specificity and negative predictive values cannot be calculated.

Even if the positive predictive value is high, the specificity, sensitivity and negative predictive value may be lower. Sensitivity may be lower because of the way that Read codes are analysed. The absence of a Read code for a disease from the electronic medical record must be interpreted as the absence of the disease in the patient; however, such a process may lead to false negative cases. The Read code

could be falsely absent in the record of a patient with hip osteoarthritis because patients did not present to their GP with disease or because GPs did not record the disease in the electronic medical record using a recognised Read code diagnostic for hip osteoarthritis, either because they recorded the disease using free text or using an unrecognised or inappropriate Read code. This possibility is especially relevant in the case of hip osteoarthritis because the disease is not included in the NHS Quality and Outcomes Framework (QOF) scheme.[187] A cohort of patients identified as having hip osteoarthritis from CPRD through the presence of a Read code for hip osteoarthritis could therefore have low sensitivity and be missing many patients with genuine hip osteoarthritis.

The implication of a high positive predictive value but unknown specificity, sensitivity and negative predictive value of Read codes diagnostic for a disease is that research undertaken on cases with the disease in CPRD will have a high internal validity but may have a lower external validity. Reassuringly, the few validation studies identified by the systematic review that did investigate sensitivity and specificity of diseases in the CPRD found high validity.[185]

An alternative method of identifying a cohort of patients with hip osteoarthritis from CPRD would be to include other 'surrogate' Read codes that do not specifically state the diagnosis of hip osteoarthritis but instead indicate the likely presence of the disease, such as Read codes for 'hip pain'. Including such broader terms would likely increase the sensitivity of the cohort, by detecting further patients missed by the original approach. Additionally, it is possible to search CPRD records for free text entries from GP consultations for terms (such as 'hip pain'), which would indicate the likely presence of hip osteoarthritis. Limiting the cohort to patients who had chronic hip pain (for example, with repeated free text entries stating 'hip pain) would increase the chance of correctly identifying patients with genuine hip osteoarthritis.

However, the limitation of including other 'surrogate' Read codes or free text is that patients may be included in the cohort who do not have hip osteoarthritis, and instead have another diagnosis such as trochanteric bursitis or referred back pain, reducing the specificity of the cases included from CPRD.[188]

A different approach to identifying a cohort of patients with hip osteoarthritis would be to identify patients with a code indicating that they underwent hip replacement, and then excluding patients with an indication other than hip osteoarthritis, such as fracture or rheumatoid arthritis. In patients with no indication recorded, it would be reasonable to assume the indication was hip osteoarthritis. This would permit the identification of patients with hip osteoarthritis but lacked a Read code. This approach was not available to the thesis since only a cohort of patients with the Read code for hip osteoarthritis was available from CPRD.

In summary, previous validations studies suggest that the quality of CPRD data on diagnostic Read codes is high, but comprehensive data quality checks must always be undertaken before analysing data. This study will therefore use CPRD as the source of electronic medical records. This study will identify the study cohort based on presence of Read codes indicating diagnosis of hip osteoarthritis in the records because this approach maximises specificity, although the limitation of unknown sensitivity is acknowledged. The date of diagnosis of hip osteoarthritis used in the study will be the date of diagnosis recorded in CPRD.

2.1.5 Verification of the diagnostic codes

To date, the validity of the Read codes indicating a diagnosis of hip osteoarthritis, and the date of diagnosis, in CPRD has not been investigated. There are two main concerns about the codes: (i) that the codes indicating a diagnosis of hip osteoarthritis were not used by GPs in a specific manner, meaning there may be false positive cases where other diseases have been incorrectly recorded using the codes indicating a diagnosis of hip osteoarthritis; and (ii) that GPs could have diagnosed patients with hip osteoarthritis when diagnostic criteria were not met, meaning there may be false positive cases where a code indicating a diagnosis of hip osteoarthritis is present but the patient does not have the disease.

Therefore, before investigating the influence of multimorbidity on access to hip replacement in patients with hip osteoarthritis, the first study in this thesis will be a validation investigation into the positive predictive value of the codes indicating a diagnosis of hip osteoarthritis in CPRD. (An investigation

into the sensitivity and specificity of the codes is beyond the resources of this thesis, because access has only been granted to cases in CPRD with Read codes indicating hip osteoarthritis.)

As discussed in Chapter 1, making a diagnosis of hip osteoarthritis in primary care is challenging. Firstly, the clinical presentation varies, and may present in a similar way to other pathologies. Secondly, there is only a weak correlation between symptomatic disease and the radiographic severity. Thirdly, there is no consensus on a radiographic definition of what constitutes a radiographic diagnosis of hip osteoarthritis. The result is that there is no single simple way to design a study to investigate whether each diagnosis of hip osteoarthritis is valid. The different methods available to the validation study are considered here.

There are a number of ways that Read codes for a diagnosis in the CPRD may be validated. A systematic review in 2010 investigated and summarised the range of methods that had been used.[185] Validation may use data entirely contained within the CPRD database (internal validation) or from outside the database (external validation). Three methods of internal validation and three methods of external validation of CPRD data have been described.

Internal validation methods

(1) Diagnostic algorithm: a diagnosis may be validated by the presence of codes indicating disease-specific symptoms, prescriptions for disease specific drugs, or test results indicative of the disease. Hip osteoarthritis does not have any such indicative codes, so this method is not appropriate here.

(2) Manual review of free text in CPRD: a disease may be validated by the presence of confirmatory evidence of disease status within the free text sections in the electronic medical records in CPRD. The evidence (either clinical or radiological or both) that led GPs to make the diagnosis of hip osteoarthritis would likely be recorded in free text entries, meaning this method is a possible option. The drawback of performing this method is that it would be very time-intensive, as it requires researchers to search through the free text.

(3) Sensitivity analysis: researchers may investigate the change in rate of disease when using a broad set of codes indicating the disease compared with a more restricted set of codes more likely to represent

true positive cases. Based on the change in rate, a 'precise' set of codes may be confirmed. To identify the cohort in the main study, only a previously defined set of codes for hip osteoarthritis with clear definitions will be used, meaning false positives could not be excluded in this manner. This method is therefore not appropriate.

External validation methods

(1) Comparison of rates: a diagnosis may be validated by comparing the disease incidence, prevalence or patterns in CPRD with those in a separate non-CPRD, UK-based data source. Unfortunately, it is not possible to compare the rate of hip osteoarthritis in CPRD to a published rate of hip osteoarthritis[3] because it is not possible to calculate the rate of hip osteoarthritis within the wider CPRD population. This is because data access was only granted by CPRD administration to records of patients identified by a Read code of hip osteoarthritis (i.e. the numerator), and so the total number of patients within the wider CPRD population (i.e. the denominator) is unknown. This method is therefore not appropriate.

(2) Record request to GP: copies of medical records or hospital discharge summaries may be requested from GPs by researchers, with the information obtained used to validate a diagnosis. The evidence that led GPs to make the diagnosis of hip osteoarthritis would likely be recorded in such documents, meaning this method is a possible option. The drawback of performing this method is that it would be time-intensive, both for researchers who would need to search through the documents and for GPs who would need to collate the relevant documents, anonymise them and submit them to researchers. This method may result in a low response rate from GPs.

(3) Questionnaire to GP: a questionnaire investigating how and when the diagnosis was made may be sent to GPs by researchers, with the information obtained used to validate a diagnosis. The evidence that led GPs to make the diagnosis of hip osteoarthritis would likely be captured by such a questionnaire, meaning this method is a possible option. The benefit of using this method is that it would be less time-intensive that the other available options.

The investigation into the validity of the codes indicating a diagnosis of hip osteoarthritis in CPRD will use the method of obtaining further information by sending a questionnaire to GPs.

2.1.6 Source of information on multimorbidity

The method to identify the cohort for the study to establish the influence of multimorbidity on access to hip replacement is confirmed. The next step is to determine what measures of multimorbidity to use and how to obtain the required data.

Chapter 1 describes the different approaches that have been developed to measure multimorbidity. Each score has strengths and weaknesses, and it is not known which score would be most appropriate in the setting of studying the likelihood of surgery. Therefore, this study will investigate a number of different types of multimorbidity score and compare their value. The measures that this study will use are (1) a simple count of coexisting diseases, (2) the Charlson Comorbidity Index, which is a count of coexisting diseases, with weighting by disease type, (3) the Electronic Frailty Index, which is a count of both coexisting diseases and functional limitations, and (4) the number of different medications prescribed in the previous 12 months and (5) the number of contacts with the GP in the previous 12 months, both of which are surrogate measures of multimorbidity burden. Score (1) is included as it is the most simple way of assessing for the presence of multimorbidity, using the traditional definition, and the influence of an increasing number of diseases can be measured. Score (2) is included as it is the most established and referenced score in the literature, with the strength of weighting by disease. Score (3) is included as a measure encompassing weighting by the impact of the multimorbidity on the patient, through the inclusion of functional limitations. Although technically this score is a score of frailty, the assessment of functional limitation will permit understanding of multimorbidity burden, making this score appropriate in this context. Scores (4) and (5) are included as such surrogate measures of multimorbidity may capture multimorbidity burden that is missed by traditional disease count methods. It was not possible to include a measure scored from a direct subjective assessment of overall health status, such as the ASA Classification System, because no such measure was routinely available in patients' records.

One method to obtain the required data on multimorbidity would be to collect the data prospectively, either directly from patients in the cohort or from their GPs. This method would require significant time

and financial resources and is not possible for this study. An alternative method would be to use the information stored in electronic medical records to derive the multimorbidity scores. Information on diseases, symptoms, disabilities, prescriptions and appointments is recorded by GPs in electronic medical records, meaning that all the proposed measures can be derived directly from the comprehensive records. This study will therefore use the available electronic medical records in CPRD to calculate multimorbidity measures on the study cohort. Other patient demographic information, such as age, sex, socio-economic status and region of the UK in which they live, will also be obtained from CPRD.

2.1.7 Source of information on study outcomes

Finally, how to obtain data on the outcomes of this study must be considered. The first outcome is whether patients are referred from primary care to orthopaedic secondary care, and the time between diagnosis of hip osteoarthritis and referral. Any such referral would be made by a patient's GP. One method to obtain information on whether a referral was made would be to contact the orthopaedic secondary care local to each patient in the cohort to see if a referral was ever received. This method would be expensive and logistically complex. Instead, the information on whether a referral was ever sent could be sought from primary care. One method would be to contact GPs of the entire study cohort directly to ask if they had ever made a referral. However, similarly this method would be expensive. The referral of a patient to secondary care for specialist opinion is a significant healthcare event and it is therefore likely that GPs would record referrals in the patient's records. An alternative method to obtain the information would therefore be to use the electronic medical records available to the study from CPRD. This method may achieve a similar data quality as contacting GPs directly, is more efficient, and is not prohibitively expensive. Therefore, data on this outcome will be obtained from CPRD.

The second outcome is whether patients undergo hip replacement, and the time between diagnosis of hip osteoarthritis and hip replacement. As before, collecting the data prospectively from patients,

primary care or secondary care is expensive and not possible for this study. Instead, the data will be collected retrospectively, from databases of routinely collected data. There are several possible sources of data.

One option is to obtain data from the National Joint Registry for England, Wales, Northern Ireland and the Isle of Man (NJR). The NJR was set up by the UK Government Department of Health and the Welsh Government in 2002 to collect information on hip replacements. Initially submission of data was voluntary; however, since 2011, it has been mandatory that all hip replacements performed in this geographical area are reported to the registry.[189] Data are collected on patient, implant and surgeon variables. An internal audit found the completeness of recording of hip replacements in the registry since 2011 to be in excess of 95% nationally when compared to levy returns for the number of implants sold, although it noted that the completeness of data in the earlier years of the registry is lower.[5] Within the UK arthroplasty research community, the NJR is regarded as the gold standard source of national data on hip replacements.[5] Access to the NJR via linkage to CPRD, however, was not available to this thesis.

Another option is to obtain data routinely recorded in secondary care. The Hospital Episode Statistics Admitted Patient Care (HES APC) database is a secondary care database that contains anonymised patient data from NHS-funded hospital admissions. The HES APC database, as with all HES databases are owned and managed by NHS Digital. NHS Digital is a public organisation with the role of national provider of digital services to the NHS in the UK, and is accountable to the UK government Department of Health and Social Care. The data recorded in HES APC is sourced from discharge summaries: upon discharge home of a patient from hospital, a clinician in the team that managed the patient completes a discharge summary that includes diagnoses made and procedures performed. The discharge summary is forwarded to the clinical coding department in the hospital where coders enter the information into a local database, using nationally standardised coding procedures. Details on diagnoses are coded using ICD-10 and on procedures using OPCS-4. Data is forwarded on a monthly basis to NHS Digital for two purposes: for hospital reimbursement and for the HES APC database. NHS digital perform data cleaning and validation, and pseudonymise information before adding data to HES APC. This process ensures

that the quality of data in HES APC is high.[190] Investigation of the recording of total hip replacement in HES APC found data to be of comparable quality to the NJR.[7]

A patient's data in HES APC may be linked to their data in CPRD. Indeed, linkage of CPRD to HES APC was available to this thesis, making HES APC a potential source of data. However, the drawback to using HES APC as the source of data on whether patients in the cohort undergo hip replacement is that some patients in the CPRD cohort may undergo hip replacement but there is no record of the hip replacement in HES APC. There are three reasons this may occur. Firstly, the CPRD cohort will be drawn from all of the UK, whereas the HES APC database only covers hospital admissions in England. Secondly, of the CPRD GP practices in England, only a subset (currently 75%) have consented to have their electronic medical records linked to other datasets, such as HES APC. Together, this would mean approximately only 58% of the study cohort could be included when investigating this outcome. Thirdly, a minority of patients may undergo hip replacement with non-NHS funding. Currently 14% of hip replacements are independently funded.[5] Any independently funded hip replacements would not be recorded in HES APC. It is possible that multimorbidity may be associated with the method of funding for hip replacement. Therefore, missing out independently funded hip replacements from the analysis could bias the results.

The third option is to use routine data recorded in primary care. The discharge summary created in secondary care upon discharge home of a patient from a hospital, whether NHS-funded or not, is sent to the GP of the patient. The GP then records the information on diagnoses and procedures in the primary care electronic medical record of their patient, because it is relevant to the ongoing management of the patient. Therefore, for this study data on the outcome of hip replacement will be obtained from CPRD.

It is, however, important to consider that it is possible that information on the hip replacements could be recorded incorrectly or not at all in the primary care electronic medical record, and therefore CPRD may not contain a complete record of all hip replacements that were performed on the study cohort. This could occur if the information was not correctly fed back from secondary care to the GP or if the GP did not record information on the hip replacement in the record.

Therefore, it is necessary to validate the recording of hip replacement in the data from the CPRD database. There are a number of ways that this could be done. One option would be to contact the GPs of the patients included in the cohort and ask them to confirm whether each patient had undergone hip replacement. Again, such a method would be prohibitively time consuming and expensive. Instead, the validation will be performed using the linkage to the HES APC database available to the thesis, with HES APC considered the reference standard. The validation will be performed on the subset of patients on whom linkage is available (expected to be approximately 58% of total cohort). In all patients who have data in CPRD and HES APC available, whether or not a hip replacement was recorded in each database will be investigated. The positive predictive power of a hip replacement recorded in CPRD also being recorded in HES APC will be calculated, and vice versa. If the positive predictive power of a hip replacement recorded in CPRD also being recorded in HES APC is over 80%, then the data on whether patients undergo hip replacement in CPRD will be deemed sufficiently accurate for the purposes of the study analysis. A consideration when performing this linkage validation is whether the entire study cohort in CPRD is comparable with the subset that have linkage to HES APC data. To answer this, the study will compare the two cohorts based on demographic variables and assess for any differences.

2.2 Objective 2 – To establish the influence of multimorbidity on the outcomes of primary total hip replacement

There are a number of steps and issues to consider in the design of the study to address this objective. These include:

- Setting of the primary outcomes
- Identification of the cohort
- Source of information on multimorbidity
- Source of information on study outcomes
- Consideration of a further study

2.2.1 Setting of the primary outcomes

Chapter 1 describes the complementary ways in which the outcome of total hip replacement may be assessed. Here, the primary outcomes to be investigated are:

i. the rate of complications, and
ii. the patient-reported outcomes of pain, function, and quality of life, and
iii. the rate of revision surgery and other reoperations.

2.2.2 Identification of the cohort

The cohort will be comprised of patients that have undergone elective primary total hip replacement. There are a number of ways the cohort could be identified.

A prospective cohort study is not feasible within the time and financial resources available to the thesis. The only viable method is a retrospective cohort study, using routinely collected patient information to identify the study cohort, measure multimorbidity and assess study outcomes. In the UK, there are a number of different potential sources of routinely collected data on patients undergoing total hip replacement.

One potential data source is a database of secondary care data. In the UK the largest database on secondary care data is the HES APC database. The database has a high degree of completeness of recording hip replacements performed in England. Therefore, HES APC would be an appropriate source of data to identify a cohort for the study.

An alternative potential data source is a database of primary care electronic medical records. Although hip replacements are not performed in primary care, information on procedures performed during hospital admissions is fed back to GPs who record the information in primary care electronic medical records. The thesis has access to data in CPRD. The completeness of recording of hip replacements in CPRD is not known. If the degree of completeness is not high, then a study cohort derived from this dataset may not be representative of the UK population undergoing total hip replacement. Therefore, CPRD may be an appropriate source of data to identify a cohort for the study; however, before CPRD

could be used, an investigation into the completeness of recording of hip replacements in CPRD would be required.

The third potential data source is the NJR. With a high degree of completeness of recording primary total hip replacements, the NJR would also be an appropriate source of data to identify a cohort for the study. However, it is not possible to use NJR data for this study due to limitations in the data available on multimorbidity. The NJR does not contain data on all the variables required to calculate all the different measures of multimorbidity required for the study. Similar to HES APC, the NJR may be linked to CPRD, which contains information to calculate all the different measures of multimorbidity required for the study. However, linkage of NJR data to CPRD data was not available to this study. There are no other databases of routinely collected data that could provide the required data on multimorbidity to which the NJR can be linked. Therefore, the NJR cannot be used as the data source to identify the cohort in this study.

In summary, there are two databases, HES APC and CPRD, that are possible options to identify a cohort of patients that have undergone total hip replacement. For this study, the HES APC database will be used as the data source and the study cohort will be identified based on the presence of an OPCS-4 code indicating primary elective total hip replacement. HES APC was determined to be the superior choice because the quality of data on the outcomes of patients in a HES APC cohort is likely to be higher than in a CPRD cohort. The reasons for this are detailed in section 2.2.4.

For this study the data on hip replacements from HES APC must be linked to data on multimorbidity in CPRD. The logical way of identifying the study cohort would be to identify all patients in HES APC with an included OPCS-4 code and then extract linked CPRD data on these patients. However, it was not possible for the thesis to obtain two separate cohorts with linked HES APC and CPRD data due to financial constraints.

As discussed in section 2.1, a cohort of patients with linked HES APC and CPRD data is required for the investigation the influence of multimorbidity on the likelihood of total hip replacement. Therefore, for this investigation of the influence of multimorbidity on outcomes of hip replacement, it is not

possible to obtain a second cohort directly from HES APC and CPRD. Instead, as the most pragmatic solution, the cohort of patients for this second study (outcomes of total hip replacement) will be identified from the larger cohort of patients obtained for the first study (likelihood of total hip replacement). Of the patients in the larger cohort for the first study, those that have an OPCS-4 code indicating primary elective total hip replacement in HES APC will therefore form the cohort for this second study.

2.2.3 Source of information on multimorbidity

This study will use the same five measures of multimorbidity as the study investigating the likelihood of total hip replacement, detailed in 2.1.6. HES APC does not contain data on all the variables required to calculate all the different measures of multimorbidity required for the study. However, via the linkage of HES APC to CPRD, all the required information on multimorbidity is available. Therefore, the records of the study cohort in HES APC will be linked to their records in CPRD, and the available CPRD data will be used to calculate the multimorbidity measures of the study cohort.

2.2.4 Source of information on study outcomes

Here, the possible sources of data on study outcomes are considered. Data from HES APC, CPRD or other databases of routinely collected data that are available via linkage to HES APC are considered.

The first outcome is the rate of post-operative complications within 90 days of total hip replacement. The complications included are death, venous thromboembolism, myocardial infarction, cerebrovascular accident, anaemia, wound infection, respiratory tract infection, and urinary tract infection. This study will also investigate length of stay and readmission to hospital. The information that HES APC and CPRD would provide on post-operative medical complications is different. The HES APC database would provide information on medical complications that were diagnosed and managed in secondary care within 90 days of the hip replacement, either prior to hospital discharge or following

a readmission to hospital. The CPRD database would provide information on those same medical complications that were diagnosed and managed in secondary care, with information fed back to the GP on hospital discharge, and additional less severe complications that were diagnosed and managed only in primary care. A possible weakness of CPRD data on complications is that secondary care information may not have been correctly fed back to the GP, and there may be date errors, as information is usually sent out on hospital discharge. This study will therefore investigate the rate of post-operative medical complications from the HES APC database. Data on length of stay and readmission to hospital will be sourced from HES APC as these data are not routinely available in CPRD.

Of note, the time period for inclusion of complications is within 90 days of total hip replacement. This time period is the most frequently selected in the current literature. This time period is selected here because it is sufficiently long to capture complications that may be directly attributable to the surgery (maintaining a high sensitivity), but it is not so long that it captures medical events that occurred irrespective of the recent surgery (so not compromising a high specificity). So that complications that occurred within this specific time period are included, it is essential that both the initial surgery and complication are recorded on the correct date. The recording of the date of events in HES APC is known to be accurate.[190] The accuracy of recording of the date of events in CPRD is known to be of lower quality.[185] Therefore, the HES APC is the preferred choice as the source of data for total hip replacements and complications in this study.

The second outcome is the patient-reported benefit of hip replacement. Chapter 1 of the thesis describes the different ways that have been developed to assess the benefit of hip replacement as perceived by patients. In the UK, since 2009 all patients undergoing total hip replacement funded by the NHS are requested to complete two Patient Reported Outcome Measures: the Oxford Hip Score and the EQ5D index. The scores are recorded in a database managed by NHS Digital, called HES PROMs. Data in HES APC may be linked to data in HES PROMs. No other national databases of PROMs routinely collected after hip replacement exist in the UK. Therefore, the HES APC is the preferred choice to

identify the study cohort for this outcome, and data on the outcome will obtained from the linked HES PROMs database.

The third outcome is the overall rate of revision surgery and other reoperations after total hip replacement. All procedures performed in NHS-funded hospital admissions in England are recorded in HES APC, with a high degree of completeness, including revision surgery and other reoperations after total hip replacement, as detailed in section 2.1.7. Thus, HES APC is an appropriate method to identify the cohort undergoing hip replacement and follow up the outcomes of revision surgery and other reoperations. While CPRD may also contain data on revision surgery and other reoperations after total hip replacement, it is possible the data may have a lower degree of completeness than in HES APC. This is because GPs may not record the detailed information on the type or side of the hip operation, since the purpose of the recording is for the future reference of the GP only. Unlike data recorded in HES APC, the coded data is not used for financial reimbursement. Therefore, the HES APC is the preferred choice to identify the study cohort and data for this outcome.

Importantly, as discussed in Chapter 1, Section 1.9, data from Dutch Arthroplasty Register suggest the increase in risk of revision in patients with multimorbidity compared to those without multimorbidity is highest within the first two years post-operatively.[145] In addition, data from the Swedish, Danish and Norwegian Arthroplasty Registers show the rate of early revision surgery (within five years of primary surgery) has increased in recent years, while data from the Swiss National Joint Registry show a proportion of early revision surgeries are performed within three months of primary surgery.[191–193] The early post-operative period therefore warrants detailed study. It is thus important to consider whether the study described above will be adequate to investigate this early post-operative period. The NJR reports that the cumulative rate of revision of all primary hip replacements at two-year post-operatively is 1.2%.[5] Because of the way that the cohort for this thesis has been obtained from CPRD, a cohort of approximately 5000 patients is anticipated with linked HES APC records for the study into the outcomes of hip replacement. A cohort of this size would be expected to have approximately 60 cases of revision surgery within two-years post-operatively, based on the NJR revision rate. Such a low number of cases of early revision surgery would likely be insufficient to power an investigation on the influence of

multimorbidity on the rate of early revision surgery. Therefore, a different larger cohort for this particular investigation is required. As a different cohort is required, this outcome will be investigated by a separate study, detailed below in Section 2.2.5.

2.2.5 Consideration of a further study

The primary outcome of this study will be the rate of early revision surgery and other reoperations after primary elective THR. As discussed in Chapter 1, recent data from several joint replacement registries suggest that the rate of early revision surgery is increasing, making this a key period for investigation.

Again, this study will be designed as a retrospective cohort study, using routinely available patient information. As detailed above, the cohort for this study must be sufficiently large for the analysis and therefore cannot be obtained from the dataset available to the thesis from HES APC and CPRD. An alternative source of routinely collected data on patients undergoing total hip replacements is joint replacement registries. Access to data in the UK NJR was not available to this study. Access to data in the Geneva Arthroplasty Register and Sweden Hip Arthroplasty Register was available. Therefore, the cohort for this study will be comprised of patients who underwent a total hip replacement that is recorded in either of these two joint replacement registries.

The next step is to determine what measure of multimorbidity to use. Linkage of the Geneva Arthroplasty Register and Sweden Hip Arthroplasty Register to any other databases was not available to this study. Therefore, any multimorbidity score must be available from the registries themselves. Both registries collect data on the ASA Classification System. As described in Chapter 1, the ASA Classification System is a direct subjective assessment of overall health status. It was developed to concisely communicate a patient's pre-anaesthesia medical comorbidities and predict perioperative risks. Although there only being one multimorbidity score available limits the depth of investigation into multimorbidity, the strength of this study design is in the larger cohort available in the joint replacement registries. This study will therefore use the ASA Classification System as the measure of multimorbidity.

Similar to the NJR, the Geneva Arthroplasty Register and Sweden Hip Arthroplasty Register record whether patients undergo revision hip replacement. In addition, the two registries record whether patients undergo other reoperations to the prosthetic hip after total hip replacements. This study will therefore use the Geneva Arthroplasty Register and Sweden Hip Arthroplasty Register as the source of data on the primary outcomes.

2.3 Objective 3 – To determine the variation in multimorbidity of patients undergoing primary total hip replacement in different countries

There are a number of steps and issues to consider in the design of the study to address this objective. These include:

- Setting of the primary outcome
- Identification of the cohort
- Measure of multimorbidity
- Reliability of the measure of multimorbidity

2.3.1 Setting of the primary outcome

Chapter 1 describes how comparisons of arthroplasty registry data internationally require controlling for the differences between the populations in different countries, and yet at present there are limited published data on differences in multimorbidity of patients undergoing total hip replacement in different countries. The primary outcome of this study therefore will be to investigate the extent of variation in multimorbidity of patients undergoing total hip replacement between arthroplasty registries internationally.

2.3.2 Identification of the study cohort

For this study, the cohort will include patients undergoing elective primary total hip replacement in different countries. Again, this study will be designed as a retrospective cohort study, using routinely available patient information. It is necessary to consider what databases are available in different countries.

One method would be to use data from primary care or secondary care databases. As described in section 2.1.6, databases of electronic medical records of primary and secondary care tend to contain broad and detailed information about patients' medical histories, enabling calculation of different measures of multimorbidity. It is not possible, however, to obtain data from primary care or secondary care databases from many different countries for two reasons. Firstly, only a small number of countries have created such databases. Secondly, in countries that have created such databases, there is no standardised method of recording data so analysing the data would be an extremely time-consuming task and beyond the time and financial resources available to the thesis.

The alternative method would be to use data from joint replacement registries. While joint replacement registries contain less detailed information on patients' medical histories, many joint replacement registries collect data on at least one measure of multimorbidity. This study will therefore investigate the variation in multimorbidity by using data from joint replacement registries.

Which joint replacement registries to include is the next consideration. All joint replacement registries worldwide may join the International Society of Arthroplasty Registries (ISAR). ISAR has a tiered membership system, based on data standards. Full membership requires the registry to be national in terms of geographical coverage, have over 90% of procedures performed within the country to be recorded in the registry and have the data collected validated. In 2017 there were 10 national joint replacement registries that were full members of ISAR. To ensure a high quality of data from joint replacement registries, only registries that are full members of ISAR will be eligible for inclusion in the study.

2.3.3 Measure of multimorbidity

The most widely collected measure of multimorbidity by joint replacement registries worldwide is the ASA Classification System.[89] Few registries record any other measure of multimorbidity. This study will therefore use the ASA Classification System as the measure of multimorbidity to maximise the number of registries that can be included. Other patient demographics will be studied.

2.3.4 Reliability of the measure of multimorbidity

For the study of variation in ASA Classification System of patients to be valid, the assignment of ASA Classification System in different countries must be consistent and equivalent. However, this has not previously been investigated. Therefore, this study must also investigate the consistency of assignment of ASA Classification System in different countries. The ASA Classification System was developed to predict which patients would have an increased mortality following major surgery. Therefore, the method of investigating the consistency of assignment of ASA Classification System will be to compare the between-population impact of ASA Classification System on 1-year mortality.

2.4 Structure of Thesis

The studies described above will be presented in the following chapters:

Chapter 3 presents the study to determine the validity of the coding of hip osteoarthritis in electronic primary care data, via a questionnaire sent to GPs. Data from CPRD are used.

Chapter 4 presents the study investigating the influence of multimorbidity on the likelihood of patients with hip osteoarthritis undergoing total hip replacement. Data from CPRD, ONS and IMD are used.

Chapter 5 presents the study investigating the influence of multimorbidity on the outcomes of total hip replacement. Data from CPRD, HES APC, HES PROMs, ONS and IMD are used.

Chapter 6 presents the study investigating the influence of multimorbidity on the rate of early revision surgery and other reoperations after total hip replacement. Data from the Geneva Arthroplasty Register and Sweden Hip Arthroplasty Register are used.

Chapter 7 presents the study investigating the variation in multimorbidity of patients undergoing total hip replacement in different countries. Data from seven national joint replacement registries (Australia, Finland, New Zealand, Norway, Sweden, Netherlands and United Kingdom) and one healthcare organisation registry (Kaiser Permanente, USA) are used.

Chapter 8 summarises the important findings and conclusions presented in the thesis. In addition, it discusses the relevance of the work presented, and provides ideas and recommendations for future work in the field.

A Patient and Public Involvement (PPI) meeting was held at the design stage of this work with participants from the Keele Osteoarthritis PPI Group. The meeting structure was a discussion with patients guided by members of the research team (RJF and AJS), with questions and answers throughout. One patient member joined the study team to give ongoing input for the studies performed in Chapters 3, 4, and 5. A presentation was given by a member of the research team (RJF) to outline the research study plan. The feedback was that patients felt it was difficult to know how their own 'other health issues' and multimorbidity would impact the outcome of hip replacement, and if they had been given more personalised information the decision of whether to go ahead would have been easier. Patients were supportive of the proposal to include a measure of 'sickness' or multimorbidity burden that included functional limitations, even though technically it would be a frailty score, rather than a multimorbidity score. Patients were keen when asked that length of stay and hospital readmission should be included when investigating postoperative outcomes of total hip replacement.

Chapter 3: Validation of the Diagnosis of Hip Osteoarthritis in CPRD

3.1 Abstract

Introduction

The diagnosis of hip osteoarthritis is subject to several uncertainties, especially in primary care. The aims of this study were to determine (i) the diagnostic accuracy of coding of hip osteoarthritis by GPs in the UK Clinical Practice Research Datalink (CPRD), (ii) the relative influence of radiographic and clinical parameters on diagnostic accuracy, and (iii) the accuracy of the diagnosis date.

Methods

An extract of all patients aged over 65 years, with a Read code for hip osteoarthritis listed between January 1995 and April 2014, was obtained from CPRD. A random sample was selected of 170 participants. A questionnaire concerning data in medical records on relevant clinical and radiographic criteria used to establish the diagnosis of hip osteoarthritis was distributed to GPs of participants. Using diagnostic criteria, thresholds for diagnosis based on clinical, radiographic and combined grounds were formulated.

Results

119 completed questionnaires were returned (70% response rate). The positive predictive value (PPV) of hip osteoarthritis codes, based on radiological criteria, was 79.8%. The PPV, based on clinical criteria, was 79.0%, with substantial but not complete overlap. Overall 12% of diagnoses were not confirmed. In 42% of cases, there was disparity between date of diagnosis in CPRD and the medical record. Median difference in date was +/-425 days (interquartile range, 18-1448 days).

Conclusions

Despite the difficulties in reaching a diagnosis of hip osteoarthritis in primary care, CPRD Read codes have a sufficiently high PPV for most research uses. However, the accuracy of diagnosis date may not be as reliable.

Work described in this chapter has been published as:

- *Ferguson RJ, Prieto-Alhambra D, Walker C, Yu D, Valderas JM, Judge A, Griffiths J, Jordan KP, Peat G, Glyn-Jones S, Silman AJ. Validation of hip osteoarthritis diagnosis recording in the UK Clinical Practice Research Datalink. Pharmacoepidemiol Drug Saf 2019 Feb; 28(2): 187-193. DOI:10.1002/pds.4673. PMID: 30375101*

3.2 Introduction

Databases of electronic medical records are widely used in observational epidemiological research. Healthcare information, including diagnoses, prescriptions, laboratory tests, symptoms, and hospital referrals, are recorded via computerised codes. The strengths of such data sources are large cohort sizes, complete records of healthcare use, follow up over many years, and lower cost than prospective investigation or manual record review. The limitation is that relying solely on computerised codes to determine the occurrence of events can lead to misclassification, due to inaccurate use of code, inaccurate recording of date, or events occurring without being recorded.

Researchers develop algorithms of codes in order to identify cases with specific diagnoses. Investigations of the validity of the algorithms are therefore key. Indeed, in 2006 an international consortium of researchers and administrative health care data users identified validation of such data coding as a research priority.[194]

To date no study has investigated the validity of the diagnosis of hip osteoarthritis within electronic medical records in the UK. NICE guidelines advise that osteoarthritis may be diagnosed on clinical grounds alone, based on the presence of appropriate symptoms. Nonetheless, the diagnosis is commonly confirmed on radiographic grounds, based on finding evidence of osteophytes, joint space narrowing and sclerosis on plain x-ray films.

This study set out to examine the validity of diagnostic codes for hip osteoarthritis recorded in the primary care electronic medical records. The CPRD GOLD database is the database of primary care electronic medical records available to this thesis.

Specifically, therefore, the study aimed to determine (i) the positive predictive value (PPV) of Read codes in CPRD GOLD records to identify 'true cases' of hip osteoarthritis, (ii) the relative influence of radiographic and clinical parameters on diagnostic recording, and (iii) the potential for error in using electronic recorded date of diagnosis.

3.3 Methods

3.3.1 Study design

This study examined the validity of the diagnostic codes to identify 'true cases' of hip osteoarthritis by obtaining further information on the diagnosis from GPs of individuals with such a diagnosis via a questionnaire.

3.3.2 Data set

The population for this study was randomly selected from the cohort of individuals whose anonymised electronic medical records were obtained from CPRD GOLD for the thesis.

Ethical approval to obtain the electronic medical records from CPRD GOLD and use them for the research planned in the thesis was obtained from the Independent Scientific Advisory Committee (ISAC). ISAC is a non-statutory expert advisory body established in 2006 by the Secretary of State for Health to provide scientific advice on research requests to access data provided by CPRD. The ISAC application number was 17_024R and approval was granted in May 2017.

The cohort of individuals for the thesis were identified by a search of all electronic medical records in the CPRD GOLD database for the presence of Read codes indicating the diagnosis of hip osteoarthritis. Individuals whose electronic medical record contained a Read code indicating the diagnosis of hip osteoarthritis were included in the cohort. The list of included Read codes is shown in Table 3-1. The list of Read codes was compiled from the CPRD Research Applications Code Browser. The included codes were reviewed and approved by a general practitioner, a consultant hip surgeon and a professor of musculoskeletal health. All included codes specifically state 'hip osteoarthritis'. This approach was chosen to maximise specificity (i.e., the chance that included patients would have a genuine diagnosis of hip osteoarthritis).

The search of the CPRD GOLD database was performed by the CPRD organisation. The full electronic medical records held in CPRD GOLD of all individuals included in the cohort were provided by CPRD.

These data were received in July 2017. The raw data of the electronic medical records were provided in the form of multiple text files, which were then cleaned and merged by a senior data manager to create a pre-analytical dataset.

Table 3-1 – Read Codes for Hip Osteoarthritis

Read code	Description
N053512	Hip osteoarthritis NOS
N05z511	Hip osteoarthritis NOS
N05zJ00	Osteoarthritis NOS, of hip
Nyu2100	[X]Other primary coxarthrosis
N051900	Primary coxarthrosis, bilateral

Certain inclusion and exclusion criteria were applied to the cohort received from CPRD:

(1) The date of first diagnosis was required to be between January 1, 1995 and April 30, 2014. The first appearance of an included Read code was considered to indicate the date of diagnosis of hip osteoarthritis. The end date of the time window was chosen to permit an adequate period of follow up after diagnosis: the last date of electronic medical records data available in the CPRD GOLD dataset provided to the thesis was January 26, 2015. In order to set the lowest maximum possible period of follow up at 8 months, the end date of April 30, 2014 was chosen. The start date of the time window was chosen to yield a time window of study of 20 years.

(2) The date of diagnosis was required to be at least one year after the start date of CPRD GOLD data availability. Start date of CPRD GOLD data availability was defined as the later date of the date the individual registered with the GP practice and of the date the GP practice became ‘up-to-standard”. “Up-to-standard” date indicates the point from which the GP practice is considered to have continuous and complete recording of patient data, based on meeting specified CPRD GOLD data submission criteria. The up-to-standard indicator is provided by CPRD GOLD. The requirement of having a minimum of one year of data available in CPRD GOLD prior to the date of diagnosis was for two reasons: (i) to maximise the likelihood that the date of diagnosis in the electronic medical record was

truly the incident, first diagnosis of hip osteoarthritis, and (ii) to permit the assessment of multimorbidity status prior to the date of diagnosis (required in a subsequent study in this thesis).

(3) Only individuals aged over 65 years were eligible. This was to maximise the likelihood that the diagnosis was primary hip osteoarthritis, and not arthritis secondary to another hip pathology.

Individuals meeting these criteria were included in the cohort for the thesis. The population for this study was then randomly selected from this cohort. To randomly select the population, each individual was assigned a consecutive integer and an online random number generator was used (Research Randomizer, USA)[195] was used.

3.3.3 Design of questionnaire

GPs of all individuals in the study population were contacted by post and asked to complete and return a questionnaire. The mailing of the questionnaires was performed by CPRD administration to preserve the anonymity of individuals and GP practices in CPRD GOLD. GPs were financially rewarded for returning a questionnaire to encourage participation.

The questionnaire was designed to confirm the code-identified diagnosis of hip osteoarthritis and verify the date of diagnosis, based on information recorded in each individual's medical records at their GP practice (GP medical record). It was acknowledged that the diagnosis of hip osteoarthritis might be made in different ways in primary care. Classically, osteoarthritis can be diagnosed based on radiographic grounds, based on radiographic features of osteophyte formation, narrowing of joint space width, sclerosis of subchondral bone and development of subchondral cysts, first described in the Kellgren-Lawrence classification system.[196] However, as discussed in Chapter 1, given the only moderate associations between structural signs of osteoarthritis and the presence of pain, NICE advises that osteoarthritis may be diagnosed clinically, from patient symptoms, without the need for confirmatory imaging.[43] The questionnaire was designed so that each diagnosis could be confirmed either on (i) radiographic grounds or (ii) clinical grounds, with criteria based broadly on each of the

radiographic and clinical features described in the Kellgren-Lawrence, American College of Rheumatology and NICE osteoarthritis diagnostic and classification schemes.

The questionnaire first sought concordance between the CPRD and the GP medical record, with a specific question on whether the GP medical record had ever had a diagnosis of hip osteoarthritis noted. If so, the questionnaire asked for (i) the date of diagnosis, (ii) whether the diagnosis was confirmed in secondary care, (ii) whether the diagnosis was subsequently revised. The second set of questions focussed on the presence or absence of the specific items used to make the diagnosis. The questions covered symptoms reported by the patient, findings from physical examination, and results from any hip radiographs that were recorded prior to the diagnosis of hip osteoarthritis. The questionnaire is shown in Figure 3-1. The questionnaire was first reviewed internally by an academic GP, a consultant hip surgeon and a professor of musculoskeletal health. The questionnaire was then reviewed by five GPs in active clinical practice, who were asked if the questions were relevant to the diagnostic process, and if any other questions should be added. No questions were added or removed at this stage.

A returned questionnaire was considered invalid if it was returned blank. A period of three months for return of questionnaires was permitted before the study was ended.

3.3.4 Sample size

The study population size was determined by a sample size calculation. To demonstrate sufficient validity, it was proposed a PPV of 70% or greater would be required. Based on previous CPRD validation studies for other diagnoses that obtained additional information from GPs[185], it was predicted that 80% of cases would be confirmed as valid. For the lower boundary of the 95% confidence interval of the proportion of valid cases to be above 70%, a minimum of 85 returned questionnaires was required Based on previous CPRD validation studies, a questionnaire response rate of 50% was predicted, meaning 170 questionnaires would need to be sent out. The population size for the study was therefore set at 170.

Figure 3-1 – Questionnaire sent to GPs

Practice ID:	Vision Patient ID:	Sex:	Birth Year:

Questionnaire into Validation of Hip Osteoarthritis

1. Diagnosis

a) Was the patient diagnosed with osteoarthritis of the hip?
□ Yes
If Yes, please provide the diagnosis date: __ / __ / ____
□ No
If No, no further responses to the questionnaire are required
b) Was the diagnosis confirmed in secondary care?
□ Yes
□ No
c) Was the diagnosis subsequently changed to an alternative diagnosis?
□ Yes
□ No

2. Presentation

a) Prior to the diagnosis of osteoarthritis of the hip, did the patient attend with any hip related symptoms?
□ Yes
□ No
□ Unknown *(If No or Unknown, please proceed to question 3)*
b) Please indicate which symptoms the patient complained of *(Please tick all that apply)*:
□ Pain
□ Stiffness
□ Restriction of movement
□ Other (please indicate): _____

3. Physical Examination

According to the patient's electronic healthcare record (including hospital letters), please indicate which best apply based on the last joint examination made prior to diagnosis or hip osteoarthritis *(Please tick all that apply)*:

□ Normal range of joint movement
□ Reduced range of hip flexion
□ Reduced range of hip internal rotation
□ No record of joint examination

4. Imaging Investigations

According to the patient's electronic healthcare record (including hospital letters), please indicate which apply based on hip or pelvis X-rays/scans taken prior to diagnosis of hip osteoarthritis *(Please tick all that apply)*:

□ Osteoarthritis
□ Osteophytes
□ Narrowing of hip joint space

Many thanks for your time in completing this questionnaire. Please return it as soon as possible to the CPRD in the freepost envelope provided.

A higher degree of precision could have been achieved with a larger study population size. However, the CPRD charge researchers £35 for each questionnaire mailed and a further £55 for each questionnaire returned. This limited the study population size to the minimum required by the sample size calculation.

3.3.5 Data analysis

The response rate was calculated as the number of the returned valid questionnaires divided by total number of questionnaires sent.

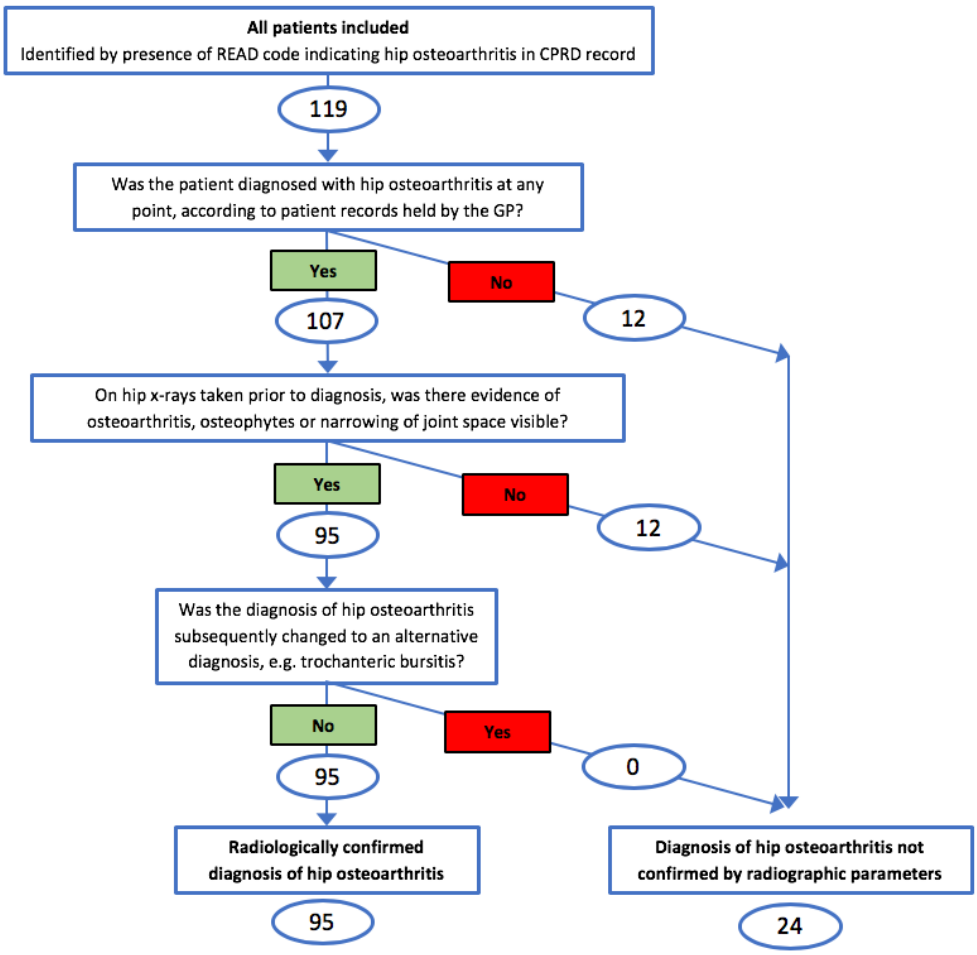
It is possible that on receiving the questionnaire and looking up their patient's medical records, GPs might have been more likely to return a completed questionnaire if the GP medical record showed the clinical details to justify the diagnosis, leading to participation bias. Conversely, in patients' whose medical records did not contain clinical details to justify the diagnosis, GPs might have been more likely to not return the questionnaire, leading to non-response bias. The characteristics of the two groups (patients whose GP responded ['responders'] and patients whose GP did not respond ['non-responders']) were investigated for any differences.

