The access to and outcomes of elective hip and knee replacement surgery for patients with comorbidities: a study using PROMs and administrative data

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ABSTRACT

Background

Joint replacement surgery is one of the most cost-effective interventions leading to considerable improvements in function and quality of life. The rise in multimorbidity in the UK is leading to an increasing number of patients with long-term conditions (LTCs) undergoing joint replacement surgery. Financially stretched commissioners of health services are seeking to restrict access to routine elective surgery, including hip and knee replacements, despite a lack of evidence to support these decisions. It is therefore important to understand the factors that limit the safety and effectiveness of surgery and how LTCs might have an impact on access to and outcomes of joint replacement.

Methods

In this thesis, national patient-level datasets and both quantitative and qualitative research methods were used to investigate the access to and outcomes of hip and knee replacement surgery for patients with 11 different comorbidities. This involved three components: a literature review, methodological work, and empirical work. The literature review explored the outcomes for patients with different comorbidities. The methodological work assessed the agreement between patient-report and administrative data derived comorbidities. Finally, the empirical work explored the severity of joint problems before surgery and the safety and effectiveness outcomes for patients with comorbidities. Semi-structured interviews with healthcare professionals that are involved in the referral and selection of patients for joint replacement surgery were undertaken to provide insight into the factors that influence the access to surgery for patients with comorbidities.

Results

The systematic review on outcomes to hip and knee replacement surgery showed that there was limited evidence of the impact of comorbidities on patient-reported outcomes related to effectiveness of joint replacement surgery. Patients with comorbidities reported more severe joint problems before surgery compared to patients without comorbidities, suggesting that patients with comorbidities may be undergoing hip and knee replacement surgery later in the course of their joint disease. This was further supported by the findings from the qualitative study that patients with comorbidities who were considered unsuitable for surgery were 'lost to the system' and left to self-manage their comorbidities before being reconsidered for joint replacement surgery. With regards to outcomes,

patients with comorbidities have a moderately increased risk of adverse outcomes after hip and knee replacement surgery but benefit almost to the same extent as patients without comorbidities. Patients with comorbidities reported only slightly smaller improvements in severity of joint problems and no difference in quality of life after surgery compared to patients without comorbidities. Patients with multiple comorbidities (two or more comorbidities) reported more severe joint problems before surgery and a slightly higher increased risk of adverse outcomes but nevertheless benefitted considerably from the surgery.

Conclusions

This thesis demonstrates that patients with comorbidities may experience inequalities in access to hip and knee replacement surgery even though they benefit almost as much as patients without comorbidities. This finding indicates that the restriction of access to joint replacement surgery based on the presence of comorbidities alone is difficult to justify considering the beneficial impact of the surgery on patients' lives.

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LIST OF ABBREVIATIONS

A&E	Accident and Emergency
AHRQ	Agency for Healthcare Research and Quality
BMI	Body Mass Index
CCI	Charlson Comorbidity Index
CCG	Clinical Commissioning Group
COPD	Chronic Obstructive Pulmonary Disease
ESP	Extended Scope Physiotherapist
EQ-5D	Euroquol 5- dimension
GP	General Practitioner
HES	Hospital Episodes Statistic
HRQoL	Health related quality of Life
ICD-10	International Classification of Diseases, Version 10
ICNARC	Intensive Care National Audit & Research Centre
LTC	Long-term condition
MID	Minimal Important Difference
MIC	Minimal Important Change
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
OKS	Oxford Knee Score
OHS	Oxford Hip Score
ONS	Office for National Statistics
OR	Odds ratio
PROMs	Patient Reported Outcome Measures
PSI	Patient Safety Indicator
WOMAC	Western Ontario and McMaster Universities Osteoarthritis Index
UK	United Kingdom

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1 INTRODUCTION

1.1 Rationale for investigating access and outcomes to hip and knee replacement surgery in patients with comorbidities

One of the biggest challenges currently facing the UK National Health Service (NHS) is the increase in the number of patients living with long-term conditions (LTCs) [1]. Elective hip and knee replacement surgery is one of the most common and effective surgeries and it is increasingly being used [2]. More and more patients undergoing hip and knee replacement surgery have LTCs. In a previous study of hip and knee replacement surgery patients in England, more than 60% of patients for these operations reported at least one LTC [3]. This number is expected to continue to rise as the number of people living with multiple LTCs is on the increase [4].

In the UK, the NHS was founded on the principle of equity in access to care. However, evidence shows that there are inequities in provision and utilisation of health services. Research has demonstrated that such inequities in healthcare provision include major surgical interventions such as cardiac surgery, liver transplantations and joint replacement [5]. The focus of research has been on sociodemographic characteristics such as age, gender, ethnicity and socioeconomic status and studies have shown these characteristics have an important impact on the likelihood of receiving surgery [6-10].

Furthermore, there are indications that access to elective surgery, such as hip and knee replacement surgery, is being restricted by commissioners of health services in a bid to cut spending budgets [11]. This could introduce inequalities in access, specifically disadvantaging patients with comorbidities and thereby may be creating inequities. For example, some Clinical Commissioning Groups (CCGs) have restricted access to elective surgery by imposing minimum eligibility criteria for severity of preoperative function [12] and pain [11], smoking status [13], the requirement that a patient's body mass index (BMI) is lower than 30kg/m^2 [14, 15] and the optimisation of pre-existing comorbidities [16]. However, there is no clinical or economic justification for any of these eligibility criterion [17, 18] and they are not supported by the National Institute for Health and Care Excellence (NICE) clinical guidelines [19].

Commissioners assume that for patients with a high BMI, surgery is less safe and effective [20, 21]. High BMI and obesity however rarely come as an isolated diagnosis and are often accompanied by other LTCs (e.g. diabetes, heart disease) that are considered to increase the risk of surgical complications after surgery [22]. For example, diabetes is considered to be a risk factor for surgical site infections after surgery [23]. Little is known however about the impact of a variety of specific LTCs on the safety and effectiveness of elective surgery.

This thesis will seek to fill this gap in the literature and focus on hip and knee replacement surgery as the healthcare resource of interest. In England, Patient Reported Outcome Measures (PROMs) survey data have been collected since 2009 for four elective surgeries: knee replacement surgery, hip replacement surgery, varicose vein surgery and hernia repair. PROMs data provide an opportunity to explore and evaluate differences in access to (focusing on patient-reported severity and duration of joint problems just before surgery) and outcomes of elective surgery. PROMs data has previously been used to assess the impact of socioeconomic status on severity and duration of joint problems before surgery [9, 24]. Joint replacement surgery, the replacement of the articulating surfaces of the hip or knee joint, is an ideal condition to choose to study evidence of inequalities in healthcare. Its provision is widely used as an indicator of equity because it is a common procedure with about 87 000 primary hip replacements and about 98 000 primary knee replacements conducted in the year 2015/16 in the UK alone [25], but also because it leads to big improvements in health-related quality of life (HRQoL) [26-28].

To determine whether there are any inequalities in provision, it is necessary to compare patterns of service provision relative to clinical need, however this is difficult as the data on the latter are not routinely available. I therefore relied on data on patients having surgery to make inferences about access to joint replacement surgery for people with different LTCs. The NHS provides a unique opportunity to investigate variation in healthcare and utilisation because of the data it collects routinely about hospital activity [29]. These administrative datasets have traditionally been used for health service planning, commissioning and performance management. It has now been recognised that they are a valuable source of data for health service research [30]. I used these administrative datasets to explore the variation in patient-reported health prior to hip or knee replacement surgery and describe the extent to which comorbidities explain observed variation in access to and outcomes for patients with and without different LTCs.

1.2 Defining terms

The next section will define the two main terms that will be used throughout the thesis: access and long-term condition/comorbidity.

1.2.1 Access

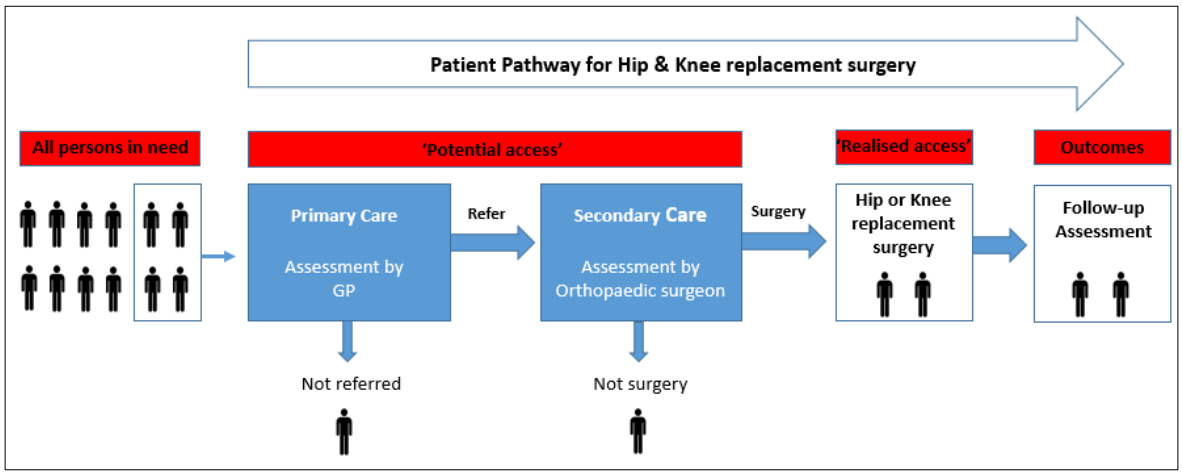
Access to healthcare has long been a term that is difficult to define and interpret. Whilst various indicators of access have been considered including availability of services and consumer satisfaction, it is very difficult to observe access directly [31]. The choice of approach to measuring access is commonly dictated by the data that is available. Direct approaches to measuring access involve collecting data directly from healthcare users' on access problems via large expensive surveys. As a result, the most common methodological approach is to measure access indirectly using the population standard approach. The population standard approach uses utilisation of health services data, rate at which services are actually used, to compare use relative to need [32]. Utilisation measures, for example, include the number of contacts with the General Practitioner (GP) and the rate of hip and knee replacement surgery. Due to data on unmet need not being routinely available, utilisation data is usually used.