An assessment of both participation bias (comparison of 'responders' versus the whole CPRD cohort) and of non-response bias (comparison of 'responders' versus 'non-responders') was done by comparing age, sex, body mass index (BMI), socio-economic status and comorbidities of the groups. These data were sourced from the electronic medical record of each individual obtained from CPRD. Socio-economic status was derived from the Index of Multiple Deprivation quintile, which was linked to the CPRD records.[197] Comorbidities were scored with the Charlson Comorbidity Index.[123]

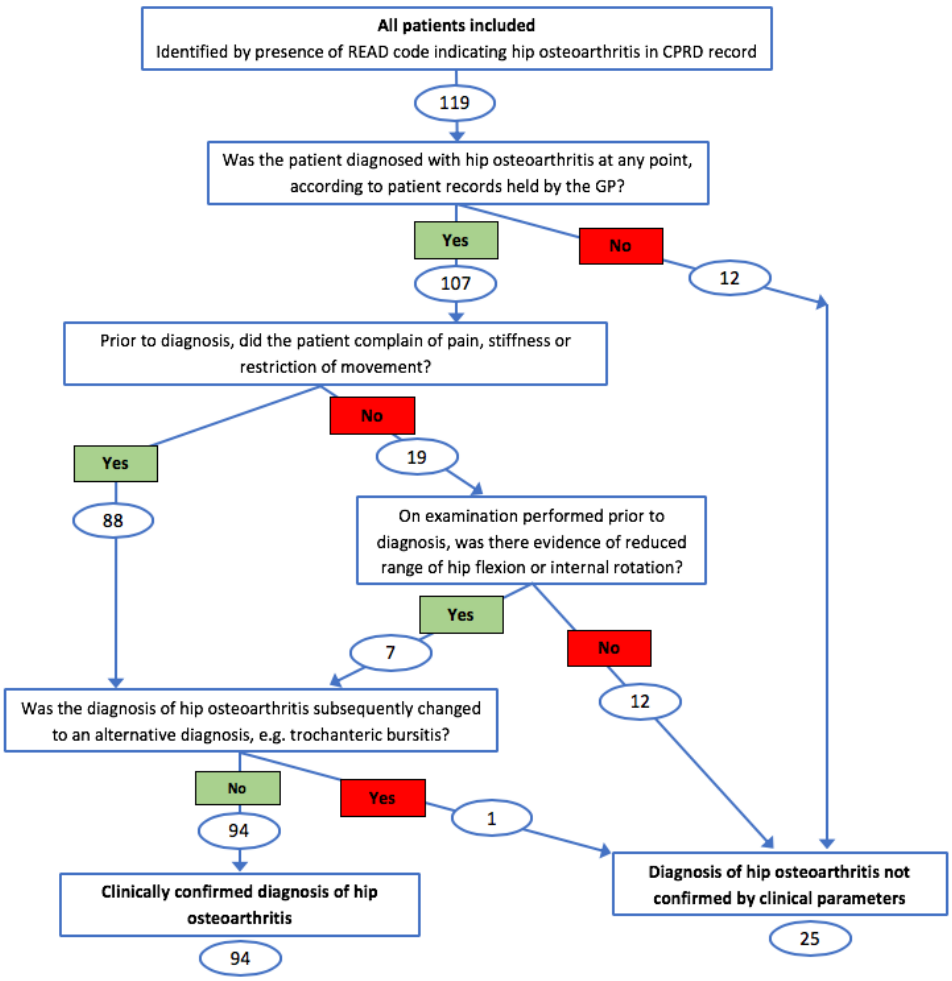
An algorithm flow chart (Figure 3-2) was used to make the diagnostic assignment of hip osteoarthritis. Cases were defined as radiologically confirmed cases of hip osteoarthritis if the report of radiographs reported evidence of 'osteoarthritis', 'osteophytes' or 'joint space narrowing'. Cases were defined as clinically confirmed cases if patients reported pain, stiffness or restriction of movement, or if physical examination found a reduced range of hip flexion or internal rotation. Cases were defined as unconfirmed cases if these radiological or clinical parameters were not met.

Figure 3-2 – Algorithms for diagnosis based on radiologic and clinical parameters

(i) Algorithm for diagnosis based on radiologic parameters



(ii) Algorithm for diagnosis based on clinical parameters



Patients could be classified as satisfying (i) radiographic criteria, (ii) clinical criteria, (iii) *either* radiographic *or* clinical criteria, and (iv) *both* radiographic *and* clinical criteria. The PPV refers to the proportion of the cases that were confirmed as actual cases, based on the information provided by the GP in the questionnaire. PPV was calculated as the number of confirmed cases divided by the total number of cases for whom a valid questionnaire was received from the patient's GP. Binomial 95% confidence intervals were calculated for the PPV.

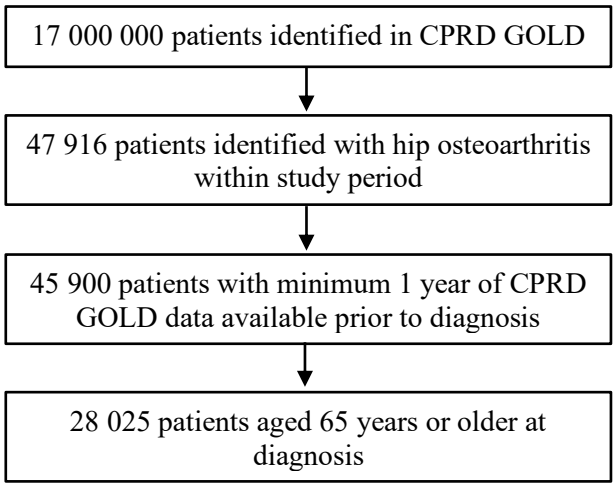
In patients with a difference in the date of diagnosis recorded between CPRD and the GP medical record, the number of days between the two dates was calculated. The distribution of the difference in date in those without an exact date match is displayed graphically.

3.4 Results

3.4.1 CPRD cohort

28,025 individuals with a Read code indicating the diagnosis of hip osteoarthritis in CPRD GOLD were identified as eligible for inclusion in the cohort for the thesis. The number of individuals included at each stage of applying the inclusion criteria are shown in Figure 3-3. The earliest included date of diagnosis was January 1, 1995, and the latest included date of diagnosis was April 30, 2014. Further demographic details on the cohort for the thesis are given in Chapter 4.

Figure 3-3 – Identification of the cohort in CPRD



3.4.2 Study population

The 170 individuals randomly selected for the study population from the 28,025 individuals in the CPRD cohort were registered at 138 GP practices. There were 112 practices with 1 participant, 20 practices with 2 participants, and 6 practices with 3 participants.

3.4.3 Returned questionnaires

A total of 125 of 170 (73.5%) questionnaires were returned. Six of the returned questionnaires were blank and therefore invalid, because GPs reported they could not access required data (in 5 cases GPs had changed computer software; in 1 case the patient was no longer registered at the practice), yielding

a final response rate of 70.0% (119/170). The response rate was higher amongst patients with a more recent diagnosis (date earlier/later than the median diagnosis date): 74% vs 66%.

3.4.4 Sample demographics

The comparison of demographic characteristics between the three populations of (i) the entire CPRD cohort with hip osteoarthritis, (ii) patients whose GPs responded to the questionnaire ('GP responders'), and (iii) patients whose GPs did not respond to the questionnaire ('GP non-responders') to the 170 questionnaires are shown in Table 3-2. The characteristics were broadly similar. The patients whose GPs were non-responders were more likely to be male, but had very similar mean age, BMI and comorbidity status. The patients whose GPs were responders had a socio-economic profile very close to the entire CPRD cohort with hip osteoarthritis.

Table 3-2 – Demographic characteristics of patients in the entire CPRD GOLD cohort, and of GP responders and non-responders to the validation questionnaire

	Entire cohort		GP responders		GP non-responders	
	Number	%	Number	%	Number	%
Cohort size	34, 656		119		51	
Gender						
Male	14183	40.9	55	46.2	26	51.0
Female	20473	59.1	64	53.8	25	49.0
Age (mean, SD)	75.2	11.5	73.7	11.7	74.3	11.4
BMI (mean, SD)	28.4	5.3	28.6	5.1	28.5	6.2
CCI (mean, SD)	0.36	0.95	0.40	0.93	0.35	1.05
IMD						
Quintile 1: Least deprived	5688	26.4	17	27.4	5	20.8
Quintile 2	5342	24.8	14	22.6	7	29.2
Quintile 3	4664	21.6	12	19.4	1	4.2
Quintile 4	3756	17.4	13	21.0	8	33.3
Quintile 5: Most deprived	2111	9.8	6	9.7	3	12.5
Missing	13095	-	57	-	27	-

BMI: body mass index (kg/m^2); CCI: Charlson Comorbidity Index; IMD: Practice level Index of Multiple Deprivation, 2004

3.4.5 Confirmation of diagnosis

In all, 95 of the 119 cases were confirmed based on radiological parameters, yielding a PPV of 79.8% (95% confidence interval [CI]: 72.6%, 87.0%), whilst 94 cases were confirmed based on clinical parameters, yielding a PPV of 79.0% (95% CI 71.7%, 86.3%). The level of agreement between radiological and clinical confirmed cases is shown in Table 3-3, with a Kappa statistic of 0.46, p value <0.001. If either clinical or radiographic criteria were required to confirm diagnosis, the PPV was 88.2% (95% CI 82.4%, 94.0%). If both clinical and radiographic criteria were required to confirm diagnosis, the PPV fell to 70.5% (95% CI 62.3%, 78.7%).

Of the 14 unconfirmed cases, in 12 cases there was no record of a diagnosis of osteoarthritis ever having been made. One case was unconfirmed because the diagnosis was subsequently changed to trochanteric bursitis. One case was unconfirmed because radiological and clinical criteria were not met; however, the GP reported that the diagnosis of hip osteoarthritis was subsequently confirmed in secondary care.

Table 3-3 – Overlap of Cases Confirmed by Radiological and Clinical Parameters

		Clinical		
		Confirmed	Unconfirmed	All
Radiological	Confirmed	84 (70.5%)	11 (9.2%)	95 (79.8%)
	Unconfirmed	10 (8.4%)	14* (11.8%)	24 (20.2%)
	All	94 (79.0%)	25 (21.0%)	119 (100%)

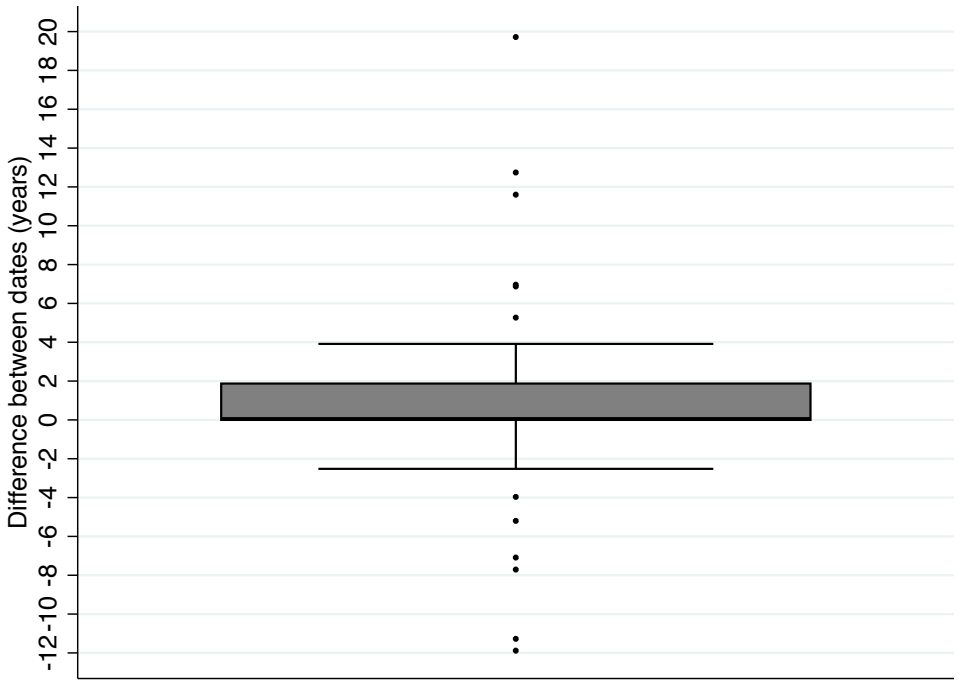
Kappa statistic = 0.46, p value <0.001
*One case was unconfirmed by radiological and clinical parameters; however, the GP reported that the case was confirmed in secondary care.

3.4.6 Date of diagnosis

In 104 of the total 105 confirmed cases (99.0%) the date of diagnosis was recorded in the GP medical record. In the majority of cases (60/104), the date of diagnosis was identical to that in CPRD. However, in the other 44 cases (42.3%) there were differences in diagnosis date. In the majority of cases with a difference in diagnosis date (32/44), the GP medical record recorded an earlier date of diagnosis than the CPRD record. For many patients, there were substantial differences between the two dates (Figure

3-4). Median difference in diagnosis date was +/-425 days (interquartile range [IQR], 18-1448 days). In 11 cases, the difference in diagnosis date was less than 30 days. In 24 cases, the difference in diagnosis date was over one year. Of the 24 cases, in 16 cases the date of diagnosis was over one year earlier in the GP medical record and in 8 cases the date of diagnosis was over one year earlier in CPRD.

Figure 3-4 – Box and whisker plot of the time in years between dates of patients with a different date of diagnosis between CPRD and GP patient record (N=44)



3.5 Discussion

3.5.1 Summary of main findings

The results of this validation study show that the diagnosis of hip osteoarthritis recorded in the CPRD has high PPV when assessed by radiological or clinical criteria (79.8% and 79.0% respectively). These findings suggest that, using the criteria described here, the diagnosis of hip osteoarthritis in patients aged over 65 years recorded in the CPRD is accurate. The level of accuracy of the diagnosis was similar between assessment by radiological and clinical criteria.

By contrast, the date of diagnosis in CPRD was identical to that in the GP medical record in only 58% (60/104). In the 42% (44/104) there was a discrepancy in date of diagnosis between the CPRD record and the GP medical record. The median difference was +/- 425 days. This suggests caution should be taken in using the date of diagnosis of hip osteoarthritis in CPRD for time-dependent research.

The presence of 12 CPRD hip osteoarthritis cases having no recorded diagnosis in the GP patient record was unexpected. Possible explanations are that there was an error in completing the questionnaire by the GP, that the code was entered into CPRD in error, or that after diagnosis was made and recorded in CPRD, the GP subsequently edited the patient record. Of note, one of the cases unconfirmed by radiological or clinical criteria but was reported to be confirmed in secondary care. The lack of evidence in the GP patient record to confirm the diagnosis may be because information was not passed back from secondary care to primary care. The analysis plan was to confirm cases based on defined radiological or clinical criteria, so this patient was treated in the analysis as an unconfirmed case because these criteria were not met. Additionally, not all patients are seen in secondary care, so permitting the confirmation of diagnoses from secondary care would have introduced bias into the results.

3.5.2 Findings in context

A literature search in PubMed did not identify any studies that have previously investigated the PPV of hip osteoarthritis diagnosis in the CPRD dataset. A further search identified three studies that investigated the validity of diagnoses of osteoarthritis of any joint recorded in any electronic databases of medical records.[198–200] Two studies validated the diagnosis in the Canadian Primary Care Sentinel Surveillance Network, which is Canada's first national database of primary care electronic medical records. One study validated the diagnosis in the British Colombia, Canada, Ministry of Health administrative database[200]. The methods of validation were expert review of original primary care records and comprehensive clinical assessment of patients. The PPV of a diagnosis of osteoarthritis ranged from 82% to 100%. These results are consistent with the results of this study.

3.5.3 Strengths and limitations

Selecting appropriate criteria to determine if a diagnosis of hip osteoarthritis is valid or not was fundamental. The approach to validate the diagnosis was based on the ways that the diagnosis of hip osteoarthritis is made in practice based on using both radiological and clinical information.

A limitation of the questionnaire was that there was no option in Question 4 on Imaging Investigations for GPs to record that a patient had not had imaging prior to the diagnosis being made. Therefore, if a questionnaire did not have ticked any of the available options in Question 4 (osteoarthritis, osteophytes, or narrowing of the hip joint space), it was not possible to determine if a patient had no imaging or had imaging that had no evidence of osteoarthritis. It would have been informative to the study to see if patients were having hip osteoarthritis diagnosed without any imaging, which is entirely appropriate under NICE guidance.

The approach to radiologically confirming the diagnosis permitted the presence of mention of 'osteoarthritis' or of osteophytes or joint space narrowing as sufficient. The latter are the radiographic features required for Kellgren-Lawrence grading to radiologically define osteoarthritis. It was not possible to obtain the radiographs to formally Kellgren-Lawrence grade them and it was unlikely such grading would be available on routine GP records. The radiologically confirmed cases did not also require any further clinical evidence. This approach is justified because x-rays of the hip would most likely have been performed to investigate symptoms in the hip region. However, it is possible that in some cases x-rays were performed for another clinical reason (for example, to investigate general surgical pathology), and that radiographic evidence of hip osteoarthritis was an incidental finding, leading to a diagnosis in the absence of clinical disease. A further limitation to the questionnaire was that it did not ask whether GPs had gathered information from a formal report on radiographs or scans written by a consultant radiologist or whether GPs had interpreted the radiographs or scans themselves. In theoretical and unknown cases where a specialist report was unavailable and a GP had interpreted radiographs or scans themselves, it is possible errors in the interpretation could have occurred, introducing error into the questionnaire results and validation process.

The approach to clinically confirming the diagnosis of hip osteoarthritis, allowed the presence of mention of either pain, stiffness or restriction of movement, or reduced range of hip flexion or internal rotation as sufficient. This differs from the NICE clinical diagnostic criteria. NICE require activity-related joint pain and less than 30 minutes of morning stiffness in patients 45 years or over. In this retrospective study, a pragmatic view was taken, after consultation with GPs, that the quality of the data in routine records would not be of sufficient quality to allow robust assignment using criteria such as those of NICE or ACR. It was unlikely that there would be any accurate measure of, for example, range of hip flexion and internal rotation, these being good markers of hip osteoarthritis[201].

In summary, both the available data on radiological evidence and clinical evidence of hip osteoarthritis have limitations in their ability to 'prove' a valid diagnosis.

There was potential for bias between the quality of coding of GPs that responded and those that did not. The study demonstrated no significant differences between the patients based on age, gender, comorbidity or their GP practice index of multiple deprivation. Of note, the profile of social demographic status of responders closely mirrored the entire CPRD cohort. However, the possibility cannot be excluded that in some of the cases of unreturned questionnaires, GPs may have chosen to not respond on finding a lack of evidence to confirm the diagnosis of hip osteoarthritis.

The sample size was sufficient to demonstrate that the diagnosis was valid using radiological and clinical parameters separately; however, a larger sample size would have enabled a more accurate PPV calculation, with a smaller 95% CI. As with many validation studies, this study was limited by costs. The period for responses was limited to three months due to time constraints and because it was predicted that the majority of responses would be received within two months. This transpired: 84% (105/125) returned questionnaires were returned within two months.

The study design attempted to ensure that only incident cases of hip osteoarthritis during the study period were included. The methodological approach to achieve this was to require a minimum of one year of data were available in CPRD prior to the date of diagnosis. It was hypothesized that any individuals with previously diagnosed hip osteoarthritis would likely have it mentioned by their GP in

their electronic medical record over the period of 12 months, and therefore any individuals without a mention of hip osteoarthritis over this period likely had not been previously diagnosed with the condition. Individuals for whom there was a mention of hip osteoarthritis in the 12 months prior to diagnosis in CPRD were therefore excluded.

However, the possibility remains that some of the patients in this analysis may have had a diagnosis of hip osteoarthritis previously. This could occur in two ways. Firstly, in the UK patients are free to move between different primary care providers. The CPRD database can only capture clinical events during the time when an individual patient is registered with a CPRD practice, and therefore some patients may have had a diagnosis of hip osteoarthritis previously in a non-CPRD practice. Secondly, patients may have had a diagnosis of hip osteoarthritis in a CPRD practice more than one year previously and had not consulted their GP for at least a year. On investigation of the date of diagnosis, 16 cases were identified where the date of diagnosis in the GP patient was more than one year earlier than in the CPRD record. These 16 cases may represent cases where the date of diagnosis in CPRD was not accurate or prevalent cases where an earlier diagnosis was recorded in CPRD but was missed because the study only investigated one year prior to the diagnosis within the study period. Because of this uncertainty, the decision was made not to exclude these 16 cases. It is unlikely that either scenario is likely to be of material impact to the results of the coding accuracy analysis. However, were it possible to identify and exclude such patients, the disparity in date of diagnosis in CPRD and the GP patient record would likely be lower.

This study aimed to assess the accuracy of "new" diagnoses of hip osteoarthritis using the Read Codes recorded by GPs in CPRD. Although there are estimates of the point prevalence of hip osteoarthritis from population surveys, it was not possible to derive any comparative estimate of the prevalence of osteoarthritis in the CPRD population, because the patient cohort only constituted new diagnoses in primary care. Further studies may attempt to investigate the proportion of hip osteoarthritis cases seen in UK primary care that are not diagnosed or coded by the GP, although this may prove challenging because there are no "gold-standard" data to compare primary care data with. Indeed, there are studies from many disorders in the literature where CPRD itself has been used as such a gold-standard.

A key limitation is that from the data it is possible calculate PPV of the diagnosis in CPRD, but not sensitivity. There may exist many cases of patients in the CPRD that have hip osteoarthritis but do not have it diagnosed or recorded. It was not possible to identify these patients, meaning a sensitivity calculation was not possible. Future studies on hip osteoarthritis in the CPRD should consider this potential source of bias.

It is also important to consider whether there were codes used by some GPs for recording the diagnosis of hip osteoarthritis that were not included in this analysis. For example, codes that mentioned osteoarthritis "of the pelvic area" but had not mentioned hip specifically were not included. It would be important in future studies to determine if such codes are widely used by some GPs for hip osteoarthritis. However, whilst excluding such cases would under-estimate the total number of hip osteoarthritis patients, a plausible conclusion is that the levels of clinical and radiographic confirmation of such cases would not necessarily be different from those where the GP preferred to use the term hip. This however remains to be proven.

The cohort of patients was restricted to patients aged over 65 years. This is because there is greater diagnostic uncertainty in patients aged under 65, and therefore more complex to validate. The findings of this paper should not be assumed to apply to diagnoses of hip osteoarthritis made in younger patients.

3.5.4 Conclusions

In conclusion, the recorded diagnosis of hip osteoarthritis was confirmed in a high proportion of patients aged over 65 years within CPRD, and therefore Read codes for hip osteoarthritis amongst all patients aged over 65 in the CPRD dataset are likely to accurately identify true cases. However, accurate diagnosis timing remains difficult to determine.

Chapter 4: Influence of Multimorbidity on the Likelihood of Total Hip Replacement

4.1 Abstract

Introduction

It is not known how patients with hip osteoarthritis and concurrent multimorbidity are currently being managed. The aim of this study was to investigate the influence of multimorbidity on the likelihood of total hip replacement in patients with hip osteoarthritis in the UK.

Methods

A cohort study was performed, with the cohort comprised of all patients aged over 65 years with a diagnosis of hip osteoarthritis recorded in CPRD GOLD. Severity of multimorbidity burden was measured using five different scores. The outcomes were (i) referral to orthopaedic secondary care and (ii) undergoing total hip replacement, with Kaplan-Meier survival and competing-risk analyses.

Results

28,025 patients were included. The quality of data on referral to orthopaedic secondary care was poor and analysis of this outcome was terminated. 10,948 patients underwent total hip replacement. Increased multimorbidity burden was associated with decreased likelihood of undergoing surgery, irrespective of the method of scoring multimorbidity. The Electronic Frailty Index had the largest difference between categories of all the multimorbidity measures. Adjusted hazard ratio (Electronic Frailty Index category of 'severe frailty' versus 'fit') was 0.34 (95% CI 0.22, 0.51).

Conclusions

Hip osteoarthritis patients with concurrent multimorbidity were up to two thirds less likely to undergo total hip replacement. Whether this difference in healthcare management is appropriate depends on

whether and to what extent multimorbidity influences the outcomes of total hip replacement. As a next step, it is essential to investigate the influence of multimorbidity on the outcome of hip replacement.

Work described in this chapter has been published as:

- *Ferguson RJ, Prieto-Alhambra D, Peat G, Delmestri A, Jordan KP, Strauss VY, Valderas JM, Walker C, Yu D, Glyn-Jones S, Silman AJ. Influence of pre-existing multimorbidity on receiving a hip arthroplasty: cohort study of 28 025 elderly subjects from UK primary care. BMJ Open. 2021 Sep 23; 11(9): e046713. DOI: 10.1136/bmjopen-2020-046713. PMID: 34556507*

4.2 Introduction

As discussed in Chapter 1, limited data are available on the influence of multimorbidity on the outcomes of total hip replacement for patients with hip osteoarthritis. The lack of clear evidence has a significant impact on patients. Patients suffering with hip osteoarthritis and their clinicians must decide whether or not to proceed with total hip replacement without personalised information available to them on the predicted risks and benefits of surgery.

At present, there is no information on how patients with hip osteoarthritis and concurrent multimorbidity are currently being managed compared with patients without multimorbidity. The aim of this chapter is to investigate how, in current practice, patients with hip osteoarthritis are having their disease managed, specifically whether patients are undergoing total hip replacement or not, and examining the influence of the presence or absence of multimorbidity in these patients on the management. There are a number of ways this subject may be investigated, as discussed in Chapter 2. This chapter will identify a cohort of patients with hip osteoarthritis from across the UK and study the clinical outcomes of referral to orthopaedic secondary care and of whether patients undergo total hip replacement. These two outcome measures were selected as they are the two key 'decision points' in a patient's pathway to undergoing total hip replacement.

4.3 Methods

4.3.1 Study design

The study was a retrospective cohort study, using routinely collected primary care data in the UK. The data source was CPRD GOLD (application ISAC-17_024R), with linked data from the Hospital Episode Statistics Admitted Patient Care database (HES APC), the English Index of Multiple Deprivation (IMD), and the Office for National Statistics (ONS).

4.3.2 Data set

The population for this study consisted of the cohort of individuals whose pseudonymised electronic primary care medical records were obtained from CPRD for the thesis. Details of how the cohort of individuals were identified in CPRD via a diagnosis of hip osteoarthritis, including inclusion and exclusion criteria, are given in Chapter 3, Section 3.3.2.

Data on the individuals' demographics were extracted from CPRD, including year of birth, sex, body mass index (BMI), ethnicity, marital status and geographical region of residence within the UK. Age was taken at date of diagnosis of hip osteoarthritis and calculated using January 1st in the year of birth as date of birth. Exact date of birth of registered individuals is not available from CPRD to preserve pseudonymisation of data. BMI was taken as the last recorded BMI measurement prior to date of diagnosis. There was no limitation placed on the earliest date of a BMI measurement, provided the patient was aged over 18 years. Ethnicity was recorded using the categories defined by the Office for National Statistics for the 2011 census, with categories then collapsed into the groupings of: white, Afro-Caribbean, Chinese, South Asian, and other. Marital status was categorised as single, in a relationship or separated, and the last mention prior to diagnosis was used. Geographical region of residence within the UK was categorised using the Health and Social Care Information Centre geographical regions of Northern Ireland, Scotland, Wales, and the 10 regions of England, which are North East, North West, Yorkshire and the Humber, East Midlands, West Midlands, East of England, South East Coast, South Central, South West and London.

The electronic medical records of the cohort from CPRD were linked with records in the English Index of Multiple Deprivation, and the Office for National Statistics (ONS) mortality dataset for data on socio-economic status and death. NHS Digital performs the linkage and uses an eight-step process to match individuals' records. NHS number, date of birth, sex and postcode are used if available. Each linkage is assigned a match rank, based on the step of the algorithm at which the linkage was established. A match rank of one indicates the strongest linkage. CPRD provided linked records for individuals with match rank of one to five. Linked records were only included in this study if the match rank was one or two.

The English Index of Multiple Deprivation contains information on socio-economic status of patients, by quintile, based on the latest available postcode of residence. The ONS mortality dataset contains national death certificate data, irrespective of whether the death occurred in hospital or in the community, including date and cause of death.

4.3.3 Multimorbidity measures

Multimorbidity was the exposure of interest in this study. As discussed in Chapter 1, there are many ways to estimate the severity of multimorbidity burden. Five different methods to measure multimorbidity were selected to be used in this study, as explained in Chapter 2, Section 2.1.6:

(1) Charlson Comorbidity Index,
(2) Count of chronic diseases,
(3) Count of different medications prescribed in the previous 12 months,
(4) Count of contacts with primary care in the previous 12 months, and
(5) Electronic Frailty Index.

All multimorbidity scores were calculated from patients' electronic medical records in CPRD, based on the presence of Read codes recorded after the start date of CPRD data availability and prior to the index date (date of diagnosis of hip osteoarthritis). The method for determining the start date of CPRD data availability is described in Chapter 3, Section 3.3.2.

The Charlson Comorbidity Index (range 0-37) was calculated using the scoring algorithm based on the presence of certain diseases, as defined by Charlson et al.[123] The diseases and scoring algorithm are shown in Table 4-1. A previous study by Khan et al created a full set of Read code lists for the Charlson Comorbidity Index and validated them using CPRD data.[202] For this study, the list of Read codes for each disease in the Charlson Comorbidity Index was obtained from the supplementary information of the Khan et al study. The code lists are shown in Appendix Table A-1. Read codes recorded in CPRD in the five years prior to the index date were included, consistent with the methodology of Khan et al.

Table 4-1 – Scoring of the Charlson Comorbidity Index

Score	Disease state	Score	Disease state
1	Myocardial infarction	2	Hemiplegia
1	Congestive heart failure	2	Renal disease, moderate or severe
1	Cerebrovascular disease	2	Diabetes with end organ damage
1	Peripheral vascular disease	2	Any malignancy
1	Dementia	2	Leukaemia
1	Chronic pulmonary disease	2	Lymphoma
1	Connective tissue disease	3	Liver disease, moderate or severe
1	Peptic ulcer disease	6	Metastatic solid malignancy
1	Liver disease, mild	6	AIDS
1	Diabetes		

The count of chronic diseases (range 0-17) was calculated from a simple unweighted count of the number of included diagnosed chronic diseases recorded in patients' electronic medical records. The chronic diseases selected to be included were the diseases included in the Quality and Outcomes Framework (QOF). The QOF, introduced in 2004, aimed to improve the quality of primary care by rewarding GPs, through a voluntary incentive payment scheme, for 'good practice'.[187] Good practice was measured in several ways, including by the quality of recording of key data items relating to common chronic diseases. An advisory committee was appointed by NICE to select the most common and clinically important chronic diseases for inclusion in the QOF. 17 diseases were selected. Subsequent to the introduction of QOF, the completeness of recording of included key data items in patients' primary care electronic medical records improved.[183] In this study, for the count of chronic diseases, the same 17 chronic diseases included in the QOF were selected for inclusion and are shown in Table 4-2. For each disease a list of Read codes was compiled using the CPRD Research Applications Code Browser. The included codes were reviewed and approved by a GP and a professor of musculoskeletal health. The code lists are shown in Appendix Table A-2. Read codes recorded in CPRD at any date prior to the index date were included due to the chronic nature of the diseases.

Table 4-2 – Diseases included in the Count of Chronic Diseases

Asthma	Atrial fibrillation	Cancer
Chronic kidney disease	COPD	Dementia
Depression	Diabetes mellitus	Epilepsy
Heart failure	Hypertension	Learning disability
Mental health disorder	Osteoporosis	Peripheral arterial disease
Rheumatoid arthritis	Stroke / TIA	

The count of different medications prescribed in the previous 12 months (range ≥0) was calculated from the number of different medications issued on prescription to each patient via CPRD prescription data. As described in Chapter 1, the number of medications a patient is prescribed may be a useful surrogate measure of multimorbidity burden. It may provide insights into the severity of multimorbidity burden that the Charlson Comorbidity Index and the count of chronic diseases cannot, because they do not indicate whether a disease is mild or severe. All medications issued on prescription, including both one-off (or 'acute') and regular (or 'repeat') prescriptions were included. It is acknowledged that other researchers have chosen to include only regular prescriptions in their assessment of polypharmacy and multimorbidity, because such prescriptions reflect the burden on chronic disease.[203] The inclusion of both one-off and regular prescriptions was chosen in this study because 'acute' healthcare events occurring are a marker of poorly controlled chronic disease and so reflect greater overall multimorbidity burden.

The count of contacts with primary care in the previous 12 months (range ≥0) was calculated from the number of consultation events recorded. This measure is not a count of clinic appointments that a patient had with a GP only, and instead includes a number of different events: consultation events include clinical events (for example, face-to-face appointments with a GP or practice nurse), referrals (for example, referral by a GP to orthopaedic secondary care services), therapies (for example, prescription of a medication or changing of a skin dressing) and test results (for example, a GP recording the result of a blood test). By including a broader range of events, this measure will give a more accurate assessment of the degree of healthcare usage in primary care. As described in Chapter 1, the degree of healthcare usage may be a useful surrogate measure of multimorbidity burden. If multiple events are

recorded during one data entry period, then only one consultation event is scored. Such events may be entered by a variety of staff at the GP practice, including a GP, nurse, other healthcare professional or an administrator.

The Electronic Frailty Index (range 0-36) was calculated from a simple unweighted count of the number of 'deficits' recorded in patients' electronic medical records. The index includes 36 deficits, which are shown in Table 4-3 and comprise diseases, symptoms and functional limitations. The list of Read codes for each deficit was obtained from the developers of the score.[128] The code lists are shown in Appendix Table A-3. Read codes recorded in CPRD at any date prior to the index date were included as per guidance issued by the developers of the Index.

Table 4-3 – Deficits included in the Electronic Frailty Index

Activity limitation	Anaemia	Arthritis
Atrial fibrillation	Cerebrovascular disease	Chronic kidney disease
Diabetes mellitus	Dizziness	Dyspnoea
Falls	Foot problems	Fragility fracture
Hearing impairment	Heart failure	Heart valve disease
Housebound	Hypertension	Hypotension
Ischaemic heart disease	Cognitive problems	Mobility problems
Osteoporosis	Tremor	Peptic ulcers
Peripheral vascular disease	Polypharmacy	Requirement for care
Respiratory disease	Skin ulcer	Sleep disturbance
Social vulnerability	Thyroid disease	Urinary incontinence
Urinary system disease	Visual impairment	Unintended weight loss

4.3.4 Outcome measures

The outcomes of interest were:

(1) referral from primary care to orthopaedic secondary care for specialist opinion, and

(2) total hip replacement.

The outcomes were identified in CPRD using Read codes. The inclusion period was from the index date (date of diagnosis of hip osteoarthritis) until either outcome event, death or end of follow up in

CPRD GOLD. The date of outcome was the first occurrence of the outcome after the index date. The list of Read codes for referral was compiled from the CPRD Research Applications Code Browser and comprises a total of four Read codes. The codes are shown in Appendix Table A-4. The list of Read codes for total hip replacement was obtained from an existing validated code list.[10] The existing code list was checked against the CPRD Research Applications Code Browser and two further codes were to the list, making a total of 39 Read codes in total. The codes are shown in Appendix Table A-5.

4.3.5 Statistical analysis

Baseline characteristic variables were checked for completeness and ranges. Data were described using frequencies, proportions, means and standard deviations (SDs).

Each multimorbidity measure was split into categories. For four of the five multimorbidity measures (Charlson comorbidity index, count of chronic diseases, count of different medications, and count of contacts with primary care), there was no existing widely agreed system of how to categorise the measure, from low to high multimorbidity. Thus, an appropriate method of categorisation was required. Each multimorbidity measure was split into four categories, from lowest to highest burden of multimorbidity. The aim was that, for each score, each category would be approximately equal in proportion, with approximately 25% of the cohort in each category.

Four was chosen for the number of categories for clinical and statistical reasons. Four categories would each have clinical relevance, representing patients with no, low, medium and high severity of multimorbidity burden. A larger number of categories would be less distinct from one another and would decrease statistical power. The reason to create categories approximately equal in proportion was to maximise statistical power and to permit investigation of whether an ordinal trend existed between the categories.

A further aim was that the proportions of the four categories would be approximately equal between the multimorbidity measures. The rationale behind this was to permit comparisons between the multimorbidity measures. It was acknowledged that the degree to which equality in proportion of each category could be achieved would be dependent on the spread of the data in each multimorbidity

measure. The cut offs for each of the four categories, in each of the four multimorbidity measures, were therefore confirmed after review of the data.

The fifth multimorbidity measure, the Electronic Frailty Index, has four categories that were defined by the creators of the score. The categories were: 'fit' (with score 0-4), 'mild frailty' (5-8), 'moderate frailty' (9-12), and 'severe frailty' (13-36). These categories were used in this study. It was acknowledged that this method of defining the categories was different to that used for the other multimorbidity measures, and as a result the Electronic Frailty Index categories might not be approximately equal proportions. Indeed, the developers of the Electronic Frailty Index reported that in the development cohort only 3% of individuals were classified into the highest 'severe frailty' category.

The distribution in length of 'lead up' in CPRD available to investigate multimorbidity (between start date of CPRD data availability and index date) was described using the median, interquartile range (IQR) and range.

The distribution in length of follow up in CPRD available to investigate outcomes (between index date and end date of CPRD data availability) was described using the median, interquartile range (IQR) and range. The end date of CPRD data availability was defined as the earliest date of date of patient removal from GP practice list, date of death, date of last data submission by GP practice, and date of extraction of CPRD data by CPRD staff for this thesis (January 26, 2015).

Analyses were performed separately for each outcome. For the outcome of referral, all individuals in the cohort were included. For the outcome of total hip replacement, all individuals in the cohort were included except for individuals whom underwent total hip replacement within 30 days of index date. This exclusion step was performed in order to exclude cases where a diagnosis of hip osteoarthritis was recorded at the time or after the decision was made for the individual to undergo total hip replacement, since such cases would introduce bias into the analysis of time between diagnosis and surgery. The cut off of 30 days was chosen after consideration of the shortest plausible duration of the pathway from diagnosis to surgery, including referral, clinic review, booking of surgery, and waiting time to surgery.

Descriptive statistics were calculated for the two outcomes, for the total population and by multimorbidity category. These were: number of patients included in analyses (total at risk), total number of person-years at risk contributed by all included patients, and median follow-up time (in years) per patient (with IQR).

To explore the relationship between multimorbidity categories and rate of referral and of total hip replacement, the number of outcome events and incidence rate (per 100 person-years) of outcome event were calculated. The cumulative incidence of referral and of total hip replacement was assessed with competing risks estimates, with death considered a competing event.

To compare the rates of referral and of total hip replacement between multimorbidity categories, survival analysis was performed. Competing risk analysis models were used, with death considered a competing event. Fine and Gray competing risks regressions models, which focus on the cumulative incidence function, were chosen ahead of cause-specific hazard models.[204] This method was most appropriate because the models provide crude estimates of absolute risk, which is more relevant when the focus is on predicting prognosis. The models are presented as subdistribution hazard ratios (HRs) with 95% confidence intervals (CIs). The lowest multimorbidity category was defined as the referent category. Univariate and multivariate models, adjusted for age, sex, region of residence in the UK, and calendar year of diagnosis, were conducted. Age was considered a continuous variable. Sex was considered a binary categorical variable. Region of residence was considered a nominal categorical variable. Calendar year of diagnosis was considered an ordinal categorical variable. Complete case analysis was used for adjusted models.

Statistical analysis was performed using STATA 14.0 (College Station, Tx, USA).

4.3.6 Sensitivity analyses

As discussed in Chapter 2, the degree of completeness of recording of true cases total hip replacement in CPRD is not known. Thus, the validity of recording of total hip replacements in CPRD was assessed by checking agreement with recording of total hip replacements in linked HES APC data. Recording of

total hip replacements in HES APC was considered the reference standard because HES APC has been shown to be comparable in completeness to the NJR in a previous validation.[7] The NJR has a near 100% compliance against levy returns for the number of implants sold, according to a recent internal audit, and is regarded as the gold standard for data on total hip replacements performed in the UK.[5] Validation against the NJR directly was not possible as access to the NJR with linkage of CPRD and NJR data was not available to the thesis.

To assess the validity of recording of total hip replacements in CPRD, the sensitivity, specificity, positive predictive value and negative predictive value were estimated. Cohen's kappa statistic was calculated to measure the degree of agreement between the two data sources (CPRD and HES APC), with 95% CIs. Included individuals in the validation analysis cohort were those in the 28,025-strong CPRD cohort that were resident in England, with linkage to HES APC available and with linkage of adequate quality. The two data sources were investigated for the recorded occurrence of total hip replacement. CPRD records were investigated for the presence of a Read code indicating total hip replacement, as described in section 5.3.4. HES APC records were investigated for the presence of an OPCS Classification of Interventions and Procedures version 4 (OPCS-4) procedure code indicating primary total hip replacement. The list of OPCS-4 codes for total hip replacement was compiled by searching the NHS Digital OPCS Classification of Interventions and Procedures version 4-8 code list, via its alphabetical index.[205] The 63 included codes are shown in Appendix Table A-6. Only total hip replacements identified in CPRD performed during the period for which follow up was available in HES APC +/- 60 days were included, and vice versa.

If an eligible total hip replacement was identified in CPRD with a corresponding HES APC event performed +/- 60 days, it was considered a true positive in CPRD (Table 4-4). The 60-day time window for agreement was set to minimise the risk of included bilateral hip replacements since laterality of surgery data was not available in CPRD. If an eligible total hip replacement was identified in CPRD with no corresponding HES APC event within the time window, it was considered a false positive in CPRD. If an eligible total hip replacement was identified in HES APC with no corresponding CPRD event within the time window, it was considered a false negative in CPRD.

Table 4-4 – Cross-tabulation for agreement between CPRD versus HES APC

		HES	
		Yes	No
CPRD	Yes	True positive	False positive
	No	False negative	True negative

As a further sensitivity analysis, the demographic and multimorbidity characteristics of the entire cohort in CPRD were compared with the subset of the cohort that had data linkage with HES APC. This was to establish whether the subset of the cohort included in the total hip replacement validation was representative of the entire cohort in CPRD.

4.4 Results

4.4.1 Study cohort

In all, 28,025 patients were included in the cohort, based on the recording of a diagnosis of hip osteoarthritis in CPRD between January 1, 1995 and April 30, 2014. The mean age of patients at diagnosis was 75.5 years (SD 6.9). The mean BMI prior to diagnosis was 27.5 (SD 4.8). Detailed demographic data are shown in Table 4-5. Data on geographical region of residence are shown in Appendix Table B-1.

The length of 'lead up' in CPRD data available to investigate multimorbidity (between start date of CPRD data availability and index date) ranged from 1.0 years to 24.7 years. The median was 8.4 years (IQR 5.0 to 12.3 years). The distribution of index date (date of diagnosis of hip osteoarthritis), by year, is shown in Appendix Table B-2. The length of follow up in CPRD data available to investigate outcomes (between index date and end date of CPRD data availability) ranged from 0 days to 20.0 years. The median was 4.8 years (IQR 2.4 to 7.9 years).

4.4.2 Multimorbidity

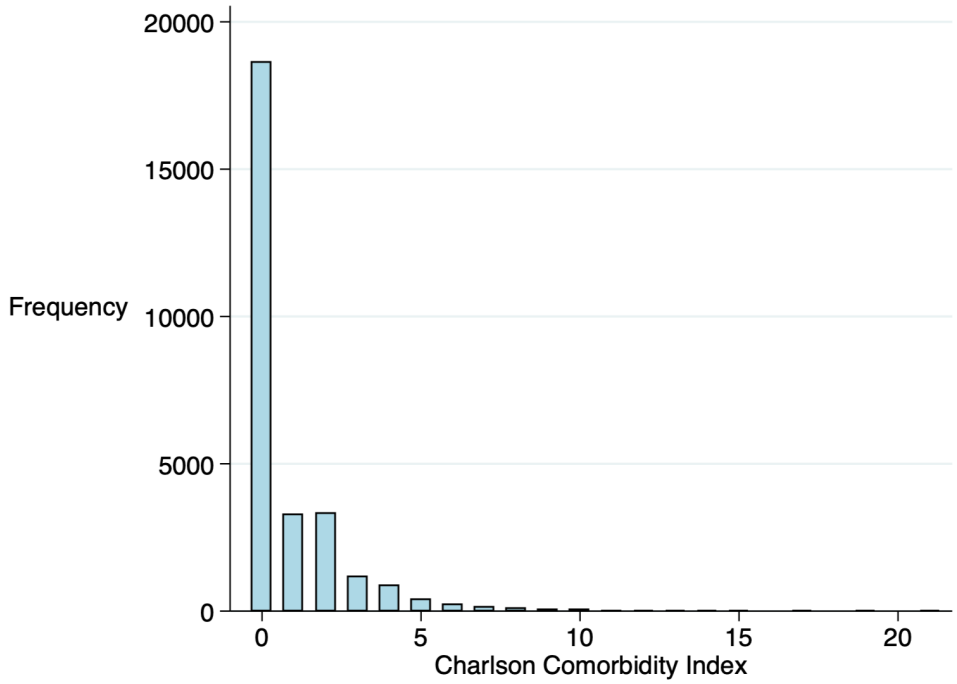
The distribution of the Charlson Comorbidity Index scores is shown in Figure 4-1. The range was 0-21 and median was 0 (IQR 0-1). Due to the distribution of scores, the Charlson Comorbidity Index categories were set at scores of 0, 1, 2 and 3+. The proportions of each category are shown in Table 4-6.