Using the terminology of Aday and Andersen, utilisation of health services reflects 'realised access' irrespective of 'potential access' [33]. 'Potential access' is influenced by the characteristics of the healthcare system (e.g. the distribution of medical resources and waiting times) and the characteristics of the population at risk (e.g. age, sex, ethnicity and perceptions of health and illness) [33]. In other words, variation in utilisation reflects variation in 'realised access' and this variation may be directly influenced by the characteristics of the healthcare system or the patient population at risk.

If I apply this to the patient pathway to joint replacement surgery, one can initially recognise a population of patients who are in need of joint replacement surgery (see Figure 1). A proportion of these patients will go to their GPs for their hip and knee pain and will have 'potential access' to joint replacement surgery. At this point, patients may not be referred on because their GP considers that their joint problems are not severe enough and can be managed in primary care or the patients do not want to be referred. For those patients who are referred to secondary care, patients again may not be selected for surgery either because the surgeon does not consider the patient suitable for surgery or the patient

is unwilling to undergo surgery. Only those who undergo the hip or knee replacement surgery will have 'realised' their access.

Figure 1 – 'Realised access' in hip and knee replacement surgery



This study will use utilisation data on patients who have undergone hip and knee replacement surgery to determine if there are any inequalities in 'realised access' for patients with comorbidities compared to patients without comorbidities. In applied health research, inequality means a difference without any moral judgement. In contrast inequity, a subset of inequality, involves a judgement of what we think is avoidable and unfair [32]. It is important to further distinguish between the vertical and horizontal dimensions of equity: vertical equity refers to access according to variation in need whilst horizontal equity refers to equal access to healthcare for people in equal need [31]. Determining the presence of inequity in access is beyond the scope of this thesis. However, whether any inequalities suggest inequities, specifically in relation to the horizontal dimension of equity, is considered in the discussion section of this thesis.

1.2.2 LTCs and comorbidities

LTCs which may also be known as chronic diseases or noncommunicable diseases, will be defined using the World Health Organisation definition which is *"any disease that tends to be of long duration and is a result of a combination of genetic, physiological, environmental and behavioural factors"* [34].

In research studies, the burden of LTCs is denoted using the term 'comorbidities'. Several definitions have been suggested for comorbidity but all are based on a single core concept: the presence of more than one distinct condition in an individual [35]. In the case of this research, comorbidity will be used to convey the notion of burden of illness or disease in addition to the primary indication for surgery (i.e. osteoarthritis). Multiple comorbidities will be used to describe the extension of this, as having two or more comorbidities. Having multiple comorbidities adds a more complex dimension but to overcome this complexity this thesis used an approach based on counting of comorbidities (2, 3 and 4 or more comorbidities).

Table 1 – Summary of definitions of terms

Term	Definition
Long-term condition (policy)	Any disease that tends to be of long duration and is a result of a combination of genetic, physiological, environmental and behavioural factors
Comorbidity (research)	Presence of additional diseases in relation to an index disease (i.e. osteoarthritis) in one individual
Multiple comorbidities (research)	Presence of two or more additional diseases in relation to an index disease (i.e. osteoarthritis) in one individual

1.3 Long-term conditions

One of the biggest challenges currently facing the NHS is the increase in the number of patients living with LTCs. Estimates from 2010 suggest that around 15 million people in England have at least one LTC [1]. Increasingly patients are also living with multiple LTCs, also known as multimorbidity [36]. This increase will likely have an important impact on healthcare utilisation. Patients with LTCs are users of all parts of the health system including community services, urgent and emergency care and acute services. They have been shown to account for at least 50% of GP appointments, outpatient appointments and inpatient bed days [1]. It is therefore important to measure accurately the presence of LTCs to quantify their impact on access to health interventions, to quantify the outcomes of such interventions, and to show the implications this has for the organisation and delivery of healthcare services that provide support for patients with LTCs.

1.3.1 Identifying patients with LTCs in epidemiological research

In epidemiology, the occurrence of comorbidity needs to be measured for multiple reasons. Firstly, to account for confounding of comorbidities and secondly to understand how comorbidity interacts with the outcome [37]. Data on comorbidities can be collected by directly interviewing patients, by patients self-reporting (patient-report), by reviewing medical records, or by extraction from administrative databases [38]. This study focused on comorbidities derived from administrative data and patient-report.

1.3.1.1 Administrative data-derived comorbidities

Administrative datasets are often large in size and used for administrative purposes in health, including reimbursement for health services or for insurance payments. In England, the Hospital Episode Statistics (HES) dataset is the administrative data that is used to reimburse NHS providers. Due to the complexity of these large databases, comorbidity indices have been developed to identify comorbidities and quantify their impact on the outcome. Comorbidities indices are a means to categorise comorbidities and the most widely used indices are based on the *International Classification of Disease* (ICD) diagnosis codes that are used in administrative data to record diagnoses.

The most commonly used comorbidity indices are the Charlson Comorbidity Index (CCI) and the Elixhauser comorbidity indices. Each comorbidity index includes different comorbidities. Each comorbidity index was also originally developed to predict a certain outcome such as 1-year mortality (CCI), length of stay, hospital charges or in-hospital mortality (Elixhauser). The majority of the studies comparing different comorbidity indices were carried out in the United States and in Canada using Medicare and Medicaid data and show that comorbidity indices vary in their predictive ability [39-41].

Due to the variability in the comorbidities included in the indices, and the outcomes they were developed to predict, researchers have been forced to modify these indices so they are more suitable to the study population they are interested in. As a result, there are many modifications of the Charlson and Elixhauser comorbidity indices (see Appendix H for more detail on different comorbidity indices).

1.3.1.2 Patient-reported comorbidities

Patient-report is an attractive alternative source of data on comorbidities to chart review and administrative data. This is because it engages the patient in their healthcare and is thought to encourage patient-centred care. Questionnaire studies are very resource-intensive to deliver however and are therefore more expensive than using already existing administrative data.

Several measures have been developed to assist the patient with objectively reporting their medical history such as the *Self-Administered Comorbidity* questionnaire, which uses not only the patient's own report of conditions but also the symptoms and their severity to be able to characterise total disease burden without depending on a current diagnosis [42]. This questionnaire has been shown to have a modest relationship with widely used medical-record-based comorbidity instruments [43].

In England, the *Patient-Reported Outcome Measures (PROMs)* questionnaire asks patients if they have ever been told by a doctor whether they had any of 12 comorbidities (see Box 1). The PROMs survey comorbidity categories were originally chosen based on the work of Bayliss et al [44]. Bayliss et al searched the literature to determine the health conditions that were most frequently assessed in measuring comorbidity and then subsequently pre-tested the instrument for clarity with patients [44].

Box 1: PROMS questionnaire comorbidities

In the PROMs pre-operative questionnaire patients were asked: "Have you ever been told by a doctor that you have any of the following conditions?"

- Heart disease (for example angina, heart attack or heart failure)
- High blood pressure
- Problems caused by stroke
- Leg pain when walking due to poor circulation
- Lung disease (for example asthma, chronic bronchitis or emphysema)
- Diabetes
- Kidney disease
- Diseases of the nervous system (for example, Parkinson's disease or multiple sclerosis)
- Liver disease
- Cancer (within the last 5 years)
- Depression

There are concerns however, that patients cannot report their comorbidities accurately due to recall bias. These scores derived from patient-reported data have therefore been validated against comorbidity indices calculated from administrative data. Several studies have specifically compared the performance of a CCI adaptation derived from patient-reported data with the same index derived from administrative data or chart review. They found that patient-reported data and administrative data adaptations had similar ability to predict various outcomes [45, 46]. Several studies have shown that patients can accurately and reliably report certain medical conditions although levels of agreement (as measured by the kappa statistics and sensitivity) varied significantly [42, 47, 48].

1.4 Factors determining access to hip and knee replacement surgery

A wide variation in the access to hip and knee replacement surgery has been reported and there are many possible reasons for this variation. These include differences in severity of joint problems, and a variety of patient-related factors such as age, socioeconomic deprivation and patients' willingness to undergo surgery. Other factors include differences in health-system related factors and differences in medical-professional related factors [49, 50]. This variation may have led to underutilisation in some areas and overutilisation in others which can lead to poor or even harmful care for some patients [51, 52].

1.4.1 Severity of joint problems

One of the main determinants of a patient's decision to undergo surgery and an orthopaedic surgeon to select a patients for surgery is the severity of the joint problem [53]. In end-stage osteoarthritis, patients reporting lower ability to function and more pain have been shown to be more likely to undergo knee replacement and hip replacement [54]. Specific problems such as getting up from a chair, climbing up stairs and walking difficulties predicted undergoing knee replacement within two years [55]. Pain however is the single most important influential factors in the decision to undergo hip or knee replacement [56]. Patients reporting worse severity of joint problems (as measured by the WOMAC score) as well as HRQoL were more likely to undergo joint replacement surgery [57].

1.4.2 Patient-related factors

Evidence suggests that patient-related factors have a large impact on the use of hip and knee replacement surgery in the UK and other countries. These include factors such as age, gender, ethnicity, socioeconomic status and patients' willingness to undergo surgery.

One of the simplest indicators of need is age. This is particularly true for LTCs whose prevalence increases with age. The primary indication for total hip or knee replacement is osteoarthritis (>90% of patients). Osteoarthritis, a progressive degeneration of the articular cartilage, is most common in elderly populations [58]. Osteoarthritis increases with age, with projections showing that ageing alone will lead to the population with osteoarthritis increasing by 50% over the next two decades [59]. Recently there has also been an increasing number of younger patients (<65 years) undergoing knee replacement surgery and a study found that this cannot be fully explained by variations in clinical decision-making [60].

Previous studies have reported that gender plays a role in the use of surgery. In both Canada and the UK, the GP is less likely to refer women to surgeons [7, 61] and this is despite reports that women have worse pain and disability than men just before surgery [24, 27, 62]. Studies have shown that the gender of the patient also affects the health professionals' treatment recommendations [6, 63]. Researchers have suggested this is likely to be a result of an unconscious gender bias already pervasive in society and healthcare professional hearing from other health professionals that women don't benefit as much as men from knee replacement surgery. Furthermore, this inappropriate preconception may be because women are more risk averse and therefore usually receive surgery at a more advanced stage of disease than men [64, 65].