Table 4-5 – Demographic details of the CPRD cohort

	Frequency	%
Age		
65-69	7200	25.7
70-74	7229	25.8
75-79	6421	22.9
80-84	4233	15.1
85-89	2161	7.7
90+	781	2.8
Missing	0	-
Sex		
Male	10,662	38.0
Female	17,363	62.0
Missing	0	-
BMI		
<18.5	257	1.2
18.5-<25	6,611	29.6
25-<30	9,569	42.8
30-<35	4,269	19.1
35+	1,638	7.3
Missing	5,681	-
Ethnicity		
White	14,674	98.7
Afro-Caribbean	54	0.4
Chinese	8	0.05
South Asian	49	0.3
Other	81	0.5
Missing	13,159	-
Total	28,025	

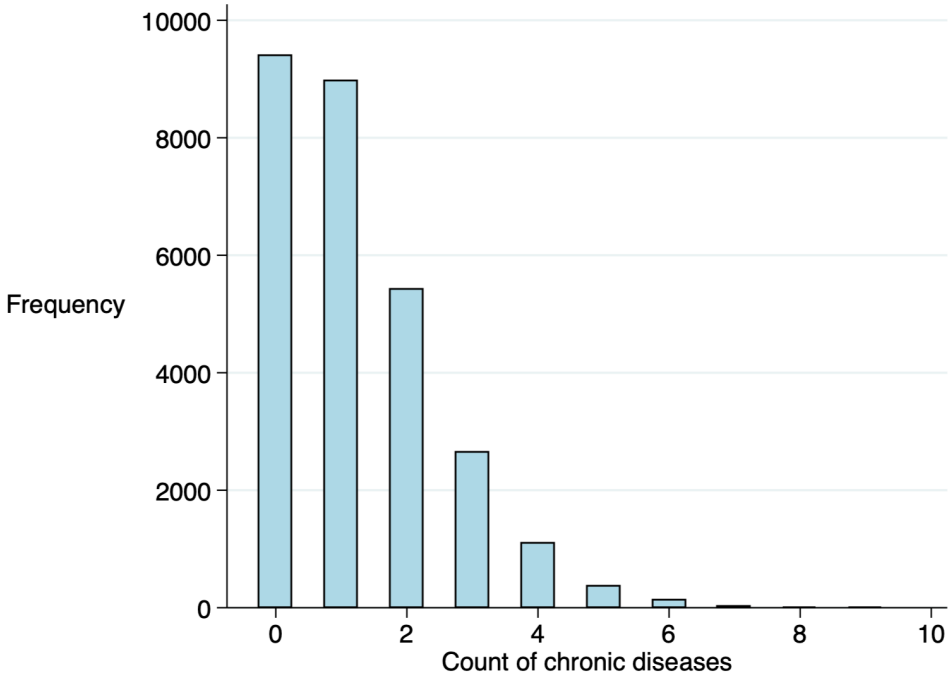
	Frequency	%
IMD quintiles		
Least deprived	4,668	25.9
2	4,503	25.0
3	3,981	22.1
4	3,190	17.7
Most deprived	1,696	9.4
Missing	9,987	-
Total	28,025	

Figure 4-1 – Charlson Comorbidity Index prior to diagnosis



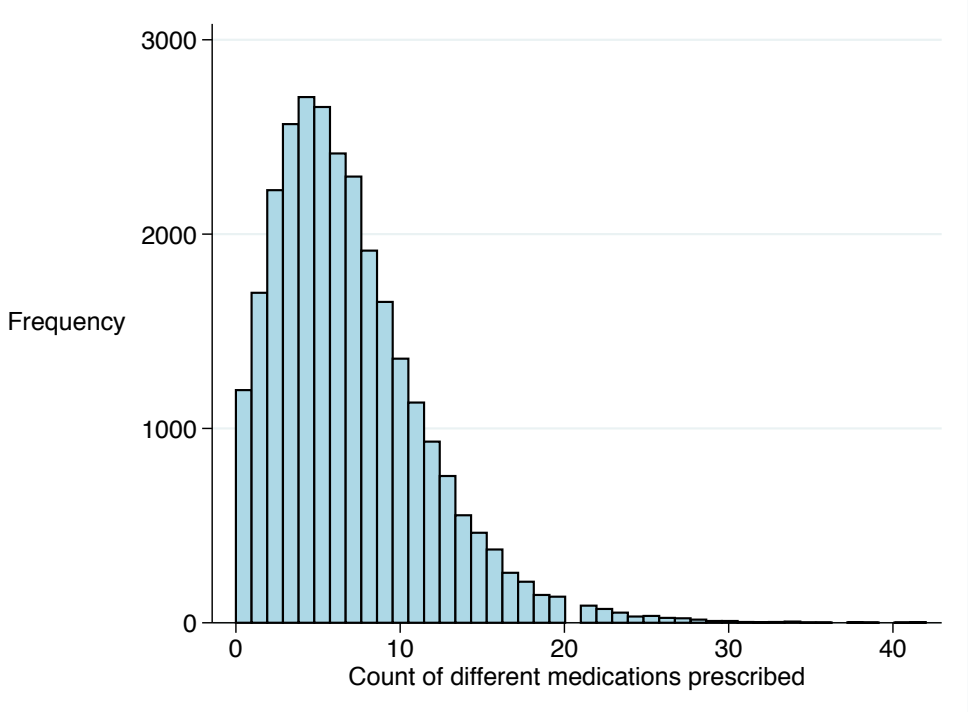
The distribution of the count of chronic diseases is shown in Figure 4-2. The range was 0-9 and median was 1 (IQR 0-2). Due to the distribution of scores, the count of chronic diseases categories were set at counts of 0, 1, 2 and 3+. The proportions of each category are shown in Table 4-6.

Figure 4-2 – Count of chronic diseases prior to diagnosis



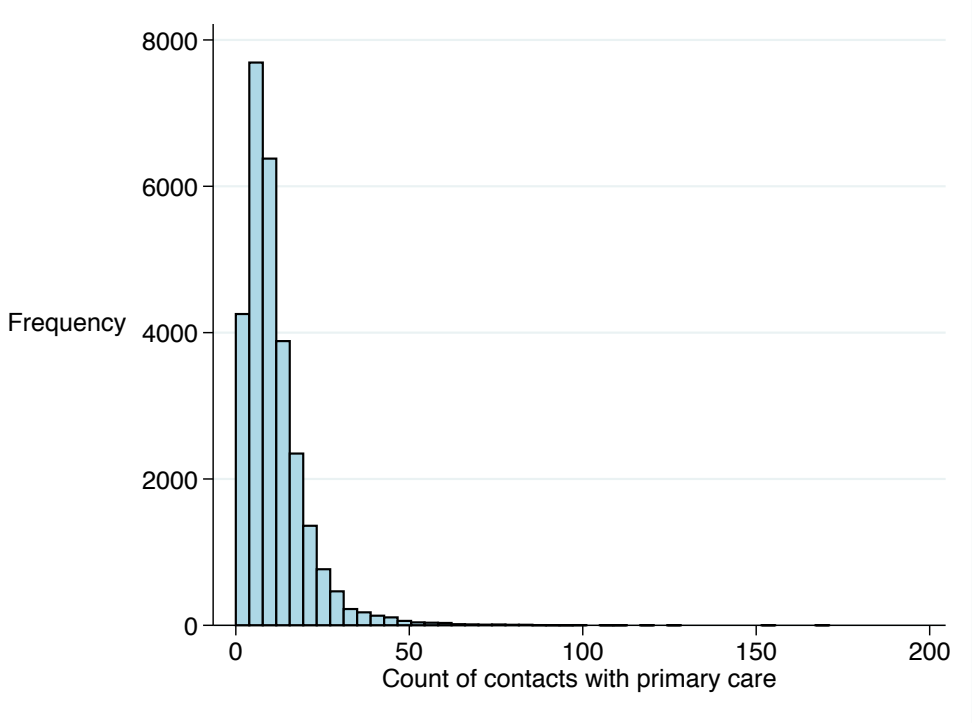
The distribution of the count of different medications prescribed in the 12 months prior to index date is shown in Figure 4-3. The range was 0-42 and median was 6 (IQR 3-9). The count of different medications prescribed categories were set in order to best match the proportions of the categories in the multimorbidity measures of Charlson Comorbidity Index and the count of chronic diseases. A further consideration was that 'polypharmacy' may be defined as the prescription of ≥5 medications. Thus, to be consistent with 'no polypharmacy', the lowest category was set at a count of 0-4. The other categories were set at counts of 5-7, 8-12, and 13+. The proportions of each category are shown in Table 4-6.

Figure 4-3 – Count of different medications prescribed prior to diagnosis



The distribution of the count of contacts with primary care in the 12 months prior to index date is shown in Figure 4-4. The range was 0-171 and median was 9 (IQR 5-14). The count of contacts with primary care categories were also set in order to best match the proportions of the categories in the multimorbidity measures of Charlson Comorbidity Index and the count of chronic diseases. The categories were set at counts of 0-7, 8-11, 12-17 and 18+. The proportions of each category are shown in Table 4-6.

Figure 4-4 – Count of contacts with primary care prior to diagnosis



The distribution of the Electronic Frailty Index scores is shown in Figure 4-5. The range was 0-19 and median was 3 (IQR 1-5). The Electronic Frailty Index categories were defined by the developers. The proportions of each category are shown in Table 4-6.

Figure 4-5 – Electronic Frailty Index prior to diagnosis

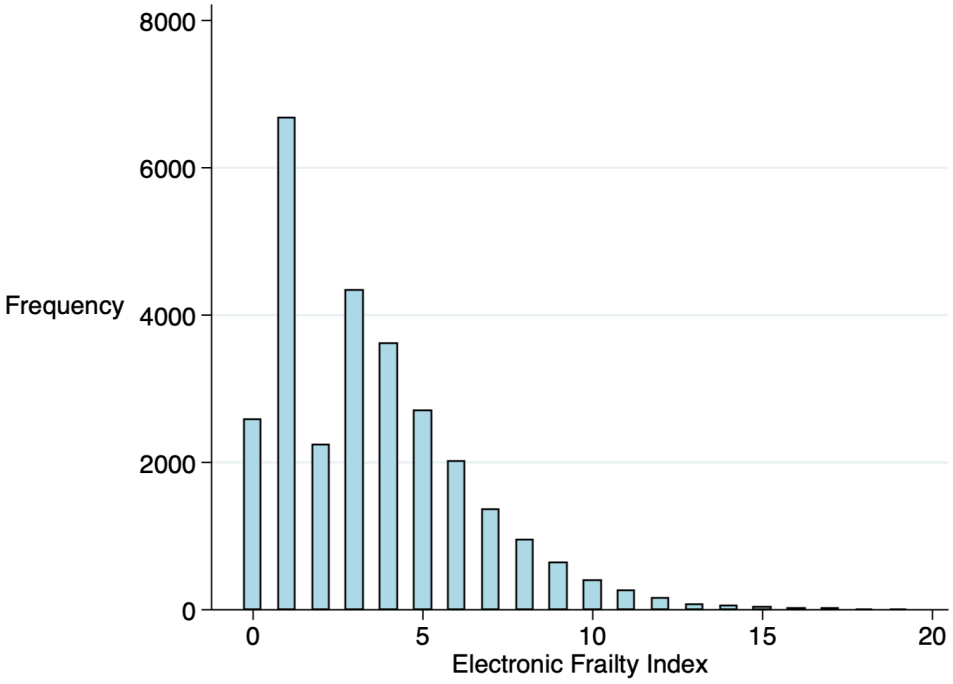


Table 4-6 – Distribution of categories of multimorbidity, by each measure

	Frequency	%
Charlson Comorbidity Index		
0	18,631	66.5
1	3,245	11.6
2	3,312	11.8
3+	2,837	10.1
Count of chronic diseases		
0	9,398	33.5
1	8,957	32.0
2	5,414	19.3
3+	4,256	15.2
Count of medications prescribed		
0-4	10,392	37.1
5-7	7,365	26.3
8-12	6,990	24.9
13+	3,278	11.7
Count of contacts with primary care		
0-7	11,945	42.6
8-11	6,378	22.8
12-17	5,212	18.6
18+	4,490	16.0
Electronic Frailty Index		
0-4	19,441	69.4
5-8	7,005	25.0
9-12	1,411	5.0
13+	168	0.6
Total	28,025	

4.4.3 Referral from primary care to orthopaedic secondary care

Of the 28,025 patients in the cohort, 1,219 had a Read code indicating such a referral in their electronic medical record.

However, 11,413 of the 28,025 patients had a Read code indication total hip replacement. All patients who underwent total hip replacement must have first been referred to a hip surgeon in orthopaedic secondary care by their GP. That 11,413 underwent total hip replacement but only 1,219 had a referral code indicates that there is a high degree of missing data on referral from primary care to orthopaedic secondary care in the electronic medical records in CPRD GOLD. This is a significant weakness in the data quality.

A further consideration is that the aim was to identify patients who were referred from primary care to orthopaedic secondary care for specialist opinion on whether they would benefit from total hip replacement for their hip osteoarthritis. However, the available Read codes relating to referral from primary care to orthopaedic secondary care were limited in their specificity. The four most accurate Read codes, which comprised the code list, specified referral to orthopaedic specialist care, but did not specify that referral was due to hip osteoarthritis or for consideration of total hip replacement. Therefore, it is possible that patients in the cohort with an included referral Read code may have been referred for a different orthopaedic problem, such as shoulder osteoarthritis. This lack of coding specificity represents a second significant weakness in the data quality.

Due to these two limitations, the analysis of the influence of multimorbidity on the likelihood of referral was terminated.

4.4.4 Total hip replacement

465 (1.7%) patients underwent total hip replacement within 30 days of diagnosis of hip osteoarthritis, and so were excluded. Of the 27,560 patients remaining in the cohort, 10,948 (39.7%) underwent total hip replacement during the follow up period.

The median time between diagnosis of hip osteoarthritis and total hip replacement was 0.8 years (IQR 0.4-1.7 years). The range was 0.1-16.9 years.

4.4.5 Association between multimorbidity measures and rate of total hip replacement

The associations between each multimorbidity measure and the rate of total hip replacement are displayed in Table 4-7. The likelihood of undergoing total hip replacement decreased with increasing degree of multimorbidity, a trend that was observed with each multimorbidity measure used. The trend remained after adjustment for age, sex, region of the UK, and year of diagnosis.

The most severe category of the Charlson Comorbidity Index, the count of chronic diseases and the count of medications prescribed all had a similar hazard ratio relative to their referent category, with a range of 0.59 (95% CI 0.55, 0.63) to 0.67 (95% CI 0.62, 0.72).

The most severe category of the count of contacts with primary care had the smallest hazard ratio relative to the referent category: 0.85 (95% CI 0.81, 0.91).

The Electronic Frailty Index had the largest hazard ratios across the categories. The most severe category (score of 13+) had an adjusted hazard ratio of 0.34 (95% CI 0.22, 0.51). This means that patients with severe frailty were approximately one third as likely to undergo total hip replacement for their hip osteoarthritis, relative to patients without frailty.

Table 4-7 – Rate of undergoing total hip replacement by multimorbidity measure

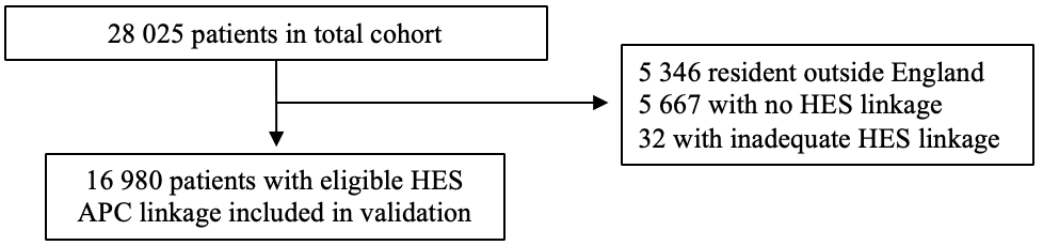
	Total at risk	Competing risk events	THR events	Person years at risk	Incidence per 100 PY	Unadjusted HR (95% CI)	Adjusted HR* (95% CI)
Charlson Comorbidity Index							
0	18,303	2,279	7,878	64,676	12.2	Ref	Ref
1	3,202	630	1,160	11,729	9.9	0.79 (0.75, 0.84)	0.84 (0.79, 0.89)
2	3,261	596	1,115	10,096	11.0	0.78 (0.74, 0.84)	0.81 (0.76, 0.87)
3+	2,794	656	795	8,628	9.2	0.63 (0.58, 0.68)	0.65 (0.60, 0.70)
Count of chronic diseases							
0	9,228	1,142	4,248	34,744	12.2	Ref	Ref
1	8,802	1,231	3,631	30,613	11.9	0.90 (0.86, 0.94)	0.91 (0.87, 0.95)
2	5,339	881	1,955	17,482	11.2	0.80 (0.76, 0.84)	0.81 (0.77, 0.86)
3+	4,191	907	1,114	12,289	9.1	0.57 (0.53, 0.61)	0.59 (0.55, 0.63)
Count of medications prescribed							
0-4	10,250	1,206	4,674	38,337	12.2	Ref	Ref
5-7	7,234	1,111	2,911	24,489	11.9	0.89 (0.85, 0.93)	0.92 (0.88, 0.97)
8-12	6,857	1,169	2,421	22,576	10.7	0.78 (0.74, 0.82)	0.81 (0.77, 0.86)
13+	3,219	675	942	9,726	9.7	0.64 (0.59, 0.68)	0.67 (0.62, 0.72)
Count of contacts with primary care							
0-7	11,790	1,570	4,946	42,662	11.6	Ref	Ref
8-11	6,272	866	2,559	21,483	11.9	1.00 (0.95, 1.04)	1.02 (0.97, 1.07)
12-17	5,097	825	1,939	16,902	11.5	0.92 (0.88, 0.97)	0.95 (0.91, 1.01)
18+	4,401	900	1,504	14,080	10.7	0.82 (0.77, 0.87)	0.85 (0.81, 0.91)
Electronic Frailty Index							
0-4	19,102	2,596	8,373	69,541	12.0	Ref	Ref
5-8	6,900	1,157	2,249	21,349	10.5	0.75 (0.71, 0.78)	0.77 (0.74, 0.81)
9-12	1,391	354	303	3,839	7.9	0.48 (0.43, 0.54)	0.52 (0.47, 0.59)
13+	167	54	23	399	5.8	0.31 (0.20, 0.46)	0.34 (0.22, 0.51)
Total	27,560	4161	10,948	95,128	11.5		

*The model was adjusted for age, sex, region of the UK, and year of diagnosis.

4.4.6 Sensitivity analyses

Figure 4-6 shows the subset of the CPRD cohort with adequate HES APC linkage. There were 16,980 individuals in total (60.6%), all of whom were included in the validation analysis. This figure is similar to the proportion of GP practices have consented to the linkage scheme, reported to be approximately 58%.

Figure 4-6 – CPRD cohort with adequate HES APC linkage



Of the 16,960 individuals included, 7,303 had total hip replacement recorded in CPRD. 195 total hip replacements were excluded as they were performed outside the period for which follow up was available in HES APC (April 1, 1997 to March 31, 2014) +/- 60 days, leaving 7,108 CPRD total hip replacements for validation. 6,682 had total hip replacement recorded in HES APC, of which all were performed inside the eligible CPRD time window. Of the 6,682 procedures recorded in HES APC, 5,382 had a corresponding record in CPRD within the 60-day time window (Table 4-8).

Table 4-8 – Cross-tabulation of total hip replacements during follow-up according to CPRD versus HES APC (with 60-day time window for agreement)

		HES		
		Yes	No	Total
CPRD GOLD	Yes	5,382	1,726	7,108
	No	1,300	8,572	9,872
	Total	6,682	10,298	16,980

Sensitivity was 80.5%. Specificity was 83.2%. Positive predictive value was 75.8%. Negative predictive value was 86.8%. The Kappa statistic was 0.63 (95% CI 0.62-0.64).

The demographic characteristics of the entire CPRD cohort and the subset of the cohort with adequate HES APC linkage are shown in Table 4-9. The multimorbidity characteristics of the two cohorts are shown in Appendix Table B-3. The two cohorts are highly similar in terms of their demographic and multimorbidity characteristics.

Table 4-9 – Demographics of CPRD cohort and subset with HES APC linkage

	CPRD	HES APC linkage
Age in years (mean, SD)	75.5 (6.9)	75.7 (6.9)
Female (%)	62.0	62.2
BMI (mean, SD)	27.5 (4.8)	27.5 (4.8)
White ethnicity (%)	98.7	98.7
In a relationship (%)	76.9	77.4
IMD quintile 1-2 (%)	50.8	50.4
Total	28,025	16,980

4.5 Discussion

4.5.1 Summary of main findings

This chapter reports on the association between multimorbidity and the likelihood of undergoing total hip replacement in a large sample of individuals diagnosed with hip osteoarthritis in the UK. The results indicate with increasing multimorbidity burden, the likelihood of undergoing total hip replacement is lower. Patients with severe multimorbidity burden were one third to two thirds less likely to undergo total hip replacement. This trend was observed irrespective of the method of measuring multimorbidity, and it persisted after adjustment for age, sex, region of the UK and year of diagnosis of hip osteoarthritis.

4.5.2 Strengths and limitations

This section considers, in turn, the study design, study cohort, predictor variables, covariates, and outcome variables.

Study design

The retrospective cohort study design enabled a large population of patients to be identified at the point of diagnosis with hip osteoarthritis, enabling study of a long follow-up period comprising the entire patient journey. As discussed in Chapter 3, a prospective study design, which would have had the advantage of reducing loss to follow up, was not feasible within the time and financial resources available to the thesis.

Study cohort

The study cohort was identified using CPRD GOLD as the data source. As discussed in Chapter 2, CPRD is a leading UK primary care database. The recording of in excess of 184 diseases has been validated and the demographics of CPRD patients have been demonstrated to be representative of the wider UK population in terms of age, sex, ethnicity and BMI.[183,185] Use of CPRD increases the external validity of the findings. Indeed, the cohort was drawn from all 13 regions of the UK. Each region contained between 3.1% and 12.5% of the cohort, a distribution that did not differ substantially from the overall UK population distribution.[206] The exception was the North East region, which contained only 1.9% of the cohort. This reflects the size of the CPRD population from the North East, which is in turn reflects the low rate of the use of the Vision computer system by GP practices in the region.[183] It was a concern that only 9% of the cohort were from the most socio-economically deprived population quintile, with a steadily increasing proportion up to 25.9% from the most affluent quintile. This implies a lower rate of diagnosis of hip osteoarthritis in areas of deprivation. It has previously been shown in ecological studies however that areas with high deprivation have higher rates of osteoarthritis.[207] The lower rate of diagnosis of hip osteoarthritis in deprived areas may therefore be due to under-diagnosis in these areas. This may reflect GP behaviour, whereby GPs may have a higher workload with more complex patients, or patient behaviour, whereby patients do not seek medical attention due to other priorities. This phenomenon is referred to as the 'inverse care law'.[208,209]

The study only included patients aged over 65 years. The reason for this was to increase the specificity of including a cohort with genuine hip osteoarthritis, as hip osteoarthritis is less common in younger

patients, and so including younger patients would risk including patients with other hip pathology that had erroneously been coded as hip osteoarthritis. The limitation of this approach is that some patients do develop hip osteoarthritis under the age of 65 years. Indeed, it is possible that younger patients with hip osteoarthritis would have an increased rate of multimorbidity compared to similarly aged patients without hip osteoarthritis. Given the outcomes in younger patients by multimorbidity are unknown, it is important to avoid generalising the outcomes from the patient cohort to all ages groups.

The study cohort were identified by the presence of a Read code for hip osteoarthritis in CPRD. The diagnosis of hip osteoarthritis in CPRD is accurate: in Chapter 3, the included list of Read codes was shown to have a positive predictive value of 79%. This study therefore accurately identified a cohort with hip osteoarthritis.

The completeness of recording of the Read codes for hip osteoarthritis in CPRD, however, is unknown. The limitation of identifying the cohort in this way, therefore, is that there may be many eligible patients in CPRD missed from the study cohort. As discussed in Chapter 3, a limitation of the methodology of the validation study was that it was not possible to calculate the number of individuals that were incorrectly missed from the cohort or to estimate the prevalence of hip osteoarthritis within the wider CPRD population. This is because access was only granted to records of patients with a Read code for hip osteoarthritis. It remains a possibility that this method of identification had low sensitivity and that selection bias occurred as a result of the method used to identify the cohort: some patients with hip osteoarthritis and increased multimorbidity burden may not have had the diagnosis of hip osteoarthritis recorded in their medical records because those patients and/or their GPs were more focussed on the management of other more serious chronic illnesses[210], and did not pursue treatment for hip osteoarthritis. If such a scenario did take place, the study findings that increased multimorbidity burden is associated with a lower rate of total hip replacement may have underestimated the true association.

The option of including broader ‘surrogate’ Read codes for hip pain to increase the detection of patients was considered but rejected due to concerns that the specificity might be low. One other method to improve the study design would have been to survey ‘regular’ GPs (not routinely involved in CPRD research and without Read code expertise) on how they would code or store information in the electronic

medical record of a patient presenting with symptoms consistent with hip osteoarthritis. This might have identified other Read codes or free text that were not considered by the research team. In addition, the inclusion of information in free text when identifying the cohort could have flagged up further appropriate patients. The option was not included due to concerns that the manual review of thousands of free text entries was beyond the time resources available to the thesis. It is acknowledged, however, that novel modelling methods, using machine learning, have been developed to predict the presence of a diagnosis through mining free text.[211] Future work should study this method identifying patients with hip osteoarthritis from CPRD.

The date of diagnosis of hip osteoarthritis is a major issue in this study. The date of clinical diagnosis likely does not represent the same point in the development of hip osteoarthritis pathology or symptoms for all patients. Indeed, there are several ways in which the date of diagnosis may be influenced by multimorbidity. First, due to patient behaviour: while there is a natural variation in when patients decide to present to their GP for management of symptoms of hip osteoarthritis, it is possible some patients with increased multimorbidity burden presented later due to placing a higher priority on another, more dominant chronic illness and so received a 'later' date of diagnosis in the hip osteoarthritis disease course.[210] Second, due to GP behaviour: it is possible that, to avoid diagnostic error, GPs may have delayed coding the diagnosis in some patients' records until referring a patient to secondary care for specialist opinion and receiving confirmation of the diagnosis from secondary care. If referrals to secondary care were influenced by multimorbidity, then patients with increased multimorbidity burden may in this way have received a 'later' date of diagnosis in their hip osteoarthritis disease course. If such a bias in date of diagnosis did occur, it would shorten the observed time between date of diagnosis and outcomes, thereby falsely increasing the rate of total hip replacement for patients with increased multimorbidity burden. It is possible therefore the findings of the study have underestimated the effect of increased multimorbidity burden on the likelihood of total hip replacement.

The date of diagnosis recording in CPRD was found to be frequently inaccurate in Chapter 3. In 42% of cases included in the validation study, there was a discrepancy between the date recorded in CPRD and the date recorded in the GP record, with a median difference of +/-425 days. Given the median time

between diagnosis and undergoing total hip replacement here was 0.8 years, the inaccuracy of diagnosis date recording is a significant limitation to the results. If there existed a relationship between inaccuracy of diagnosis date recording and multimorbidity, this would have introduced bias into the results. Whether there was a difference in multimorbidity between patients with a correct and incorrect date of diagnosis in CPRD was not investigated. This would be an important next step.

Predictor variables

Measurement of multimorbidity was a key challenge in the design of the study. The recent report by the UK Academy of Medical Sciences highlighted the lack of a uniformly agreed definition for multimorbidity.[27] Indeed, multimorbidity is a heterogeneous concept and can be used to "describe a wide array of patients experiencing a multitude of different combinations of conditions". As described in Chapter 1, in this thesis multimorbidity is defined as "being affected by two or more chronic health conditions in the same individual". This simple definition is that used by the World Health Organization.

The Academy's report also highlighted the complexity of identifying a valid approach to measure the summative severity of multimorbidity burden.[27] An important consideration is that the most appropriate or relevant method of measuring multimorbidity may depend on the population and outcome being studied. The report concluded "there appears to be no single optimal weighted count that is uniformly relevant to all studies". It was not known which method of measuring severity of multimorbidity would be most appropriate in the setting of this study and, thus, five different ways of measuring multimorbidity were implemented.

Two traditional disease count methods were used: the Charlson Comorbidity Index and a count of chronic diseases. However, the limitation of these methods is that they do not accommodate the severity of diseases present. Data on the severity of each disease present in CPRD was not available, and so, as an alternative, two surrogate measures of multimorbidity burden were included. First, a count of different medications prescribed in the 12-month period prior to index date was included. The rationale for inclusion was that with increased severity of multimorbidity burden, patients would require more

medications prescribed. This proxy measure for multimorbidity has previously been validated in predicting poor outcomes after surgery.[212,213] A limitation of this method, however, is that some patients with a severe multimorbidity burden may require only a small number of medications or receive long-lasting prescriptions, and so this score would not accurately reflect their true multimorbidity burden. Second, a count of contacts with primary care in the 12-month period prior to index date was included. The rationale for inclusion was that with increased severity of multimorbidity burden, patients would require increased care from GPs and so have increased frequency of contact with primary care. A limitation of this method, however, is that contact with the GP may be highly influenced be a patient's personality type or strength of relationship with their GP, which may mask the association with multimorbidity severity. A further significant limitation to this method is that it was not possible to study what type of 'contact' was recorded at each recorded contact episode. On review of the data, some patients had many 'contacts' recorded on the same date while others did not. This may reflect the way in which GPs record information: some GPs may record multiple bits of information about a patient's health (e.g., diagnoses, test results, personal discussions held during consultations, prescriptions) in one single 'contact episode', while other GPs may record the same number of bits of information across multiple 'contact episodes'. Indeed, there is no formal guidance on how GPs should structure their medical record keeping. As a result, it is possible that the count of contacts with primary care was not strongly related to the severity of multimorbidity burden. The results from analyses using this multimorbidity measure should therefore be interpreted with caution.

The fifth measure of multimorbidity studied was the Electronic Frailty Index, developed as a measure of frailty, rather than multimorbidity. The score includes both the presence of certain diseases (similar to the traditional disease counts) and of functional limitations, such as being housebound and a requirement for care. The rationale for inclusion was that this score may provide a truer estimation of patients' overall health status and multimorbidity burden than traditional disease counts, by virtue of accounting for both the presence of chronic diseases and their impact on physical and mental function.

An alternative option would have been to identify patients with 'complex multimorbidity'. This recently proposed concept is defined as "the co-occurrence of three or more chronic conditions affecting three

or more different body systems within one person", with an increasing score for each body system affected.[214] The proposed benefit of only counting chronic conditions that affect different body systems is that the count would only include distinct disease entities (rather than, for example, myocardial infarction and cardiac failure), and so yield a more accurate stratification of multimorbidity burden. It is a limitation of this study that this approach was not considered or included at the outset, and was only discovered after the analysis was performed. Future work should explore whether stratifying patients by complex multimorbidity leads to the identification of a subset of patients at highest risk.

A limitation of all these methods of measuring multimorbidity is that they are calculated from historical medical records and, because multimorbidity may change over time, the methods may not provide an accurate assessment of the burden of multimorbidity severity at the time point of interest, which in this study is the date of diagnosis of hip osteoarthritis. Another type of multimorbidity score is a direct subjective assessment of overall multimorbidity burden, such as the ASA classification system. This type of score offers a snapshot of a patient's health status at a particular point in time. Unfortunately, no score of this type was routinely available to this study on patients at the point of diagnosis of hip osteoarthritis.

The rate of multimorbidity studied in this cohort varied slightly by each measure, from 31% for the Electronic Frailty Index up to 67% for the count of chronic diseases. These rates are broadly equivalent to those reported by a global systematic review that reported rates of multimorbidity of 40-60% at age 60 years and 60-80% at age 80 years.[1] A UK-based study of CPRD records identified similar rates of multimorbidity, of 55% at age 65-74 years and 82% at age above 85 years.[215]

Another limitation of the methods of measuring multimorbidity is that the length of follow up in CPRD data available to investigate multimorbidity (between start date of CPRD data availability and index date) varied between patients. It is possible that patients with a shorter follow up period available might not have had all their multimorbidity recorded and so the multimorbidity scores for these patients would be falsely low. However, a previous investigation using CPRD data found calculating multimorbidity measures over a five-year look-back period gave a similar result to a one-year look-back period.[216] This

suggests the method of scoring multimorbidity burden in this study was reliable because all patients had a minimum of a one-year follow up period available to investigate multimorbidity.

It was not possible to categorise each multimorbidity measure into four approximately equal groups (from least to most severe multimorbidity) as planned due to the data distribution of the Charlson Comorbidity Index and the count of chronic diseases. For the four multimorbidity measures where categories were defined here, all reference strata included ≥33.5% of the cohort and all strata included ≥10% of the cohort. These minimum group sizes maintain the clinical relevance of all groups. The most severe category of the Electronic Frailty Index, which had pre-defined categories, contained only 0.6% of the cohort, and is thus likely identifying a 'very severe' subset. The moderate frailty category (score of 9-12) contained 5.0% of the cohort, which was comparable in size to the most severe categories of the other multimorbidity scores. When comparing the multimorbidity scores in terms of their associations with total hip replacement stratified by severity of multimorbidity, it is thus important to consider the differences in group sizes. An alternative approach would have been to make groups similar in size across all multimorbidity measures (by changing the Electronic Frailty Index categories to match the other measures, or vice versa) to facilitate comparison of multimorbidity measures; however, the a priori statistical plan was not changed.

Covariates

The multivariate regression models were adjusted for age, sex, region of residence in the UK and year of diagnosis of hip osteoarthritis. This was to control for any potential confounding effect of each of these variables, since all four variables are associated with multimorbidity, and likelihood of or access to total hip replacement.[1,40,217–219]

A limitation of the data on age is that date of birth data were not available from CPRD due to data protection regulations and so year of birth data were supplied instead. Age at index date was estimated using January 1st in the year of birth as date of birth. For some patients, the estimated date of birth may be up to 365 days out. Instead, using the date in the middle of the calendar year (July 2nd) would have reduced the error.

Models were not adjusted for BMI and index of multiple deprivation because these factors were judged to be on the causal pathway of multimorbidity and so their inclusion would have constituted over adjustment and could have masked the true association between multimorbidity and likelihood of surgery.[220–223] Models were not adjusted for ethnicity because the rate of missing data was high (47%) and the cohort was overwhelmingly from one ethnicity (99% white), and so such an adjustment would have reduced the precision of the models without increasing the accuracy.

Finally, it remains possible that other unmeasured patient factors had a confounding effect on the observed association between multimorbidity and the likelihood of hip replacement.

Outcome variables

The length of follow up in CPRD (between date of diagnosis and end date of CPRD data availability) was sufficiently long to investigate the clinical outcomes. NICE guidelines advise that patients with hip osteoarthritis should not be referred to secondary care for consideration of surgery until patients have been offered the core non-surgical treatment options, a process that would take substantially less time than the lower quartile follow up time of 2.4 years, even accounting for long waiting times to surgery.[43]

The end date of CPRD data availability was used as the end point of follow up. However, it remains possible that some patients were registered with a NHS GP practice that submitted data to CPRD but, after diagnosis of hip osteoarthritis, sought medical care elsewhere (such as a private GP or abroad) and this information was not fed back to the registered NHS GP. Such patients would have been lost to follow up, but this would not be accounted for in the analysis. Reassuringly, the number of such patients is likely to be low because this scenario could only happen if patients sought medical care privately or abroad, as if patients sought medical care via a different NHS GP, the original GP would have been notified and the patient removed from their patient list. Such loss to follow up is therefore unlikely to have affected the study findings.

The study aimed to investigate the association between multimorbidity and the likelihood of referral by GPs to orthopaedic secondary care. This would have permitted analysis of where the ‘barriers’ to patients with multimorbidity seeking joint replacement were occurring: either in primary care, where

GPs are the 'gate-keepers' of access to orthopaedic surgeons, or in secondary care, where orthopaedic surgeons are the 'gate-keepers' of surgery. Regrettably this analysis was not possible due to the low quality of the referral data available. This remains an important knowledge gap and future studies should aim to investigate the influence of multimorbidity on the rate of referral. In view of the poor quality routinely collected data currently available in patients' electronic medical records, future studies would either need to collect data prospectively from GPs directly or to start by pushing for national guidelines regarding the coding of referrals in primary care computer systems to drive up the quality of the data.

A sensitivity analysis was performed to investigate the validity of recording of total hip replacements in CPRD. The sensitivity, relative to recording of total hip replacements in linked HES APC data, was 80.5%. Reasons for the cases missing from CPRD may be that the GP in primary did not receive information on the total hip replacement carried out in a secondary care setting, or that the GP did not correctly code the total hip replacement in the primary care record. Nonetheless, the Kappa statistic of 0.63 (95% CI 0.62, 0.64) demonstrated good agreement between total hip replacements recorded in CPRD and HES APC. Furthermore, the subset included in the sensitivity analysis matched the wider cohort in terms of demographic and multimorbidity characteristics. In addition, this is a similar result to a previously published validation in a cohort of rheumatoid arthritis patients.[224] This suggests the recording of total hip replacements in CPRD has a high degree of completeness. This indicates the study findings are unlikely to have been affected by follow up bias.

The finding that the median time between diagnosis of hip osteoarthritis and total hip replacement was 0.8 years was unexpected. In the NHS, the pathway from referral by a GP to undergoing total hip replacement commonly takes approximately 0.8 years. The NHS target is that patients undergo elective surgery within 18 weeks (0.35 years) of being added to the waiting list for surgery by the surgeon in secondary care. Data on NHS performance shows many patient wait longer than the 18 weeks target.[225] This does not include the time between referral by a GP to review in clinic by the surgeon in secondary care. Although there are limitations in the accuracy of the diagnosis date, this finding raises questions about the timing of the diagnosis coding. It is possible that it is very common for patients to present late in the disease process and are immediately referred to secondary care. However, NICE Guidance

advises that patients should undergo a period of conservative management before referral. The alternative possibility is that GPs are only coding the diagnosis at the point that a referral is made. The implication of this possibility therefore is that there may exist patients with hip osteoarthritis symptoms who did not have it recorded by GPs because they were unsuitable for referral. This may be associated with multimorbidity, and as a result it is possible that the influence of multimorbidity on the rate of surgery has been underestimated.

4.5.3 Findings of different multimorbidity measures

The most severe category, using the Charlson Comorbidity Index as the multimorbidity measure, had an adjusted hazard ratio of 0.65 (95% CI 0.60, 0.70). When using the count of chronic diseases, the equivalent category had a lower, albeit similar, likelihood of surgery, with a hazard ratio of 0.59 (95% CI 0.55, 0.63). While these two measures are very similar in design, the larger difference between categories with the count of chronic diseases may indicate that it was superior at identifying patients within the cohort with a severe multimorbidity burden. The measure includes 17 chronic diseases that are very common and clinically important at present and have high data quality in CPRD as a result of the NHS QOF scheme[187], whereas the Charlson Comorbidity Index was developed in 1987 and adapted in 1992[202], and includes diseases, such as peptic ulcer disease and HIV/AIDS, for which treatment has improved substantially since 1992 and so have less of an impact on the health of modern patients.[226,227]

The most severe category when using the count of different medications prescribed in the previous 12 months had a hazard ratio of 0.67 (95% CI 0.62, 0.72), a similar result to the two traditional multimorbidity measures. The results suggest it is of similar value to the traditional multimorbidity measures in this context.

The other proxy multimorbidity score, the count of contacts with primary care in the previous 12 months, had a most severe category with hazard ratio of 0.85 (95% CI 0.81, 0.91). This lower difference between categories may not represent the true relationship between multimorbidity and rate of total hip replacement. Instead, this measure may have been the least effective at stratifying patients by severity

multimorbidity burden. A possible reason for this is that the count may be influenced by patient behaviour. Another reason, discussed above in the limitations section, is that there may be inconsistent ways of documenting patient contact in medical records by GPs, thus masking an association between count of contacts and multimorbidity severity.

The most severe category of the Electronic Frailty Index had a hazard ratio of 0.34 (95% CI 0.22, 0.51), which was substantially smaller than that of the other multimorbidity measures. This may indicate that this score was the best at identifying patients with a severe multimorbidity burden, by virtue that it accounts for functional disabilities as well as the presence of diseases. As discussed above, however, the most severe category is much smaller than of the other scores so likely represents a 'very severe' subset. Nonetheless, the moderate frailty category (score of 9-12), comparable in size to the most severe categories of the other multimorbidity scores, had a hazard ratio of 0.52 (95% CI 0.47, 0.59), which is smaller than that of the other multimorbidity measures. This shows the merit of the Electronic Frailty Index in this context.

4.5.4 Findings in context

This study found that patients with hip osteoarthritis with concurrent multimorbidity in the UK were substantially less likely to undergo total hip replacement, a procedure that leads to significant reduction in pain and improvement in quality of life. Patients with severe multimorbidity burden were one third to two thirds less likely to undergo total hip replacement. This study is the first to quantitatively study the influence of multimorbidity on the clinical management of patients with hip osteoarthritis in the UK. No previous studies are available for comparison.

Previous qualitative studies have suggested that such patients were being treated in this way. One study reported that some orthopaedic surgeons believed the presence of comorbidities should sway the decision towards not to proceeding with total hip replacement.[177] The reason given by the surveyed surgeons was that comorbidities reduced the likelihood of an excellent outcome. Another recent study in the UK found that a sample of 20 clinicians, including orthopaedic surgeons, GPs and physiotherapists, did not see the presence of comorbidities as a barrier to being referred or selected for

joint replacement, however, the study identified that the different professional groups disagreed on their responsibilities regarding the management of patients with comorbidities.[178] The authors suggested this disagreement may create an implicit barrier at the overall pathway-level such that patients with comorbidities get 'lost' to the system and miss out on total hip replacement, despite no formal decision that total hip replacement would be inappropriate. Such a scenario would be a failure of the NHS to deliver appropriate and fair, and indeed respectful, care and a failure to this group of patients, especially since evidence has demonstrated that poor continuity of care is associated with higher rates of adverse outcomes for patients with multimorbidity.[228,229] The data in this study did not contain sufficient detail to permit analysis of why the patients with multimorbidity were less likely to undergo total hip replacement. Further prospective research should investigate the reasons that certain patients with hip osteoarthritis did not undergo total hip replacement, and in particular focus on whether this was a decision taken by the GP, surgeon and/or patient, and what guided the decision.

4.5.5 Implications of findings

When considering the implications of the findings of this study, that is the different rate of total hip replacement for patients with multimorbidity, the key question is whether the different management of these patients is appropriate and fair, relative to patients without multimorbidity. This depends primarily on the influence of multimorbidity on the different outcomes of total hip replacement, namely the rate of post-operative complications, the degree of functional benefit, and the rate of revision surgery and other reoperations after surgery. For, if the likelihood of an excellent outcome is substantially lower for patients with multimorbidity (and this information were available), a lower rate of total hip replacement in these patients would be expected: clinicians would counsel patients on the predicted outcomes and fewer patients would likely choose to undergo surgery. However, if the likelihood of an excellent outcome for patients with multimorbidity were similar to that of patients without multimorbidity, the observed lower rate of total hip replacement for patients with multimorbidity becomes a concern: it would suggest that the patients have been receiving incorrect information or inappropriate management from their clinicians. The influence of multimorbidity on the outcomes of total hip replacement will be

investigated in the next two chapters, and the informed discussion on the appropriateness and fairness of the observed differing rate of surgery will be held in Chapter 8.

4.5.6 Conclusions

Hip osteoarthritis patients with concurrent severe multimorbidity burden are one third to two thirds less likely to undergo total hip replacement. Whether this difference in healthcare management is appropriate depends on whether and to what extent multimorbidity influences the outcomes of total hip replacement. As a next step, it is essential to investigate the influence of multimorbidity on the outcome of total hip replacement.

Chapter 5: Influence of Multimorbidity on Outcomes of Total Hip Replacement

5.1 Abstract

Introduction

Limited data are available on the risks and benefits of total hip replacement for patients with hip osteoarthritis and concurrent multimorbidity. As a result, patients and clinicians across the UK are making decisions on whether or not to proceed with total hip replacement, in the context of multimorbidity, without clear personalised evidence available to them. The aim of this study was to investigate the influence of multimorbidity on the outcomes of total hip replacement in patients with hip osteoarthritis in the UK.

Methods

A cohort study was performed, with the cohort comprised of all patients aged over 65 years with a diagnosis of hip osteoarthritis recorded in CPRD and receipt of primary total hip replacement recorded in HES APC. Severity of pre-operative multimorbidity burden was measured using five different scores. The outcomes were (i) the risks of total hip replacement, assessed by post-operative complications, length of stay and hospital readmission; (ii) the benefits of surgery, assessed by post-operative OHS and EQ-5D; and (iii) the need for further surgery, assessed by rate of revision surgery and other reoperations to the prosthetic hip.

Results

6,682 patients were included. Patients with multimorbidity were at increased risk of serious complications. Those with severe multimorbidity burden were at 1.5 to 2.5 times increased risk. There was no clinically meaningful difference in the benefits of surgery between patients with and without multimorbidity, in terms of postoperative hip pain and function or health-related quality of life. Patients with multimorbidity appear to have a mildly increased risk of revision surgery; however, the observed differences between revision rate were not statistically significant.

Conclusions

Even for patients with severe multimorbidity burden, the potential benefits of surgery remain high, while the increase in risks is relatively small. This information will be of value to patients and clinicians when deciding whether or not to proceed with hip joint surgery.

Work described in this chapter has been published as:

- *Ferguson RJ, Prieto-Alhambra D, Peat G, Delmestri A, Jordan KP, Strauss VY, Valderas JM, Walker C, Yu D, Glyn-Jones S, Silman AJ. Does pre-existing morbidity influences risks and benefits of total hip replacement for osteoarthritis: a prospective study of 6682 patients from linked national datasets in England. BMJ Open. 2021 Sep 23; 11(9): e046712. DOI: 10.1136/bmjopen-2020-046712. PMID: 34556506*

5.2 Introduction

As discussed in Chapter 1, across a variety of surgical specialties, multimorbidity influences the outcome of surgery. Depending on the severity, multimorbidity may increase the risk of complications from surgery and constrain the benefits in quality of life.[28,30,31,154,165,166] Evidence on the influence of multimorbidity on the outcome of total hip replacement specifically is limited.

In an ideal scenario, patients with severe hip osteoarthritis would decide whether to proceed with total hip replacement following discussions with their GP, orthopaedic surgeon and anaesthetist about the expected risks and benefits of surgery, based on evidence personalised to the patient. However, the ability of the evidence to inform this decision is currently limited. This increases the chance of inappropriate or unfair healthcare management occurring and increases decision-stress for patients.

The aim of this chapter is to investigate how, in patients with hip osteoarthritis, multimorbidity influences the outcome of total hip replacement. There are a number of ways this investigation may be performed, as discussed in Chapter 2. This chapter will identify a cohort of patients with hip osteoarthritis from across the UK and study the clinical outcomes of (i) the risks of total hip replacement, assessed by post-operative complications, length of stay and hospital readmission; (ii) the benefits of surgery, assessed by post-operative pain, function and quality of life; and (iii) the need for further surgery, assessed by rate of revision surgery and other reoperations to the prosthetic hip.

5.3 Methods

5.3.1 Study design

The study was a retrospective cohort study, using routinely collected linked primary care data and secondary care data in the UK. The data source was CPRD GOLD (application ISAC-17_024R), with linked data from the Hospital Episode Statistics Admitted Patient Care database (HES APC), the HES Patient Reported Outcome Measures database (HES PROMs), the English Index of Multiple Deprivation (IMD), and the Office for National Statistics (ONS) mortality data.

5.3.2 Data set

The population for this study were individuals undergoing elective primary total hip replacement, drawn from the cohort obtained for this thesis, described in Chapter 3, of 28,025 individuals aged over 65 years with a diagnosis of hip osteoarthritis recorded in CPRD.