Studies have also found that there are ethnic disparities in the provision of hip and knee replacement surgery. In a large-scale study using Medicare data in 1991 the use of knee replacement surgery was 36% lower for patients from a Black ethnic background compared to a White ethnic background and this difference persisted over an 18-year study period. In 2008, it was 40% lower for patients with Black ethnic backgrounds compared to White ethnic backgrounds [66]. Another study in the UK found that symptoms also tended to be more severe and of a longer duration in patients from South Asian and Black ethnic backgrounds than in patients from White ethnic background just before surgery [67].

Studies have found that there is an under-provision of surgery in socioeconomically deprived areas, compared to estimates of the need for surgery [68-74]. A study found that more socioeconomically disadvantaged patient groups are less likely to undergo primary total hip replacement than more affluent groups [75]. This may be in part due to the differences in patients' perceptions, preferences for care and differences in their expectations of a positive outcome of surgery. Another possible reason is that socioeconomically deprived people generally have worse health, often have several LTCs and therefore may be considered inappropriate candidates for surgery [76].

Patient's willingness to undergo surgery also plays a role in the access to surgery. A number of studies have reported differences in patient preferences and expectations for joint replacement surgery according to sex, ethnic group and socioeconomic status [77-79]. Some patients may decide not to want a major surgery which requires a long recovery period. In particular, some elderly people may prefer to manage the pain and to live with limited mobility [80]. Similarly, more socioeconomically deprived people are thought to be more willing to accept chronic pain and functional limitations before seeking help or having surgery [81].

1.4.3 Health system-related factors

Another possible reason for the observed disparity in access is the differences in regional availability of orthopaedic surgeons in a rapidly ageing population with the concomitant increase in rates of joint replacement surgery. The suggested optimal provision of orthopaedic surgeons for the UK is 4-6.7 FTE per 100,000 but the actual figure, 3 surgeons per 100,000 for the UK falls well below this [82, 83]. In a study of access to primary care practitioners and orthopaedic surgeons in Canada the findings suggest that in areas with fewer available orthopaedic surgeons patients were less likely to have an orthopaedic consultation and less likely to receive surgery [84].

1.4.4 Medical-professional related factors

Disparities in access to hip and knee replacement surgery can occur at several points in the patient's trajectory from access to referring health professionals and referral to orthopaedic surgeons through to entering the waiting list for surgery and subsequent progression along this list. In general, differences in access to surgery appears more likely

to occur at the referring health professional stage due to a variation in clinical decision-making.

Specifically, research has suggested the variation is due to the clinical indication criteria used when referring or selecting patients for surgery [85-87]. In most countries, the indication criteria for total knee replacement and total hip replacement surgery are not clearly defined or evidence-based [88]. For example, in a study of 15 hospitals in Spain, the researchers estimated that as many as 25% of the knee replacement and hip replacement could be considered inappropriate [89]. A lack of consensus will lead to disparities in the provision of joint replacement surgery.

In many countries, GPs act as gatekeepers for referral to hip replacement surgery and studies have found that GPs and orthopaedic surgeons do not have the same views on who should have joint replacement surgery. In a multi-centred survey study of 304 orthopaedic surgeons and 314 referring practitioners across 12 European countries, the study found that the latter think that patients need to have more severe symptoms to offer surgery than do the surgeons. In addition, referring physicians were more likely to associate age and obesity with a less favourable outcome than the orthopaedic surgeons [90]. The referring physicians may therefore be holding back patients who might have been offered surgery, had they consulted an orthopaedic surgeon [85].

There is also evidence of wide variation in orthopaedic surgeons' indications for total joint replacement and that comorbidities play a role in the selection of patients for surgery [91, 92]. In 1996, a study carried out a postal survey of orthopaedic surgeons in which the surgeons reported no consensus but agreed that the key indication for knee replacement surgery was severe daily pain. A patient's willingness to undergo surgery and motivation to improve was also reported as a common reason for proceeding with surgery. Comorbidities however was given as a reason for avoiding recommendation for surgery [91]. Similarly, in a qualitative study with four surgeons and two Extended Scope Physiotherapists (ESPs) in England, intermediate care professionals that work in musculoskeletal assessment centres, one of the key indicators for referral or selection for surgery, was the presence or absence of comorbidity. Comorbidities were considered when assessing whether a hip replacement would be a worthwhile investment for the patient [93]. Another study found that after adjustment for confounders the deciding indications

for the surgeon's decisions were the presence or absence of severe cardiovascular disease and the SF-36 (HRQoL) physical score [92].

1.5 Outcomes after hip and knee replacement surgery

The three pillars of quality in healthcare are thought to be patient safety clinical effectiveness and patient experience [94]. In this thesis, the approach to measuring outcomes was to look at all of the domains of quality of healthcare that reflect outcomes of the care received. Due to data on patient experience being unavailable, the focus was therefore on outcomes relating to patient safety and clinical effectiveness after hip or knee replacement surgery. To ensure the patient perspective was captured the focus was on investigating patient-reported outcomes.

Outcomes after hip and knee replacement have been improving over the last few decades. Hip and knee replacement surgery now offers considerable improvement in function and HRQoL in patients suffering with osteoarthritis or inflammatory arthritis [95-98]. In 2014, of the 76 576 PROMs hip replacements and 79 769 knee replacement that were performed in England, over 80% showed improvements in function and HRQoL [99]. Despite the success of joint replacement surgery and the reduction in mortality, a small number of patients continue to have surgical complications, pain and in some cases no improvement in function after surgery [100].

1.5.1 Patient safety outcomes

In this thesis, patient safety outcomes refers to outcomes that measure the risk of short-term (<90 days) adverse outcomes after surgery related to the exposure to medical care. These include: surgical complications, short-term mortality, readmissions and length of stay (LOS) [101].

1.5.1.1 Surgical complications

Surgical complications after total knee replacement are rare. For example, infective complications of the prosthesis occurs in 1-3% of patients undergoing hip and knee arthroplasty [102]. If they do occur they can lead to significant patient morbidity and cost to the healthcare system [102]. As with other major surgery, complications may occur, and

these include anaesthesia-related risks, exacerbating comorbidities such as a myocardial infarction, infections, medication and allergic reactions and venous thromboembolism [103].

1.5.1.2 Short-term mortality

All surgery carries risk of some kind, including death. In England and Wales, the risk of death in the 90 days following hip replacement surgery is less than 1% and is lower than in the age and sex matched population [104]. In a systematic review of 32 studies published between 2003 and 2013 looking at 30-day or 90-day mortality following hip replacement, the estimated incidence of mortality during the first 30 days was 0.30% (95% CI 0.22 to 0.38) and 0.65% (95% CI 0.50 to 0.81) in the 90 days following the surgery [105]. The risk factors for early mortality most commonly identified were increasing age, male gender and comorbidities, particularly cardiovascular disease. Cardiovascular complications appear to be the lead cause of death followed by embolism after hip replacement [105].

1.5.1.3 Readmissions

The 30-day or 90-day readmission rate after hip and knee replacement is commonly used as a surrogate measure of adverse outcomes such as surgical complications [106]. A large study in England looking at readmission rates over a 10-year period for patients undergoing hip and knee arthroplasty, found that readmissions rates have been decreasing [107]. Specifically, readmission rates decreased for patients with acute myocardial infarction, chronic obstructive pulmonary disease and heart failure, but increased for patients with pneumonia and diabetes [107]. The most common causes of readmissions have been shown to be infections and surgical complications such as venous thromboembolism [108].

1.5.1.4 Length of stay (LOS) in hospital

LOS in hospital following joint replacement surgery measured in days is a common outcome measure and a key outcome in the measure of the overall cost of the procedure. LOS has fallen substantially between 1997 and 2014 in England following joint replacement surgery [109]. In previous studies of hip and knee patients, prolonged LOS has been associated with advanced age [110], social deprivation [110], gender [111] and comorbidities [112]. Concerns have been reported however about the approach to

measuring LOS. Most studies on LOS after joint replacement are limited by small sample sizes and as such using mean LOS can be misleading [112]. In addition, it is difficult to ascertain what constitutes prolonged LOS as a previous study found that some measures of prolonged LOS do not agree with coded complications [113].

1.5.2 Clinical effectiveness outcomes

In this thesis, *clinical effectiveness outcomes* refers to long-term outcomes (>90 days after surgery) that reflect the act of achieving optimum process and outcomes of healthcare services for patients. These include patient-reported outcome measures such as function, pain, HRQoL, patient satisfaction with the outcome as well as the likelihood of revision surgery.

1.5.2.1 Patient-reported outcome measures (PROMs)

PROMs, such as disease-specific and general quality of life measures, are new tools which have been proposed to strengthen patient engagement and enable patient-centred care [114]. PROMs were initially developed in clinical trials to measure people's subjective health and HRQoL and are now used widely to measure the performance and quality of healthcare services.

There are challenges to using PROMs data to measure outcomes for patients with comorbidities however. There is a general assumption that the impact of comorbidities is not captured by these PROMs such as disease-specific measures like the Oxford Hip (OHS) or Knee (OKS) Score. This notion is not properly understood so must be further explored.

1.5.2.1.1 Hip or knee function

The main aim of hip and knee replacement surgery is to improve hip or knee function and it has been effective in doing so. Hip and knee function is commonly measured using disease-specific quality of life measures such as the OHS/OKS and the WOMAC score. In a literature review of 62 studies published between 1995 and 2003 looking at the function and HRQoL after joint replacement it was found that hip and knee replacement leads to significantly improved function. This benefit was perceived as greater by healthcare professionals than by patients [115]. In a European collaborative study of 1327 patients with total hip replacement, it was found that, despite hip replacement being effective in

the majority of cases, between 14% and 36% of patients reported no improvement or being worse 12 months after surgery [116]. Factors such as age and socioeconomic status have been found to have an impact on the improvement in function reported by patients after total joint replacement surgery. A study looking at a sample of 121 893 patients in England, found that patients living in socioeconomically deprived areas reported less improvements in function after surgery due to differences in overall health and joint disease severity than patients from more affluent areas [9].

1.5.2.1.2 Pain

Alongside function, pain is also measured when using patient-reported disease-specific outcome measures. Despite the significant improvements in function, patients continue to report pain after total joint replacement and reports of persistent pain are not uncommon [117, 118]. In an in-depth interview study with 10 patients 6-months after their joint replacement surgery, 8 out of these 10 patients still experienced pain and mobility issues [117]. In a systematic review of 14 articles published up until January 2011 investigating the proportion of patients reporting long-term pain after hip or knee replacement for osteoarthritis the best quality studies reported 9% of patients after hip replacement and about 20% of patients after knee replacement reported long-term pain after surgery [118].