Inclusion criteria were (1) linkage of individuals' electronic medical records in CPRD to records in HES APC, (2) the presence of a code indicating primary total hip replacement in HES APC records, and (3) the date of the recorded total hip replacement was between 1st April 1997, and 31st March 2014, and occurred after the date of diagnosis of hip osteoarthritis in CPRD. Details of the linkage methodology are given in Chapter 4, Section 4.3.2. Primary total hip replacements were identified in HES APC by a recorded OPCS-4 procedure code. The list of included OPCS-4 codes for primary total hip replacement was compiled from the NHS Digital OPCS-4 code list, as described in Chapter 4, Section 4.3.6. Data on date and side of procedure were extracted. Where an individual underwent primary total hip replacement on both hips, the date of the first total hip replacement recorded in their HES APC record only was taken as the index date. Procedures for which the date was lacking were excluded.

Data on the individuals' demographics were extracted from CPRD, including year of birth, sex, body mass index (BMI), ethnicity, marital status and geographical region of residence within the UK. Age was taken at date of primary total hip replacement and calculated using January 1st in the year of birth as date of birth. BMI was taken as the last recorded BMI measurement prior to date of primary total hip replacement. Other demographics were collected using methodology described in Chapter 4, Section 4.3.2. Data on socio-economic status and death were extracted from the IMD and ONS mortality dataset.

5.3.3 Multimorbidity measures

Multimorbidity was the exposure of interest in this study. As discussed in Chapter 1, there are many ways to estimate the severity of multimorbidity burden. Five different methods to measure multimorbidity, as in Chapter 4, were selected to be used in this study:

(1) Charlson Comorbidity Index,

(2) Count of chronic diseases,

(3) Count of different medications prescribed in the previous 12 months,

(4) Count of contacts with primary care in the previous 12 months, and

(5) Electronic Frailty Index.

All multimorbidity scores were calculated from data extracted from CPRD, based on the presence of Read codes recorded after the start date of CPRD data availability and prior to the index date (date of primary total hip replacement). The methodology to calculate each score was the same as that described in Chapter 4, Section 4.3.3.

5.3.4 Outcome measures

The outcomes of interest were:

(1) at least one serious complication within 90 days of index total hip replacement,

(2) readmission to hospital within 90 days of index surgery,

(3) length of stay in hospital for the index surgery,

(4) hip pain and function at least 6 months post-operatively,

(5) quality of life at least 6 months post-operatively,

(6) revision surgery, and

(7) any other reoperation to the prosthetic hip.

Outcome (1) of serious complications within 90 days was identified from HES APC and ONS mortality data. A serious complication was defined as either myocardial infarction, stroke, venous thromboembolism (pulmonary embolism or deep vein thrombosis), anaemia, surgical wound infection or dehiscence, respiratory tract infection, urinary tract infection, or death. These complications were selected for inclusion because they represent the most common major medical complications that occur after THR.[230] Serious complications (excluding death) were identified by the presence of an included ICD-10 code in HES APC recorded within 90 days of index THR. The list of included ICD-10 codes

for serious complications was compiled from the NHS Digital ICD-10 4th edition code list. The codes are shown in Appendix Table A-7. Data on death and date of death were extracted from ONS mortality data.

Outcome (2) of readmission within 90 days was identified from HES APC. Readmission was defined as all-cause admission to hospital that occurred after the first discharge from hospital after index total hip replacement. HES APC records were searched for a code indicating hospital admission within 90 days of index THR.

Outcome (3) of length of stay was identified from HES APC. Length of stay was calculated as the number of days from last date of admission to hospital prior to index primary total hip replacement to first date of discharge after index primary total hip replacement inclusive. It was recorded as an integer since times of admission and discharge were not available. HES APC records were searched for codes indicating hospital admission and discharge before and after index THR date.

Outcome (4) of hip pain and function at least 6 months post-operatively was identified from HES PROMs. The outcome was measured using the Oxford Hip Score (OHS).[78] The OHS was developed to assess hip pain and function in patients undergoing total hip replacement. The score (range 0-48) is calculated from the answers given by patients to 12 questions. The questionnaire is shown in Appendix Table B-4. Patients undergoing total hip replacement funded by NHS England are requested to complete the questionnaire before surgery and at least six months after surgery, with responses recorded in HES PROMs. Collection and recording of PROMs data in HES PROMs began in April 2009, so no routinely collected PROMs data is available prior to this date. Data on the score and date of the preoperative and postoperative OHS entries recorded were extracted from patients' HES PROMs records.

Outcome (5) of quality of life at least 6 months post-operatively was identified from HES PROMs. The outcome was measured using the three level EuroQol 5-dimension (EQ-5D) descriptive system score.[81] The EQ-5D was developed to assess health-related quality of life. It is a questionnaire that asks if individuals have problems in five dimensions of their life: mobility, self-care, usual activities, pain and discomfort, and anxiety and depression. The questionnaire is shown in Appendix Table B-5. A single

summative score (or global health index) is calculated from responses to the questionnaire. The summative score is calculated differently in different countries; in HES PROMs, the UK value set is used (summative score range -0.48 to 1.0).[231] Patients undergoing total hip replacement funded by NHS England are requested to complete the questionnaire before surgery and at least six months after surgery, with responses recorded in HES PROMs. Data on the single summative score and date of the preoperative and postoperative EQ-5D entries recorded were extracted from patients' HES PROMs records.

Outcome (6) of revision surgery was identified from HES APC. Revision surgery was defined as any surgery that involved the addition, removal or replacement of one or more components of the prosthetic hip. The inclusion period was from the index date (date of primary total hip replacement) until either outcome event, death or end of follow up in HES APC available. Revision total hip replacement operations were identified by the presence of an included OPCS-4 procedure code. The list of included OPCS-4 codes for revision total hip replacement was compiled from the NHS Digital OPCS-4 code list and are shown in Appendix Table A-8. Data on date and side of procedure were extracted. The date of outcome was the first occurrence of revision total hip replacement after the index date.

Outcome (7) of any other reoperation to the prosthetic hip, hereafter termed 'other reoperation', was identified from HES APC. Other reoperation was defined as any surgery to the prosthetic hip that did not involve the addition, removal or replacement of any components of the prosthetic hip. The inclusion period was from the index date (date of primary total hip replacement) until either outcome event, death or end of follow up in HES APC available. Other reoperations were identified by the presence of an included OPCS-4 procedure code. The list of included OPCS-4 codes for other reoperations was compiled from the NHS Digital OPCS-4 code list and are shown in Appendix Table A-9. Other reoperations include, but are not limited to, joint debridement, washout, and manipulation, and osteosynthesis of periprosthetic fracture. Data on date and side of procedure were extracted. The date of outcome was the first occurrence of an included other reoperation after the index date.

5.3.5 Statistical analysis

Data handling and descriptive statistics

Each multimorbidity measure was split into four categories. The cut offs for the categories in each of the five multimorbidity measures were set at the same thresholds as used in Chapter 4. The rationale for categorising the multimorbidity measures in this way is described in Section 4.3.5. The number of patients included in analyses (total at risk) was calculated for each category in all five multimorbidity measures. The lowest multimorbidity category was defined as the referent category for statistical analyses.

Baseline characteristic data were described using frequencies, proportions, means and standard deviations (SDs). Ranges of age (0-120 years) and BMI data (10-100 kg/m^2) were checked for plausibility.

The distribution in length of 'lead up' in CPRD available to investigate multimorbidity (between start date of CPRD data availability and index date) was described using the median, interquartile range (IQR) and range.

The distribution in length of follow up in HES APC available to investigate outcomes (between index date and end date of HES APC data availability) was described using the median, interquartile range (IQR) and range. The end date of HES APC data availability was March 31, 2014. This represents the last date of data submission (from hospitals to NHS Digital) of data that had been processed and approved by NHS Digital at the point at which data for this thesis were extracted by NHS Digital staff.

The start date of HES PROMs data availability was April 1, 2009, which is the date that HES PROMs was created and data recording began. No PROMs data are available prior to this date. The end date of HES PROMs data availability was February 29, 2016. This represents the last date of data submission (from hospitals to NHS Digital) of data that had been processed and approved by NHS Digital at the point at which data for this thesis were extracted by NHS Digital staff.

Analysis of associations between multimorbidity and outcomes

Outcome (1) of at least one serious complication within 90 days of index total hip replacement was treated as a binary variable. The rate of having a serious complication was calculated with 95% CIs for patients in each multimorbidity category. To compare the rates of having a serious complication by multimorbidity category, logistic regression analysis was used. The models are presented as odds ratios (ORs) with 95% CIs. The lowest multimorbidity category was defined as the referent category. Univariate and multivariate models, adjusted for age, sex, region of residence, and calendar year of surgery, were generated.

Outcome (2) of readmission to hospital within 90 days of index total hip replacement was treated as a binary variable. ORs were calculated using the same methods as in Outcome (1).

Outcome (3) of length of stay in hospital was treated as a count variable (with positive integer data points). Mean length of stay was calculated for patients by multimorbidity category. Regression analysis was used to compare the length of stay between multimorbidity categories. First, the distribution of data was visually assessed using a kernel density plot (Appendix Figure B-1). As data were non-negative and positively skewed, Poisson regression analysis models were used. The models are presented as incidence rate ratios (IRRs) with 95% CIs. Univariate and multivariate models, adjusted for age, sex, region of residence, and calendar year of surgery, were generated.

Outcome (4) of OHS, including pre-operative score, post-operative score and change in score, was described using mean and SD for patients in each multimorbidity category. The scores were investigated for statistically significant differences between multimorbidity categories using a one-way analysis of variance (ANOVA), with alpha of 0.05 as the threshold for significance. To compare the post-operative OHS between multimorbidity categories, regression analysis was used. First, the distribution of data was visually assessed using kernel density and Q-Q plots of regression residuals (Appendix Figures B-2 and B-3). As the residuals were approximately normally distributed, linear regression analysis models were used. The models are presented as coefficients with 95% CIs, adjusted for pre-operative OHS.

Univariate and multivariate models, adjusted for age, sex, region of residence, and calendar year of surgery, were generated.

Outcome (5) of EQ-5D measured at least 6 months post-operatively was analysed using the same methods as outcome (4). As Q-Q and kernel density plots of regression residuals (Appendix Figures B-4 and B-5) indicated residuals were approximately normally distributed, linear regression analysis models were used.

Outcome (6) of revision surgery was first explored by calculating the total number of person-years at risk contributed by all included patients, the number of revision surgery events and incidence rate (per 100 person-years) of revision surgery in each multimorbidity category. The cumulative incidence of revision surgery was assessed with competing risks estimates, with death considered a competing event. To compare the rate of revision surgery between multimorbidity categories, survival analysis was performed. Competing risk analysis models were used, with death considered a competing event. Fine and Gray competing risks regressions models, which focus on the cumulative incidence function, were chosen ahead of cause-specific hazard models.[204] Since the focus was on predicting prognosis, these methods were most appropriate as the models provide crude estimates of absolute risk. The models are presented as subdistribution hazard ratios (HRs) with 95% confidence intervals (CIs). Univariate and multivariate models, adjusted for age, sex, region of residence, and calendar year of surgery, were generated.

Outcome (7) of other reoperations was analysed using the same methods as outcome (6).

Statistical analysis was performed using STATA 14.0 (College Station, Tx, USA).

5.3.6 Sensitivity analysis of readmission to hospital

Outcome (2) investigated whether patients with multimorbidity were more likely to be readmitted to hospital within 90 days. However, patients with multimorbidity have a higher rate of unplanned admission to hospital compared with patients without multimorbidity even when they have not

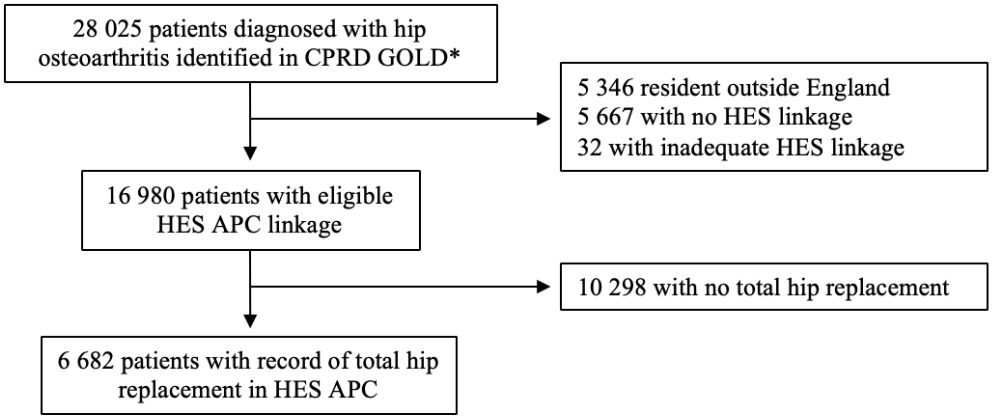
undergone surgery, with one recent study of 180,000 patients in Scotland reporting an odds ratio of 5.9 (95% CI 5.5, 6.3) of admission for patients with 4 or more diseases compared to patients with no diseases.[232] Therefore, to truly understand the results of outcome (2), it was necessary to understand in patients with multimorbidity what rate of readmission was 'normal' (i.e. the rate of admission that was not related to total hip replacement) and what rate of readmission was related to total hip replacement. Thus, to provide a comparator, the same cohort of patients was studied over an equivalent 90-day period not following total hip replacement. A period of 90 days beginning exactly one year prior to the date of total hip replacement was selected. The rate of hospital admission was analysed using the same methods as outcome (2) and the results were compared with those of outcome (2).

5.4 Results

5.4.1 Study cohort

In all, 6,682 patients were included in the cohort, based on the recording of elective primary total hip replacement in HES APC between April 1, 1997, and March 31, 2014. Figure 5-1 shows the cohort selection process.

Figure 5-1 – Flow diagram showing the selection of patients for inclusion



*28 025 patients eligible for inclusion as described in Section 3.4.1

Table 5-1 – Demographic details of patients in the CPRD cohort that underwent THR

	N.	%
Age		
65-69	1294	19.4
70-74	1976	29.6
75-79	1736	26.0
80-84	1095	16.4
85-89	465	7.0
90+	116	1.7
Missing	0	-
Sex		
Male	2592	38.8
Female	4090	61.2
Missing	0	-
BMI		
<18.5	54	1.0
18.5-<25	1615	28.8
25-<30	2444	43.6
30-<35	1124	20.0
35+	373	6.7
Missing	1072	-
Ethnicity		
White	5926	99.2
Afro-Caribbean	14	0.2
Chinese	10	0.16
Other	24	0.4
Missing	708	-
IMD quintiles		
Least deprived	1706	25.5
2	1718	25.7
3	1539	23.0
4	1144	17.1
Most deprived	573	8.6
Missing	2	-
Total	6682	

The mean age of patients at surgery was 75.9 years (SD 6.1). The mean BMI prior to surgery was 27.5 (SD 4.5). Detailed demographic data are shown in Table 5-1. Data on geographical region of residence are shown in Appendix Table B-6.

The length of 'lead up' in CPRD data available to investigate multimorbidity (between start date of CPRD data availability and index date) ranged from 1.1 years to 24.3 years. The median was 10.0 years and the interquartile range was 6.6 to 13.8 years. The distribution of index date (date of primary total hip replacement), by year, is shown in Appendix Table B-7. The length of follow up in HES APC data available to investigate outcomes (between index date and end date of HES APC data availability) ranged from 0 days to 17.0 years. The median was 4.7 years and the interquartile range was 2.3 to 7.6 years. For 196 patients (2.9%), the duration of follow up after primary total hip replacement was less than 90 days.

5.4.2 Multimorbidity

The proportions of the cohort in each multimorbidity category are shown in Table 5-2. Excluding the Electronic Frailty Index, the proportion of the cohort in the most severe category of the different multimorbidity measures ranged from 9.4 to 20.8%. The most severe category of the Electronic Frailty Index contained only 0.6% of the cohort, matching the proportion in the larger cohort in Chapter 4.

Table 5-2 – Distribution of categories of multimorbidity, by each measure

	N.	%
Charlson Comorbidity Index		
0	4490	67.2
1	682	10.2
2	880	13.2
3+	630	9.4
Count of chronic diseases		
0	1901	28.5
1	2286	34.2
2	1430	21.4
3+	1065	15.9

Count of medications prescribed		
0-4	1963	29.4
5-7	1832	27.4
8-12	1992	29.8
13+	895	13.4
Count of contacts with primary care		
0-7	2167	32.4
8-11	1598	23.9
12-17	1528	22.9
18+	1389	20.8
Electronic Frailty Index		
0-4	4184	62.6
5-8	2064	30.9
9-12	393	5.9
13+	41	0.6
Total	6682	

5.4.3 Serious complications

Of the 6,682 patients in the cohort, 216 (3.2% [95% CI 2.81, 3.66]) suffered at least one serious complication within 90 days of index total hip replacement. 57 patients (0.85% [CI 0.63, 1.07]) died within 90 days of index procedure. The numbers of events of all serious complications are shown in Table 5-3.

Table 5-3 – Serious complications within 90 days

	No. events	% (95% CI)
Myocardial infarction	20	0.30 (0.17, 0.43)
Stroke	8	0.12 (0.04, 0.20)
Venous thromboembolism	54	0.81 (0.59, 1.02)
Anaemia	12	0.18 (0.08, 0.28)
Surgical wound infection	37	0.55 (0.38, 0.73)
Respiratory tract infection	28	0.42 (0.26, 0.57)
Urinary tract infection	12	0.18 (0.08, 0.28)
Death	57	0.85 (0.63, 1.07)
Any serious complication	216	3.23 (2.81, 3.66)

The number and risk of serious complications by multimorbidity are displayed in Table 5-4. For patients without multimorbidity, the rate of a serious complication was approximately 3%. The risk of a serious complication increased modestly with increasing degree of multimorbidity in all five different methods of measuring multimorbidity. The pattern remained after adjustment for age, sex, region of the residence, and year of surgery.

Table 5-4 – Risk of any serious complication within 90 days by multimorbidity.

	No. patients	Events	% Events	Unadjusted OR (95% CI)	Adjusted OR* (95% CI)
Charlson Comorbidity Index					
0	4490	120	2.67	Ref	Ref
1	682	27	3.96	1.50 (0.98, 2.30)	1.43 (0.93, 2.20)
2	880	43	4.89	1.87 (1.31, 2.67)	1.78 (1.24, 2.56)
3+	630	26	4.13	1.57 (1.02, 2.42)	1.46 (0.94, 2.26)
Count of chronic diseases					
0	1901	53	2.79	Ref	Ref
1	2286	53	2.32	0.83 (0.56, 1.22)	0.80 (0.54, 1.18)
2	1430	57	3.99	1.45 (0.99, 2.12)	1.41 (0.96, 2.08)
3+	1065	53	4.98	1.83 (1.24, 2.69)	1.74 (1.16, 2.61)
Count of medications prescribed					
0-4	1963	49	3.09	Ref	Ref
5-7	1832	55	2.75	1.21 (0.82, 1.79)	1.17 (0.79, 1.73)
8-12	1992	68	3.53	1.38 (0.95, 2.00)	1.28 (0.88, 1.87)
13+	895	33	3.67	2.02 (1.33, 3.06)	1.85 (1.21, 2.83)
Count of contacts with primary care					
0-7	2167	67	3.09	Ref	Ref
8-11	1598	44	2.75	0.89 (0.60, 1.31)	0.85 (0.58, 1.25)
12-17	1528	54	3.53	1.15 (0.80, 1.65)	1.09 (0.76, 1.58)
18+	1389	51	3.67	1.19 (0.82, 1.73)	1.07 (0.74, 1.57)
Electronic Frailty Index					
0-4	4184	112	2.68	Ref	Ref
5-8	2064	75	3.63	1.37 (1.02, 1.85)	1.31 (0.96, 1.78)
9-12	393	26	6.62	2.58 (1.66, 4.00)	2.26 (1.42, 3.62)
13+	41	3	7.32	2.87 (0.87, 9.44)	2.50 (0.74, 8.41)
Total	6682	216	3.2		

*The model was adjusted for age, sex, region of the residence, and year of surgery.

The most severe category of the Charlson Comorbidity Index, the count of chronic diseases and the count of medications prescribed all had a similar odds ratio relative to their referent category, with a range of 1.46 (95% CI 0.94, 2.26) to 1.85 (95% CI 1.21, 2.83). The Electronic Frailty Index had the highest odds ratio across the categories. The wide 95% CI of the most severe EFI category (0.74, 8.41) reflects the low proportion in the category. The multimorbidity measure with the weakest trend in odds ratios between categories was the count of contacts with primary care.

For patients with multimorbidity that was not severe (hereafter defined as patients with multimorbidity that were not in top two categories of the Electronic Frailty Index [excluding 6.5% of patients with the most severe multimorbidity] or in the top category of the other multimorbidity scores [excluding between 9.4 and 20.8% of patients with the most severe multimorbidity]), there was generally a small increase in risk of serious complications. The range of odds ratios was 0.80 (95% CI 0.54, 1.18) to 1.78 (95% CI 1.24, 2.56).

The number of deaths and risk of death by multimorbidity are displayed in Appendix Table B-8. The risk of death increased modestly with increasing degree of multimorbidity. Patients with severe multimorbidity burden were at 1.1 to 2.8 times increased risk than patients without multimorbidity.

5.4.4 Readmission to hospital

In total 786 (11.8% [95% CI 11.0, 12.5]) were readmitted to hospital after discharge within 90 days of index total hip replacement.

The number and risk of hospital readmission by multimorbidity score are displayed in Table 5-5. For patients without multimorbidity, the rate of readmission was approximately 10%. The risk of hospital readmission increased modestly with increasing degree of multimorbidity, in all five different methods of measuring multimorbidity. The pattern remained after adjustment for age, sex, region of the residence, and year of surgery.

The odds ratio of the most severe category relative to the referent category was similar for all multimorbidity measures. The Charlson Comorbidity Index had the lowest ratio, at 1.45 (95% CI 1.14, 1.84), while the Electronic Frailty Index had the highest, at 2.15 (95% CI 0.97, 2.73). For patients with multimorbidity that was not severe, there was generally a small increase in risk of readmission. The range of odds ratios was 1.01 (95% CI 0.82, 1.23) to 1.47 (95% CI 1.19, 1.83).

Table 5-5 – Risk of hospital readmission within 90 days by multimorbidity

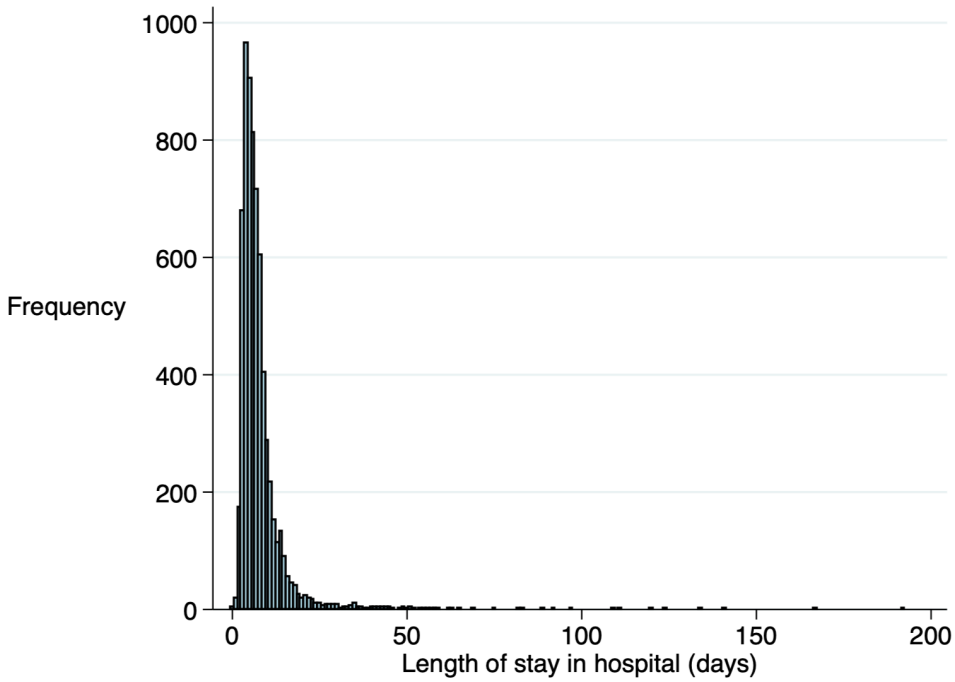
	No. patients	Events	% Events	Unadjusted OR (95% CI)	Adjusted OR* (95% CI)
Charlson Comorbidity Index					
0	4490	477	10.6	Ref	Ref
1	682	82	12.0	1.15 (0.90, 1.48)	1.09 (0.85, 1.40)
2	880	131	14.9	1.47 (1.19, 1.81)	1.41 (1.14, 1.74)
3+	630	96	15.2	1.51 (1.19, 1.92)	1.45 (1.14, 1.84)
Count of chronic diseases					
0	1901	192	10.1	Ref	Ref
1	2286	232	10.2	1.01 (0.82, 1.23)	1.01 (0.82, 1.23)
2	1430	205	14.3	1.49 (1.21, 1.84)	1.47 (1.19, 1.83)
3+	1065	157	14.7	1.54 (1.23, 1.93)	1.53 (1.21, 1.94)
Count of medications prescribed					
0-4	1963	180	9.2	Ref	Ref
5-7	1832	201	11.0	1.22 (0.99, 1.51)	1.22 (0.99, 1.51)
8-12	1992	257	12.9	1.47 (1.20, 1.80)	1.45 (1.18, 1.78)
13+	895	148	16.5	1.96 (1.55, 2.48)	1.96 (1.54, 2.49)
Count of contacts with primary care					
0-7	2167	204	9.4	Ref	Ref
8-11	1598	172	10.8	1.16 (0.94, 1.44)	1.15 (0.93, 1.43)
12-17	1528	192	12.6	1.38 (1.12, 1.70)	1.37 (1.11, 1.69)
18+	1389	218	15.7	1.79 (1.46, 2.20)	1.75 (1.42, 2.15)
Electronic Frailty Index					
0-4	4184	432	10.3	Ref	Ref
5-8	2064	270	13.1	1.31 (1.11, 1.54)	1.30 (1.10, 1.55)
9-12	393	76	19.3	2.08 (1.59, 2.73)	2.01 (1.51, 2.67)
13+	41	8	19.5	2.11 (0.97, 4.59)	2.15 (0.97, 4.73)
Total	6682	786	11.8		

*The model was adjusted for age, sex, region of the residence, and year of surgery.

5.4.5 Length of stay

The distribution in length of stay in hospital for index total hip replacement is shown in Figure 5-2. The median length of stay was 6 days (IQR 4-9 days). The range was 0-192 days.

Figure 5-2 – Distribution in length of stay in hospital



The associations between in length of stay in hospital and multimorbidity are displayed in Table 5-6. For patients without multimorbidity, the median length of stay was 6 days. The duration of length of stay increased modestly with increasing degree of multimorbidity, in all five different methods of measuring multimorbidity. The pattern remained after adjustment for age, sex, region of the residence, and year of surgery.

Patients in most severe category of the Charlson Comorbidity Index had the lowest incidence rate ratio relative to the referent category, at 1.21 (95% CI 1.18, 1.24), indicating these patients had a hospital stay approximately 20% longer. Patients in most severe category of the Electronic Frailty Index had the highest incidence rate ratio relative to the referent category, at 2.07 (95% CI 1.91, 2.25), indicating these patients had a hospital stay approximately twice as long. For patients with multimorbidity that

was not severe, there was generally a small increase in length of stay. The range of incidence rate ratio was 1.02 (95% CI 1.00, 1.05) to 1.21 (95% CI 1.18, 1.24).

Table 5-6 – Length of stay in hospital by multimorbidity

	Total at risk	Median length of stay (IQR)	Unadjusted IRR (95% CI)	Adjusted IRR* (95% CI)
Charlson Comorbidity Index				
0	4490	6 (4, 9)	Ref	Ref
1	682	6 (5, 9)	1.10 (1.07, 1.13)	1.05 (1.02, 1.08)
2	880	6 (4, 9)	1.08 (1.06, 1.11)	1.11 (1.08, 1.14)
3+	630	7 (5, 9)	1.18 (1.14, 1.21)	1.21 (1.18, 1.24)
Count of chronic diseases				
0	1901	6 (4, 8)	Ref	Ref
1	2286	6 (4, 9)	1.06 (1.03, 1.08)	1.06 (1.04, 1.09)
2	1430	6 (4, 9)	1.13 (1.10, 1.16)	1.19 (1.16, 1.22)
3+	1065	7 (5, 10)	1.22 (1.19, 1.26)	1.32 (1.29, 1.36)
Count of medications prescribed				
0-4	1963	6 (4, 8)	Ref	Ref
5-7	1832	6 (4, 9)	1.09 (1.06, 1.11)	1.08 (1.05, 1.10)
8-12	1992	7 (5, 9)	1.22 (1.19, 1.25)	1.21 (1.18, 1.24)
13+	895	7 (5, 10)	1.44 (1.40, 1.48)	1.46 (1.42, 1.50)
Count of contacts with primary care				
0-7	2167	6 (4, 8)	Ref	Ref
8-11	1598	6 (4, 9)	1.03 (1.00, 1.05)	1.02 (1.00, 1.05)
12-17	1528	6 (4, 9)	1.04 (1.02, 1.07)	1.04 (1.01, 1.06)
18+	1389	7 (5, 10)	1.25 (1.22, 1.28)	1.23 (1.20, 1.26)
Electronic Frailty Index				
0-4	4184	6 (4, 9)	Ref	Ref
5-8	2064	6 (4, 9)	1.12 (1.10, 1.14)	1.17 (1.15, 1.19)
9-12	393	8 (5, 11)	1.36 (1.32, 1.41)	1.38 (1.34, 1.43)
13+	41	8 (7, 13)	1.99 (1.83, 2.16)	2.07 (1.91, 2.25)
Total	6682	6 (4, 9)		

*The model was adjusted for age, sex, region of the residence, and year of surgery.

5.4.6 Oxford Hip Score

In total, 1474 patients (22%) had an OHS score recorded in HES PROMs. Of these, 1460 had preoperative OHS recorded, 1416 had postoperative OHS recorded, and 1402 had both preoperative and postoperative OHS recorded.

Table 5-7 – Oxford Hip Score by multimorbidity

	No. patients	Preop score	Postop score	Change in score	Unadjusted coefficient (95% CI)	Adjusted coefficient* (95% CI)
Charlson Comorbidity Index						
0	960	18.5 (8.0)	39.9 (8.0)	21.4 (9.6)	Ref	Ref
1	113	17.6 (8.4)	37.5 (9.7)	20.1 (10.5)	-2.03 (-3.56, -0.49)	-2.03 (-3.55, -0.52)
2	199	16.0 (7.5)	37.8 (8.3)	21.9 (9.4)	-1.37 (-2.58, -0.16)	-1.02 (-2.22, 0.18)
3+	130	16.8 (7.1)†	38.5 (8.1)†	21.5 (10.0)	-1.05 (-2.49, -0.40)	-0.60 (-2.04, 0.83)
Count of chronic diseases						
0	358	18.9 (7.8)	40.7 (7.9)	21.7 (9.9)	Ref	Ref
1	481	18.6 (8.1)	39.9 (7.9)	21.3 (9.6)	-0.70 (-1.77, 0.37)	-0.42 (-1.48, 0.64)
2	324	17.6 (7.9)	38.7 (8.2)	21.0 (9.6)	-1.62 (-2.80, -0.44)	-1.15 (-2.33, 0.04)
3+	239	15.7 (7.5)†	36.9 (8.9)†	21.2 (9.7)	-3.01 (-4.31, -1.71)	-2.28 (-3.58, -0.98)
Count of medications prescribed						
0-4	407	19.9 (7.4)	41.4 (7.1)	21.4 (9.3)	Ref	Ref
5-7	383	19.4 (8.1)	40.4 (7.4)	20.9 (9.5)	-0.84 (-1.92, 0.25)	-0.48 (-1.55, 0.60)
8-12	406	16.6 (7.7)	38.2 (8.5)	21.7 (9.9)	-2.32 (-3.41, -1.24)	-1.96 (-3.04, -0.88)
13+	206	14.1 (7.3)†	35.4 (9.2)†	21.3 (10.3	-4.55 (-5.89, -3.21)	-3.99 (-5.34, -2.64)
Count of contacts with primary care						
0-7	447	18.9 (7.8)	39.9 (7.8)	21.0 (8.9)	Ref	Ref
8-11	318	18.3 (8.1)	40.1 (7.8)	21.7 (10.0)	0.32 (-0.81, 1.45)	0.56 (-0.56, 1.67)
12-17	366	17.8 (7.8)	39.4 (8.1)	21.7 (9.9)	-0.08 (-1.16, 1.01)	0.41 (-0.70, 1.50)
18+	271	16.1 (8.1)†	37.2 (9.2)†	21.1 (10.3)	-2.01 (-3.21, -0.82)	-1.46 (-2.65, -0.26)
Electronic Frailty Index						
0-4	798	18.8 (7.9)	40.7 (7.5)	21.8 (9.4)	Ref	Ref
5-8	511	17.3 (7.9)	37.7 (8.8)	20.5 (10.2)	-2.53 (-3.40, -1.66)	-2.03 (-2.91, -1.15)
9-12	86	14.6 (7.0)	35.8 (8.1)	21.4 (8.8)	-3.62 (-5.37, -1.88)	-2.88 (-4.66, -1.10)
13+	7	14.7 (8.2)†	39.1 (10.4)†	24.4 (8.7)	-0.45 (-6.25, 5.35)	0.99 (-4.76, 6.74)
Mean		17.9 (7.9)	39.2 (8.2)	21.3 (9.7)		
Total	1402	1460	1416	1402		

† Denotes significance ($p<0.05$), based on one-way ANOVA comparing multimorbidity categories

*The model was adjusted for age, sex, region of the residence, and year of surgery.

Table 5-7 shows the mean (and SD) preoperative, postoperative and change in OHS by multimorbidity. Preoperatively, patients with increased severity of multimorbidity had a lower OHS (indicating more pain and worse function), a finding consistent in all multimorbidity measures used. Similarly, the postoperative score was lower in patients with increased severity of multimorbidity. Notably, however, the change in OHS was substantial for patients in all multimorbidity categories (mean change of 21.3 [SD 9.7]). Indeed, there was no significant difference in change in OHS between multimorbidity categories, irrespective of the multimorbidity measure used.

Table 5-7 also shows the associations between postoperative OHS, adjusted for preoperative OHS, and multimorbidity. The broad pattern across the different multimorbidity measures was that as severity of multimorbidity increases, the OHS outcome was lower.

The range in coefficient of the most severe category relative to the referent category for the different multimorbidity scores (excluding the Electronic Frailty Index) was -0.60 (-2.04, 0.83) to -3.99 (-5.34, -2.64). The interpretation of this finding is that, after allowing for differences in preoperative OHS, patients with severe multimorbidity would have a postoperative OHS of up to 4 points lower than patients without multimorbidity. The equivalent coefficient for the Electronic Frailty Index was positive, at 0.99 (-4.76, 6.74), suggesting patients with an increased Electronic Frailty Index have an increased postoperative OHS, however, the low number of cases and wide 95% CI should be noted. Indeed, the coefficient for the second most severe category was -2.88 (-4.66, -1.10), which is consistent with the other multimorbidity measures.

5.4.7 EQ-5D

In total, 1462 patients (22%) had an EQ-5D descriptive system summative score recorded in HES PROMs. Of these, 1380 had preoperative EQ-5D recorded, 1367 had postoperative EQ-5D score recorded, and 1285 had both preoperative and postoperative EQ-5D recorded.

Table 5-8 shows the mean (and SD) preoperative, postoperative and change in EQ-5D by multimorbidity. Preoperatively, patients with increased severity of multimorbidity had a lower EQ-5D

(indicating worse health-related quality of life), a finding consistent in all multimorbidity measures used. Similarly, the postoperative score was lower in patients with increased severity of multimorbidity.

Table 5-8 – EQ-5D score by multimorbidity

	No. patients	Preop score	Postop score	Change in score	Unadjusted coefficient (95% CI)	Adjusted coefficient* (95% CI)
Charlson Comorbidity Index						
0	880	.37 (.31)	.82 (.22)	.45 (.34)	Ref	Ref
1	108	.33 (.32)	.77 (.25)	.44 (.33)	-.04 (-.08, .01)	-.04 (-.08, .01)
2	178	.29 (.31)	.76 (.22)	.48 (.34)	-.04 (-.07, .00)	-.03 (-.06, .01)
3+	119	.33 (.29)†	.74 (.24)†	.40 (.33)	-.07 (-.11, -.03)	-.06 (-.10, -.02)
Count of chronic diseases						
0	330	.39 (.31)	.85 (.19)	.46 (.34)	Ref	Ref
1	429	.38 (.31)	.81 (.20)	.43 (.32)	-.04 (-.07, -.01)	-.03 (-.06, .00)
2	306	.33 (.31)	.78 (.23)	.45 (.35)	-.06 (-.09, -.03)	-.05 (-.08, -.02)
3+	220	.26 (.32)†	.71 (.28)†	.45 (.36)	-.12 (-.16, -.08)	-.11 (-.14, -.07)
Count of medications prescribed						
0-4	378	.42 (.30)	.85 (.20)	.44 (.34)	Ref	Ref
5-7	351	.41 (.30)	.83 (.20)	.42 (.32)	-.02 (-.05, .01)	-.02 (-.05, .01)
8-12	372	.30 (.30)	.77 (.22)	.47 (.34)	-.07 (-.10, -.04)	-.06 (-.09, -.03)
13+	184	.19 (.31)†	.69 (.28)†	.50 (.37)†	-.14 (-.18, -.10)	-.13 (-.17, -.09)
Count of contacts with primary care						
0-7	417	.39 (.31)	.82 (.22)	.44 (.33)	Ref	Ref
8-11	294	.36 (.30)	.83 (.21)	.46 (.34)	0.00 (-.03, .04)	0.01 (-.03, .04)
12-17	337	.36 (.31)	.80 (.21)	.44 (.35)	-.02 (-.05, .01)	-.01 (-.04, .02)
18+	237	.26 (.32)†	.72 (.26)†	.47 (.35)	-.08 (-.11, -.04)	-.07 (-.11, -.03)
Electronic Frailty Index						
0-4	735	.39 (.31)	.83 (.20)	.45 (.33)	Ref	Ref
5-8	464	.32 (.31)	.76 (.23)	.45 (.36)	-.06 (-.08, -.03)	-.05 (-.07, -.02)
9-12	79	.20 (.29)	.69 (.28)	.47 (.34)	-.14 (-.19, -.09)	-.13 (-.18, -.07)
13+	7	.20 (.35)†	.78 (.35)†	.59 (.32)	-.02 (-.18, .14)	.00 (-.16, .17)
Mean		.35 (.31)	.80 (.23)	.45 (.34)		
Total	1285	1380	1367	1285		

† Denotes significance ($p<0.05$), based on one-way ANOVA comparing multimorbidity categories
*The model was adjusted for age, sex, region of the residence, and year of surgery.

Notably, the change in EQ-5D was substantial for patients in all multimorbidity categories (mean change of 0.45 [SD 0.34]). There was no significant difference in change in EQ-5D between

multimorbidity categories, except for when measuring multimorbidity with the count of medication prescribed, which found patients with increased severity of multimorbidity had a greater change in EQ-5D, indicating a greater improvement in quality of life.

Table 5-8 also shows the associations between postoperative EQ-5D, adjusted for preoperative EQ-5D, and multimorbidity. The broad pattern across the different multimorbidity measures was that as severity of multimorbidity increases, the EQ-5D outcome was slightly lower.

Excluding the Electronic Frailty Index, the range in adjusted coefficient of the most severe category relative to the referent category was -0.06 (-0.10, -0.02) to -0.13 (-0.17, -0.09). The interpretation of this finding is that, after allowing for differences in preoperative EQ-5D, patients with severe multimorbidity would have a postoperative EQ-5D of up to 0.13 points lower than patients without multimorbidity. The equivalent coefficient for patients in most severe category of the Electronic Frailty Index was 0.00 (-0.16, 0.17), suggesting no difference in EQ-5D outcome between patients in the least and most severe multimorbidity categories. However, the low number of cases and wide 95% CI should be noted. Indeed, patients in the second and third categories had a poorer EQ-5D outcome relative to patients in the least multimorbidity category (coefficients of -0.05 [-0.07, -0.02) and -0.13 [-0.18, -0.07] respectively).

5.4.8 Revision surgery

Out of 6,682 patients, 104 (1.56%) underwent revision surgery to their index primary total hip replacement during the available follow up period, according to HES APC records. Figure 5-3 shows the process of selecting revision total hip replacements for inclusion. The cumulative incidence of revision is shown in Figure 5-4.

Figure 5-3 – Flow diagram showing the inclusion process for revision surgeries

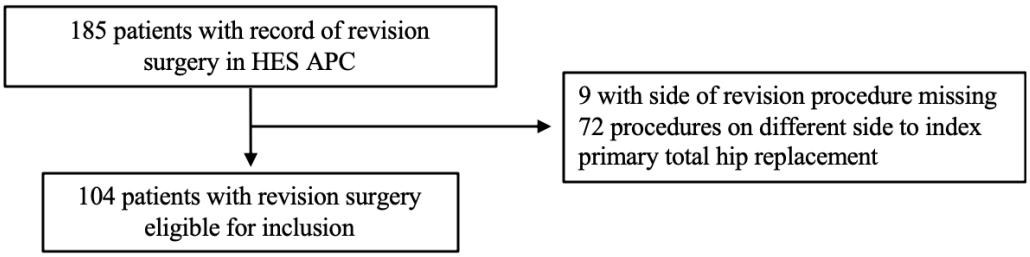
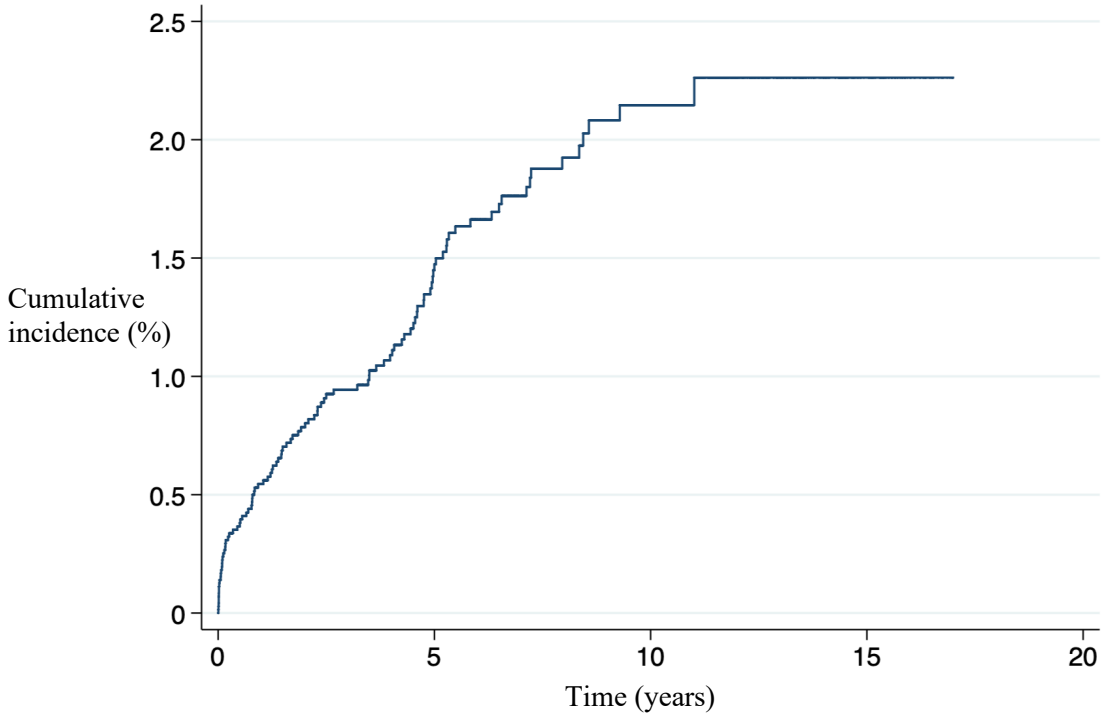


Figure 5-4 – Cumulative incidence of revision in HES APC



The associations between each multimorbidity measure and the rate of revision surgery are displayed in Table 5-9. There was no statistically significant difference in rate of revision surgery between patients in different categories of multimorbidity, for all multimorbidity measures except the count of contacts with primary care.

Table 5-9 – Rate of undergoing revision surgery by multimorbidity measure

	Total at risk	Competing risk events	Revision events	Person years at risk	Incidence per 100 PY	Unadjusted HR (95% CI)	Adjusted HR* (95% CI)
Charlson Comorbidity Index							
0	4490	800	63	25,643	0.27	Ref	Ref
1	682	175	15	3,847	0.29	1.53 (0.87, 2.68)	1.54 (0.88, 2.72)
2	880	188	12	2,942	0.37	1.06 (0.57, 1.96)	1.11 (0.59, 2.10)
3+	630	152	14	2,259	0.62	1.69 (0.95, 3.02)	1.70 (0.96, 3.02)
Count of chronic diseases							
0	1901	352	29	14,679	0.25	Ref	Ref
1	2286	439	33	11,647	0.27	0.99 (0.60, 1.63)	1.03 (0.63, 1.68)
2	1430	282	24	5,485	0.38	1.25 (0.73, 2.15)	1.31 (0.76, 2.25)
3+	1065	242	18	2,879	0.49	1.36 (0.75, 2.45)	1.45 (0.79, 2.65)
Count of medications prescribed							
0-4	1963	327	27	16,012	0.19	Ref	Ref
5-7	1832	361	18	9,251	0.27	0.72 (0.40, 1.31)	0.75 (0.41, 1.35)
8-12	1992	408	41	7,086	0.51	1.59 (0.98, 2.57)	1.68 (1.04, 2.73)
13+	895	219	18	2,342	0.51	1.64 (0.90, 2.96)	1.81 (0.98, 3.34)
Count of contacts with primary care							
0-7	2167	399	26	16,400	0.23	Ref	Ref
8-11	1598	292	27	7,792	0.28	1.42 (0.83, 2.43)	1.44 (0.84, 2.48)
12-17	1528	299	18	5,970	0.35	1.02 (0.56, 1.85)	1.05 (0.57, 1.91)
18+	1389	325	33	4,529	0.51	2.07 (1.24, 3.45)	2.17 (1.30, 3.64)
Electronic Frailty Index							
0-4	4184	814	66	27,842	0.27	Ref	Ref
5-8	2064	393	32	6,978	0.44	1.15 (0.75, 1.75)	1.26 (0.81, 1.95)
9-12	393	99	6	734	0.27	1.21 (0.52, 2.78)	1.44 (0.60, 3.47)
13+	41	9	0	37.0	0	-	-
Total	6682	1315	104	34,691	0.30		

*The model was adjusted for age, sex, region of the residence, and year of surgery.

5.4.9 Other reoperations

Out of 6,682 patients, 178 (2.66%) underwent an 'other reoperation' to their index primary total hip replacement during the available follow up period, according to HES APC records. Figure 5-5 shows

the process of selecting other reoperations for inclusion. The cumulative incidence of other reoperations is shown in Figure 5-6.

Figure 5-5 – Flow diagram showing the inclusion process for other reoperations

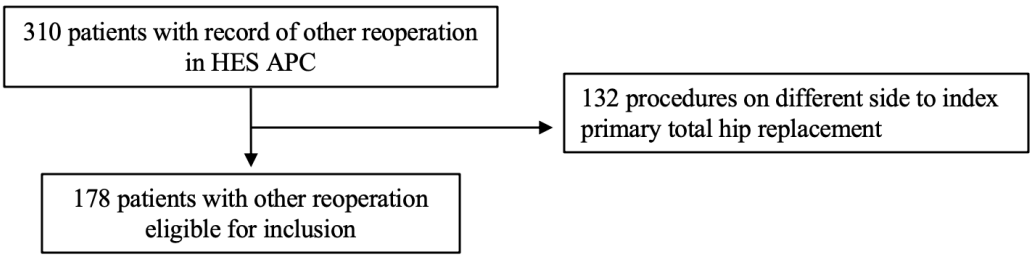
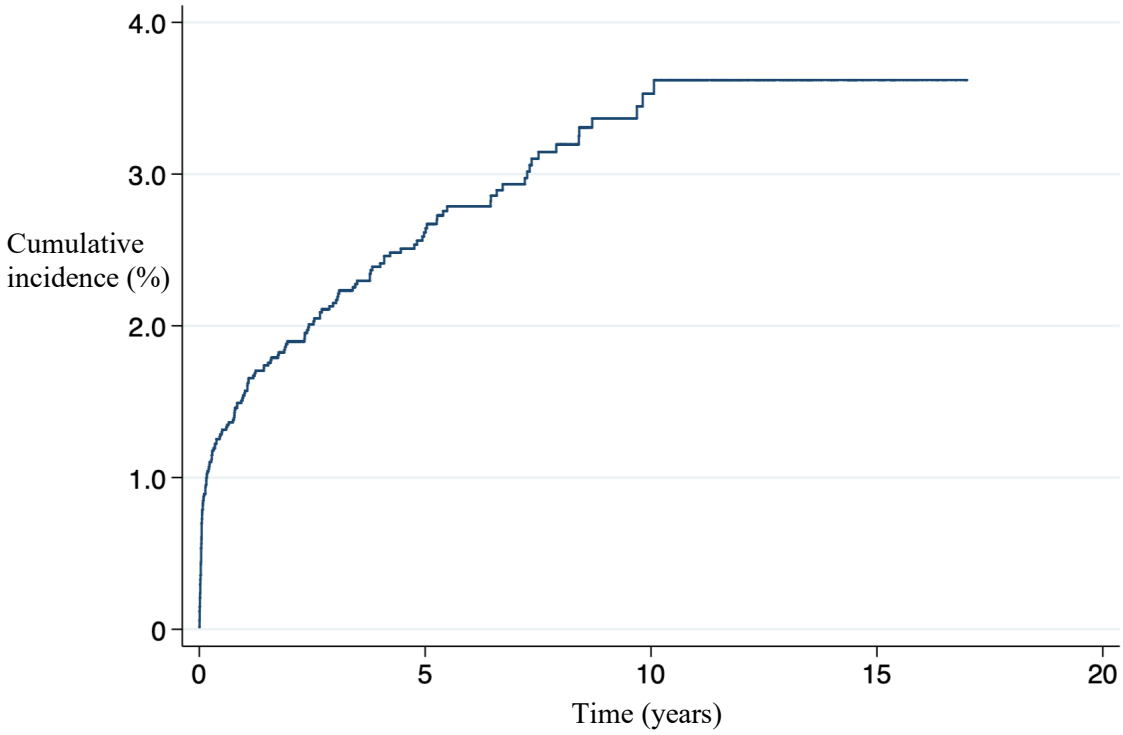


Figure 5-6 – Cumulative incidence of other reoperations in HES APC



The associations between each multimorbidity measure and the rate of other reoperation are displayed in Table 5-10.

When measuring multimorbidity using the Charlson Comorbidity Index, the count of chronic diseases and the count of medications prescribed, there was no statistically significant difference in rate of other

reoperation between patients in different categories of multimorbidity. Patients in the most severe category of the Electronic Frailty Index had an increased rate of other reoperation (adjusted HR 3.41 [95% CI 1.11, 10.47]). However, the low number of patients in this category and wide CI is acknowledged.

Table 5-10 – Rate of undergoing other reoperation by multimorbidity measure

	Total at risk	Competing risk events	Reop events	Person years at risk	Incidence per 100 PY	Unadjusted HR (95% CI)	Adjusted HR* (95% CI)
Charlson Comorbidity Index							
0	4490	783	120	25,373	0.47	Ref	Ref
1	682	172	22	3,779	0.69	1.18 (0.75, 1.86)	1.17 (0.74, 1.84)
2	880	185	25	2,914	0.69	1.12 (0.73, 1.73)	1.10 (0.71, 1.71)
3+	630	154	11	2,256	0.58	0.68 (0.36, 1.25)	0.67 (0.36, 1.24)
Count of chronic diseases							
0	1901	346	48	14,539	0.43	Ref	Ref
1	2286	431	62	11,474	0.54	1.11 (0.76, 1.61)	1.11 (0.76, 1.62)
2	1430	277	38	5,465	0.51	1.15 (0.75, 1.76)	1.15 (0.75, 1.76)
3+	1065	240	30	2,845	0.88	1.27 (0.81, 2.00)	1.27 (0.80, 2.01)
Count of medications prescribed							
0-4	1963	324	42	15,881	0.34	Ref	Ref
5-7	1832	358	39	9,118	0.49	1.00 (0.65, 1.55)	1.00 (0.65, 1.56)
8-12	1992	395	73	6,991	0.86	1.79 (1.23, 2.62)	1.77 (1.20, 2.60)
13+	895	217	24	2,333	0.81	1.35 (0.82, 2.23)	1.34 (0.80, 2.23)
Count of contacts with primary care							
0-7	2167	394	50	16,290	0.34	Ref	Ref
8-11	1598	292	35	7,683	0.55	0.95 (0.62, 1.47)	0.93 (0.60, 1.44)
12-17	1528	291	45	5,872	0.77	1.31 (0.88, 1.96)	1.27 (0.85, 1.91)
18+	1389	317	48	4,478	0.78	1.55 (1.04, 2.29)	1.50 (1.01, 2.23)
Electronic Frailty Index							
0-4	4184	804	109	27,510	0.48	Ref	Ref
5-8	2064	384	54	6,045	0.65	1.11 (0.80, 1.54)	1.09 (0.77, 1.53)
9-12	393	97	12	732	0.68	1.36 (0.75, 2.46)	1.29 (0.69, 2.43)
13+	41	9	3	36	5.60	3.37 (1.09, 10.42)	3.41 (1.11, 10.47)
Total	6682	1294	178	34,322	0.52		

*The model was adjusted for age, sex, region of the residence, and year of surgery.

5.4.10 Sensitivity analysis of readmission to hospital

Appendix Table B-9 shows the rate of admission to hospital over a 90-day period beginning exactly one year prior to index total hip replacement, stratified by multimorbidity. Overall, the proportion of patients who were admitted to hospital over the 90-day period beginning exactly one year prior to index total hip replacement was 9.5%, compared with 11.8% for the 90-day period following total hip replacement. The proportion of patients with severe multimorbidity burden who were admitted to hospital over the prior 90-day period ranged from 15.6% to 19.6% depending on the multimorbidity measure used. This compares with 14.7% to 19.5% of the same group of patients who were readmitted to hospital in the 90-day period following total hip replacement. Patients with severe multimorbidity burden were more likely to be admitted to hospital than patients without multimorbidity, with an adjusted odds ratio of 2.2 to 3.5, in the period one year prior to surgery. This compares with an odds ratio of 1.5 to 2.2 of readmission 90-day period following total hip replacement for the same cohort of patients.

5.5 Discussion

5.5.1 Summary of main findings

This chapter reports on the association between multimorbidity and the outcomes of total hip replacement in a large sample of individuals diagnosed with hip osteoarthritis in the UK.

The results indicate that with increasing multimorbidity burden, patients are at increased risk of suffering a serious complication within 90 days of surgery. The rate of complications for patients with multimorbidity was approximately 4-7%, compared with 3% for patients without multimorbidity. Patients with multimorbidity that was not severe were at 0.8 to 1.8 times increased risk than patients without multimorbidity. Patients with severe multimorbidity burden were at 1.5 to 2.5 times increased risk.

With increasing multimorbidity burden, patients are at increased risk of requiring readmission to hospital within 90 days of surgery. Patients with multimorbidity that was not severe were at 1.0 to 1.5 times increased risk. Patients with severe multimorbidity burden were at 1.5 to 2.2 times increased risk.

With increasing multimorbidity burden, patients require a longer stay in hospital after surgery. Patients with multimorbidity that was not severe had stays of 1.0 to 1.2 times as long. Patients with severe multimorbidity burden had stays of 1.2 to 2.1 times as long.

With increasing multimorbidity burden, patients have a lower OHS outcome after surgery. However, it is important to consider whether the observed difference is clinically important. A study by the developers of the score presented estimates of the minimum clinically important difference and the minimum detectable change of the OHS, using both anchor-based and distribution-based methods. The smallest minimum clinically important difference was 5.[174] In this study, the difference in outcome was only between 0.6 and 4.0 points lower (depending on multimorbidity score) for patients with severe multimorbidity burden compared with those without multimorbidity. Thus, the patient-reported difference in OHS outcome between patients with and without multimorbidity was not sufficiently large that patients would be able to detect any difference in pain and hip function. Furthermore, irrespective of multimorbidity burden, patients had a large positive change in OHS after surgery and there was no difference in change between multimorbidity categories. This suggests that patients benefit substantially from total hip replacement, in terms of hip pain and function, whether or not they have concurrent multimorbidity.

With increasing multimorbidity burden, patients have a lower EQ-5D outcome after surgery. However, again, it is important to consider whether the observed difference is clinically important. A literature review identified numerous studies that have attempted to calculate the minimum clinically important difference of the EQ-5D score. A systematic review in 2014 identified 18 studies that had estimated the minimum clinically important difference of the three-level EQ-5D score, with an overall average of 0.18 points and a range of 0.03 to 0.54.[175] In this study, the difference in outcome was only between 0.06 and 0.13 points lower (depending on multimorbidity score) for patients with severe multimorbidity burden than those without multimorbidity. Thus, taking the average of 0.18 points as the minimum

clinically important difference would mean that the patient-reported difference in EQ-5D outcome between patients with and without multimorbidity was not sufficiently large that patients would be able to detect any difference in their health-related quality of life. Furthermore, irrespective of multimorbidity burden, patients had a large positive change in EQ-5D after surgery and there was no difference in change between multimorbidity categories. (The one exception was the multimorbidity score of the count of medications prescribed, which found that patients in the most severe category actually had a greater improvement than patients in other categories.) This suggests that patients benefit substantially from total hip replacement, in terms of health-related quality of life, whether or not they have concurrent multimorbidity.

With increasing multimorbidity burden, there appeared to be a mildly increased risk of revision surgery (up to 1.5 to 2.2 times higher), however, the differences between the categories were not statistically significant.

There was no consistent pattern between severity of multimorbidity burden and rate of other reoperations. There was no statistically significant difference in the rate of other reoperations by severity of multimorbidity burden.

5.5.2 Strengths and limitations

Study cohort

The study cohort was identified using HES APC as the data source. As described in Chapter 2, HES APC contains data from all NHS-funded hospital admissions in England. HES APC recording of THRs has been validated and found to have comparable completeness with the NJR.[7] The NJR in turn has been audited and found to have near 100% compliance against levy returns for the number of implants sold.[5] Thus, HES APC is a near complete source of data on THR in England, minimising selection bias.

Each year in the UK, in excess of 70,000 primary total hip replacements are performed.[5] However, the cohort for this study only included 6,682 individuals that had undergone total hip replacement identified

in HES APC over a 17-year period. This means therefore, given the completeness of HES APC, that many hip replacements recorded in HES APC were not included in the cohort here. There were several factors in the cohort identification process that led to this reduced total cohort size. Only one cohort of patients with linked CPRD and HES APC data was available to this thesis from CPRD due to financial resources. CPRD holds data from primary care records of approximately 7% of the UK population. CPRD charges for access to the data it holds on a 'fee per data extract' basis and only one data extract could be purchased. The single cohort obtained from CPRD was therefore designed to best provide cohorts to permit the studies described in Chapters 4 and 5. The cohort from CPRD were all patients aged over 65 years with a diagnosis of hip osteoarthritis recorded in CPRD, which totalled 28,025. For this study, all patients in that cohort who had linkage to HES APC and had undergone total hip replacement were included. The key issue is whether the included cohort of 6,682 individuals are representative of the wider UK population that have undergone total hip replacement over the same time period. Appendix Table B-6 demonstrates the cohort was drawn broadly equally from all 10 geographical areas of England covered by HES APC, and the mean age and BMI, and sex makeup of the cohort (75 years old, BMI 28, 39% men) were similar to that reported by the UK NJR (68 years old, BMI 28, 40% men).[5] It is not possible to compare the multimorbidity of the cohort with the wider population that have undergone hip replacement as no data are available. Nonetheless, there is unlikely to be any relationship between multimorbidity and each of the cohort inclusion steps, making the risk of selection bias low.

Predictor variables

The selection of ways of measuring multimorbidity that accurately score the true multimorbidity burden of patients was a crucial step in this study. A discussion of the strengths and limitations of the five measures chosen in this study is found in Chapter 4, Section 4.5.2.

The results of this study describe the outcomes of total hip replacement in patients with moderate and severe multimorbidity burden compared to patients without multimorbidity. However, an important limitation of this study is that the cohort only included patients that underwent total hip replacement, indicating they had gone through a selection process and were judged by their clinicians to be

appropriate candidates for surgery. Another group of patients exists with hip osteoarthritis and concurrent multimorbidity that did not undergo total hip replacement. Some of these patients will have not undergone surgery because their clinicians advised, after assessment and examination, that surgery was not appropriate due to a severe burden of multimorbidity. Indeed, it is acknowledged there may be weaknesses in the ability of the five included multimorbidity scores of routinely collected patient data to identify patients' true burden of multimorbidity. Although in this study the measures of multimorbidity classified some patients as having more severe multimorbidity, these patients may not have as severe a multimorbidity burden compared to certain other patients that did not undergo total hip replacement. The results of this study for patients with multimorbidity that was classified as severe may not actually represent what the outcomes of surgery would be for patients with a true severe burden of multimorbidity. Care must therefore be taken before extrapolating the outcomes of surgery in patients in this cohort that were judged to have multimorbidity, to all future patients with hip osteoarthritis and concurrent multimorbidity whom are considering surgery.

Covariates

The multivariate regression models were adjusted for age, sex, region of residence in the UK and year of total hip replacement. This was to control for any potential confounding effect of each of these variables. Age and sex are known to be associated with multimorbidity and with outcomes of THR.[87,233–235] Region of residence in the UK is associated with certain comorbid diseases and there is evidence outcome of THR varies between hospitals, thus it was decided to adjust models for region of residence of patients undergoing THR.[217,218,236] A limitation of these data was that region of residence recorded on the date of THR was not available in HES APC, and instead the most recent available recording of region of residence in CPRD was used. Thus, data would be incorrect for patients that changed region of residence prior to THR without informing their GP. It is expected the data of only a small minority of patients would be affected and any potential information bias would be negligible. Year of surgery was included as an adjustment factor because both multimorbidity rates and outcomes of surgery have changed over time.[5,237]

It remains possible that other unmeasured variables had a confounding effect on the observed association between multimorbidity and the outcomes of hip replacement; however, any effect is likely to be small.

Outcome variables

A strength of this study is that it was able to investigate all of the complementary ways in which the outcome of total hip replacement may be evaluated, yielding a comprehensive analysis of the influence of multimorbidity on the outcomes of surgery. However, before drawing conclusions, it remains essential to evaluate the outcome variables studied, included whether appropriate variables were studied, whether data were complete, whether data were accurate, and whether there was any bias in the data.

(1) At least one serious complication within 90 days of total hip replacement:

Whether this study investigated the 'correct' or most relevant serious complications is an important consideration. The choice to include the eight complications here (myocardial infarction, stroke, venous thromboembolism, anaemia, surgical wound infection or dehiscence, respiratory tract infection, urinary tract infection, or death) was based on the fact they represent the most common medical adverse events after total hip replacement.[230] Certainly, other medical adverse events may occur after hip replacement. Examples are Clostridium Difficile-associated diarrhoea and cardiac arrhythmias. The reason other medical adverse events were not included is because they are less common and there may be increased ambiguity on whether they occurred as a result of the total hip replacement.

An alternative strategy in investigating complications would have been to include all complications of specified graded severity, recorded according to a complication classification system. One complication classification system is the Clavien-Dindo system, which has become widely used in General Surgery since its development in 2004.[238] Despite an adaptation by Sink et al in 2012 for use in orthopaedic surgery,[239] the classification system (or any other complication classification system) is not routinely used in arthroplasty surgery and so it was not possible here to extract data on complications based on recording of a complication classification system in the primary care records.

It is acknowledged that the included complications, with the exception of death, may occur with varying severity and can indeed have only minor and temporary effects on patients' health status. However, it was not possible to determine from the HES APC data whether each recording of the eight included complications represented a severe complication or only a minor one. This is because to do so would have required extraction and review of free text data entries following each recorded complication and this was beyond the resources available to this thesis. This is a limitation because the lack of detail regarding whether each complication was mild or severe may have masked the true relationship between patients with multimorbidity and the clinically important severe post-operative complications. Nonetheless the results of the study remain valid because each recording of one of the eight included complications represents a serious event in the post-operative care of the patient, carrying the potential for significant morbidity or death.

To investigate the influence of multimorbidity on the risk of severe complications, death was analysed separately (Appendix Table B-8). Patients with multimorbidity were at 1.0 to 2.8 times increased risk of death than patients without multimorbidity. This is a similar risk to the risk of serious complications, although it is acknowledged the odds ratio estimates have wider confidence intervals due to the lower number of death events. This result suggests the inability to assess the severity of each complication did not introduce substantial information bias into the results of the analysis of the risk of serious complications.

Whether the data on complications were complete and accurate are the next considerations. The outcomes of serious complications within 90 days were analysed as a binary outcome and not as survival analysis. 97% of the cohort had a minimum 90 days follow up. For patients with 90-day follow up data available, it was not possible to directly assess whether data on serious complications were missing because the absence of a relevant code in HES APC was interpreted as the event not occurring. Instead, to evaluate whether the results were plausible and by extension whether the data were accurate, comparisons were made between the rates of serious complications found here and the rates reported in recent publications of similar patient groups. A search of the literature found three relevant papers that reported the rate of different serious complications after primary total hip replacement in a large cohort,

of which one was based on UK patients and two based on USA patients, with a range of cohort size of 5,000 to 31,000 (Table 5-11).[15,240,241]

Table 5-11 – Comparison of rate of serious complications

	Event rate in study (%) (95% CI)	Rate in literature[15,240,241] (%)
Myocardial infarction	0.30 (0.17, 0.43)	0.2-0.5
Stroke	0.12 (0.04, 0.20)	0.1-0.5
Venous thromboembolism	0.81 (0.59, 1.02)	0.6-2.9
Anaemia	0.18 (0.08, 0.28)	2.4
Surgical wound infection	0.55 (0.38, 0.73)	0.2-2.2
Respiratory tract infection	0.42 (0.26, 0.57)	0.1-0.5
Urinary tract infection	0.18 (0.08, 0.28)	1.2-2.3
Death	0.85 (0.63, 1.07)	0.1-1.0

For each of the included serious complications, with the exception of anaemia, the rate found in the study was within the range reported by the comparison studies. Of note, the comparison studies had a range of included follow up time, of within hospital, within 30 days and within 6 months. The comparison is therefore not exactly like-with-like; however, nonetheless, the comparison suggests the rates found in this study are likely to be broadly accurate, or, at worst, consistent with inaccuracies made by others.

In this study, the recorded rate of post-operative anaemia was 0.18%. Comparison to other reports suggests this may be an underestimate of the true rate. Wallace et al reported a post-operative anaemia rate of 2.4%. Indeed, other studies have reported an allogenic blood transfusion rate after total hip replacement in excess of 20%.[242–244] It is acknowledged that thresholds for definitions of anaemia vary and that the rate of post-operative anaemia has decreased substantially in the past 20 years due to improvement in peri-operative medical care. Nonetheless, these comparisons suggest the rate of 0.18% found here in HES APC is inaccurately low. One possible explanation for this is that the occurrence of anaemia was recorded in patients' hospital discharge letters and hence HES APC record via ICD-10 codes and that the code was missed in this study due to the flawed methodology. However, the list of included codes for anaemia was compiled as an inclusive, exhaustive list from the most recent NHS

Digital ICD-10 4th edition code list, in order to minimise the chance of missing anaemia events, making this possibility unlikely. An alternative explanation is that the occurrence of anaemia was not recorded in patients' hospital discharge letters and hence was lacking in the HES APC record. This could have happened if the clinician that wrote the discharge letter either chose not to record anaemia because it had resolved prior to discharge (either spontaneously or after a blood transfusion) or chose to record anaemia indirectly, such as recording that a blood transfusion had taken place. Indeed, the list of included codes for anaemia did include codes for blood transfusion. The underestimation of the rate of anaemia is a weakness of the analysis methodology. It is possible that the risk of anaemia, and, by extension, serious complications, in patients with multimorbidity was underestimated.

(2) Readmission to hospital within 90 days of total hip replacement:

Readmission to hospital was defined as all-cause admission to hospital. This definition was chosen because it negated the need for subjective assessments of whether each readmission was related to the index surgery or not.

The data on readmission to hospital were extracted and analysed in a similar way to the data on serious complications: the absence of a relevant code in HES APC was interpreted as the event not occurring. Thus, to evaluate whether the data were likely accurate, comparisons were made between the rates of readmission found here and the rates reported in recent publications. The rate of readmission to hospital within 90 days found here was 11.8% (95% CI 11.0, 12.5). A search of the literature found three relevant papers that reported the rate of readmission to hospital after primary total hip replacement in a large cohort, of which one was based on UK patients and two based on USA patients, with a range of cohort size of 274,000 to 500,000.[245–247] The two USA cohorts had a 90-day readmission rate of 10.2% and 12.7%. The UK cohort had a 30-day readmission rate of 5.9%. These comparisons are consistent with the rate of readmission to hospital reported in this study.

One concern when analysing the rate of readmission was that patients could be wrongly counted as being readmitted to hospital when they were not. This could happen if, during a patient's original hospital admission, the consultant in charge of their care changed, and this event was coded as "hospital

admission" under a different consultant. To minimise the risk of this data error occurring, only hospital admission events that occurred later that the date of hospital discharge were included. A second concern remains: that patients readmitted within 90 days to a hospital that was not an NHS funded were not identified; however, the rate of such an event occurring is likely to be very low.

When interpreting the findings of the analysis of rate of readmission to hospital, it is important to consider what a patient with multimorbidity considering total hip replacement would want to know: what the impact of THR is on the subsequent rate of admission to hospital, and how does multimorbidity affect it. It is thus important to acknowledge that not all the observed cases of admission to hospital following total hip replacement occurred as a result of the surgery, and that some admissions might theoretically have occurred anyway without surgery having been performed. Indeed, patients with multimorbidity have a higher rate of unplanned admission to hospital at baseline[232], and therefore would have an equivalently higher rate of 'readmission' to hospital within 90 days of surgery. The sensitivity analysis performed here demonstrated that the proportion of patients with severe multimorbidity burden who were readmitted to hospital within 90 days of total hip replacement (between 14.7% and 19.5%, depending on multimorbidity score) was similar to the proportion of patients with severe multimorbidity burden who were admitted to hospital over a 90-day period exactly one year prior (between 15.6% and 19.6%). Together, these data suggest that while patients with severe multimorbidity burden have a higher rate of admission to hospital within 90 days of total hip replacement than patients without multimorbidity, this higher rate of admission appears to be the 'normal rate' for such patients, and is unchanged following total hip replacement.

(3) Length of stay in hospital for total hip replacement:

Data on length of stay, calculated from dates of admission to and discharge from hospital listed in HES APC, were available on all patients. Completeness of recording date of admission and discharge are high because hospitals must record these variables for reimbursement purposes.

Data accuracy relies on correct recording of the dates of admission to and discharge from hospital. Similar to the approach with serious complications, to gain insights into whether the results were

plausible, comparisons were made with the average lengths of stay reported in recent publications of similar patient groups. On a national level, the average length of stay after total hip replacement decreased significantly over the study period (1997 to 2014) due to advances in peri-operative medical care,[248] thus comparisons of length of stay after total hip replacement must consider the year in which included cases were performed. A search of the literature found one relevant paper that reported the length of stay after primary total hip replacement in a larger cohort of patients also using HES APC data and including the same years of surgery.[248] The overall mean length of stay was 8.2 days, similar to the mean length of stay in this study of 7.9 days (SD 7.9). A comparison of length of stay by year of surgery between the cohort in this study and previously published data, shown in Appendix Table B-10, found similar results. A further search of the literature for studies based in the UK that did not use HES APC data found two single-centre case series. One reported mean length of stay of 8.1 days after procedures carried out from 1998 to 2006.[249] The other reported mean length of stay of 11.4 days after procedures carried out prior to 2010.[250] Together, these results suggest the data of length of stay in this study were likely accurate.

(4) Hip pain and function and (5) Quality of life at least 6 months post-operatively:

Data on OHS and EQ-5D PROMs were obtained from the HES PROMs database. NHS providers are required to contact patients directly to distribute and collect PROMs questionnaires, which are then submitted to NHS Digital for processing, before cleaned data is added to the database. The central processing of nationwide data is designed to minimise data errors.

Data on PROMs were only available on a subset of the cohort. In all, 45% of procedures were performed during the period that the PROMs data was collected (2008-2014). Pre- and post-operative OHS and EQ-5D scores available for 21% and 19% of the total cohort respectively, indicating that approximately just under half of all individuals that were requested to complete PROMs questionnaires did so. The completion rate observed here is similar to that reported by other national PROMs registers.[251] That the completion rate of PROMs data is often low in datasets reflects the fact collection of PROMs requires significant time and financial resources by the collector, and time and willingness on the part of the patient.

To investigate the possibility that patients with increased multimorbidity may be less likely to complete the PROMs questionnaires, which would introduce non-response bias to the results, the proportions in each multimorbidity category were compared between the total cohort and the subset whom completed pre- and post-operative OHS score. Appendix table B-11 shows the proportions in each multimorbidity category were similar, suggesting that there was no difference in PROMs questionnaire completion rate by multimorbidity and that the results were not affected by non-response bias.

(6) Revision surgery:

The data on revision surgery were extracted and analysed in a similar way to the data on serious complications: the absence of a relevant code in HES APC was interpreted as the event not occurring. Thus, to evaluate whether the data were likely accurate, comparisons were made between the rate of revision surgery found here and that reported by the UK National Joint Registry. Data on revision surgeries recorded by the National Joint Registry have been audited and found to have a completeness of 90% when compared to levy returns for the number of implants sold, indicating the National Joint Registry is a reasonably reliable comparator.

The cumulative rate of revision after five years, using Kaplan Meier estimates, in this cohort was 1.67% (95%CI 1.34, 2.08%), whereas the cumulative rate of revision after five years, also using Kaplan Meier estimates, reported by the National Joint Registry in 2015 was 2.51% (95%CI 2.47, 2.55%). The cumulative rate of revision after 10 years in this cohort was 2.60% (95%CI 2.08, 3.26%), whereas the cumulative rate of revision after 10 years reported by the National Joint Registry was 5.39% (95%CI 5.30, 5.49%). Clearly, the revision rate found in this cohort was significantly lower than that reported by the National Joint Registry, suggesting the true revision rate in this cohort was higher than that identified.

One possible explanation is that revision surgery was recorded in patients' discharge letters and hence their HES APC record via OPCS-4 codes, and that the code was missed because the code list here did not include all the appropriate codes. However, the list of includes codes of revision hip replacement was compiled using the OPCS-4 code book and reviewed by two orthopaedic surgeons, making this

possibility unlikely. The alternative explanation is that there was a substantial proportion of missing data on revision surgery events in the HES APC database. It appears unlikely that there was an association between missing data on revision surgery and presence of multimorbidity. Nonetheless, the missing data are a concern because the substantial proportion of missing data may have masked the true relationship between multimorbidity and the rate of revision surgery. Thus, the missing data constitute a significant weakness in the strength of the results of revision surgery and so results should be interpreted with caution.

(7) Other reoperations:

This outcome was included because undergoing any further surgery to the prosthetic hip represents a significant adverse outcome for patients, and therefore it is important to be able to counsel patients on whether multimorbidity affects the rate of other reoperations after THR. This outcome, however, has not been widely investigated as a single entity previously. This is because (1) revision surgery is a more major procedure and study of revision surgery has taken precedence, and (2) other reoperations, as defined, includes a wide range of procedures. In order to include all possible reoperations to the prosthetic hip, the NHS Digital list of OPCS-4 procedure codes was comprehensively reviewed by two researchers and a list of all possible reoperations was compiled. The list was then independently reviewed by two orthopaedic surgeons. The list includes, but is not limited to, manipulation of the joint under anaesthetic, joint stabilisation, osteosynthesis of peri-prosthetic fracture, debridement of infection, and drainage of hematoma. Due to the way data was extracted from HES APC, it was not possible to study the rate of each type of reoperation individually. The rate of other reoperations after total hip replacement could not be compared to other studies because a literature search identified no studies that reported the cumulative rate of all types of reoperation after primary total hip replacement, excluding revision surgery. In the absence of any external validation, it is important to note that the rate of other reoperations was analysed with similar methods to the rate of revision surgery. It is highly possible therefore that, similarly, there was a substantial proportion of missing data on other reoperation events. Thus, results should be interpreted with caution.

5.5.3 Findings in context

This section considers the results of each outcome according to multimorbidity in turn in the context of previously published evidence.

(1) At least one serious complication within 90 days of total hip replacement:

This study found that patients with severe multimorbidity burden were 1.5 to 2.5 times more likely to suffer a serious complication. This result is broadly similar to results reported in previously published studies. Table 1-4, in Chapter 1, summarises the results of 12 previous studies.

The six studies that measured multimorbidity with a count of coexisting diseases, with weighting by disease type (Charlson Comorbidity Index) reported that patients with multimorbidity were more likely to suffer a complication, with a range in odds ratio from 1.2 to 2.3.[19,87,143,155,168,169] Within these six studies, there was some variation in the outcome studied (all complications or focussed on cardiac, thromboembolic or joint infection, at either 30 or 90 days) and the handling of the Charlson Comorbidity Index (≥1 vs 0, ≥2 vs 0, or continuous), which may partially explain the variation in odds ratio.

Two studies that measured multimorbidity with the Charlson Comorbidity Index also used the ASA classification system.[155,168] Both studies reported a higher odds ratio with the ASA classification system. A study of post-operative cardiac complications in 1,200 patients in the USA reported an odds ratio of 1.2 (95% CI 1.0, 1.4) for the Charlson Comorbidity Index, handled as a continuous variable, and 6.1 (95% CI 1.6, 22.8) for the ASA classification system, handled as a categorical variable with ASA grade ≥3 vs ≤2. The other study of post-operative complications in 1,600 patients in Switzerland reported a coefficient of 0.21 (P 0.01) for the Charlson Comorbidity Index and 0.56 (P <0.001) for the ASA classification system, both handled as continuous variables. One possible reason for the larger observed difference in complication rate with the ASA classification system is that the system is superior at identifying patients with increased multimorbidity, by virtue of accounting for the severity of disease and its impact on overall health, compared with the Charlson Comorbidity Index, which is simply a count of coexisting diseases.

Four studies used a count of coexisting diseases, with weighting by disease severity or functional limitation.[163,170,172,173] Three studies that investigated complications of patients in the USA using the Modified Frailty Index reported an odds ratio of between 1.3 and 3.6. The higher odds ratios with the Modified Frailty Index compared with the Charlson Comorbidity Index may, again, be because the weighting of the score by functional limitation means that the score is superior at identifying patients with increased multimorbidity. Of note, one study that used the Modified Frailty Index reported a high odds ratio of 5.1 (95% CI 1.4, 18.9).[172] This ratio is higher than that associated with the most severe category of the Electronic Frailty Index in this study, which was 2.50 (95% CI 0.74, 8.41). This study, of 14,000 patients, was focussed on life-threatening complications only (Clavien-Dindo score IV) and handled the Modified Frailty Index as a binary variable, with the threshold score of >0.45 vs ≤0.45. As a result, the odds ratio of 5.1 only represented the outcome for 0.2% of the cohort, which may partially explain the higher odds ratio.

No previous studies were found for comparison that reported the influence of the two surrogate measures of multimorbidity (the count of medications prescribed and the count of contacts with primary care) on complications after total hip replacement. However, one previous study of 260,000 patients in Canada reported that polypharmacy (defined as five or more medications prescribed in three months prior) increased the rate of complications after non-cardiac elective surgery (of which total hip replacement comprised 25% of cases) by 1.4 times (odds ratio 1.40 [CI 1.37, 1.43]), which is a similar result to this study.[213]

In summary, this study is consistent with previously published evidence in finding that patients with severe burden of multimorbidity are approximately 1.5 to 2.5 times more likely to suffer a serious complication compared with patients without multimorbidity. In addition, a very small group of the patients with the most severe burden of multimorbidity (approximately 0.2-0.6% of all patients undergoing total hip replacement) may have a higher rate of complications, up to 2.5 to 5 times greater than patients without multimorbidity. Furthermore, this study is consistent with previously published evidence in finding that multimorbidity scores that account for disease severity or functional limitation are superior to simple counts of coexisting diseases in identifying patients at most risk of complications.

This study is the first to demonstrate this finding in patients in the UK. It is acknowledged, nonetheless, that in this study the proportions in each category of the different multimorbidity measures were not equal, which limits the comparisons of the different measures.

(2) Readmission to hospital within 90 days of total hip replacement:

This study found that patients with severe multimorbidity burden were 1.5 to 2.2 times more likely to be readmitted to hospital. A literature search identified one study that used a simple count of coexisting diseases as the multimorbidity measure when investigating the rate of readmission, and three studies that used a count of coexisting diseases with weighting by disease type (Charlson Comorbidity Index). The study of 9,000 patients in the USA that used a simple count of coexisting diseases reported that patients with two or more comorbid disease were 2.5 times more likely to be readmitted after hip replacement than patients without comorbid disease.[252] The three studies that used the Charlson Comorbidity Index had broadly similar findings, considering the different methods of analysis (Charlson Comorbidity Index was treated as a continuous variable and as a categorical variable with scores of ≥2 and ≥3 compared with score of 0): patients with multimorbidity were approximately 1.3 to 2.8 times more likely to be readmitted than patients without multimorbidity.[253–255]

No previous studies were found for comparison that reported the influence of the surrogate multimorbidity measure of the count of contacts with primary care on readmission after total hip replacement. One study of 250 patients in Denmark investigated polypharmacy (defined as ≥5 regular medications) and frailty (defined as ≥2 functional limitations), and reported that patients with polypharmacy and without frailty were 1.7 times more likely to be readmitted than patients without polypharmacy and frailty.[256] The same study reported patients without polypharmacy and with frailty were 2.3 times more likely to be readmitted, while those with both polypharmacy and frailty were 5.0 times more likely to be readmitted. These findings demonstrate the importance of functional limitations when assessing the overall multimorbidity burden of patients that are candidates for surgery.

Three other studies used counts of coexisting diseases, with weighting by disease severity or functional limitation. Two studies of >50,000 patients in the USA using the Modified Frailty Index reported an

odds ratio of 1.3 and 1.4 for readmission with increasing frailty, while a study of 415 patients in the USA using the Frailty Index reported a relative risk of 1.1.[170,171,257]

In summary, this study is broadly consistent with previously published evidence in finding that patients with severe multimorbidity burden have a higher rate of readmission within 90 days of total hip replacement, in the order of 1-3 times. However, the sensitivity analysis in this study clearly demonstrated that the rate of readmission to hospital after total hip replacement for patients with multimorbidity was the same as the rate of admission to hospital over an equivalent period one year prior. Together, these data suggest the observed higher rate of admission to hospital after total hip replacement appears to be the 'normal rate' for patients with multimorbidity and is not any different despite recent total hip replacement.

(3) Length of stay in hospital for total hip replacement:

This study found that patients with severe multimorbidity burden had a length of stay 1.2 to 2.1 times as long as those without multimorbidity. A literature search identified one study that used a simple count of coexisting diseases as the multimorbidity measure when investigating length of stay, and two studies that used a count of coexisting diseases with weighting by disease type (Charlson Comorbidity Index). [248,258,259] A study of 500,000 patients in the USA reported that patients with 3 comorbid disease had a length of stay 1.2 times as long, while the studies using the Charlson Comorbidity Index reported a length of stay 1.4 times as long (for score ≥2 vs 0; 11,000 patients in the UK) and 2.5 times more likely to stay longer than 3 days (for score ≥3 vs 0; 1,900,000 patients in the USA).

No previous studies were found for comparison that reported the influence of the two surrogate measures of multimorbidity on length of stay after THR. Two studies used a count of coexisting diseases, with weighting by disease severity or functional limitation. One study of 125,000 patients in Canada used the Johns Hopkins Adjusted Clinical Groups frailty-defining diagnoses indicator, which is a binary variable that defines patients as frail based on the presence of at least one frailty-defining diagnosis. Frail patients had a length of stay 1.6 (95% CI 1.59, 1.65) times as long as non-frail patients.[260] Another study of 87 patients in Canada used the Clinical Frailty Scale, which is based on

Rockwood's frailty model of accumulated deficits, similar to the Electronic Frailty Index. The study found 49% of frail patients had a length of stay of ≥5 days, while only 18% of non-frail patients did.[261]

In summary, this study is consistent with previously published evidence in finding that patients with multimorbidity have a length of stay 1.2 to 2.1 times as long. Furthermore, this study suggests that multimorbidity scores that account for disease severity or functional limitation are superior than simple counts of coexisting diseases in identifying patients likely to require a longer stay in hospital after total hip replacement. The presence of functional limitations may be associated with longer post-operative hospital stays because those patients recover from surgery more slowly and because those patients require more complex discharge planning. This study is the first to demonstrate this finding in patients in the UK.

(4) Hip pain and function at least 6 months post-operatively:

This study found that patients with severe multimorbidity burden had a lower OHS outcome; however, the difference was so small that it was not clinically meaningful (<5 points).[174] This indicates there was no reduction in benefit of surgery in terms of pain reduction and hip function for patients with multimorbidity compared with those without. This finding was consistent for all multimorbidity scores.

A literature search identified 11 relevant studies, summarised in Table 1-3, in Chapter 1, with broadly consistent findings.[153–163] Six studies used a simple count of coexisting diseases, four used a count of coexisting diseases, with weighting by disease type (Charlson Comorbidity Index), and one used a count of coexisting diseases, with weighting by disease severity and functional impairment (Index of Co-Existent Diseases).

While the majority of studies reported an association between increased multimorbidity and poorer pain or function outcome, only one study reported a difference that was clinically meaningful. This study of 251 patients at a single centre in the UK in 2014 reported that patients with a Charlson Comorbidity Index of ≥1 had 1-year post-operative OHS 5.1 points lower than patients with score of 0; however, importantly, the primary outcome of the study was pre- to post-operative change in OHS, for which there was no difference by multimorbidity. The single study that used a count of coexisting diseases,

with weighting by disease severity and functional impairment was of 517 patients in 1992-3 and found conflicting results between the UK (poorer post-operative function with increased multimorbidity) and Japan (no difference), and so is of limited relevance to modern patients.

This study is the first multi-centre UK study that has investigated, using a range of complementary measures of multimorbidity, the influence of multimorbidity on hip pain and function after total hip replacement. The key results are that patients benefit substantially in terms of post-operative hip pain and function, regardless of whether they have concurrent multimorbidity, and that there is no clinically important difference in outcome based on preoperative multimorbidity burden. This finding remains even when multimorbidity is measured using a count of coexisting diseases, with weighting by disease severity and functional impairment. This is novel evidence that will be informative to clinicians and patients when deciding whether to proceed with total hip replacement.

(5) Quality of life at least 6 months post-operatively:

This study found that patients with severe multimorbidity burden had a lower EQ-5D outcome; however, the difference was so small that it was not clinically meaningful (<0.18 points). This indicates there was no reduction in benefit of surgery in terms of health-related quality of life for patients with multimorbidity compared with those without. This finding was consistent for all multimorbidity scores.

A literature search identified four relevant studies, summarised in Table 1-3, in Chapter 1, with broadly consistent findings.[154,164–166] All four studies used a count of coexisting diseases, with weighting by disease type (Charlson Comorbidity Index) as the measure of multimorbidity. Two studies found no association between Charlson Comorbidity Index and post-operative health-related quality of life, while two studies reported that increased multimorbidity was associated with a lower quality of life outcome, although the difference remained smaller than the minimum clinically important difference. No studies were identified that used a count of coexisting diseases, with weighting by disease severity or functional limitation, or used the two surrogate measures of multimorbidity when investigating quality of life after hip replacement.

This study is the first multi-centre UK study that has investigated, using a range of complementary measures of multimorbidity, the influence of multimorbidity on health-related quality of life after total hip replacement. The key results are that patients benefit substantially in terms of health-related quality of life, regardless of whether they have concurrent multimorbidity, and that there is no clinically important difference in outcome based on preoperative multimorbidity burden. This finding remains even when multimorbidity is measured using a count of coexisting diseases, with weighting by disease severity and functional impairment.

(6) Revision surgery:

This study found that patients with severe multimorbidity burden appeared to have a mildly increased risk of revision surgery (up to 1.5 to 2.2 times higher), although the differences between the categories were not statistically significant. This reflects the low number of revision events captured by the data source. This estimated odds ratio is broadly similar to results reported in previously published studies. Table 1-2, in Chapter 1, summarises the results of 6 previous studies.[138–143]

All six studies used a count of coexisting diseases, with weighting by disease type (five used the Charlson Comorbidity Index, one used the Elixhauser Comorbidity Index) to measure multimorbidity. Across four of the six studies, increased multimorbidity was associated with an increased rate of revision, with the reported hazard ratios varying between 1.1 and 2.8. However, two studies did not find any significant association. A limitation of the six studies is that multimorbidity was only measured with a count of coexisting diseases, with weighting by disease type, which may have reduced their ability to identify patients with the most severe multimorbidity burden. In addition, it is acknowledged that the risk of requiring revision surgery associated with multimorbidity may change over follow-up, in the months and years following total hip replacement. For example, the risk of infection or peri-prosthetic fracture necessitating revision in the immediate post-operative period (<30 days) may be higher in patients with multimorbidity, whereas the risk of aseptic loosening from implant wear necessitating revision in the late post-operative period (>10 years) may be lower in patients with multimorbidity. The variation in follow up length of the studies may explain the variation in risk of revision observed. Indeed, one study reported subhazard ratios at two time points: 1.5 (95% CI 1.1, 2.2)

was reported at 1-year follow up for Elixhauser Comorbidity Index >2 vs 0, while a lower ratio of 1.3 (95% CI 1.0, 1.7) at 5 years.

No previous studies were found for comparison that reported on a measure of multimorbidity with weighting by disease severity or functional limitation, or a surrogate measure of multimorbidity on the rate of revision surgery.

In summary, previously published evidence suggests patients with multimorbidity have a mildly increased risk of revision after primary THR, in the order of 1-3 times, however, there is inconsistency in the evidence and the available evidence is based on very limited assessments of multimorbidity. Due to limitations in data quality, this study was unable to add meaningfully to the evidence base. The next step to improve the evidence base would be to repeat the investigation using a different data source. Such a study, using registry data, is reported in Chapter 6.

(7) Other reoperations:

This study found no consistent pattern between severity of multimorbidity burden and rate of other reoperations. No previous studies were found for comparison that reported the influence of multimorbidity on the risk of other reoperation after total hip replacement. This reflects the fact that other reoperations (other than revision surgery) have only recently been acknowledged to be an important outcome measure. As described in Chapter 1, the risk of needing to undergo other reoperations to the prosthetic hip after total hip replacement is a relevant and important issue to patients, and thus the absence of evidence on any increased risk due to multimorbidity is a deficiency in patient care. The next step to improve the evidence base would be to repeat the investigation using a different data source. Such a study, using registry data, is reported in Chapter 6.

5.5.4 Conclusions

This study investigated the influence of multimorbidity on the outcomes of total hip replacement for patients diagnosed with hip osteoarthritis in England. A multimodal approach was taken to the

assessment of surgical outcomes, in order to provide evidence on all the different ways that patients may wish to consider their predicted outcome of total hip replacement. A multimodal approach was also taken to the assessment of multimorbidity, using five different ways of measuring the severity of multimorbidity, in order to maximise the insights gained about the influence of multimorbidity, and minimise the limitations related to each individual multimorbidity measure. The study was national in scope, with drawn patients from all 10 regions of England. This study, broad in approach to outcomes, multimorbidity measurement and the cohort, is truly novel, providing new information for the 100,000 patients that undergo THR in England each year. Despite the limitations of the data and the methodology discussed in detail above, the findings are robust.

With the exceptions of the outcomes of revision surgery and of other reoperations, which were affected by substantial missing data, this study was able to answer the objectives set. Patients with multimorbidity that underwent total hip replacement were at up to 1.5 to 2.5 times increased risk of suffering a post-operative complication compared with patients without multimorbidity. Patients with multimorbidity that underwent total hip replacement were at up to 1.5 to 2.2 times increased risk of admission to hospital within 90 days of surgery compared with patients without multimorbidity, however the rate of admission to hospital was not substantially increased within 90 days of surgery than when not following surgery. Patients with multimorbidity required a stay in hospital after total hip replacement up to 1.2 to 2.1 times as long compared with patients without multimorbidity. There was no clinically meaningful difference in the benefits of surgery between patients with and without multimorbidity, in terms of postoperative hip pain and function as measured by the OHS and postoperative health-related quality of life as measured by the EQ-5D. Indeed, patients of all levels of multimorbidity reported substantial benefits of surgery.

A key strength of this study is the multimodal approach to multimorbidity. Within each outcome studied, there was broad consistency between the multimorbidity measure, in terms of the direction and the magnitude of the trend seen. This consistency adds strength to the conclusions about the influence of multimorbidity on each outcome.

There was also broad consistency between each outcome studied on which multimorbidity measure had the strongest association with the outcome: the Electronic Frailty Index. Although the smaller proportion of the cohort in most severe category for this measure than for the other multimorbidity measures is acknowledged, these results suggest that the Electronic Frailty Index was the 'best' score at predicting the outcomes of THR for patients with multimorbidity. As discussed, this finding was not a surprise because the measure includes functional limitations as well as a count of diseases, enriching the understanding of a patient's multimorbidity.