1.5.2.1.3 Health related quality of life (HRQoL)

Linked to the aim to improve hip and knee function is the aim to improve the HRQoL of patients with hip or knee pain. A large systematic review of 74 prospective cohort studies published between 1980 and 2003 concluded that total hip and knee arthroplasties were effective in improving HRQoL [119]. Another study looking at overall improvement in HRQoL after knee replacement surgery found an overall improvement which seemed to continue six months after the procedure [120]. The main predictors of improved HRQoL were function, pain, patient satisfaction, better quality of sleep and adequate social and familial support after surgery. The factors that predicted poor improvements in HRQoL were obesity, advanced age, comorbidities, persistence of pain after the procedure and waiting a long time for the operation [120].

1.5.2.1.4 Patient satisfaction with the outcomes

An additional aspect of patients' perception of the impact of their surgery is their level of satisfaction with the outcome of the surgery. Research has predominantly focused on satisfaction with the processes of care rather than patients' satisfaction with their condition and the outcome of their treatment [121]. The most common causes of dissatisfaction include pain and limited function and poor recovery after surgery. The possible determinants of dissatisfaction that have been explored include age, gender, patient's expectations and comorbidities [122]. There is little consensus on the impact of age and gender as predictors of dissatisfaction. A patient's expectations however has found to be the strongest predictor of dissatisfaction suggesting managing patients' expectations before surgery is important [123, 124]. Comorbidities have also been found to have an impact on satisfaction. Patients with depression have been shown to be more dissatisfied with their surgery although conflicting findings have been reported [125, 126].

1.5.2.2 Revisions

Hip and knee replacements may require revision surgery in both the short-term and the long-term. The rate of revisions in the first couple of years following hip and knee replacement surgery remain low. A study in England found that in the first three years of surgery only about one in 75 patients needed a revision of their joint replacement [127]. The risk factors for short-term implant failures include age, high comorbidity score, an uncemented prosthesis as well as complications (e.g. infections) [128]. Hip and knee prostheses however, do not continue to function effectively for the lifetime of patients. Implants are likely to require revision surgery after 20 years of use due to wear and prosthetic loosening with a 20-year implant survival rate of 85% for hip replacement and 89.7% for knee replacement [129]. As a consequence, surgery is recommended to be avoided in younger patients [130, 131].

In a systematic review of 86 papers published between 2000 and 2010, factors found to be associated with revision included younger age, greater comorbidity, fewer surgeons available, and, anatomically, the femoral head size. Men also had a higher rate of revisions due to aseptic loosening (the failure of the bond between bone and hip or knee implant) and post-operative infection. Longer operating time was associated with revision due to the higher risk of infection. Smaller femoral head size was associated with revision due to an increased risk of dislocation [132].

2 RESEARCH DESIGN OVERVIEW

To determine if there were any inequalities in access to and outcomes of hip and knee replacement surgery, literature review, administrative data analysis, and qualitative methods were used. First, a literature review of published articles on access to and outcomes of hip and knee replacement surgery for patients with comorbidities was conducted. In parallel, a qualitative study was conducted to explore the complexity of the patient pathway to access hip and knee replacement surgery for patients with comorbidities. Administrative data along with patient-reported data were used to quantitatively assess the variation in access and outcomes related to both safety and effectiveness of hip and knee replacement surgery.

This chapter gives an overview of the research design. Further detail of the methods for each study can be found in each of the individual chapters.

2.1 Aims and objectives

The overall aim of this research was to use both administrative and patient-reported data and qualitative study to assess the impact of comorbidities on access to and safety and effectiveness outcomes of hip and knee replacement surgery for patients with comorbidities.

The specific objectives were:

Objective 1 (RP1): To conduct a systematic review of the literature on access to and outcomes of hip and knee replacement surgery for patients with different comorbidities.

Objective 2 (RP2): To conduct a qualitative study to understand the barriers to and facilitators for accessing elective hip and knee replacement surgery for patients with comorbidities.

Objective 3 (RP3): To investigate how comorbidities reported by patients agree with comorbidities recorded in administrative datasets.

Objective 4 (RP4): To investigate the variation in access to hip and knee replacement surgery for patients with different comorbidities.

Objective 5 (RP5): To investigate the variation in outcomes related to the safety of hip and knee replacement surgery for patients with different comorbidities.

Objective 6 (RP6): To investigate the variation in outcomes related to the effectiveness of hip and knee replacement surgery for patients with different comorbidities.

The outputs of this research are in the form of six **research papers (RP1-6)** which are expected to provide further understanding of the variation in access to and outcomes for patients with comorbidities and the implications this has for further organisation and delivery of healthcare services to support this group of patients.

2.2 Data sources

This section gives an overview of the data sources used in each study of this programme of research.

Existing published research (RP1)

A literature review on the outcomes of hip and knee replacement for patients with 11 different comorbidities was conducted. Three databases, Medline, Embase and CINAHL Plus, were searched for all relevant papers in the English language up until May 2017 that compared the outcomes of hip and knee replacement surgery between patients with and without comorbidities. Search terms for hip and knee replacement were combined with search terms for health outcomes and search terms for 11 common comorbid conditions: heart disease, high blood pressure, stroke, leg pain due to poor circulation, lung disease, diabetes, kidney disease, diseases of the nervous system, liver disease, cancer and depression. 14 894 studies were identified through this search (after deduplication) and 70 studies were eligible for inclusion.