This study also demonstrated the validity of the count of medications prescribed as a surrogate multimorbidity measure. Indeed, for each outcome measure, the count of medications prescribed had a stronger association than the Charlson Comorbidity Index. The count of medications prescribed is simple to calculate and does not require detailed knowledge of a patient's medical history or assessment of function. This measure therefore is recommended to researchers for future use. The other surrogate multimorbidity measure (the count of contacts with primary care), however, was less consistent in the associations with each outcome. The count of contacts with primary care may still be useful as a measure of multimorbidity, but regrettably, as discussed, the quality of the data on it available here was suspected to be poor.

Chapter 6: Influence of ASA Class on Early Revision and Other Reoperations

6.1 Abstract

Introduction

Data from several joint replacement registries suggest that patients with multimorbidity have an increased risk of revision after total hip replacement, particularly within the early post-operative period. The aim of this study was to investigate the influence of multimorbidity on the risk of revision and other reoperations within three months and within five years of primary total hip replacement.

Methods

A cohort study was performed, with the cohort comprised of all patients that underwent primary total hip replacement recorded in the Geneva and Swedish Hip Arthroplasty Registries, performed in 1996-2016 and 2008-2016 respectively. The ASA Classification System was used as the measure of multimorbidity. The outcomes were all-cause revision and other reoperations evaluated using Kaplan Meier survival and Cox regression analyses.

Results

5,319 and 122,241 total hip replacements were included respectively. Within three months after surgery, higher ASA class was associated with greater risk of revision and other reoperation. Three-month cumulative incidences of revision by ASA class I, II and III-IV respectively, were 0.6%, 0.7% and 2.3% in Geneva and 0.5%, 0.8% and 1.6% in Sweden. Three-month cumulative incidences of other reoperations were 0.4%, 0.7% and 0.9% in Geneva and 0.2%, 0.4% and 0.7% in Sweden. Adjusted hazard ratios (ASA III-IV vs. I) for revision within three months were 2.7 (95% CI 1.2, 5.9) in Geneva and 3.3 (95% CI 2.6, 4.0) in Sweden. Adjusted hazard ratios (ASA III-IV vs. I) for other reoperation within three months were 1.1 (95% CI 0.5, 2.4) in Geneva and 2.7 (95% CI 2.0, 3.7) in Sweden.

Conclusions

Patients with multimorbidity, assessed with the ASA Classification System, were at increased risk of early revision surgery and other reoperations after total hip replacement, with the highest risk within the first three months of surgery. This information will be of value to patients and clinicians when deciding whether to proceed with hip replacement. In addition, the systematic recording of ASA class in joint replacement registries will permit risk adjustment and facilitate future comparison of revision rates internationally.

Work described in this chapter has been published as:

- *Ferguson RJ, Silman AJ, Combescure C, Bulow E, Odin D, Hannouche D, Glyn-Jones S, Rolfson O, Lübbeke A. ASA class is associated with early revision and reoperation after total hip arthroplasty: an analysis of the Geneva and Swedish Hip Arthroplasty Registries. Acta Orthopaedica 2019; 90(4): 324-330. DOI: 10.1080/17453674.2019.1605785. PMID 31035846*

6.2 Introduction

As discussed in Chapter 1, recent evidence suggests that patients with multimorbidity have an increased risk of revision after total hip replacement (THR). However, estimates of the effect size are conflicting, with studies reporting hazard ratios between 1.0 and 2.8 for patients with multimorbidity versus those without. In addition, the approach to measuring multimorbidity has been limited, based only on counts of coexisting diseases, with weighting by disease type, but not by disease severity or functional limitation.[138,140,142,262] Regrettably, the investigation into the outcome of revision surgery described in Chapter 5 was unable to add to the evidence base due to limitations in the quality of data on revision surgery in the HES APC dataset. Similarly, although no external validation was possible, it appeared likely that there were limitations in the quality of data on other reoperations in the HES APC dataset.

This chapter will repeat the investigation into the need for further surgery after primary THR using different data sources from those used in Chapter 5. Specifically, the aim of this chapter is to investigate how, in patients with end-stage hip osteoarthritis, multimorbidity influences the risks of revision and other reoperations after THR. Instead of using patients' electronic medical records as the source of data, this study will use data recorded in hip arthroplasty registries. Registries are databases of systematically collected data on a predefined number of variables from a predefined cohort of patients. Recording of primary and revision THRs in hip arthroplasty registries is generally of high accuracy and completeness because the databases are designed specifically to record these data and undergo frequent audit against levy returns for implants sold.[5]

A key time period to study is the early post-operative period. Evidence from the New Zealand Joint Registry suggests that patients with poor preoperative health status (ASA class of III or more) are at increased risk of revision within two years of THR than patients with good preoperative health (ASA class of I or II), but by three years the results were the same.[144] Furthermore, recent data have shown that a high proportion of all early revision surgeries is performed within three months.[193] However, there are little data on the influence of multimorbidity on very early revision, specifically within three months of primary THR. This chapter will therefore investigate the influence of multimorbidity both

within three months of primary THR and between three months and five years following primary THR. In cases of revision and other reoperation, the indication for surgery will be investigated.

The most widely collected scoring system on patients' preoperative physical health status by arthroplasty registries worldwide is the ASA Physical Status Classification System.[89] The ASA Classification System is not technically a measure of multimorbidity; however, because it is designed to assess and communicate a patient's overall health status and pre-anaesthesia comorbidities, by considering the severity of systemic diseases, it gives an indirect assessment of multimorbidity. This chapter will therefore use the ASA Classification System as a surrogate measure of multimorbidity burden.

6.3 Methods

6.3.1 Study design

The study was a retrospective cohort study, using data recorded in two hip arthroplasty registries. The registries whose data were available to this thesis were the Geneva Arthroplasty Registry (GAR) and the Swedish Hip Arthroplasty Register (SHAR). Two registries were included to increase the external validity of the results. The registry data collection was approved by the Geneva University Hospital Institutional Review Board and the Gothenburg Regional Ethical Review Board.

GAR is a hospital-based registry that collects data on all THRs performed at Geneva University Hospitals, the only public hospital of the canton of Geneva, Switzerland serving a population of 500,000 inhabitants. Data on patient demographics and surgical intervention are recorded by operating surgeons on data collection forms and submitted to the registry. Completeness of recording eligible primary THRs in GAR up to 2016 was >99% according to an audit of hospital operation records.[263] GAR records revision, other reoperation and mortality data continuously as data are submitted by surgeons. In addition, GAR actively follows up patients at one, five, 10, 15, and 20 years and questions them regarding further surgery. Revision and other reoperation events are therefore captured by the registry unless patients are lost to follow up. The completeness of capture of revision surgery following primary

THRs recorded in GAR was 100% in 2013-2016, based an audit of all revision THRs performed within Switzerland using the Swiss National Joint Registry (SIRIS) as the data source. GAR reports it has not been possible to directly calculate the completeness of capture of revision surgery in GAR prior to 2013 using SIRIS because SIRIS was only established in 2012. However, loss to follow up in GAR at five years after primary THR during 1996-2012 was 6%, hence it is estimated the completeness of capture of revision surgery was ≥94% over this period.

SHAR is a national registry that collects data on all THRs performed in Sweden, covering 80 hospitals and clinics.[264] Data on patient demographics and surgical intervention are recorded by operating surgeons on data collection forms and submitted to registry staff. Completeness of recording eligible primary THRs in SHAR up to 2016 was 98%, according to an audit of linked data from Sweden's National Board of Health and Welfare's Patient Register, which is a database of secondary care provided across Sweden, equivalent to England's HES APC. SHAR records revision and other reoperation data continuously as data are submitted by surgeons. The completeness of capture of revision surgery following primary THRs recorded in SHAR was 92%, according to an audit of linked data from Sweden's National Board of Health and Welfare's Patient Register. Mortality data are obtained from the Board of Health and Welfare.

6.3.2 Data set

The population for this study were individuals identified in GAR or SHAR that underwent primary THR during the period that the registries collected data on ASA Classification System. This period was March 1996 to December 2016 for GAR and January 2008 to December 2016 for SHAR. Included cases were elective primary THRs only. Data on date and side of procedure were extracted. Bilateral cases were included. THRs in individuals with missing data on ASA class were excluded. Two groups of cases were excluded: first, THRs with metal-on-metal bearings were excluded because they have a substantially higher revision rate than other bearings and are no longer used except in rare and particular circumstances.[263–265] In addition, patients with lower ASA class received metal-on-metal prostheses

more than other patients, meaning inclusion of such cases would have introduced selection bias. Second, THRs were excluded for which the indication was trauma or malignancy because such cases are not strictly elective.

Data on the individuals' demographics were extracted from the registries, including age at surgery (in years), sex, BMI, and diagnosis. BMI is measured as part of standard care for patients undergoing THR in pre-operative assessment clinics in all hospitals and clinics covered by GAR and SHAR. Diagnosis for patients undergoing elective primary THR is recorded as primary or secondary osteoarthritis by GAR and SHAR. Secondary osteoarthritis is defined as osteoarthritis occurring as a result of a previously existing condition, including (but not limited to) avascular necrosis, congenital hip dysplasia, history of infection, history of trauma, inflammatory arthropathy, Perthes disease, and slipped upper femoral epiphysis.

6.3.3 Multimorbidity measures

Multimorbidity was measured in this investigation using the ASA Physical Status Classification System.[134] The ASA Classification System classifies patients into six classes, shown in Table 6-1. ASA classes V and VI are not appropriate to patients undergoing elective THR, thus individuals in this cohort had a range of ASA classes I-IV.

Table 6-1 – Categories of the ASA Physical Status Classification System

ASA class	Definition
I	A normal healthy patient
II	A patient with mild systemic disease
III	A patient with severe systemic disease
IV	A patient with severe systemic disease that is a constant threat to life
V	A moribund patient who is not expected to survive without the operation
VI	A declared brain-dead patient whose organs are being removed for donor purposes

The ASA Classification System is the only measure of preoperative physical health status recorded by GAR and SHAR. All patients undergoing THR in Switzerland and Sweden have their ASA class measured and recorded by the anaesthetist immediately prior to the operation, as required by the WHO surgical safety checklist.[266] The ASA class is then recorded by operating surgeons on registry data collection forms. Data on ASA class of included individuals was extracted from GAR and SHAR.

6.3.4 Outcome measures

The outcomes of interest were:

(1) incidence of revision, and

(2) incidence of other reoperation, within 3 months and within 5 years of index THR.

Revision surgery was defined, as in Chapter 5, as any surgery that involved the addition, removal or replacement of one or more components of the prosthetic hip. Other reoperation was defined as any surgery to the prosthetic hip that did not involve the addition, removal or replacement of any components of the prosthetic hip. Closed reduction of dislocation was not included as an other reoperation.

Data on outcome events, including date and side, were extracted from GAR and SHAR. The date of outcome was the first occurrence of revision or of other reoperation after the index date. If an individual underwent other reoperation, follow up continued to permit analysis of whether the patient underwent revision. If an individual underwent revision, follow up was terminated. Indication for revision and other reoperation was extracted.

The inclusion period of follow up was from the index date (date of primary THR) until either outcome event, death, or end of follow up in GAR and SHAR (December 2016), or until 5 years of follow up.

6.3.5 Statistical analysis

Analyses were conducted independently for each registry. The outcomes of revision surgery and of other reoperation were analysed separately. Baseline characteristics were described using frequencies, proportions, means, and standard deviations (SDs). The proportion of THRs in individuals of ASA class IV (0.56% in GAR and 0.41% in SHAR) was too small for meaningful analysis on its own. Thus, ASA was categorised into 3 groups: class I, II and III-IV.

The cumulative incidence of revision and of other reoperation by ASA class after index THR was assessed with competing risks estimates, with death was considered a competing event.

To compare the rate of revision and of other reoperation by ASA class, competing risk analysis models were used, with death was considered a competing event. Cause-specific Cox proportional hazard models were chosen because these models provide estimates of the relative rate of the outcomes, which is helpful when evaluating the influence of ASA class. ASA class I was defined as the referent category. The models are presented as cause-specific hazard ratios (HRs) with 95% confidence intervals (CIs). The proportionality of hazards was checked by plotting the log of Kaplan-Meier survival versus the log of follow up time. In order to investigate the periods of within 3 months of index THR and after 3 months separately, all univariate models were checked for a difference in hazard ratio within 3 months of index THR and after 3 months. In models where the proportional hazards assumption over follow up time was violated, a time-varying hazard ratio was introduced to the model: hazard ratio within 3 months of index THR and hazard ratio after 3 months and within 5 years of index THR. Univariate models for ASA class and multivariate models, adjusted for age, sex, BMI, and diagnosis, are presented. Complete case analysis was used for adjusted models.

It was unknown whether having undergone a previous primary THR on the contralateral hip would affect the outcome of a patient's second primary THR. Thus, it was possible that including both procedures where patients had undergone bilateral THR would introduce selection bias to the results. Therefore, as a sensitivity analysis, the survival analyses were re-run with only the first primary THR procedure in each patient included.

Data were analysed using STATA 14.0 (College Station, Tx, USA) and R (R Foundation for Statistical Computing, Vienna, Austria) with alpha of 0.05 as the statistical threshold for significance (all tests were 2-sided).

6.4 Results

In GAR, 5,319 procedures in 4,501 patients were eligible for inclusion. In SHAR, 122,241 procedures in 106,522 patients were eligible for inclusion (Table 6-2). In both cohorts the proportions of cases in obese patients (BMI≥30), in those over 85 years of age, and in patients with secondary osteoarthritis were highest in ASA classes III-IV.

Table 6-2 – Preoperative Patient Characteristics by ASA Class

	Geneva cohort				Sweden cohort			
	ASA I	ASA II	ASA III-IV	Total	ASA I	ASA II	ASA III-IV	Total
	N=481	N=3496	N=1342	N=5319	N=29280	N=72857	N=20104	N=122241
Women (N, %)	259 (54)	2106 (60)	767 (57)	3132 (59)	16112 (55)	41460 (59)	9885 (53)	67149 (57)
Age (mean, SD)	60.1 (12.3)	68.8 (11.7)	76.1 (10.1)	69.9 (12.2)	62.5 (10.7)	69.2 (9.7)	72.9 (9.8)	68.2 (10.5)
Age categories								
< 55 (N, %)	150 (31)	393 (11)	42 (3.1)	585 (11)	6325 (22)	5152 (7.1)	863 (4.3)	12340 (10)
55-64	127 (26)	667 (19)	109 (8.1)	903 (17)	9679 (33)	15756 (22)	2701 (13)	28136 (23)
65-74	152 (32)	1226 (35)	357 (27)	1735 (33)	9766 (33)	29660 (41)	6999 (35)	46425 (38)
75-84	49 (10)	1024 (29)	550 (41)	1623 (31)	3225 (11)	19423 (27)	7648 (38)	30296 (25)
≥ 85	3 (0.6)	186 (5.3)	284 (21)	473 (8.9)	285 (1.0)	2866 (3.9)	1893 (9.4)	5044 (4.1)
BMI (mean, SD)	24.8 (3.3)	26.8 (4.7)	27.3 (5.6)	26.8 (4.9)	26.1 (3.8)	27.4 (4.4)	28.7 (5.6)	27.3 (4.6)
BMI categories								
< 18.5 (N, %)	13 (2.7)	63 (1.8)	43 (3.3)	119 (2.3)	195 (0.6)	531 (0.7)	240 (1.2)	966 (0.8)
18.5-24	245 (51)	1280 (37)	437 (33)	1962 (37)	11405 (38)	20933 (29)	5008 (26)	37346 (31)
25-29	193 (40)	1303 (38)	441 (33)	1937 (37)	12868 (43)	31374 (44)	6955 (36)	51197 (43)
30-34	27 (5.6)	642 (19)	288 (22)	957 (18)	3476 (12)	14512 (20)	4520 (23)	22508 (19)
35-39	2 (0.4)	156 (4.5)	85 (6.4)	243 (4.6)	416 (1.3)	3234 (4.5)	2115 (11)	5765 (4.8)
≥ 40	0 (0.0)	26 (0.7)	27 (2.0)	53 (1.0)	66 (0.2)	529 (0.7)	629 (3.2)	1224 (1.0)
Missing data	1	26	21	48	854	1744	637	3235
Diagnosis (N, %)								
Primary OA	375 (78)	2817 (81)	1007 (75)	4199 (79)	26644 (91)	67221 (92)	17666 (88)	111531 (92)
Secondary OA	106 (22)	679 (19)	335 (25)	1120 (21)	2636 (9.0)	5636 (7.7)	2438 (12)	10710 (8.8)

In GAR, 126 cases of revision were recorded within 5 years, with 59 (47% of total) within 3 months, (Table 6-3). The incidence of death within 5 years was 12.8% (95% CI 11.8, 13.8). In SHAR, 2,353 cases of revision were recorded within 5 years, with 1,030 (44% of total) within 3 months. The incidence of death within 5 years was 8.3% (95% CI 8.1, 8.5). In both cohorts, the cumulative incidence of revision within 3 months and within 5 years was higher in ASA class III-IV than in ASA class I. The cumulative incidence was lower for other reoperation than for revision in both cohorts.

Table 6-3 – Cumulative incidence of revision and other reoperation by ASA Class

	Revision			Reoperation		
	Total number (%)	Cumulative incidence (95% CI)		Total number (%)	Cumulative incidence (95% CI)	
		3 months	5 years		3 months	5 years
Geneva						
All patients	126 (2.4)	1.1 (0.8 - 1.4)	2.6 (2.1 - 3.0)	95 (1.8)	0.7 (0.5 - 0.9)	1.9 (1.5 - 2.3)
ASA I	10 (2.1)	0.6 (0.0 - 1.3)	2.3 (0.9 - 3.8)	9 (1.9)	0.4 (0.0 - 1.0)	2.0 (0.7 - 3.4)
ASA II	73 (2.1)	0.7 (0.4 - 1.0)	2.3 (1.8 - 2.8)	58 (1.7)	0.7 (0.4 - 0.9)	1.8 (1.3 - 2.2)
ASA III-IV	43 (3.2)	2.3 (1.5 - 3.1)	3.3 (2.3 - 4.3)	28 (2.1)	0.9 (0.4 - 1.4)	2.2 (1.4 – 3.0)
Sweden						
All patients	2353 (1.9)	0.9 (0.8 - 0.9)	2.3 (2.2 - 2.4)	878 (0.7)	0.4 (0.4 - 0.4)	0.8 (0.8 - 0.9)
ASA I	444 (1.5)	0.5 (0.4 - 0.6)	1.9 (1.7 - 2.1)	145 (0.5)	0.2 (0.2 - 0.3)	0.6 (0.5 - 0.7)
ASA II	1364 (1.9)	0.8 (0.7 - 0.9)	2.3 (2.2 - 2.4)	522 (0.7)	0.4 (0.3 - 0.4)	0.8 (0.8 - 0.9)
ASA III-IV	545 (2.7)	1.6 (1.4 - 1.7)	3.3 (3.0 - 3.6)	211 (1.0)	0.7 (0.6 - 0.8)	1.2 (1.0 - 1.4)

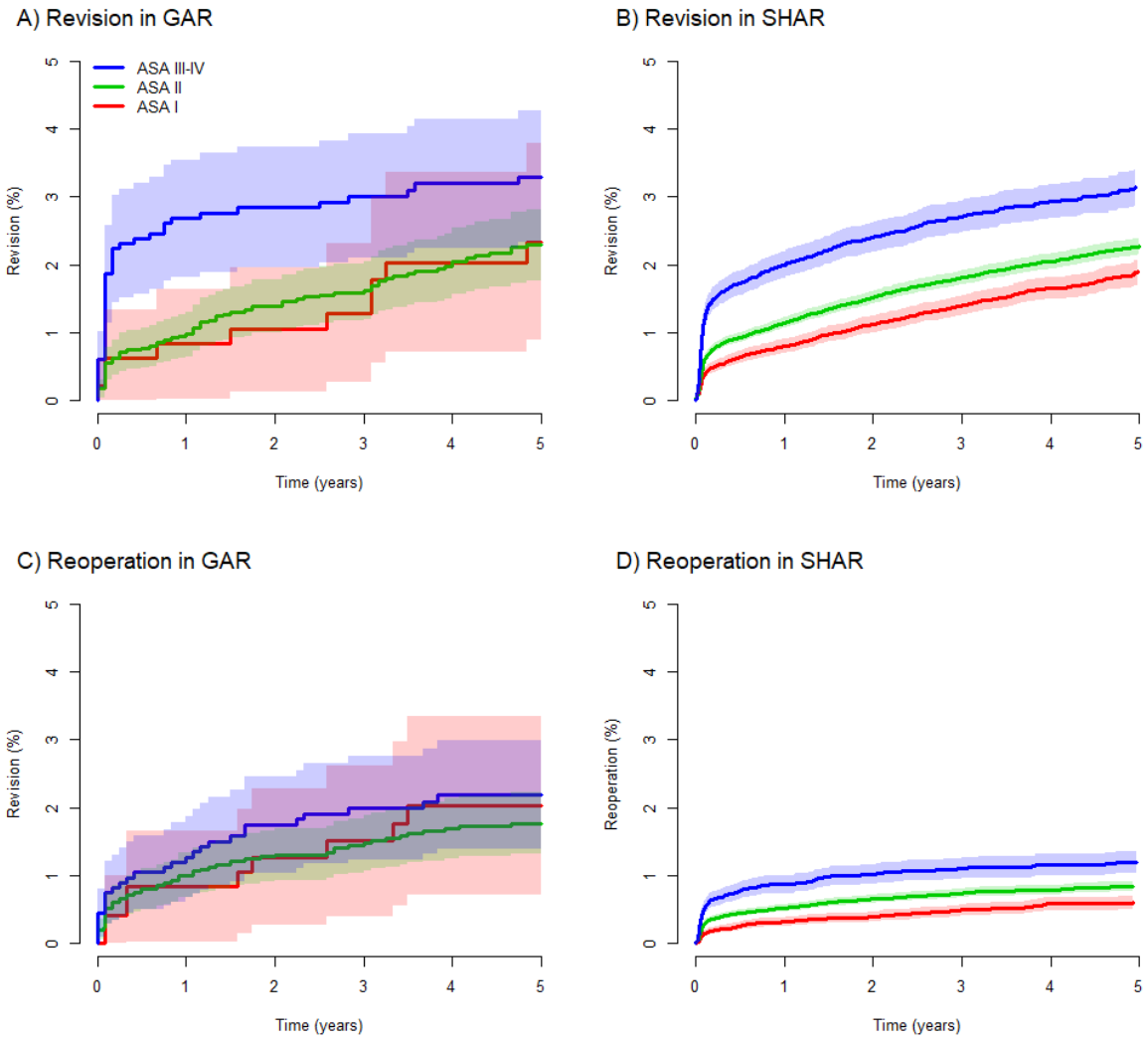
There was a positive association between ASA class and the risk of revision within 5 years (Figure 6-1) (GAR: P=0.02 for the comparison between ASA class I or II vs. III-IV; SHAR: P<0.001 for the comparison between all ASA classes). Results were unchanged by including only the first procedure in each patient (Appendix Figure B-6). An association between ASA class and risk of reoperation within 5 years was only detected in SHAR (GAR: P=0.6; SHAR: P<0.001).

In GAR, ASA class III-IV was associated with a higher risk of revision (Table 6-4). However, the association was restricted to within 3 months after primary THR (unadjusted HR: 3.4, 95% CI 1.6, 7.4). The risk of revision was also higher in patients with a diagnosis of secondary osteoarthritis and in obese patients.

In SHAR, the association of ASA class III-IV with revision within 3 months was confirmed (unadjusted HR: 3.2, 95% CI 2.6, 3.9). The association decreased after 3 months but remained statistically

significant (unadjusted HR: 1.3, 95% CI 1.1, 1.6). In contrast to GAR, an association with ASA class II was also detected within 3 months (unadjusted HR: 1.6, 95% CI 1.4, 2.0). Adjustment for differences in the preoperative baseline characteristics did not importantly modify the associations. In contrast to GAR, sex and age were also associated with the risk of revision. Women had a lower risk of revision.

Figure 6-1 – Cumulative incidence of Revision in (A) GAR and (B) SHAR and cumulative incidence of Other Reoperation in (C) GAR and (D) SHAR by ASA class



Patients aged over 85 years had a higher risk within 3 months but a lower risk thereafter. The associations between the risk of revision and both the diagnosis of secondary osteoarthritis and obesity were confirmed in SHAR. Results were not significantly changed by including only the first procedure in each patient (Appendix Table B-12).

In GAR, ASA class was not associated with the risk of other reoperations (unadjusted HR ASA III-IV vs. ASA I: 1.2, 95% CI 0.6, 2.5) (Table 6-5). In SHAR, ASA class was associated with a greater risk of reoperation within 3 months following primary THR than after 3 months and within 5 years (unadjusted HR ASA III-IV vs. ASA I within 3 months: 3.2, 95% CI 2.3, 4.3; after 3 months and within 5 years: 1.6, 95% CI 1.2, 2.1). Results were not significantly changed by including only the first procedure in each patient (Appendix Table B-13).

Table 6-4 – Associations between ASA Class and Risk of Revision Surgery (time-invariant HR unless specified)

	Geneva cohort HR (95% CI)	Sweden cohort HR (95% CI)
Univariable model		
ASA class		
I	1 (ref)	1 (ref)
II	1.0 (0.5, 2.0)	1.6 (1.4, 2.0)*[d]
		1.1 (0.9, 1.3)**[d]
III-IV	3.4 (1.6, 7.4)*[a]	3.2 (2.6, 3.9)*[d]
	0.7 (0.3, 1.7)**[a]	1.3 (1.1, 1.6)**[d]
Multivariable model		
ASA class		
I	1 (ref)	1 (ref)
II	1.0 (0.5, 1.9)	1.7 (1.4, 2.1)*[e]
		1.2 (1.0, 1.3)**[e]
III-IV	2.7 (1.2, 5.9)*[b]	3.3 (2.6, 4.0)*[e]
	0.7 (0.3, 1.7)**[b]	1.4 (1.1, 1.6)**[e]
Sex		
Male	1 (ref)	1 (ref)
Female	0.8 (0.6, 1.1)	0.7 (0.6, 0.7)
Diagnosis		
Primary OA	1 (ref)	1 (ref)
Secondary OA	2.4 (1.7, 3.5)	1.4 (1.3, 1.6)
BMI		
<35	1 (ref)	1 (ref)
≥35	3.7 (2.3, 6.0)	2.6 (2.2, 3.1)*[f]
		1.2 (1.0, 1.5)**[f]
Age		
<85 y	1 (ref)	1 (ref)
≥85 y	1.6 (0.8, 3.3)*[c]	1.9 (1.5, 2.4)*[g]
	0.2 (0.1, 1.7)**[c]	0.6 (0.4, 0.8)**[g]

**: HR within the first 3 months. **: HR after 3 months and within 5 years*

[a]: the change in HR within the first 3 months and after was statistically significant (p<0.001)

[b]: the change in HR within the first 3 months and after was statistically significant (p=0.002)

[c]: a change in HR within the first 3 months and after was suspected (p=0.07)
[d]: the change in HR within the first 3 months and after was statistically significant (ASA II: p<0.001, ASA III-IV: p<0.001)
[e]: the change in HR within the first 3 months and after was statistically significant (ASA II: p<0.001, ASA III-IV: p<0.001)
[f]: a change in HR within the first 3 months and after was statistically significant (p<0.001)
[g]: a change in HR within the first 3 months and after was statistically significant (p<0.001)

Table 6-5 – Associations between ASA Class and Risk of Other Reoperations (time-invariant HR unless specified)

	Geneva cohort HR (95% CI)	Sweden cohort HR (95% CI)
Univariable model		
ASA class		
I	1 (ref)	1 (ref)
II	0.9 (0.5 - 1.8)	1.8 (1.3 - 2.4)*[d]
		1.2 (1.0 - 1.6)**[d]
III-IV	1.2 (0.6 - 2.5)	3.2 (2.3 - 4.3)*[d]
		1.6 (1.2 - 2.1)**[d]
Multivariable model		
ASA class		
I	1 (ref)	1 (ref)
II	0.9 (0.4 - 1.7)	1.7 (1.2 - 2.2)*[e]
		1.1 (0.9 - 1.5)**[e]
III-IV	1.1 (0.5 - 2.4)	2.7 (2.0 - 3.7)*[e]
		1.4 (1.0 - 1.8)**[e]
Sex		
Male	1 (ref)	1 (ref)
Female	0.8 (0.4 - 1.6)*[a]	0.6 (0.5 - 0.8)*[f]
	1.8 (1.0 - 3.2)**[a]	1.0 (0.8 - 1.2)**[f]
Diagnosis		
Primary OA	1 (ref)	1 (ref)
Secondary OA	3.1 (1.6 - 6.0)*[b]	1.8 (1.5 - 2.2)
	0.7 (0.4 - 1.5)**[b]	
BMI		
<35	1 (ref)	1 (ref)
≥35	4.5 (1.9 - 10.3)*[c]	2.6 (1.9 - 3.4)*[g]
	1.1 (0.4 - 2.9)**[c]	1.2 (0.8 - 1.7)**[g]
Age		
<85 y	1 (ref)	1 (ref)
≥85 y	0.9 (0.4 - 2.0)	1.9 (1.4 - 2.4)

**: HR within the first 3 months*
***: HR after 3 months and within 5 years*
[a]: the change in HR within the first 3 months and after was suspected (p=0.08)
[b]: the change in HR within the first 3 months and after was statistically significant (p=0.003)
[c]: a change in HR within the first 3 months and after was suspected (p=0.05)
[d]: the change in HR within the first 3 months and after was statistically significant (ASA II: p=0.05, ASA III-IV: p=0.001)

[e]: the change in HR within the first 3 months and after was statistically significant for ASA II (p=0.05) and close to statistical significance for ASA III-IV (p=0.05)
[f]: a change in HR within the first 3 months and after was statistically significant (p<0.001)
[g]: a change in HR within the first 3 months and after was statistically significant (p=0.001)

The most frequent indications for revision in both cohorts were dislocation, infection and periprosthetic fracture, and for other reoperation in both cohorts were infection, periprosthetic fracture and hematoma (Table 6-6).

Table 6-6 – Indications for Revision and Other Reoperations within 3 months by ASA grade

	Geneva cohort				Sweden cohort			
	ASA I N=481	ASA II N=3496	ASA III-IV N=1342	Total N=5319	ASA I N=29280	ASA II N=72857	ASA III-IV N=20104	Total N=122241
Indications for revision								
Dislocation, N (%)	1 (0.2)	5 (0.1)	12 (0.9)	18 (0.3)	30 (0.1)	103 (0.1)	57 (0.3)	190 (0.2)
Infection	1 (0.2)	8 (0.2)	7 (0.5)	16 (0.3)	81 (0.3)	356 (0.5)	195 (1)	632 (0.5)
Periprosthetic fracture	0	6 (0.2)	7 (0.5)	13 (0.2)	24 (0.1)	80 (0.1)	42 (0.2)	146 (0.1)
Aseptic loosening	0	4 (0.1)	3 (0.2)	7 (0.1)	8 (<0.1)	21 (<0.1)	8 (<0.1)	37 (<0.1)
Implant malposition	0	1 (<0.1)	1 (0.1)	2 (<0.1)	3 (<0.1)	8 (<0.1)	3 (<0.1)	14 (<0.1)
Other*	1 (0.2)	1 (<0.1)	1 (0.1)	3 (0.1)	1 (<0.1)	2 (<0.1)	3 (<0.1)	6 (<0.1)
Unknown	0	0	0	0	2 (<0.1)	3 (<0.1)	0	5 (<0.1)
Total	3 (0.6)	25 (0.7)	31 (2.3)	59 (1.1)	149 (0.5)	573 (0.8)	308 (1.5)	1030 (0.8)
Indications for reoperation								
Infection, N (%)	1 (0.2)	11 (0.3)	3 (0.2)	15 (0.3)	45 (0.2)	219 (0.3)	106 (0.5)	370 (0.3)
Periprosthetic fracture	0	3 (0.1)	6 (0.4)	9 (0.2)	4 (<0.1)	16 (<0.1)	10 (<0.1)	30 (<0.1)
Hematoma	1 (0.2)	4 (0.1)	1 (0.1)	6 (0.1)	1 (<0.1)	9 (<0.1)	8 (<0.1)	18 (<0.1)
Abductor avulsion	0	2 (0.1)	1 (0.1)	3 (0.1)	1 (<0.1)	1 (<0.1)	0	2 (<0.1)
Dislocation	0	0	0	0	3 (<0.1)	8 (<0.1)	1 (<0.1)	12 (<0.1)
Cement problem	0	0	0	0	1 (<0.1)	3 (<0.1)	2 (<0.1)	6 (<0.1)
Other**	0	3 (0.1)	1 (0.1)	4 (0.1)	2 (<0.1)	7 (<0.1)	1 (<0.1)	10 (<0.1)
Unknown	0	0	0	0	1 (<0.1)	3 (<0.1)	2 (<0.1)	6 (<0.1)
Total	2 (0.4)	23 (0.7)	12 (0.9)	37 (0.7)	58 (0.2)	266 (0.4)	130 (0.6)	454 (0.4)

** Other includes: infection suspected but not confirmed; hematoma; other material left in joint; nerve injury; delayed healing; pain*
*** Other includes: infection suspected but not confirmed; pain; allergy to suture; other material left in joint; aseptic loosening*

6.5 Discussion

6.5.1 Summary of main findings

This study has three important findings on outcomes within three months after primary THR. First, preoperative ASA class III-IV compared to ASA class I was associated with a more than three times higher risk of very early revision. Second, preoperative ASA class III-IV compared to ASA class I was associated with a more than two times higher risk of very early other reoperation in SHAR. These risks were independent of age, sex, BMI and diagnosis. Third, a substantial proportion of early revision and other reoperation procedures in patients with ASA class III-IV were performed within three months of primary THR. In addition, beyond three months and within five years after primary THR, patients with increased ASA class were not at increased risk of revision or other reoperation in GAR and were only at a slightly higher risk of revision or other reoperation in SHAR.

6.5.2 Strengths and limitations

This study has limitations. First, the ASA Classification System has been criticised because of the subjective nature of the assessment, which has poor inter-observer correlation[146,147] Despite this, the ASA Classification System has remained the most widely used anaesthetic preoperative assessment and the most widely collected tool for measuring multimorbidity by arthroplasty registries worldwide.[89] It is acknowledged that there may be poor inter-observer reliability when determining between ASA class I and II, however, as suggested by Hooper et al.[144], the difference between ASA class I and III is so profound (a normal healthy patient compared with a patient with severe systemic disease) that it appears unlikely that the significance of the results, when comparing ASA class I with ASA class III-IV, was affected by this potential error. Furthermore, it is acknowledged that the ASA Classification System is not a true measure of multimorbidity, and was designed to assess and communicate pre-anaesthesia co-morbidities. A recent study reported a strong association between ASA class and a traditional count of comorbid diseases.[267] The ASA Classification System is used here as a surrogate for multimorbidity burden. BMI was treated as a binary variable around BMI of 35 because of the non-linear relationship between BMI and revision surgery. Data from the UK national registry showed that patients with BMI over 35 had higher rates of revision than those with lower BMI.[268]

Second, the ASA class recorded in the registries only represents a snapshot of the physical health status of each patient, taken immediately prior to primary THR. This is a general drawback of using ASA class because it is only assessed in the context of surgery. It is unknown whether physical health status changed subsequent to THR, and if this had an influence on revision and reoperation rates. With increasing follow up, other health changes might intervene that would attenuate the influence of a single baseline measure. However, this study aimed to determine the influence of preoperative physical health status, to enable the identification of high-risk patients preoperatively, so the possibility of subsequent changes should not detract from the results.

Third, the results were adjusted for age, sex, BMI and diagnosis, but other factors may have had a confounding effect. The study did not adjust for surgical factors, such as surgical approach and implant fixation, which are known to also influence early revision and reoperation rates.[269,270] The reason for this decision is that each of these factors is chosen by the surgeon, and these choices may be influenced by ASA class, age, and BMI. Therefore, the inclusion of surgical factors in the models may have led to over-adjustment. BMI was included as a covariate here because the aim was to understand the influence of ASA class on revision, independent of BMI. It is acknowledged that BMI is on the causal pathway of multimorbidity and increased ASA class, and so its inclusion as a covariate would to some extent mitigate the effect of ASA class. Nonetheless, that a substantial effect of ASA class on revision remained after adjustment for BMI is informative, as it will support the consent process of obese patients with and without multimorbidity.

Both procedures were included in patients whom had undergone bilateral THR. This is because the ASA class may change between the two operations. Indeed, a sensitivity analysis in GAR and SHAR including only the first procedure in each patient showed similar results to the analyses including bilateral cases. Nevertheless, since ASA class is associated with outcome, the preoperative ASA class of the second THR would influence the outcome of both the first and second THRs. Thus, a degree of correlation in patients with bilateral THRs cannot be excluded.

Fourth, GAR is a small registry and cases were included since 1996. This might limit the applicability to modern patients. However, the results on revision were compared with results in the larger SHAR

with recent data and the results were similar. It is acknowledged the cumulative incidence of other reoperation was higher in GAR than in SHAR. Whilst there may be a real difference in other reoperation rate between the two registries, this observed difference alternatively may reflect greater completeness of capture of reoperations in GAR.

6.5.3 Findings in context

As discussed in Chapter 5, six previous studies were identified that investigated the influence of multimorbidity on the rate of revision surgery after THR. All studies used a count of coexisting diseases, with weighting by disease type (five used the Charlson Comorbidity Index, one used the Elixhauser Comorbidity Index) to measure multimorbidity. Four of the six studies reported multimorbidity was associated with an increased rate of revision, with the reported hazard ratios varying between 1.1 and 2.8, while two studies did not find any significant association. Five of the six studies investigated risk of revision at between four and 12 years follow up. This study has demonstrated that beyond three months of follow up, the increase in risk of revision associated with multimorbidity is small to non-existent, which may partially explain the inconsistent findings of these studies at longer term follow up. Only one study investigated early post-operative revision, within one year of THR, and interestingly found no significant association by multimorbidity. This unexpected finding may relate to the limitations of the Charlson Comorbidity Index in capturing the severity of multimorbidity.

In addition, two reports from Arthroplasty Registries were identified that investigated the association between a multimorbidity score and all-cause revision surgery, with both using the ASA Classification System. The New Zealand Joint Registry reported an adjusted hazard ratio of 1.4 (95% CI 1.0, 2.0) when comparing revision rates of patients with ASA class III versus I within two years postoperatively.[144] This agrees with the findings of this study, however, the effect of increased ASA class on revision rate in the Registry was less than in this study. A possible reason for the difference is that the New Zealand Joint Registry reported revision rates at two years post-operatively, and data from this study indicate that the effect of increased ASA class is highest within 3 months and decreases

thereafter. The Dutch Arthroplasty Register reported graphically that patients with ASA class III-IV have approximately double the rate of revision of patients with ASA class I within one year postoperatively, although beyond eight years postoperatively the rate of revision in patients with ASA class I is higher.[145] This early post-operative result is similar to that observed here in GAR and SHAR.

Data on the rate of reoperations are scarce and no previous study was identified for comparison that investigated the influence of multimorbidity on other reoperation rate. This study is the first to demonstrate that preoperative multimorbidity, as measured with the ASA Classification System, is associated with increased risk of early other reoperation.

That a substantial proportion of early revision and other reoperation procedures, performed in patients with ASA class III-IV, occur within three months of primary THR is a clinically important finding. It identifies this period of three months as critical to efforts to reduce revision and other reoperation rates. Infection, periprosthetic fracture and dislocation were the most frequent indications for very early revision and reoperation. Strategies to reduce the risk of revision targeted to these complications during this very early postoperative period may be designed and implemented for patients with ASA class III-IV most at risk, and are a key focus for future work. For example, intensive preoperative optimisation with physiotherapy, weight loss, anaemia management and diabetes control, as required. Postoperative measures might include careful management with increased monitored physiotherapy to reduce the risk of fall or dislocation, and wound management by specialist nurses to reduce infection. Such intensive strategies may be appropriate and acceptable in this cohort of patients over this time frame with regards to patient preference and resource constraints.

6.5.4 Conclusions

In summary, our study has identified that within three months of primary elective THR patients with pre-operative ASA class III-IV have a higher risk of revision and other reoperation. The proposed benefits are improved patient counselling, targeted risk reduction strategies and improved risk adjustment between datasets.

Chapter 7: International Variation in Distribution of ASA Class in Patients undergoing Total Hip Replacement and its Influence on Mortality: Data from an international consortium of arthroplasty registries

7.1 Abstract

Introduction

A challenge in comparing outcomes from total hip replacement between countries is the variation in preoperative characteristics, particularly multimorbidity. Therefore, this study investigated between-country variation in multimorbidity in patients undergoing total hip replacement based on distribution of ASA class, and investigated variation in assignment of ASA class, by investigating the consistency between ASA class and mortality in different countries.

Methods

All arthroplasty registries collecting ASA class and mortality data in patients with elective primary THRs performed 2012–2016 were invited to participate. Survival analyses of the influence of ASA class on 1-year mortality were performed by individual registries, followed by meta-analysis of aggregated data.

Results

Six national registries and one US healthcare organisation registry with 418,916 THRs were included. There was substantial variation in the proportion of ASA class III/ IV, ranging from 14% in the Netherlands to 39% in Finland. Overall, 1-year mortality was 0.93% (95% CI 0.87–1.01) and increased from 0.2% in ASA class I to 8.9% in class IV. The association between ASA class and mortality measured by hazard ratios (HR) was strong in all registries even after adjustment for age and sex, which reduced them by half in all registries. Combined adjusted HRs were 2.0, 6.1, and 22 for ASA class II–IV vs. I, respectively. Associations were moderately heterogeneous across registries.

Conclusions

Large variation in distribution of ASA class between registries was observed, possibly explained by between-country differences in underlying health status and in healthcare access. The similar, strong mortality trends by ASA class between countries enhance the relevance of its use as an indicator of multimorbidity in international registry studies.

Work described in this chapter has been published as:

- *Silman AJ, Combescure C, Ferguson RJ, Graves SE, Paxton EW, Frampton C, Furnes O, Fenstad AM, Hooper G, Garland A, Spekenbrink-Spooren A, Wilkinson JM, Mäkelä K, Lübbeke A, Rolfson O. International variation in distribution of ASA class in patients undergoing total hip arthroplasty and its influence on mortality: Data from an international consortium of arthroplasty registries. Acta Orthopaedica. 2021 Jun; 92(3): 304-310. DOI: 10.1080/17453674.2021.1892267. PMID: 33641588*

7.2 Introduction

The value of arthroplasty registries is well recognised. They provide population-wide, real-world data on the outcomes of joint replacement surgery and yield insights into the factors that influence the benefits and risks of the intervention.[271] In recent years, there has been a growing interest in comparing outcomes of total hip replacement (THR) between joint replacement registries, including rates of revisions and complications, and patient-reported benefits of surgery.[272–276] Comparing aggregate-level registry data internationally allows examination of variation in practice and outcomes due to differences in implant use, populations, and healthcare systems.

However, registry populations may differ substantially in patients' preoperative characteristics, such as multimorbidity, that influence the outcome of surgery. At present, there are few published data on international variation in multimorbidity in patients undergoing THR.[277] For comparisons of outcomes between joint replacement registries to be valid, controlling for the differences between the populations in different countries in the statistical analysis is required. Furthermore, controlling relies on a consistent approach to the scoring of the variable in question in all populations.

The most widely collected measure of multimorbidity by joint replacement registries worldwide is the ASA Classification System.[89] Few registries record any other measure of multimorbidity. The system classifies patients into six classes from normal health to brain dead, shown in Chapter 6, Table 6-1, and was originally validated in predicting postoperative mortality.[129] However, studies of anaesthetists have demonstrated only fair inter-observer consistency in the score, due to the nature of the subjective assessment.[146,147] It is possible that due to different attitudes and practices, the ASA Classification System may be scored differently in different countries. As an example, the same theoretical patient with diabetes mellitus and chronic kidney disease could be scored at class II in the UK, but class III in Sweden. To date, this potential variation in assignment of ASA class has not been investigated.

The aims of this chapter therefore are (i) to investigate the extent of variation in the distribution of ASA class in patients undergoing THR between joint replacement registries internationally; (ii) to explore how far any variation identified is related to age; and (iii) to study potential variation in assignment of

ASA class, by investigating the consistency between ASA class and death within the first year after surgery between the registries included.

7.3 Methods

7.3.1 Study design

This study consisted of an analysis of aggregated data prospectively collected from participating arthroplasty registries. The distribution of primary THRs by ASA class were compared between registries. The influence of ASA class on one-year mortality after elective primary THR was investigated.

7.3.2 Data set

Arthroplasty registries were eligible and invited to take part in this study if they were full members of the International Society of Arthroplasty Registries and collected data on ASA class of patients. To ensure comparability between registries, given the variable start date that registries collected ASA class, inclusion criteria were restricted to cases that were elective primary THRs performed within the period January 1, 2012 and December 31, 2016. THRs for which the indication was trauma or malignancy were excluded. Only the first THR in each patient was included. For included cases, the following patient characteristics were extracted: age, sex, BMI, diagnosis (primary or secondary osteoarthritis [OA]) and ASA class. Data on death from any cause within one-year of THR were obtained.

7.3.3 Statistical analysis

Patient level analysis was performed by the individual registries following a standardised protocol, detailed below. The aggregated data from each registry was subsequently analysed centrally.

Individual registries analysis

All registries described the distribution of baseline characteristics using frequencies and proportions. Registries calculated the cumulative incidence of mortality at one year after index THR, both overall and by ASA class, using Kaplan-Meier survival estimates with 95% confidence intervals (95%CIs). Patients were censored at loss to follow-up or end of one year follow-up. Registries then investigated the association between ASA class and risk of one year mortality with Cox proportional hazards models (presented as hazard ratios [HRs] with 95%CIs) with ASA class I defined as the referent category. The proportionality of hazards was checked visually by plotting log-log of survival against time. Regression coefficients of the Cox models were reported with their variance-covariance matrix. The univariable model was accompanied by a multivariable model adjusting for age and sex.

Aggregate analysis across registers

Kaplan Meier tables submitted by each participating registry were combined to create a summary life table of mortality up to one year. For this purpose, effective numbers of at-risk patients and estimates of mortality at intervals during follow-up were collected from each registry. The conditional mortality estimates from each registry were derived and combined using the DerSimonian model with random effects.[278] The summary mortality estimates were obtained by the product-limit of the conditional mortality estimates.

The regression coefficients of the Cox models from the individual registries' analysis, both univariate and multivariate, were combined also using the DerSimonian model with random effects for multivariate analyses.[279] With DerSimonian and Laird's model, the logarithms of HRs are combined across studies by calculating a weighted average. The weight of a study depends on the precision of the estimated HR: the higher the precision, the higher the weight of the study. The advantage is that studies with a larger sample size tend to have a larger weight in the meta-analysis. In addition, the between-studies variability is accounted for in the calculation of the weights. The extension of DerSimonian and Laird's model for multivariate analyses has been used to account for the correlation between the combined HRs. Cochran Q tests and I^2 statistics were used to assess the heterogeneity across registries as described previously.[280] I^2 values of 25%, 50% and 75% indicate low, moderate and high levels of heterogeneity, respectively.

Statistical analyses were performed with R 4.0.2 for Windows (Foundation for Statistical Computing, Vienna, Austria). The R package mvmeta (v1.0.3)[281] was used to combine logarithm of hazard ratios and the R package MetaSurv (v0.3)[278] to combine mortality curves. The two-sided statistical threshold for significance was 0.05.

As this was a study of anonymised aggregated data, with no individual patient data passed to the researchers, there were no ethical issues and consent was not necessary. All data collection and analysis was funded by the core funding to the arthroplasty registries.

7.4 Results

7.4.1 International variation

Overall, seven registries were included in the study. Six were national and population-based (Australia, Finland, Netherlands, New Zealand, Norway, and Sweden) and one was from a healthcare organisation (Kaiser Permanente, USA).

The baseline demographic data varied by registry (Table 7-1). The proportion of women ranged from 53% in Australia to 66% in the Netherlands. Only 9% of patients were aged under 55 years in the Netherlands compared with 30% in Kaiser Permanente. The proportion of obese patients (BMI≥30) ranged from 25% in the Netherlands and Sweden to 40% in Australia, Kaiser Permanente, and New Zealand. The proportion of THRs performed for primary OA ranged from 81% in Norway to 95% in Kaiser-Permanente.

Substantial variation in the proportion in each ASA class was observed (Table 7-2). The Netherlands and Sweden had the lowest proportions of ASA class III-IV (14% and 17% respectively), while Australia, Finland and Kaiser Permanente had twice those proportions (34%, 39% and 35% respectively).

Table 7-1 – Patient Demographics by Arthroplasty Registry

	Australia	Finland	Kaiser Permanente	Netherlands	New Zealand	Norway	Sweden
Age category							
<55 (N, %)	15306 (13.4)	2726 (12.2)	13176 (30.1)	10866 (9.2)	6304 (16.4)	3750 (12.6)	7025 (10.7)
55-64	27580 (24.1)	5356 (23.9)	15485 (35.4)	24960 (21.1)	10510 (27.3)	6930 (23.2)	14273 (21.7)
65-74	39978 (35)	8214 (36.6)	7704 (17.6)	44703 (37.8)	13054 (33.9)	11008 (36.9)	25228 (38.4)
75-84	25907 (22.6)	5318 (23.7)	6018 (13.8)	32657 (27.6)	7429 (19.3)	6877 (23)	16447 (25)
>=85	5610 (4.9)	801 (3.6)	1355 (3.1)	5150 (4.4)	1165 (3)	1274 (4.3)	2742 (4.2)
Missing	0	0	33	155	0	0	0
Age, mean (SD)	67.2 (11.5)	67.3 (10.9)	65.7 (10.6)	68.9 (11.8)	66.6 (11.3)	67.8 (11.4)	68.2 (10.6)
BMI category							
<18.5 (N, %)	475 (0.9)	118 (0.6)	351 (0.8)	603 (0.8)	222 (0.8)	-*	491 (0.8)
18.5-24.9	11384 (21.9)	5093 (26.5)	9370 (22.3)	24730 (31.1)	5974 (21.2)	-	19931 (31.1)
25-29.9	19296 (37.1)	7983 (41.5)	15318 (36.5)	34449 (43.3)	10748 (38.2)	-	27664 (43.2)
30-34.9	12812 (24.7)	4353 (22.6)	10762 (25.6)	14920 (18.7)	6981 (24.8)	-	12275 (19.1)
35-39.9	5350 (10.3)	1379 (7.2)	4893 (11.6)	3906 (4.9)	3181 (11.3)	-	3173 (4.9)
>=40	2636 (5.1)	328 (1.7)	1327 (3.2)	1000 (1.3)	1054 (3.7)	-	570 (0.9)
Missing	62428	3161	1750	38883	10302	-	1611
BMI, mean (SD)	29.4 (6.2)	28.2 (4.8)	29.1 (5.6)	27.4 (4.5)	29.0 (5.6)	-	27.3 (4.4)
Sex (N, %)							
Women	60923 (53.3)	12724 (56.8)	25148 (57.5)	77566 (65.6)	20345 (52.9)	18961 (63.5)	37148 (56.5)
Men	53458 (46.7)	9681 (43.2)	18593 (42.5)	40677 (34.4)	18117 (47.1)	10878 (36.5)	28567 (43.5)
Missing	0	10	30	248	0	0	0
Diagnosis (N, %)							
Primary OA	107480 (94.0)	19336 (90.4)	41599 (95.0)	107230 (90.5)	36080 (93.8)	24075 (80.9)	60466 (92.0)
Secondary OA	6901 (6.0)	2059 (9.6)	2172 (5.0)	11261 (9.5)	2382 (6.2)	5677 (19.1)	5249 (8.0)
Missing	0	1020	0	0	0	87	0

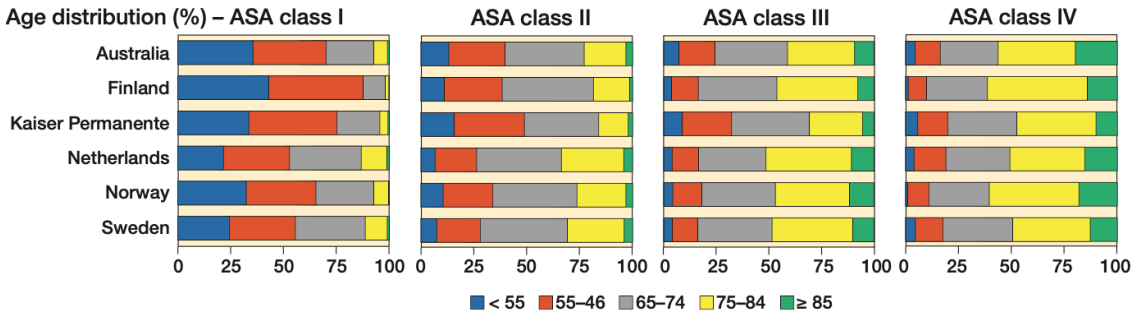
**Denotes no data*

Across all registries, the percentage of patients aged under 55 years decreased with ASA class (from 27% in ASA class I to 4.1% in ASA class IV) and the percentage of patients 85 years or older increased (from 0.7% in ASA class I to 17% in ASA class IV) (Figure 7-1). Although these broad age patterns were observed in all registries, there were substantial differences between registries in the actual proportions of patients within the same ASA class. The percentage of patients aged under 55 years in ASA class I ranged from 22% (Netherlands) to 43% (Finland), and the percentage of patients over 85 years in ASA class IV ranged from 10% (Kaiser Permanente) to 20% (Australia).

Table 7-2 – Distribution of ASA Class by Arthroplasty Registry. Values are count (%)

	Australia	Finland	Kaiser Permanente	Netherlands	New Zealand	Norway	Sweden	Total
ASA class I	11092 (10.6)	2773 (12.8)	1390 (3.3)	23750 (20.1)	5972 (15.7)	4586 (15.5)	15116 (23.4)	64679(15.4)
ASA class II	57616 (55.2)	10515 (48.4)	26634 (62.3)	77245 (65.5)	23039 (60.7)	19319 (65.2)	38483 (59.5)	252851(60.4)
ASA class III	33969 (32.6)	8076 (37.2)	14212 (33.3)	16586 (14.1)	8718 (23.0)	5600 (18.9)	10793 (16.7)	97954 (23.4)
ASA class IV	1676 (1.6)	339 (1.6)	499 (1.2)	286 (0.2)	238 (0.6)	111 (0.4)	283 (0.4)	3432 (0.8)
Any class	104353	21703	42735	117867	37967	29616	64675	418916
Missing	10028	712	1036	624	495	223	1040	14158
Total	114381	22415	43771	118491	38462	29839	65715	433074

Figure 7-1 – Distribution of age (years) in registries, by ASA class



7.4.2 ASA class and mortality within one-year after THR

Across all registries combined the overall mortality was 0.93% (95% CI 0.87, 1.01). This rose with increasing ASA class, from 0.18, 0.52, 2.2, to 8.9%, respectively from class I to class IV. Although this trend was observed in all individual registries (Table 7-3), ASA class specific one-year mortality varied. Whereas mortality rates for classes I and II were almost identical between registries, there was modest variation between registries in those in classes III ranging from 1.3% to 3.1%. Variation was most extensive in class IV (range 4.5% to 16%).

Unadjusted and age- and sex-adjusted hazard ratios for the association between ASA class and one-year mortality are shown in Table 7-4. The pooled unadjusted hazard ratio confirmed an increasing one-year mortality with increasing ASA class. This rose from an HR 3.2 (95% CI 2.3, 4.3) when comparing ASA class II to I, to a substantially higher HR of 59.1 (95% CI 37.8, 94.8) when comparing ASA class IV to I. There was moderate heterogeneity in the individual registries (I^2 around 50%), with lowest HRs

in Kaiser Permanente and the Netherlands. As an example, the unadjusted HRs in Netherlands were half those in Sweden and Finland.

Table 7-3 – 1-year mortality in percentage (95% CI) by registry & combined across registries

	Australia	Finland	Kaiser Permanente	Netherlands	New Zealand	Norway	Sweden	Combined
ASA class I	0.10 (0.04, 0.16)	0.12 (0.00, 0.26)	0.25 (0.00, 0.54)	0.30 (0.23, 0.37)	0.15 (0.05, 0.25)	0.15 (0.03, 0.28)	0.16 (0.10, 0.23)	0.18 (0.12, 0.25)
ASA class II	0.46 (0.40, 0.52)	0.40 (0.27, 0.53)	0.37 (0.29, 0.45)	0.70 (0.64, 0.76)	0.54 (0.45, 0.64)	0.46 (0.35, 0.56)	0.71 (0.63, 0.80)	0.52 (0.43, 0.64)
ASA class III	1.68 (1.54, 1.82)	1.88 (1.57, 2.19)	1.31 (1.11, 1.51)	2.74 (2.49, 2.99)	2.62 (2.28, 2.95)	3.10 (2.61, 3.58)	2.53 (2.23, 2.83)	2.21 (1.79, 2.74)
ASA class IV	6.83 (5.60, 8.04)	7.62 (4.70, 10.5)	4.54 (2.57, 6.47)	9.35 (5.86, 12.7)	13.5 (9.00, 17.7)	15.9 (8.07, 23.0)	8.31 (5.00, 11.5)	8.93 (6.74, 11.7)
All classes	0.92 (0.87, 0.98)	1.02 (0.89, 1.16)	0.73 (0.64, 0.81)	0.92 (0.87, 0.98)	1.04 (0.94, 1.14)	0.96 (0.84, 1.08)	0.93 (0.86, 1.08)	0.93 (0.87, 1.01)

Table 7-4 – Meta-analysis of unadjusted and age- and sex-adjusted hazard ratios for the association between ASA classes and one-year mortality (ASA class I as reference)

	Unadjusted HR (95% CI)			Adjusted HR (95% CI)		
	ASA II	ASA III	ASA IV	ASA II	ASA III	ASA IV
Registries						
Australia	4.5 (2.5 to 8.2)	17 (9.1 to 30)	70 (38 to 129)	2.7 (1.4 to 4.9)	6.9 (3.8 to 13)	22 (12 to 41)
Finland	3.3 (1.0 to 11)	16 (5.0 to 50)	69 (21 to 229)	2.0 (0.6 to 6.4)	6.8 (2.1 to 22)	24 (7.0 to 84)
Kaiser Permanente	1.5 (0.5 to 4.7)	5.3 (1.7 to 17)	19 (5.6 to 64)	1.0 (0.3 to 3.2)	2.7 (0.9 to 8.4)	7.3 (2.1 to 25)
Netherlands	2.2 (1.7 to 2.8)	8.8 (6.9 to 11)	32 (20 to 50)	1.4 (1.1 to 1.8)	4.2 (3.2 to 5.4)	14 (8.9 to 22)
New Zealand	3.6 (1.8 to 7.1)	18 (9.0 to 34)	97 (47 to 204)	2.3 (1.2 to 4.5)	8.0 (4.0 to 16)	34 (16 to 74)
Norway	3.1 (1.3 to 7.1)	21 (9.5 to 48)	120 (47 to 309)	1.7 (0.7 to 3.9)	7.7 (3.3 to 18)	34 (13 to 91)
Sweden	4.4 (2.9 to 6.6)	16 (10 to 24)	54 (30 to 95)	3.0 (2.0 to 4.6)	8.6 (5.6 to 13)	28 (16 to 50)
Pooled HR	3.2 (2.3 to 4.3)	14 (9.7 to 19)	59 (38 to 93)	2.0 (1.4 to 2.7)	6.1 (4.4 to 8.5)	22 (15 to 32)
P-value*	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Heterogeneity						
Q Cochran	11	14	14	12	13	10
Cochran test (p)	0.06	0.03	0.03	0.06	0.05	0.11
I^2 (%)	50	57	58	51	53	42

**P-value for testing the null hypothesis that the pooled HR equals 1*

After age and sex adjustment the HRs were lowered by half, in both the pooled as well as registry-level HRs. However, not all of the effect of ASA class on mortality could be captured by this adjustment: the increases in the pooled HRs with increasing ASA classes were attenuated but there were still 2.0 fold,

6.1 fold and 21.6 fold increases in mortality in ASA classes II, III and IV respectively compared to class I (Table 7-4). Although all registries showed this trend, there was moderate heterogeneity across registries, and I^2 statistics were around 50%, with flatter rises in adjusted HR in Kaiser Permanente and in the Netherlands compared to the other registries.

7.5 Discussion

7.5.1 Summary of main findings

Firstly, the results from the seven registries demonstrate large variation in the distribution of ASA class in patients undergoing THR internationally. Secondly, given the demographic differences between registries, there were also differences in age distribution of the registry populations within ASA classes. The third conclusion relates to the association between ASA classes and one-year mortality. Across all registries, increased ASA class was associated with greater one-year mortality, but the magnitude of the unadjusted relationship differed between registries. Age- and sex-adjustment was only able to capture about half to two thirds of the impact of ASA class on mortality, though this was consistent. After adjustment, a moderate between-registry heterogeneity between ASA classes and mortality remained. This suggests there exists a degree of variation in assignment of ASA class by anaesthetists in different countries.

7.5.2 Strengths, limitations, and interpretations

There are a number of methodological issues to consider in interpreting these findings, some of which could lead to bias in the results. The underlying aim of the study was to investigate the extent of variation in multimorbidity of patients undergoing THR, recorded in arthroplasty registries in different countries. The ASA Classification System was used as the measure of multimorbidity because it is a score well-validated in predicting post-operative mortality and complications, and because it is the most widely collected multimorbidity measure by arthroplasty registries internationally.[282–284]

To evaluate whether the observed variation in the distribution of ASA class of different registries represented true differences in multimorbidity between the populations, it was necessary to investigate whether the assignment of ASA class was consistent in the different populations. The concern was that there might exist systematic differences in the practice of assigning ASA class by anaesthetists in the different countries. The outcome chosen to investigate the consistency of assignment of ASA class was the association of ASA class with mortality at one year after primary THR. This outcome was most appropriate because the ASA Classification System was originally validated in predicting post-operative mortality.[129] A strength of the methodology was the use of meta-analysis, which pooled survival data from all the registries and was able to detect heterogeneity between the populations. A further strength was the inclusion of seven registries: to date, this represents the largest collaboration and data-sharing project between arthroplasty registries globally.

The meta-analysis was performed on hazard ratios that were adjusted for age and sex. The models were not adjusted for BMI, given the role of obesity in ASA class assignment.[134]. Adjustment for BMI could have masked the effect of multimorbidity that was the underlying aim of the study. There may be other unknown confounders that could have been adjusted for, such as socio-economic status. More deprived socio-economic status is associated with both increased multimorbidity and increased mortality.[42,285] However, comparable socio-economic status data from each registry were not available to permit adjustment for this variable.

Of note, there was a modest amount of missing data on ASA class (3% overall), but with completeness at 90% or greater in all the registries studied it is unlikely to be important. There were also minor differences in the number of years with available data in the different registries, but not of sufficient magnitude to warrant concern about secular changes.

The meta-analysis identified moderate between-registry heterogeneity between ASA classes and one-year mortality. One explanation for the heterogeneity is that it reflects differences in mortality rates for equivalent patients in the different countries where the registries are located; however, such differences are unlikely to be substantial because the countries involved have similarly developed healthcare systems and similar mortality rates according to OECD data.[286] An alternative explanation is that the

heterogeneity reflects a small but true variation in assignment of ASA class by anaesthetists in different countries. Why such variation might exist remains speculation. It has been proposed that 'upcoding' or 'downcoding' of ASA class may occur: at different times and in different jurisdictions, there may be advantages or disadvantages, financial or otherwise, for health care providers to under- or over-estimate the ASA class to support their service. Alternatively, certain health or disease factors may be viewed differently in different countries, such as an acceptable 'social alcohol' intake, leading to differences in assignment of ASA class. Nonetheless, despite the moderate heterogeneity between ASA class and mortality in the different registries, there remained substantial differences in distribution of ASA class in the different registries, indicating differences in the preoperative multimorbidity of patients undergoing THR in the different countries.

The natural next question is why were there substantial differences in distribution of ASA class in the registries of different countries. Aside from differences in assignment of ASA class, factors may be categorised into two groups: (i) underlying differences in health and multimorbidity of the wider population, with the population undergoing THR reflecting the wider population, and (ii) differences in healthcare systems that influence whether patients with multimorbidity are more or less likely to undergo THR.

Regarding the former, there are no published data on distribution of ASA class in the general populations in these countries, given that the tool is used only in patients selected for surgery. Instead, it was necessary to consider other data to investigate whether there are country-level differences in general health. The higher ASA classes focus particularly on cardiovascular disease. The Global Burden of Disease initiative publishes data on cardiovascular disease deaths by country.[287] The rate of cardiovascular disease deaths does vary between the countries included in this study and appears to be broadly consistent with the observed distribution of ASA class in different countries. In this study, the countries with the lowest and highest proportions of patients with ASA class III-IV were the Netherlands and Finland, respectively. The Global Burden of Disease data show the Netherlands has the lowest rate of cardiovascular disease deaths of the included countries, while Finland has the highest.

These data therefore suggest the observed differences in distribution of ASA class in the different registries, to some extent, reflect the general health of the wider populations.

Regarding the latter, the healthcare systems in each country will be different from each other in many ways of varying significance, and the differences challenging to account for. One major difference between the registries was that six registries were national in scope, covering patients treated in both public (free-to-access, universal) and private (self-paying or enrolled via insurance) healthcare systems, whereas the Kaiser Permanente Registry covers only patients enrolled in the Kaiser Permanente private healthcare scheme, within the USA.

The Kaiser Permanente Registry did show some differences: the registry contained the lowest proportion of ASA class I and the highest proportion of age <55 years. In addition, it had the lowest one-year mortality in ASA classes III and IV and the lowest age and sex-adjusted HRs, meaning there was a lower rate of mortality for patients in ASA classes III and IV (relative to ASA class I) in the Kaiser Permanente Registry compared to the other six registries. One possible explanation is that patients appropriately assigned to ASA class III the Kaiser Permanente Registry represent a 'healthier' cohort than patients in the same class in other registries that were not enrolled in a private healthcare scheme. Indeed, previous studies have shown lower rates of mortality in patients with health insurance compared to those without.[288,289] The caveat, of course, is that these studies were based in a setting (the USA) without a free-to-access, universal healthcare system, meaning that the reference population of uninsured patients is not directly comparable to the populations in the other registries here. Nonetheless, it remains possible that enrolling in a private healthcare scheme leads to patients making healthcare choices that influence mortality. An alternative explanation for the lower rate of mortality in the Kaiser Permanente Registry is that there may be increased unknown loss-to-follow-up compared with the national registries, due to it comprising of patients enrolled in the Kaiser Permanente private healthcare scheme. However, the Kaiser Permanente Registry reports a low rate of patients leaving the scheme, according to enrolment data, making this unlikely to be a significant factor. Only 8% of all patients in the Kaiser Permanente Registry have left the scheme.[290]

7.5.3 Conclusions

Substantial variation was observed in the distribution of ASA class in patients undergoing THR between arthroplasty registries internationally. The most plausible explanation is between-country differences in the underlying health status and healthcare access. The similar and strong mortality trends by ASA class between countries, enhances the relevance of the use of ASA class as an indicator of multimorbidity in international arthroplasty registry studies.

Chapter 8: Conclusions and Future Work

The aim of this thesis was to investigate the influence of multimorbidity on whether patients with hip osteoarthritis go on to have total hip replacement (THR) and, in those patients that do, the influence of multimorbidity on the outcomes of surgery. There were three main objectives:

1. To establish the influence of multimorbidity on the likelihood of patients with hip osteoarthritis undergoing primary THR.
2. To establish the influence of multimorbidity on the outcomes of THR, including:
    i. the rate of complications,
    ii. the patient-reported outcomes of pain, function, and quality of life, and
    iii. the rate of revision surgery and other reoperations.
3. To determine the variation in multimorbidity of patients undergoing primary THR in different countries.

In order to address the first and second objectives, data on a cohort of patients aged over 65 years with hip osteoarthritis was obtained from the CPRD, a research database of primary care electronic medical records owned by the UK Department of Health. The cohort was identified by the presence of Read codes indicating diagnosis of hip osteoarthritis in CPRD records; however, the Read codes had not previously been validated. A study was therefore performed to determine the positive predictive value of the Read codes via a questionnaire sent to the GPs of 170 patients randomly selected from the cohort. The results of Chapter 3 demonstrated the Read code for the diagnosis of hip osteoarthritis had a high validity, with a positive predictive value of 80% and 79% when assessed by radiological and clinical criteria respectively. This study had similar results to equivalent investigations of a database of primary care records in Canada.[198,199]

To address the first objective, a cohort study was performed that followed up patients from diagnosis of hip osteoarthritis to (i) referral to orthopaedic secondary care and (ii) receipt of total hip replacement. Multimorbidity was measured in five different ways. The quality of data on referral was poor and this

analysis was terminated. The results of Chapter 4 demonstrated that with increasing multimorbidity burden, the likelihood of undergoing THR was lower. Patients with increased multimorbidity burden were one third to two thirds less likely to undergo THR than patients without multimorbidity. This trend was observed irrespective of the method of measuring multimorbidity, and it persisted after adjustment for age, sex, region of the UK and year of diagnosis of hip osteoarthritis. This study is the first to quantitatively study the influence of multimorbidity on the clinical management of patients with hip osteoarthritis in the UK. The results were not unexpected, however, because previous qualitative studies have found beliefs amongst surgeons that the presence of comorbidities should sway the decision towards not to proceeding with THR.[177] Whether this observed difference in healthcare management is appropriate and fair depends on whether and to what extent multimorbidity influences the outcomes of total hip replacement.

To address the second objective, a cohort study was performed that investigated the outcomes of THR recorded in HES APC and HES PROMs, the linked databases of secondary care records, in the patients within the CPRD cohort that underwent surgery. Again, multimorbidity was measured in five different ways. The results of Chapter 5 demonstrated that patients with multimorbidity that underwent THR were at up to 1.5 to 2.5 times increased risk of suffering a post-operative complication compared with patients without multimorbidity. The results were consistent with previous studies in that multimorbidity scores that account for disease severity or functional limitation are superior to simple counts of coexisting diseases in identifying patients at most risk of complications. This study was the first to demonstrate this finding in patients in England.

Patients with multimorbidity that underwent total hip replacement were at up to 1.5 to 2.2 times increased risk of admission to hospital within 90 days of surgery compared with patients without multimorbidity, a finding consistent with previous studies. However, this study included a sensitivity analysis whereby the rate of admission to hospital within 90 days of THR was compared with the rate during the same period exactly one year earlier. The very similar rates suggest the higher rate of admission to hospital within 90 days of THR for patients with multimorbidity appears to be the ‘normal rate’ for such patients, and is unchanged following THR.

Patients with multimorbidity required a stay in hospital after total hip replacement up to 1.2 to 2.1 times as long compared with patients without multimorbidity. Consistent with previous studies, the measure of multimorbidity used here that included functional limitations as well as a count of coexisting diseases had a stronger association with length of stay than the simple counts of coexisting diseases: the Electronic Frailty Index had an incident rate ratio of 2.1 for severe multimorbidity versus no multimorbidity, whereas for Charlson Comorbidity Index the ratio was only 1.2.

In terms of patient-reported outcomes of surgery, the results of this study suggested there was no clinically meaningful difference in the benefits of surgery between patients with and without multimorbidity, in terms of postoperative hip pain and function as measured by the OHS and postoperative health-related quality of life as measured by the EQ-5D. This result was irrespective of the multimorbidity measure. Indeed, patients of all levels of multimorbidity reported substantial benefits of surgery. These findings are novel for patients in England.

Regrettably, there was substantial missing data on revision surgery and other reoperations, meaning this study was unable to add to the evidence base regarding these outcomes. The available data suggested there was a mildly increased risk of revision surgery with multimorbidity (up to 1.5 to 2.2 times higher), however, the differences between the categories were not statistically significant.

Therefore, in order to address the objective regarding rate of revision surgery and other reoperations, a further cohort study was performed using data from the Geneva and Sweden Arthroplasty Registries. The results of Chapter 6 demonstrated that patients with multimorbidity, assessed with the ASA Classification System, were at increased risk of early revision surgery and other reoperations after primary THR, with the highest risk within the first three months of surgery. Patients with ASA class III-IV had a three times higher risk of revision surgery and two times higher risk of other reoperation compared with ASA class I within three months of primary THR. Beyond three months and within five years after primary THR, patients with increased ASA class were not at increased risk of revision or other reoperation in the Geneva Arthroplasty Registry and were only at a slightly higher risk of revision or other reoperation in the Sweden Arthroplasty Registry. These findings are consistent with data on

early revision rate from two other arthroplasty registries, but novel in demonstrating the highest risk was within the first three months after primary THR.

Together, these findings on the influence of multimorbidity on the outcomes of THR will be very valuable to patients with multimorbidity and their clinicians in deciding whether to proceed with THR. These findings also provide a context for reflections on the results of Chapter 4: that patients with multimorbidity were less likely to undergo THR. Given that the increase in risk of complications, revision surgery and other reoperations was relatively small, between 1-3 times higher, and that there was no clinically meaningful difference in the benefits of surgery between patients with and without multimorbidity, it is therefore a concern that the rate of THR in patients with multimorbidity was one third to two thirds lower.

Of course, the final decision to proceed with THR truly lies with the patient, and each patient may have a different threshold for proceeding with surgery when balancing the risks of surgery against living with the symptoms of osteoarthritis. Indeed, the observed lower rate of surgery in patients with multimorbidity may reflect decisions made by patients in response to accurately estimated higher risks associated with multimorbidity. However, in a Patient and Public Involvement meeting held to discuss and disseminate the results of the study in Chapter 5, the informal feedback obtained from the nine osteoarthritis patients present was that they viewed these risks as small, and given the pain caused by osteoarthritis, they would still be keen for THR given the level of risks identified, even if they had a severe burden of multimorbidity. It therefore appears likely that the lower rate of THR was because patients decided to or were advised to avoid surgery due to inaccurate estimations of excessive risk or minimal benefit. This would constitute inappropriate management, and unfair care relative to patients without multimorbidity.

To address the third objective, a study was performed of aggregated data from seven arthroplasty registries internationally. The results of Chapter 7 demonstrated substantial variation in the distribution of ASA class in patients undergoing THR in different countries. The most plausible explanations for the between-country differences are (i) underlying differences in health and multimorbidity of the wider population of each country, with the population undergoing THR reflecting the wider population, and

(ii) differences in healthcare systems that influence whether patients with multimorbidity are more or less likely to undergo THR. The consistency in assignment of ASA class in different countries was checked by investigating the association with one-year mortality. There was broad consistency in the mortality rates, with only moderate between-registry heterogeneity between ASA classes and mortality, suggesting that ASA class is assigned in a consistent manner in different countries. The variation in distribution of ASA class and the consistency of assignment of ASA class underlines the importance of controlling for ASA class in future comparisons between arthroplasty registries.

Considering further work, a key step would be to investigate the completeness of the cohort of patients identified in CPRD, using the defined diagnosed Read codes for hip osteoarthritis. As discussed, it is not directly possible to identify false negative cases of patients missed from the cohort, to permit a sensitivity estimation. Instead, calculating the rate of osteoarthritis in the wider CPRD population, using the Read codes included here, and comparing it to the wider UK population would give a sense of the proportion of patients with hip osteoarthritis who had been successfully identified by the included Read codes and of the proportion of patients missed from the cohort.

It is problematic when medical coding is not complete or accurate because it impacts the accuracy of research such as the studies in this thesis and, also of great importance, it gives underestimates of the prevalence of a disease and so influences healthcare planning. Underestimates of the societal burden of hip osteoarthritis will negatively affect patients as insufficient resource allocation to their management may result. Furthermore, if patients do not know their diagnosis, their quality of life may be directly negatively affected as they may have poorer conservative symptom management or increased symptom-related health anxiety. Improving the quality of data recording is an important step, therefore. The quality of data recording has been shown to be improved in conditions added to the NHS Quality and Outcomes Framework. Lobbying NHS Digital for the inclusion of osteoarthritis in the included conditions should therefore be a priority.

It would be possible to improve the completeness of the study cohort, however, using other methods to identify the cohort. A recent study in the Netherlands investigated the prevalence of osteoarthritis in electronic medical records using narrative data stored in free text boxes, analysed with machine learning

algorithms. The authors reported a higher prevalence of osteoarthritis with this method than by identifying patients via the presence Read codes.[291]

It would be worthwhile therefore to re-identify a cohort of patients with hip osteoarthritis in CPRD using narrative data stored in free text boxes, and subsequently re-run the analyses with the likely larger cohort, including cross-tabulation to assess the false negative rates of the original Read codes.

The aim of the work in this thesis was to understand how multimorbidity influences the outcomes of total hip replacement, with a view to providing better information to patients considering surgery. It therefore would be beneficial to identify certain patient phenotypes, with particular disease patterns. Such 'clustering' of certain comorbidities in patients with osteoarthritis has recently been reported, using UK CPRD data.[292] For example, patients with osteoarthritis may fall into a cardiovascular-musculoskeletal cluster of diseases, which is associated with a higher rate of mortality than other clusters such as a metabolic cluster. Further work should therefore include cluster analysis to investigate whether particular patient phenotypes can be identified that are at highest risk of poor outcomes from total hip replacement.

It was beyond the scope of thesis to investigate the reasons why patients with multimorbidity did not undergo THR, including whether the choice was offered to them, and what advice they were given by their clinicians. Similarly, it was not possible to determine how patients with multimorbidity would view the novel information on risks and benefits of THR reported here, and whether it would affect their decision-making. A qualitative study into these two subjects, consisting of structured interviews with patients, GPs and surgeons, would be valuable in furthering understanding of the differential rate of THR, and whether patients had truly been given inappropriate management. This information would 'complete the circle', and the full set of information about the influence of multimorbidity on access to total hip replacement could then be communicated clearly to health service planners, with the likely message that patients with multimorbidity are currently receiving unfair care, being denied total hip replacement.

In order to make the evidence from the studies in this thesis as easy to communicate to clinicians and patients as possible, one option for further work would be to develop the regression models into a risk prediction tool, whereby patient information can be entered directly and a personalised estimation of the likely outcome of hip replacement delivered.

References

1 Fortin M, Stewart M, Poitras M, Almirall J, Maddocks H. A systematic review of prevalence studies on multimorbidity: toward a more uniform methodology. *Ann Fam Med* 2012; **10**: 142–51.

2 Valderas JM, Starfield B, Sibbald B, Salisbury C, Roland M. Defining comorbidity: implications for understanding health and health services. *Ann Fam Med*; **7**: 357–63.

3 Adomaviciute S, Soljak M, Watt H, Foley K, Newson R. Osteoarthritis prevalence models for small populations: Technical document produced for Arthritis Research UK. 2018 https://www.versusarthritis.org/media/21947/osteoarthritis-technical-document.pdf (accessed June 6, 2021).

4 Glyn-Jones S, Palmer AJR, Agricola R, *et al.* Osteoarthritis. *Lancet* 2015; **386**: 376–87.

5 National Joint Registry. National Joint Registry for England, Wales, Northern Ireland and the Isle of Man: 17th Annual Report. 2020.

6 Phillips CB, Barrett JA, Losina E, *et al.* Incidence Rates of Dislocation, Pulmonary Embolism, and Deep Infection During the First Six Months After Elective Total Hip Replacement. *J Bone Jt Surg* 2003; **85**: 20–6.

7 Hunt LP, Ben-Shlomo Y, Clark EM, *et al.* 90-day mortality after 409 096 total hip replacements for osteoarthritis, from the National Joint Registry for England and Wales: a retrospective analysis. *Lancet* 2013; **382**: 1097–104.

8 Kandala N-B, Connock M, Pulikottil-Jacob R, *et al.* Setting benchmark revision rates for total hip replacement: analysis of registry evidence. *BMJ* 2015; **350**: h756.

9 Judge A, Arden NK, Kiran A, *et al.* Interpretation of patient-reported outcomes for hip and knee replacement surgery: identification of thresholds associated with satisfaction with surgery. *J Bone Joint Surg Br* 2012; **94**: 412–8.

10 Bayliss LE, Culliford D, Monk AP, *et al.* The effect of patient age at intervention on risk of implant revision after total replacement of the hip or knee: a population-based cohort study. *Lancet* 2017; **389**: 1424–30.

11 Wuerz TH, Kent DM, Malchau H, Rubash HE. A Nomogram to Predict Major Complications After Hip and Knee Arthroplasty. *J Arthroplasty* 2014; **29**: 1457–62.

12 de Vries LM, Sturkenboom MCJM, Verhaar JAN, Kingma JH, Stricker BHC. Complications after hip arthroplasty and the association with hospital procedure volume. *Acta Orthop* 2011; **82**: 545–52.

13 Pedersen AB, Mehnert F, Sorensen HT, Emmeluth C, Overgaard S, Johnsen SP. The risk of venous thromboembolism, myocardial infarction, stroke, major bleeding and death in patients undergoing total hip and knee replacement. *Bone Joint J* 2014; **96-B**: 479–85.

14 Belmont PJ, Goodman GP, Kusnezov NA, *et al.* Postoperative Myocardial Infarction and Cardiac Arrest Following Primary Total Knee and Hip Arthroplasty: Rates, Risk Factors, and Time of Occurrence. *J Bone Jt Surgery-American Vol* 2014; **96**: 2025–31.

15 Wallace G, Judge A, Prieto-Alhambra D, de Vries F, Arden NKNK, Cooper C. The effect of body mass index on the risk of post-operative complications during the 6 months following total hip replacement or total knee replacement surgery. *Osteoarthr Cartil* 2014; **22**: 918–27.

16 Evans JT, Evans JP, Walker RW, Blom AW, Whitehouse MR, Sayers A. How long does a hip replacement last? A systematic review and meta-analysis of case series and national registry reports with more than 15 years of follow-up. *Lancet* 2019; **393**: 647–54.

17 Beswick AD, Wylde V, Gooberman-Hill R, Blom AW, Dieppe P. What proportion of patients

report long-term pain after total hip or knee replacement for osteoarthritis? A systematic review of prospective studies in unselected patients. *BMJ Open* 2012; **2**: e000435.

18 Ferguson RJ, Palmer AJ, Taylor A, Porter ML, Malchau H, Glyn-Jones S. Hip replacement. *Lancet* 2018; **392**: 1662–71.

19 SooHoo NF, Farng E, Lieberman JR, Chambers L, Zingmond DS. Factors That Predict Short-term Complication Rates After Total Hip Arthroplasty. *Clin Orthop Relat Res* 2010; **468**: 2363–71.

20 Elwyn G, Frosch D, Rollnick S. Dual equipoise shared decision making: Definitions for decision and behaviour support interventions. *Implement Sci* 2009; **4**: 75.

21 General Medical Council UK. Ethical guidance for doctors: Decision making and consent. 2020.

22 Abad-Díez JM, Calderón-Larrañaga A, Poncel-Falcó A, *et al.* Age and gender differences in the prevalence and patterns of multimorbidity in the older population. *BMC Geriatr* 2014; **14**: 75.

23 van den Akker M, Buntinx F, Metsemakers JFM, Roos S, Knottnerus JA. Multimorbidity in General Practice: Prevalence, Incidence, and Determinants of Co-Occurring Chronic and Recurrent Diseases. *J Clin Epidemiol* 1998; **51**: 367–75.

24 Swain S, Sarmanova A, Coupland C, Doherty M, Zhang W. Comorbidities in Osteoarthritis: A Systematic Review and Meta-Analysis of Observational Studies. *Arthritis Care Res (Hoboken)* 2020; **72**: 991–1000.

25 Swain S, Coupland C, Mallen C, *et al.* Temporal relationship between osteoarthritis and comorbidities: a combined case control and cohort study in the UK primary care setting. *Rheumatology (Oxford)* 2021; **60**: 4327–39.

26 Fortin M, Soubhi H, Hudon C, Bayliss EA, van den Akker M. Multimorbidity's many challenges. *BMJ* 2007; **334**: 1016–7.

27 The Academy of Medical Sciences. Multimorbidity: A Priority for Global Health Research. 2018 https://acmedsci.ac.uk/file-download/82222577 (accessed April 4, 2019).

28 Gijsen R, Hoeymans N, Schellevis FG, Ruwaard D, Satariano WA, van den Bos GA. Causes and consequences of comorbidity: a review. *J Clin Epidemiol* 2001; **54**: 661–74.

29 Ghali WA, Hall RE, Rosen AK, Ash AS, Moskowitz MA. Searching for an improved clinical comorbidity index for use with ICD-9-CM administrative data. *J Clin Epidemiol* 1996; **49**: 273–8.

30 Grossman R, Mukherjee D, Chang DC, *et al.* Preoperative Charlson Comorbidity Score Predicts Postoperative Outcomes Among Older Intracranial Meningioma Patients. *World Neurosurg* 2011; **75**: 279–85.

31 Atkins BZ, Shah AS, Hutcheson KA, *et al.* Reducing Hospital Morbidity and Mortality Following Esophagectomy. *Ann Thorac Surg* 2004; **78**: 1170–6.

32 Dunbar M, Robertsson O, Ryd L. What's all that noise?The effect of co-morbidity on health outcome questionnaire results after knee arthroplasty. *Acta Orthop Scand* 2004; **75**: 119–26.

33 Merle-Vincent F, Couris CM, Schott A-M, *et al.* Factors predicting patient satisfaction 2 years after total knee arthroplasty for osteoarthritis. *Jt Bone Spine* 2011; **78**: 383–6.

34 Greenfield S, Apolone G, McNeil BJ, Cleary PD. The importance of co-existent disease in the occurrence of postoperative complications and one-year recovery in patients undergoing total hip replacement. Comorbidity and outcomes after hip replacement. *Med Care* 1993; **31**: 141–54.

35 Bell DE. Regret in Decision Making under Uncertainty. *Oper Res* 1982; **30**: 961–81.

36 Stacey D, Bennett CL, Barry MJ, *et al.* Decision aids for people facing health treatment or screening decisions. In: Stacey D, ed. Cochrane Database of Systematic Reviews. Chichester, UK: John Wiley & Sons, Ltd, 2011: CD001431.

37 Sanmartin C, Murphy K, Choptain N, *et al.* Appropriateness of healthcare interventions: Concepts and scoping of the published literature. *Int J Technol Assess Health Care* 2008; **24**: 342–9.

38 Raine R, Or Z, Prady S, Bevan G. Evaluating health-care equity. Health Services and Delivery Research, 2016.

39 UK Government. The NHS Constitution for England. 2015. https://www.gov.uk/government/publications/the-nhs-constitution-for-england/the-nhs-constitution-for-england (accessed March 7, 2020).

40 Judge A, Welton NJ, Sandhu J, Ben-Shlomo Y, J S, Ben-Shlomo Y. Equity in access to total joint replacement of the hip and knee in England: cross sectional study. *BMJ* 2010; **341**: c4092.

41 Dreinhöfer KE, Dieppe P, Stürmer T, *et al.* Indications for total hip replacement: Comparison of assessments of orthopaedic surgeons and referring physicians. *Ann Rheum Dis* 2006; **65**: 1346–50.

42 Barnett K, Mercer SW, Norbury M, Watt G, Wyke S, Guthrie B. Epidemiology of multimorbidity and implications for health care, research, and medical education: a cross-sectional study. *Lancet* 2012; **380**: 37–43.

43 National Institute for Health and Clinical Excellence. Osteoarthritis: Care and Management Guidelines. 2014. https://www.nice.org.uk/guidance/cg177.

44 Hunter DJ, Bierma-Zeinstra S. Osteoarthritis. Lancet. 2019; **393**: 1745–59.

45 Vincent TL. Targeting mechanotransduction pathways in osteoarthritis: A focus on the pericellular matrix. Curr. Opin. Pharmacol. 2013; **13**: 449–54.

46 Agricola R, Heijboer MP, Roze RH, *et al.* Pincer deformity does not lead to osteoarthritis of the hip whereas acetabular dysplasia does: Acetabular coverage and development of osteoarthritis in a nationwide prospective cohort study (CHECK). *Osteoarthr Cartil* 2013; **21**: 1514–21.

47 Agricola R, Waarsing JH, Arden NK, *et al.* Cam impingement of the hip-a risk factor for hip osteoarthritis. Nat. Rev. Rheumatol. 2013; **9**: 630–4.

48 Kim C, Nevitt M, Guermazi A, *et al.* Brief Report: Leg Length Inequality and Hip Osteoarthritis in the Multicenter Osteoarthritis Study and the Osteoarthritis Initiative. *Arthritis Rheumatol* 2018; **70**: 1572–6.

49 Tallroth K, Ristolainen L, Manninen M. Is a long leg a risk for hip or knee osteoarthritis?: A 29-year follow-up study of 193 individuals. *Acta Orthop* 2017; **88**: 512–5.

50 Lievense AM, Bierma-Zeinstra SMA, Verhagen AP, Bernsen RMD, Verhaar JAN, Koes BW. Influence of sporting activities on the development of osteoarthritis of the hip: A systematic review. Arthritis Care Res. 2003; **49**: 228–36.

51 Palmer A, Fernquest S, Gimpel M, *et al.* Physical activity during adolescence and the development of cam morphology: A cross-sectional cohort study of 210 individuals. *Br J Sports Med* 2018; **52**: 601–10.

52 Cooper C, Inskip H, Croft P, *et al.* Individual risk factors for hip osteoarthritis: Obesity, hip injury, and physical activity. *Am J Epidemiol* 1998; **147**: 516–22.

53 Prieto-Alhambra D, Judge A, Javaid MK, Cooper C, Diez-Perez A, Arden NK. Incidence and risk factors for clinically diagnosed knee, hip and hand osteoarthritis: Influences of age, gender and osteoarthritis affecting other joints. *Ann Rheum Dis* 2014; **73**: 1659–64.

54 Mork PJ, Holtermann A, Nilsen TIL. Effect of body mass index and physical exercise on risk of knee and hip osteoarthritis: longitudinal data from the Norwegian HUNT Study. *J Epidemiol Community Health* 2012; **66**: 678–83.

55 Zeggini E, Panoutsopoulou K, Southam L, *et al.* Identification of new susceptibility loci for osteoarthritis (arcOGEN): A genome-wide association study. *Lancet* 2012; **380**: 815–23.

56 Pereira D, Peleteiro B, Araújo J, Branco J, Santos RA, Ramos E. The effect of osteoarthritis definition on prevalence and incidence estimates: a systematic review. *Osteoarthr Cartil* 2011; **19**: 1270–85.

57 Cross M, Smith E, Hoy D, *et al.* The global burden of hip and knee osteoarthritis: estimates from the Global Burden of Disease 2010 study. *Ann Rheum Dis* 2014; **73**: 1323–30.

58 Turkiewicz A, Petersson IF, Björk J, *et al.* Current and future impact of osteoarthritis on health care: A population-based study with projections to year 2032. *Osteoarthr Cartil* 2014; **22**: 1826–32.

59 Postler A, Luque Ramos A, Goronzy J, *et al.* Prevalence and treatment of hip and knee osteoarthritis in people aged 60 years or older in Germany: An analysis based on health insurance claims data. *Clin Interv Aging* 2018; **13**: 2339–49.

60 Swain S, Sarmanova A, Mallen C, *et al.* Trends in incidence and prevalence of osteoarthritis in the United Kingdom: findings from the Clinical Practice Research Datalink (CPRD). *Osteoarthr Cartil* 2020; **28**: 792–801.

61 Guermazi A, Niu J, Hayashi D, *et al.* Prevalence of abnormalities in knees detected by MRI in adults without knee osteoarthritis: Population based observational study (Framingham Osteoarthritis Study). *BMJ* 2012; **345**. DOI:10.1136/bmj.e5339.

62 Altman R, Alarcón G, Appelrouth D, *et al.* The American College of Rheumatology criteria for the classification and reporting of osteoarthritis of the hip. *Arthritis Rheum* 1991; **34**: 505–14.

63 Bedson J, Croft PR. The discordance between clinical and radiographic knee osteoarthritis: A systematic search and summary of the literature. *BMC Musculoskelet Disord* 2008; **9**: 116.

64 Schiphof D, Oei EHG, Hofman A, Waarsing JH, Weinans H, Bierma-Zeinstra SMA. Sensitivity and associations with pain and body weight of an MRI definition of knee osteoarthritis compared with radiographic Kellgren and Lawrence criteria: A population-based study in middle-aged females. *Osteoarthr Cartil* 2014; **22**: 440–6.

65 Nelson AE, Allen KD, Golightly YM, Goode AP, Jordan JM. A systematic review of recommendations and guidelines for the management of osteoarthritis: The Chronic Osteoarthritis Management Initiative of the U.S. Bone and Joint Initiative. *Semin Arthritis Rheum* 2014; **43**: 701–12.

66 Learmonth ID, Young C, Rorabeck C. The operation of the century: total hip replacement. *Lancet* 2007; **370**: 1508–19.

67 Smith-Petersen MN. The classic: Evolution of mould arthroplasty of the hip joint. *J Bone Jt Surg* 1948; **30B**: L59.

68 Wiles P. The surgery of the osteo-arthritic hip. *Br J Surg* 1958; **45**: 488–97.

69 Charnley J. Arthroplasty Of The Hip: A New Operation. *Lancet* 1961; **277**: 1129–32.

70 Charnley J. Total Hip Replacement. *JAMA* 1974; **230**: 1025–8.

71 Berry D, Harmsen W, Cabanela M, MorreyBF. Twenty-five-year survivorship of two thousand consecutive primary Charnley total hip replacements: factors affecting survivorship of acetabular and femoral components. *J Bone Joint Surg Am* 2002; **84**: 171–7.

72 Callaghan J, Albright J, Goetz D, Olejniczak J, Johnston R. Charnley total hip arthroplasty with cement. Minimum twenty-five-year follow-up. *J Bone Joint Surg Am* 2000; **82**: 487–97.

73 Kynaston-Pearson F, Ashmore a M, Malak TT, *et al.* Primary hip replacement prostheses and their evidence base: systematic review of literature. *BMJ* 2013; **347**: f6956.

74 The four health systems of the United Kingdom | The Health Foundation. https://www.health.org.uk/publications/the-four-health-systems-of-the-united-kingdom-how-do-they-compare (accessed July 12, 2021).

75 National Institute for Health and Care Excellent. NICE Guidance on Joint replacement (primary): hip, knee and shoulder. https://www.nice.org.uk/guidance/ng157 (accessed July 10,

2021).

76 NHS England. Musculoskeletal Elective Care Transformation Programme. https://www.england.nhs.uk/elective-care-transformation/best-practice-solutions/musculoskeletal/ (accessed July 16, 2021).

77 Nugent M, Young S, Frampton C, Hooper G. The lifetime risk of revision following total hip arthroplasty. *Bone Joint J* 2021; **103-B**: 479–85.

78 Dawson J, Fitzpatrick R, Carr AJ, Murray D. Questionnaire on the perceptions of patients about total hip replacement. *J Bone Joint Surg Br* 1996; **78-B**: 185–90.

79 Söderman P, Malchau H. Is the Harris hip score system useful to study the outcome of total hip replacement? *Clin Orthop Relat Res* 2001; : 189–97.

80 Bellamy N, Buchanan W, Goldsmith C, Campbell J, Stitt L. Validation study of WOMAC: a health status instrument for measuring clinically important patient relevant outcomes to antirheumatic drug therapy in patients with osteoarthritis of the hip or knee - PubMed. *J Rheumatol* 1988; **15**: 1844–1840.

81 EuroQol Group. EuroQol - a new facility for the measurement of health-related quality of life. *Health Policy (New York)* 1990; **16**: 199–208.

82 Rolfson O, Bohm E, Franklin P, *et al.* Patient-reported outcome measures in arthroplasty registries Report of the Patient-Reported Outcome Measures Working Group of the International Society of Arthroplasty Registries Part II. Recommendations for selection, administration, and analysis. *Acta Orthop* 2016; **87**: 9–23.

83 Whittle, Steinberg E, Anderson G, Herbert R, Hochberg M. Mortality after elective total hip arthroplasty in elderly Americans. Age, gender, and indication for surgery predict survival. *Clin Orthop Relat Res* 1993; : 119–26.

84 Dale H, Børsheim S, Kristensen T, *et al.* Perioperative, short-, and long-term mortality related to fixation in primary total hip arthroplasty: a study on 79,557 patients in the -Norwegian Arthroplasty Register. *Acta Orthop* 2020; **91**: 152–8.

85 Hunt L, Whitehouse M, Howard P, Ben-Shlomo Y, Blom A. Using long term mortality to determine which perioperative risk factors of mortality following hip and knee replacement may be causal. *Sci Rep* 2018; **8**. DOI:10.1038/S41598-018-33314-0.

86 Pedersen A, Baron J, Overgaard S, Johnsen S. Short- and long-term mortality following primary total hip replacement for osteoarthritis: a Danish nationwide epidemiological study. *J Bone Joint Surg Br* 2011; **93**: 172–7.

87 Mahomed NN, Barrett JA, Katz JN, *et al.* Rates and Outcomes of Primary and Revision Total Hip Replacement in the United States Medicare Population. *J Bone Jt Surg* 2003; **85**.

88 Mufarrih S, Ghani M, Martins R, *et al.* Effect of hospital volume on outcomes of total hip arthroplasty: a systematic review and meta-analysis. *J Orthop Surg Res* 2019; **14**: 468.

89 Lübbeke A, Silman AJ, Barea C, Prieto-Alhambra D, Carr AJ. Mapping existing hip and knee replacement registries in Europe. *Health Policy (New York)* 2018; **122**: 548–57.

90 Greene ME. [Thesis] Who should have total hip replacement? Use of patient-reported outcome measures in identifying the indications for and assessment of total hip replacement. 2015. https://gupea.ub.gu.se/handle/2077/38458 (accessed July 15, 2021).

91 Rolfson O, Dahlberg LE, Nilsson J-Å, Malchau H, Garellick G. Variables determining outcome in total hip replacement surgery. *Bone Joint J* 2009; **91-B**.

92 Gordon M, Frumento P, Sköldenberg O, Greene ME, Garellick G, Rolfson O. Women in Charnley class C fail to improve in mobility to a higher degree after total hip replacement. *Acta Orthop* 2014; **85**: 335–41.

93 Greene ME, Rolfson O, Nemes S, Gordon M, Malchau H, Garellick G. Education Attainment is Associated With Patient-reported Outcomes: Findings From the Swedish Hip Arthroplasty Register. *Clin Orthop Relat Res* 2014; **472**: 1868–76.

94 Krupic F, Eisler T, Garellick G, Kärrholm J. Influence of ethnicity and socioeconomic factors on outcome after total hip replacement. *Scand J Caring Sci* 2013; **27**: 139–46.

95 Nwachukwu BU, Kenny AD, Losina E, Chibnik LB, Katz JN. Complications for Racial and Ethnic Minority Groups After Total Hip and Knee Replacement: A Review of the Literature. *J Bone Jt Surgery Am Vol* 2010; **92**: 338.

96 Sayers A, Steele F, Whitehouse M, Price A, Ben-Shlomo Y, Blom A. Association between surgical volume and failure of primary total hip replacement in England and Wales: findings from a prospective national joint replacement register. *BMJ Open* 2020; **10**: e033045.

97 Fowler T, Blom A, Reed M, Aquilina A, Sayers A, Whitehouse M. The association between surgeon training grade and risk of revision following total hip arthroplasty. *Orthop Proc* 2021; **103-B**: Supplement 10.

98 Higgins BT, Barlow DR, Heagerty NE, Lin TJ. Anterior vs. Posterior Approach for Total Hip Arthroplasty, a Systematic Review and Meta-analysis. *J Arthroplasty* 2015; **30**: 419–34.

99 Evans J, Blom A, Timperley A, *et al.* Factors associated with implant survival following total hip replacement surgery: A registry study of data from the National Joint Registry of England, Wales, Northern Ireland and the Isle of Man. *PLoS Med* 2020; **17**: e1003291.

100 National Institute for Health and Care Excellence. Guidance on Multimorbidity: clinical assessment and management. https://www.nice.org.uk/guidance/ng56 (accessed July 16, 2021).

101 Calderón-Larrañaga A, Vetrano D, Ferrucci L, *et al.* Multimorbidity and functional impairment-bidirectional interplay, synergistic effects and common pathways. *J Intern Med* 2019; **285**: 255–71.

102 Marengoni A, Pasina L, Concoreggi C, *et al.* Understanding adverse drug reactions in older adults through drug-drug interactions. *Eur J Intern Med* 2014; **25**: 843–6.

103 Pasina L, Brucato A, Falcone C, *et al.* Medication non-adherence among elderly patients newly discharged and receiving polypharmacy. *Drugs Aging* 2014; **31**: 283–9.

104 Fortin M, Dionne J, Pinho G, Gignac J, Almirall J, Lapointe L. Randomized Controlled Trials: Do They Have External Validity for Patients With Multiple Comorbidities? *Ann Fam Med* 2006; **4**: 104–8.

105 Kenning C, Coventry PA, Bower P. Self-Management Interventions in Patients with Long-Term Conditions: A Structured Review of Approaches to Reporting Inclusion, Assessment, and Outcomes in Multimorbidity: *J Multimorbidity Comorbidity* 2014; **4**: 37–45.

106 Sinnott C, McHugh S, Browne J, Bradley C. GPs' perspectives on the management of patients with multimorbidity: systematic review and synthesis of qualitative research. *BMJ Open* 2013; **3**: e003610.

107 Marengoni A, von Strauss E, Rizzuto D, Winblad B, Fratiglioni L. The impact of chronic multimorbidity and disability on functional decline and survival in elderly persons. A community-based, longitudinal study. *J Intern Med* 2009; **265**: 288–95.

108 Cheung C-L, Nguyen U-SDT, Au E, Tan KCB, Kung AWC. Association of handgrip strength with chronic diseases and multimorbidity. *Age (Omaha)* 2013; **35**: 929–41.

109 Jackson C, Jones M, Tooth L, Mishra G, Byles J, Dobson A. Multimorbidity patterns are differentially associated with functional ability and decline in a longitudinal cohort of older women. *Age Ageing* 2015; **44**: 810–6.

110 Fried LP, Tangen CM, Walston J, *et al.* Frailty in older adults: evidence for a phenotype. *J Gerontol A Biol Sci Med Sci* 2001; **56**: M146-56.

111 Vetrano DL, Palmer K, Marengoni A, *et al.* Frailty and Multimorbidity: A Systematic Review and Meta-analysis. *Journals Gerontol Ser A* 2019; **74**: 659–66.

112 Bunn F, Burn A, Goodman C, *et al.* Comorbidity and dementia: a scoping review of the literature. *BMC Med* 2014; **12**: 192.

113 Biessels G, Staekenborg S, Brunner E, Brayne C, Scheltens P. Risk of dementia in diabetes mellitus: a systematic review. *Lancet Neurol* 2006; **5**: 64–74.

114 Savva G, Stephan B. Epidemiological studies of the effect of stroke on incident dementia: a systematic review. *Stroke* 2010; **41**: 41–6.

115 Marengoni A, Angleman S, Melis R, *et al.* Aging with multimorbidity: a systematic review of the literature. *Ageing Res Rev* 2011; **10**: 430–9.

116 Feinstein A. The Pre-Therapeutic Classification of Co-Morbidity in Chronic Disease. *J Chronic Dis* 1970; **23**: 455–68.

117 Van Den Akker M, Buntinx F, Knottnerus JA. Comorbidity or multimorbidity: What's in a name? A review of literature. *Eur J Gen Pract* 1996; **2**: 65–70.

118 Clegg A, Young J, Iliffe S, Rikkert MO, Rockwood K. Frailty in elderly people. *Lancet* 2013; **381**: 752–62.

119 Rockwood K, Song X, MacKnight C, *et al.* A global clinical measure of fitness and frailty in elderly people. *Can Med Assoc J* 2005; **173**: 489–95.

120 Yarnall A, Sayer A, Clegg A, Rockwood K, Parker S, Hindle J. New horizons in multimorbidity in older adults. *Age Ageing* 2017; **46**: 882–8.

121 Nardi R, Scanelli G, Corrao S, Iori I, Mathieu G, Cataldi Amatrian R. Co-morbidity does not reflect complexity in internal medicine patients. *Eur J Intern Med* 2007; **18**: 359–68.

122 Elixhauser A, Steiner C, Harris DR, Coffey RM. Comorbidity Measures for Use with Administrative Data. *Med Care* 1998; **36**: 8–27.

123 Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987; **40**: 373–83.

124 van Walraven C, Austin PC, Jennings A, Quan H, Forster AJ. A Modification of the Elixhauser Comorbidity Measures Into a Point System for Hospital Death Using Administrative Data. *Med Care* 2009; **47**: 626–33.

125 Klabunde C, Potosky A, Legler J, Warren J. Development of a comorbidity index using physician claims data. *J Clin Epidemiol* 2000; **53**: 1258–67.

126 Fortin M, Steenbakkers K, Hudon C, Poitras ME, Almirall J, Van Den Akker M. The electronic Cumulative Illness Rating Scale: a reliable and valid tool to assess multi-morbidity in primary care. *J Eval Clin Pract* 2011; **17**: 1089–93.

127 Velanovich V, Antoine H, Swartz A, Peters D, Rubinfeld I. Accumulating deficits model of frailty and postoperative mortality and morbidity: Its application to a national database. *J Surg Res* 2013; **183**: 104–10.

128 Clegg A, Bates C, Young J, *et al.* Development and validation of an electronic frailty index using routine primary care electronic health record data. *Age Ageing* 2016; **45**: 353–60.

129 Dripps R. New classification of physical status. *Anesthesiology* 1963; **24**: 111.

130 Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. *J Clin Epidemiol* 1992; **45**: 613–9.

131 Sharabiani M, Aylin P, Bottle A. Systematic review of comorbidity indices for administrative data. *Med Care* 2012; **50**: 1109–18.

132 Southern D, Quan H, Ghali W. Comparison of the Elixhauser and Charlson/Deyo methods of comorbidity measurement in administrative data. *Med Care* 2004; **42**: 355–60.

133 Stukenborg G, Wagner D, Connors A. Comparison of the performance of two comorbidity measures, with and without information from prior hospitalizations. *Med Care* 2001; **39**: 727–39.

134 American Society of Anesthesiologists (ASA). ASA Physical Status Classification System. 2014. https://www.asahq.org/standards-and-guidelines/asa-physical-status-classification-

system (accessed Feb 20, 2019).

135 Von Korff M, Wagner E, Saunders K. A chronic disease score from automated pharmacy data. *J Clin Epidemiol* 1992; **45**: 197–203.

136 Stirland L, González-Saavedra L, Mullin D, Ritchie C, Muniz-Terrera G, Russ T. Measuring multimorbidity beyond counting diseases: systematic review of community and population studies and guide to index choice. *BMJ* 2020; **368**: m160.

137 Hauswaldt J, Hummers-Pradier E, Junius-Walker U. Health service use among patients with chronic or multiple illnesses, and frequent attenders: secondary analysis of routine primary care data from 1996 to 2006. *Dtsch Arztebl Int* 2012; **109**: 814–20.

138 Arias-De La Torre J, Smith K, Dregan A, *et al.* Impact of comorbidity on the short- And medium-term risk of revision in total hip and knee arthroplasty. *BMC Musculoskelet Disord* 2020; **21**: 447.

139 Johnsen SP, Sørensen HT, Pedersen AB, Lucht U, Søballe K, Overgaard S. Patient-related predictors of implant failure after primary total hip replacement in the initial, short- and long-term: A nationwide Danish follow-up study including 36 984 patients. *J Bone Jt Surg - Br Vol* 2006; **88**: 1303–8.

140 Katz JN, Wright EA, Wright J, *et al.* Twelve-Year Risk of Revision After Primary Total Hip Replacement in the U.S. Medicare Population. *J Bone Jt Surgery-American Vol* 2012; **94**: 1825–32.

141 Losina E, Barrett JA, Mahomed NN, Baron JA, Katz JN. Early failures of total hip replacement: Effect of surgeon volume. *Arthritis Rheum* 2004; **50**: 1338–43.

142 Ong KL, Lau E, Suggs J, Kurtz SM, Manley MT. Risk of Subsequent Revision after Primary and Revision Total Joint Arthroplasty. *Clin Orthop Relat Res* 2010; **468**: 3070–6.

143 Paterson JM, Williams JI, Kreder HJ, *et al.* Provider volumes and early outcomes of primary total joint replacement in Ontario. *Can J Surg* 2010; **53**: 175–83.

144 Hooper GJ, Rothwell AG, Hooper NM, Frampton C. The relationship between the American Society Of Anesthesiologists physical rating and outcome following total hip and knee arthroplasty: an analysis of the New Zealand Joint Registry. *J Bone Joint Surg Am* 2012; **94**: 1065–70.

145 Dutch Arthroplasty Register. Landelijke Registratie Orthopedische Implantaten Annual Report. 2018 www.lroi-rapportage.nl.

146 Ranta S, Hynynen M, Tammisto T. A survey of the ASA physical status classification: significant variation in allocation among Finnish anaesthesiologists. *Acta Anaesthesiol Scand* 1997; **41**: 629–32.

147 Mak PHK, Campbell RCH, Irwin MG, American Society of Anesthesiologists. The ASA Physical Status Classification: inter-observer consistency. American Society of Anesthesiologists. *Anaesth Intensive Care* 2002; **30**: 633–40.

148 Rhee C, Lethbridge L, Richardson G, Dunbar M. Risk factors for infection, revision, death, blood transfusion and longer hospital stay 3 months and 1 year after primary total hip or knee arthroplasty. *Can J Surg* 2018; **61**: 165.

149 Bottle A, Parikh S, Aylin P, Loeffler M. Risk factors for early revision after total hip and knee arthroplasty: National observational study from a surgeon and population perspective. *PLoS One* 2019; **14**: e0214855.

150 Bozic KJ, Lau E, Ong K, *et al.* Risk Factors for Early Revision After Primary Total Hip Arthroplasty in Medicare Patients. *Clin Orthop Relat Res* 2014; **472**: 449–54.

151 Dy C, Bozic K, Pan T, Wright T, Padgett D, Lyman S. Risk factors for early revision after total hip arthroplasty. *Arthritis Care Res (Hoboken)* 2014; **66**: 907–15.

152 Podmore B, Hutchings A, Van Der Meulen J, Aggarwal A, Konan S. Impact of comorbid conditions on outcomes of hip and knee replacement surgery: A systematic review and meta-

analysis. BMJ Open. 2018; **8**: e021784.

153 Judge A, Arden NK, Batra RN, *et al.* The association of patient characteristics and surgical variables on symptoms of pain and function over 5 years following primary hip-replacement surgery: a prospective cohort study. *BMJ Open* 2013; **3**: e002453.

154 Loth FL, Giesinger JM, Giesinger K, *et al.* Impact of Comorbidities on Outcome After Total Hip Arthroplasty. *J Arthroplasty* 2017; **32**: 2755–61.

155 Mannion AF, Nauer S, Arsoy D, Impellizzeri FM, Leunig M. The Association Between Comorbidity and the Risks and Early Benefits of Total Hip Arthroplasty for Hip Osteoarthritis. *J Arthroplasty* 2020; **35**: 2480–7.

156 Zhang L, Lix LM, Ayilara O, Sawatzky R, Bohm ER. The effect of multimorbidity on changes in health-related quality of life following hip and knee arthroplasty. *Bone Joint J* 2018; **100-B**: 1168–74.

157 Dowsey M, Nikpour M, Choong P. Outcomes following large joint arthroplasty: does socio-economic status matter? *BMC Musculoskelet Disord* 2014; **15**: 148.

158 Hawker G, Badley E, Borkhoff C, *et al.* Which patients are most likely to benefit from total joint arthroplasty? *Arthritis Rheum* 2013; **65**: 1243–52.

159 Nilsdotter A-K, Petersson IF, Roos EM, Lohmander LS. Predictors of patient relevant outcome after total hip replacement for osteoarthritis: a prospective study. *Ann Rheum Dis* 2003; **62**: 923–30.

160 Stevens M, Paans N, Wagenmakers R, *et al.* The influence of overweight/obesity on patient-perceived physical functioning and health-related quality of life after primary total hip arthroplasty. *Obes Surg* 2012; **22**: 523–9.

161 Quintana JM, Escobar A, Aguirre U, Lafuente I, Arenaza JC. Predictors of Health-related Quality-of-life Change after Total Hip Arthroplasty. *Clin Orthop Relat Res* 2009; **467**: 2886–94.

162 Peter W, Dekker J, Tilbury C, *et al.* The association between comorbidities and pain, physical function and quality of life following hip and knee arthroplasty. *Rheumatol Int* 2015; **35**: 1233–41.

163 Imamura K, Black N. Does comorbidity affect the outcome of surgery? Total hip replacement in the UK and Japan. *Int J Qual Heal care J Int Soc Qual Heal Care* 1998; **10**: 113–23.

164 Glassou EN, Pedersen AB, Aalund PK, Mosegaard SB, Hansen TB. Is gain in health-related quality of life after a total hip arthroplasty depended on the comorbidity burden? *Acta Orthop* 2018; **89**: 374–9.

165 Gordon M, Paulsen A, Overgaard S, Garellick G, Pedersen AB, Rolfson O. Factors influencing health-related quality of life after total hip replacement - a comparison of data from the Swedish and Danish hip arthroplasty registers. *BMC Musculoskelet Disord* 2013; **14**: 316.

166 Greene ME, Rolfson O, Gordon M, Garellick G, Nemes S. Standard Comorbidity Measures Do Not Predict Patient-reported Outcomes 1 Year After Total Hip Arthroplasty. *Clin Orthop Relat Res* 2015; **473**: 3370–9.

167 Boniello A, Simon M, Emenari C, Courtney P. Complications and Mortality Following Total Hip Arthroplasty in the Octogenarians: An Analysis of a National Database. *J Arthroplasty* 2018; **33**: S167–71.

168 Singh JA, Jensen MR, Harmsen WS, Gabriel SE, Lewallen DG. Cardiac and thromboembolic complications and mortality in patients undergoing total hip and total knee arthroplasty. *Ann Rheum Dis* 2011; **70**: 2082–8.

169 Rasouli MR, Restrepo C, Maltenfort MG, Purtill JJ, Parvizi J. Risk Factors for Surgical Site Infection Following Total Joint Arthroplasty. *J Bone Jt Surgery-American Vol* 2014; **96**: e158-1–5.

170 Bellamy JL, Runner RP, Vu CPCL, Schenker ML, Bradbury TL, Roberson JR. Modified Frailty Index Is an Effective Risk Assessment Tool in Primary Total Hip Arthroplasty. *J Arthroplasty* 2017; **32**: 2963–8.

171 Dharmasukrit C, Chan S, Applegate R, Tancredi D, Harvath T, Joseph J. Frailty, Race/Ethnicity, Functional Status, and Adverse Outcomes After Total Hip/Knee Arthroplasty: A Moderation Analysis. *J Arthroplasty* 2021; **36**: 1895–903.

172 Shin JI, Keswani A, Lovy AJ, Moucha CS. Simplified Frailty Index as a Predictor of Adverse Outcomes in Total Hip and Knee Arthroplasty. *J Arthroplasty* 2016; **31**: 2389–94.

173 Traven S, Reeves R, Sekar M, Slone H, Walton Z. New 5-Factor Modified Frailty Index Predicts Morbidity and Mortality in Primary Hip and Knee Arthroplasty. *J Arthroplasty* 2019; **34**: 140–4.

174 Beard DJ, Harris K, Dawson J, *et al.* Meaningful changes for the Oxford hip and knee scores after joint replacement surgery. *J Clin Epidemiol* 2015; **68**: 73–9.

175 Coretti S, Ruggeri M, McNamee P. The minimum clinically important difference for EQ-5D index: A critical review. Expert Rev. Pharmacoeconomics Outcomes Res. 2014; **14**: 221–33.

176 Podmore B, Hutchings A, Konan S, Robson J, Van Der Meulen J. Access to hip and knee replacement surgery in patients with chronic diseases according to patient-reported pain and functional status. *BMC Health Serv Res* 2020; **20**: 602.

177 Mancuso CA, Ranawat CS, Esdaile JM, Johanson NA, Charlson ME. Indications for total hip and total knee arthroplasties: Results of orthopaedic surveys. *J Arthroplasty* 1996; **11**: 34–46.

178 Podmore B, Hutchings A, Durand MA, *et al.* Comorbidities and the referral pathway to access joint replacement surgery: An exploratory qualitative study. *BMC Health Serv Res* 2018; **18**: 754.

179 Birrell F, Afzal C, Nahit E, *et al.* Predictors of hip joint replacement in new attenders in primary care with hip pain. *Br J Gen Pract* 2003; **53**: 26–30.

180 Kontopantelis E, Stevens RJ, Helms PJ, Edwards D, Doran T, Ashcroft DM. Spatial distribution of clinical computer systems in primary care in England in 2016 and implications for primary care electronic medical record databases: a cross-sectional population study. *BMJ Open* 2018; **8**: e020738.

181 NHS Digital. SNOMED CT. https://digital.nhs.uk/services/terminology-and-classifications/snomed-ct (accessed May 5, 2019).

182 Clinical Practice Research Datalink. https://www.cprd.com/intro.asp (accessed Sept 6, 2017).

183 Herrett E, Gallagher AM, Bhaskaran K, *et al.* Data Resource Profile: Clinical Practice Research Datalink (CPRD). *Int J Epidemiol* 2015; **44**: 827–36.

184 Carbonari DM, Saine ME, Newcomb CW, *et al.* Use of demographic and pharmacy data to identify patients included within both the Clinical Practice Research Datalink (CPRD) and The Health Improvement Network (THIN). *Pharmacoepidemiol Drug Saf* 2015; **24**: 999–1003.

185 Herrett E, Thomas SL, Schoonen WM, Smeeth L, Hall AJ. Validation and validity of diagnoses in the General Practice Research Database: a systematic review. *Br J Clin Pharmacol* 2010; **69**: 4–14.

186 Chun DS, Lund JL, Stürmer T. *Pharmacoepidemiology and Drug Safety* 's special issue on validation studies. *Pharmacoepidemiol Drug Saf* 2019; **28**: 123–5.

187 NHS Digital. Quality and Outcomes Framework Programme. http://content.digital.nhs.uk/qof (accessed Oct 5, 2017).

188 Chamberlain R. Hip Pain in Adults: Evaluation and Differential Diagnosis - PubMed. *Am Fam Physician* 2021; **103**: 81–9.

189 Healthcare Quality Improvement Partnership. National Joint Registry overview. https://www.hqip.org.uk/national-programmes/joint-replacement-surgery-the-national-joint-registry/#.XNBY69NKhPU (accessed May 6, 2019).

190 Herbert A, Wijlaars L, Zylbersztejn A, Cromwell D, Hardelid P. Data Resource Profile: Hospital Episode Statistics Admitted Patient Care (HES APC). *Int J Epidemiol* 2017; **46**: 1093-1093i.

191 Cnudde P, Nemes S, Bülow E, *et al.* Trends in hip replacements between 1999 and 2012 in Sweden. *J Orthop Res* 2017; **36**: 432–42.

192 Thien TM, Chatziagorou G, Garellick G, *et al.* Periprosthetic femoral fracture within two years after total hip replacement: analysis of 437,629 operations in the nordic arthroplasty register association database. *J Bone Joint Surg Am* 2014; **96**: e167.

193 Swiss National Joint Registry. Swiss National Joint Registry: Annual Report. 2018 http://www.siris-implant.ch/de/index.php?section=media1&path=%2Fmedia%2Farchive1%2FJahresberichte%2F.

194 De Coster C, Quan H, Finlayson A, *et al.* Identifying priorities in methodological research using ICD-9-CM and ICD-10 administrative data: report from an international consortium. *BMC Health Serv Res* 2006; **6**: 77.

195 Urbaniak GC, Plous S. Research Randomizer (Version 4.0) [Computer software]. http://www.randomizer.org (accessed July 18, 2019).

196 Kellgren JH, Lawrence JS. Radiological assessment of osteo-arthrosis. *Ann Rheum Dis* 1957; **16**: 494–502.

197 UK Government. Indices of Deprivation. https://www.gov.uk/government/statistics/english-indices-of-deprivation-2015 (accessed Dec 22, 2017).

198 Kadhim-Saleh A, Green M, Williamson T, Hunter D, Birtwhistle R. Validation of the Diagnostic Algorithms for 5 Chronic Conditions in the Canadian Primary Care Sentinel Surveillance Network (CPCSSN): A Kingston Practice-based Research Network (PBRN) Report. *J Am Board Fam Med* 2013; **26**: 159–67.

199 Williamson T, Green ME, Birtwhistle R, *et al.* Validating the 8 CPCSSN case definitions for chronic disease surveillance in a primary care database of electronic health records. *Ann Fam Med* 2014; **12**: 367–72.

200 Rahman MM, Kopec JA, Goldsmith CH, Anis AH, Cibere J. Validation of Administrative Osteoarthritis Diagnosis Using a Clinical and Radiological Population-Based Cohort. *Int J Rheumatol* 2016; **2016**: 1–7.

201 Birrell F, Croft P, Cooper C, *et al.* Predicting radiographic hip osteoarthritis from range of movement. *Rheumatology (Oxford)* 2001; **40**: 506–12.

202 Khan NF, Perera R, Harper S, Rose PW. Adaptation and validation of the Charlson Index for Read/OXMIS coded databases. *BMC Fam Pract* 2010; **11**: 1.

203 Gallacher KI, Batty GD, McLean G, *et al.* Stroke, multimorbidity and polypharmacy in a nationally representative sample of 1,424,378 patients in Scotland: implications for treatment burden. *BMC Med* 2014; **12**. DOI:10.1186/S12916-014-0151-0.

204 Fine JP, Gray RJ. A Proportional Hazards Model for the Subdistribution of a Competing Risk. *J Am Stat Assoc* 1999; **94**: 496–509.

205 NHS Digital. OPCS Classification of Interventions and Procedures. https://digital.nhs.uk/data-and-information/information-standards/information-standards-and-data-collections-including-extractions/publications-and-notifications/standards-and-collections/dcb0084-opcs-classification-of-interventions-and-procedures (accessed Oct 29, 2019).

206 Office for National Statistics. Population and migration. https://www.ons.gov.uk/peoplepopulationandcommunity/populationandmigration (accessed March 4, 2020).

207 Reyes C, Garcia-Gil M, Elorza JM, *et al.* Socio-economic status and the risk of developing hand, hip or knee osteoarthritis: A region-wide ecological study. *Osteoarthr Cartil* 2015; **23**:

1323–9.

208 Mercer SW, Guthrie, Hart AJ. Multimorbidity and the inverse care law in primary care. *BMJ* 2012; **344**: e4152.

209 Mercer SW, Patterson J, Robson JP, Smith SM, Walton E, Watt G. The inverse care law and the potential of primary care in deprived areas. *Lancet (London, England)* 2021; **397**: 775–6.

210 Bratzke LC, Muehrer RJ, Kehl KA, Lee KS, Ward EC, Kwekkeboom KL. Self-management priority setting and decision-making in adults with multimorbidity: A narrative review of literature. Int. J. Nurs. Stud. 2015; **52**: 744–55.

211 Van Olmen J, Van Nooten J, Philips H, Sollie A, Daelemans W. Predicting COVID-19 Symptoms From Free Text in Medical Records Using Artificial Intelligence: Feasibility Study. *JMIR Med informatics* 2022; **10**. DOI:10.2196/37771.

212 Härstedt M, Rogmark C, Sutton R, Melander O, Fedorowski A. Polypharmacy and adverse outcomes after hip fracture surgery. *J Orthop Surg Res* 2016; **11**: 151.

213 McIsaac DI, Wong CA, Bryson GL, van Walraven C. Association of Polypharmacy with Survival, Complications, and Healthcare Resource Use after Elective Noncardiac Surgery. *Anesthesiology* 2018; **128**: 1140–50.

214 Harrison C, Britt H, Miller G, Henderson J. Examining different measures of multimorbidity, using a large prospective cross-sectional study in Australian general practice. *BMJ Open* 2014; **4**. DOI:10.1136/BMJOPEN-2013-004694.

215 Cassell A, Edwards D, Harshfield A, *et al.* The epidemiology of multimorbidity in primary care: a retrospective cohort study. *Br J Gen Pract* 2018; **68**: e245–51.

216 Metcalfe D, Masters J, Delmestri A, *et al.* Coding algorithms for defining Charlson and Elixhauser co-morbidities in Read-coded databases. *BMC Med Res Methodol* 2019; **19**: 115.

217 Morris RW, Whincup PH, Lampe FC, Walker M, Wannamethee SG, Shaper AG. Geographic variation in incidence of coronary heart disease in Britain: The contribution of established risk factors. *Heart* 2001; **86**: 277–83.

218 Hansell A, Ghosh R, Bakolis I, Strachan D. Geographical variation in the respiratory health of Great Britain. In: European Respiratory Journal. European Respiratory Society (ERS), 2016: PA4914.

219 The Health Foundation. Returning NHS waiting times to 18 weeks for routine treatment. 2020 https://www.health.org.uk/publications/long-reads/returning-nhs-waiting-times-to-18-weeks (accessed Nov 19, 2021).

220 Sailer D. Obesity: Entrance port to multimorbidity. Wiener Medizinische Wochenschrift. 1998; **148**: 388–92.

221 Agborsangaya CB, Ngwakongnwi E, Lahtinen M, Cooke T, Johnson JA. Multimorbidity prevalence in the general population: The role of obesity in chronic disease clustering. *BMC Public Health* 2013; **13**: 1–6.

222 Lebenbaum M, Zaric GS, Thind A, Sarma S. Trends in obesity and multimorbidity in Canada. *Prev Med (Baltim)* 2018; **116**: 173–9.

223 McLean G, Gunn J, Wyke S, *et al.* The influence of socioeconomic deprivation on multimorbidity at different ages: a cross-sectional study. *Br J Gen Pract* 2014; **64**: e440–7.

224 Hawley S, Cordtz R, Dreyer L, *et al.* Association between NICE guidance on biologic therapies with rates of hip and knee replacement among rheumatoid arthritis patients in England and Wales: An interrupted time-series analysis. *Semin Arthritis Rheum* 2018; **47**: 605–10.

225 Royal College of Surgeons of England. More than 2 million people waiting longer than statutory 18 weeks for NHS treatment. https://www.rcseng.ac.uk/news-and-events/media-centre/press-releases/waiting-times-press-notice-november-2021/ (accessed Sept 13, 2022).

226 Lanas A, Chan FKL. Peptic ulcer disease. *Lancet* 2017; **390**: 613–24.

227 Maartens G, Celum C, Lewin SR. HIV infection: Epidemiology, pathogenesis, treatment, and prevention. *Lancet* 2014; **384**: 258–71.

228 Bayliss EA, Ellis JL, Shoup JA, Zeng C, McQuillan DB, Steiner JF. Effect of continuity of care on hospital utilization for seniors with multiple medical conditions in an integrated health care system. *Ann Fam Med* 2015; **13**: 123–9.

229 Hussey PS, Schneider EC, Rudin RS, Fox DS, Lai J, Pollack CE. Continuity and the costs of care for chronic disease. *JAMA Intern Med* 2014; **174**: 742–8.

230 Bagaria V. Total Hip Replacement - An Overview. Intech Open, 2018.

231 Dolan P. Modeling Valuations for EuroQol Health States. *Med Care* 1997; **35**: 1095–108.

232 Payne RA, Abel GA, Guthrie B, Mercer SW. The effect of physical multimorbidity, mental health conditions and socioeconomic deprivation on unplanned admissions to hospital: A retrospective cohort study. *CMAJ* 2013; **185**: E221–8.

233 Rizza A, Kaplan V, Senn O, *et al.* Age- and gender-related prevalence of multimorbidity in primary care: the Swiss FIRE project. *BMC Fam Pract* 2012; **13**: 113.

234 Rocca WA, Boyd CM, Grossardt BR, *et al.* Prevalence of multimorbidity in a geographically defined American population: Patterns by age, sex, and race/ethnicity. *Mayo Clin Proc* 2014; **89**: 1336–49.

235 Inacio MCS, Ake CF, Paxton EW, *et al.* Sex and risk of hip implant failure: Assessing total hip arthroplasty outcomes in the United States. *JAMA Intern Med* 2013; **173**: 435–41.

236 Garriga C, Leal J, Sánchez-Santos MT, *et al.* Geographical Variation in Outcomes of Primary Hip and Knee Replacement. *JAMA Netw open* 2019; **2**: e1914325.

237 Uijen AA, van de Lisdonk EH. Multimorbidity in primary care: Prevalence and trend over the last 20 years. *Eur J Gen Pract* 2008; **14**: 28–32.

238 Dindo D, Demartines N, Clavien PA. Classification of surgical complications: A new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann. Surg. 2004; **240**: 205–13.

239 Sink EL, Leunig M, Zaltz I, Gilbert JC, Clohisy J. Reliability of a complication classification system for orthopaedic surgery hip. *Clin Orthop Relat Res* 2012; **470**: 2220–6.

240 Pulido L, Parvizi J, Macgibeny M, *et al.* In Hospital Complications After Total Joint Arthroplasty. *J Arthroplasty* 2008; **23**: 139–45.

241 Mantilla CB, Horlocker TT, Schroeder DR, Berry DJ, Brown DL. Frequency of myocardial infarction, pulmonary embolism, deep venous thrombosis, and death following primary hip or knee arthroplasty. *Anesthesiology* 2002; **96**: 1140–6.

242 Pedersen AB, Mehnert F, Overgaard S, Johnsen SP. Allogeneic blood transfusion and prognosis following total hip replacement: A population-based follow up study. *BMC Musculoskelet Disord* 2009; **10**: 1–12.

243 Hart A, Khalil JA, Carli A, Huk O, Zukor D, Antoniou J. Blood Transfusion in Primary Total Hip and Knee Arthroplasty. Incidence, Risk Factors, and Thirty-Day Complication Rates. *J Bone Jt Surg* 2014; **96**: 1945–51.

244 Holt JB, Miller BJ, Callaghan JJ, Clark CR, Willenborg MD, Noiseux NO. Minimizing Blood Transfusion in Total Hip and Knee Arthroplasty Through a Multimodal Approach. *J Arthroplasty* 2016; **31**: 378–82.

245 White RS, Sastow DL, Gaber-Baylis LK, Tangel V, Fisher AD, Turnbull ZA. Readmission Rates and Diagnoses Following Total Hip Replacement in Relation to Insurance Payer Status, Race and Ethnicity, and Income Status. *J Racial Ethn Heal Disparities* 2018; **5**: 1202–14.

246 Kurtz SM, Lau EC, Ong KL, Adler EM, Kolisek FR, Manley MT. Hospital, Patient, and Clinical Factors Influence 30- and 90-Day Readmission After Primary Total Hip Arthroplasty. *J Arthroplasty* 2016; **31**: 2130–8.

247 Ali AM, Loeffler MD, Aylin P, Bottle A. Factors associated with 30-day readmission after primary total hip arthroplasty analysis of 514 455 procedures in the UK National Health Service. *JAMA Surg* 2017; **152**: e173949–e173949.

248 Burn E, Edwards CJ, Murray DW, *et al.* Trends and determinants of length of stay and hospital reimbursement following knee and hip replacement: evidence from linked primary care and NHS hospital records from 1997 to 2014. *BMJ Open* 2018; **8**: e019146.

249 Foote J, Panchoo K, Blair P, Bannister G. Length of stay following primary total hip replacement. *Ann R Coll Surg Engl* 2009; **91**: 500–4.

250 Dall GF, Ohly NE, Ballantyne JA, Brenkel IJ. The influence of pre-operative factors on the length of in-patient stay following primary total hip replacement for osteoarthritis: A multivariate analysis of 2302 patients. *J Bone Jt Surg - Ser B* 2009; **91**: 434–40.

251 Wilson I, Bohm E, Lübbeke A, *et al.* Orthopaedic registries with patient-reported outcome measures. *EFORT Open Rev* 2019; **4**: 357–67.

252 Mednick RE, Alvi HM, Krishnan V, Lovecchio F, Manning DW. Factors Affecting Readmission Rates Following Primary Total Hip Arthroplasty. *J Bone Jt Surgery-American Vol* 2014; **96**: 1201–9.

253 Zmistowski B, Restrepo C, Hess J, Adibi D, Cangoz S, Parvizi J. Unplanned Readmission After Total Joint Arthroplasty. *J Bone Jt Surg* 2013; **95**: 1869–76.

254 Ayers DC, Fehring TK, Odum SM, Franklin PD. Using Joint Registry Data from FORCE-TJR to Improve the Accuracy of Risk-Adjustment Prediction Models for Thirty-Day Readmission After Total Hip Replacement and Total Knee Replacement. *J Bone Jt Surgery-American Vol* 2015; **97**: 668–71.

255 Voskuijl T, Hageman M, Ring D. Higher Charlson comorbidity index scores are associated with readmission after orthopaedic surgery. *Clin Orthop Relat Res* 2014; **472**: 1638–44.

256 Rosted E, Schultz M, Sanders S. Frailty and polypharmacy in elderly patients are associated with a high readmission risk. *Dan Med J* 2016; **63**: A5274.

257 Cooper Z, Rogers SO, Ngo L, *et al.* Comparison of Frailty Measures as Predictors of Outcomes After Orthopedic Surgery. *J Am Geriatr Soc* 2016; **64**: 2464–71.

258 Pugely AJ, Martin CT, Gao Y, Belatti DA, Callaghan JJ. Comorbidities in Patients Undergoing Total Knee Arthroplasty: Do They Influence Hospital Costs and Length of Stay? *Clin Orthop Relat Res* 2014; **472**: 3943–50.

259 El Bitar YF, Illingworth KD, Scaife SL, Horberg J V., Saleh KJ. Hospital Length of Stay following Primary Total Knee Arthroplasty: Data from the Nationwide Inpatient Sample Database. *J Arthroplasty* 2015; **30**: 1710–5.

260 McIsaac DI, Beaulé PE, Bryson GL, Van Walraven C. The impact of frailty on outcomes and healthcare resource usage after total joint arthroplasty. *Bone Joint J* 2016; **98-B**: 799–805.

261 Wang HT, Fafard J, Ahern S, Vendittoli P-A, Hebert P. Frailty as a predictor of hospital length of stay after elective total joint replacements in elderly patients. *BMC Musculoskelet Disord* 2018; **19**: 14.

262 Johnsen SP, Sørensen HT, Pedersen AB, Lucht U, Søballe K, Overgaard S. Patient-related predictors of implant failure after primary total hip replacement in the initial, short- and long-term: A nationwide Danish follow-up study including 36 984 patients. *J Bone Jt Surg - Br Vol* 2006; **88**: 1303–8.

263 Geneva Joint Arthroplasty Registry. Geneva Joint Arthroplasty Registry: Annual Report. 2017; : Available on request: christophe.barea@hcuge.ch.

264 Swedish Hip Arthroplasty Register. The Swedish Hip Arthroplasty Register: Annual Report. 2020.

265 National Joint Registry. National Joint Registry for England, Wales, Northern Ireland and the Isle of Man: 14th Annual Report. 2017.

266 World Health Organization. WHO Surgical Safety Checklist. https://www.who.int/patientsafety/topics/safe-surgery/checklist/en/ (accessed Dec 6, 2020).

267 Cavalli L, Angehrn L, Schindler C, *et al.* Number of comorbidities and their impact on perioperative outcome and costs - a single centre cohort study. *Swiss Med Wkly* 2022; **152**: w30135.

268 Mouchti S, Whitehouse MR, Sayers A, Hunt LP, Macgregor A, Blom AW. The Association of Body Mass Index with Risk of Long-Term Revision and 90-Day Mortality Following Primary Total Hip Replacement: Findings from the National Joint Registry for England, Wales, Northern Ireland and the Isle of Man. *J Bone Joint Surg Am* 2018; **100**: 2140–52.

269 Jämsen E, Eskelinen A, Peltola M, Mäkelä K. High Early Failure Rate After Cementless Hip Replacement in the Octogenarian. *Clin Orthop Relat Res* 2014; **472**: 2779–89.

270 Meneghini RM, Elston AS, Chen AF, Kheir MM, Fehring TK, Springer BD. Direct Anterior Approach: Risk Factor for Early Femoral Failure of Cementless Total Hip Arthroplasty. *J Bone Jt Surg* 2017; **99**: 99–105.

271 Berry DJ. Joint registries: what can we learn in 2016. *Bone Joint J* 2017; **99-B**: 3–7.

272 Paxton EW, Mohaddes M, Laaksonen I, *et al.* Meta-analysis of individual registry results enhances international registry collaboration. *Acta Orthop* 2018; **89**: 369–73.

273 Paxton EW, Furnes O, Namba RS, Inacio MC, Fenstad AM, Havelin LI. Comparison of the Norwegian Knee Arthroplasty Register and a United States Arthroplasty Registry. *J Bone Jt Surgery-American Vol* 2011; **93**: 20–30.

274 Hughes RE, Batra A, Hallstrom BR. Arthroplasty registries around the world: valuable sources of hip implant revision risk data. *Curr Rev Musculoskelet Med* 2017; **10**: 240–52.

275 Springer BD, Cahue S, Etkin CD, Lewallen DG, McGrory BJ. Infection burden in total hip and knee arthroplasties: an international registry-based perspective. *Arthroplast Today* 2017; **3**: 137–40.

276 McGrory BJ, Etkin CD, Lewallen DG. Comparing contemporary revision burden among hip and knee joint replacement registries. *Arthroplast today* 2016; **2**: 83–6.

277 Franklin PD, Miozzari H, Christofilopoulos P, Hoffmeyer P, Ayers DC, Lübbeke A. Important patient characteristics differ prior to total knee arthroplasty and total hip arthroplasty between Switzerland and the United States. *BMC Musculoskelet Disord* 2017; **18**: 14.

278 Combescure C, Foucher Y, Jackson D. Meta-analysis of single-arm survival studies: a distribution-free approach for estimating summary survival curves with random effects. *Stat Med* 2014; **33**: 2521–37.

279 Jackson D, White IR, Thompson SG. Extending DerSimonian and Laird's methodology to perform multivariate random effects meta-analyses. *Stat Med* 2010; **29**: 1282–97.

280 Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003; **327**: 557–60.

281 Gasparrini A, Armstrong B, Kenward MG. Multivariate meta-analysis for non-linear and other multi-parameter associations. *Stat Med* 2012; **31**: 3821–39.

282 Hackett NJ, De Oliveira GS, Jain UK, Kim JYS. ASA class is a reliable independent predictor of medical complications and mortality following surgery. *Int J Surg* 2015; **18**: 184–90.

283 Visser A, Geboers B, Gouma DJ, Goslings JC, Ubbink DT. Predictors of surgical complications: A systematic review. *Surgery* 2015; **158**: 58–65.

284 Rauh MA, Krackow KA. In-hospital deaths following elective total joint arthroplasty. *Orthopedics* 2004; **27**: 407–11.

285 Jensen NL, Pedersen HS, Vestergaard M, Mercer SW, Glümer C, Prior A. The impact of socioeconomic status and multimorbidity on mortality: a population-based cohort study. *Clin Epidemiol* 2017; **9**: 279–89.

286 Organisation for Economic Co-operation and Development. OECD Health Data. 2017. http://dx.doi.org/10.1787/health-data-en.

287 Institute for Health Metrics and Evaluation. Global Buden of Disease. 2017. http://www.healthdata.org/gbd (accessed March 19, 2019).

288 Wilper AP, Woolhandler S, Lasser KE, McCormick D, Bor DH, Himmelstein DU. Health Insurance and Mortality in US Adults. *Am J Public Health* 2009; **99**: 2289–95.

289 Woolhandler S, Himmelstein DU. The Relationship of Health Insurance and Mortality: Is Lack of Insurance Deadly? *Ann Intern Med* 2017; **167**: 424–31.

290 Kaiser Permanente National Implant Registries. https://national-implantregistries.kaiserpermanente.org/ (accessed Dec 4, 2021).

291 Arslan IG, Damen J, de Wilde M, *et al.* Estimating incidence and prevalence of hip osteoarthritis using electronic health records: a population-based cohort study. *Osteoarthr Cartil* 2022; **30**: 843–51.

292 Swain S, Coupland C, Strauss V, *et al.* Clustering of comorbidities and associated outcomes in people with osteoarthritis - A UK Clinical Practice Research Datalink study. *Osteoarthr Cartil* 2022; **30**: 702–13.