Semi-structured interviews (RP2)

20 healthcare professionals along the orthopaedic referral pathway (orthopaedic surgeons, GPs and intermediate care professionals) were interviewed to understand the impact of comorbidities on the referral and selection for joint replacement surgery. Orthopaedic surgeons were selected from a list of all orthopaedic surgeons specialising in hip or knee replacements in the NIHR CLAHRC North Thames (North Central and East London, Essex and Hertfordshire) area. Consultant orthopaedic surgeons (senior surgeons who have completed all their specialist training) were contacted via email. GPs were recruited

through the local teaching networks using snowballing techniques from a sample of GP practices across the NIHR CLAHRC North Thames area. Intermediate care professionals were recruited, using snowballing techniques, from intermediate services used by GPs and surgeons who had been interviewed. The interviews were recorded and then transcribed.

Datasets (RP3-6)

The three datasets used were Patient Reported Outcome Measures (PROMs) data, Hospital Episode Statistics (HES) and Office for National Statistics (ONS) mortality data. Further detail on the data linkage and data cleaning is available in Appendix J.

1. PROMs dataset

In England, PROMs data have been collected before and after four elective surgeries since 2009. The ones currently in use are for knee replacement surgery, hip replacement surgery, varicose vein surgery and hernia repair. Patients complete a questionnaire before their operation either at the preoperative assessment clinic or on admission to hospital (Q1). They are then sent a questionnaire six months (3 months for varicose vein surgery and hernia repair) after surgery (Q2). The questionnaires include both a disease-specific instrument, a generic instrument and additional questions about the patients' health, symptoms and experience. This dataset provides a new opportunity to explore and monitor variation in access and outcomes of elective surgery between groups.

2. HES Admitted Patient Care dataset

The HES database has been in existence since 1989 and records all patients currently admitted to NHS hospitals in England. It includes several separate datasets which cover hospital admissions, outpatient appointments, and A&E attendances in NHS hospitals. The data includes records of diagnoses and procedures during a patients stay in hospital and it is predominantly used to reimburse hospitals for the care they deliver. In this programme of work, only the HES Admitted Patient Care dataset was used.

The unit of care in HES data is a single consultant episode of care (the total time a patient spends under the care of an individual consultant). The dataset, therefore, a large

collection of separate unique records of these episodes. A record can include data on diagnoses and operations, hospital site where the patients was admitted, patient characteristics, administrative information such as time waited, admission and discharge methods, and geographical information of where the patient lives.

3. ONS mortality dataset

ONS mortality data is a database of all deaths registered in England and Wales broken down by age, sex and cause of death.

2.2.1 Dataset linkage (RP3-6)

The programme of research required linkage of all three datasets: HES Admitted Patient Care data, PROMs data and ONS mortality data. PROMs data were linked with the corresponding HES episode for the hip or knee replacement procedure, historical and subsequent HES episodes (from 2003/04 to current) and ONS mortality data. Linkage to historical HES episodes was required to identify comorbidities recorded in HES and compare these with comorbidities reported in the pre-operative PROMs questionnaires. Linkage to subsequent HES episodes and ONS mortality data is required to identify patient outcomes following surgery (see further detail in Appendix J).

The study population consist of patients who have undergone hip or knee replacement surgery and who have participated in the PROMs programme from April 2009 (programme start date) to November 2016. Patients were excluded if they do not have a linked HES episode for their PROMs procedure.

Table 2 – Datasets used in RP3-6

Research paper	Datasets used
RP3 - Identifying comorbidities	- HES Admitted Patient Care data - Pre-operative (Q1) PROMs data
RP4 - Access	- HES Admitted Patient Care data - Pre-operative (Q1) PROMs data
RP5 - Safety	- HES Admitted Patient Care data - Pre-operative (Q1) PROMs data - ONS mortality data
RP6 - Effectiveness	- HES Admitted Patient Care data - Post-operative (Q2) PROMs data

2.3 Study Design

This section provides a summary of the research design used in each chapter of the thesis. All studies described achieved their specific research objectives outlined above and have been presented in the form of six research papers (RP1-6). At the time of submission, two papers have been published, one is under review while three are in preparation for submission.

RP1: "Impact of comorbid conditions on outcomes of hip and knee replacement surgery: a systematic review and meta-analysis."

See Chapter 3, Pages 37-48

The **first** research paper (objective 1) was a systematic review and meta-analysis of published literature on 10 short-term and long-term outcomes after hip and knee replacement for patients with 11 different comorbidities. This involved the grouping of heterogeneous studies as definitions of outcomes and comorbidities varied. To make the results comparable and to be able to conduct any form of meta-analysis, some comorbid conditions were grouped together, outcomes were categorised as short and long-term, and continuous outcomes were converted to odds ratio using the Hasselblad and Hedges approach. The systematic review was intended to inform the quantitative components, and understand the outcomes that were commonly measured after hip and knee replacement surgery. The output of this study was a published research paper which is presented in chapter 3.

RP2: "Comorbidities and the referral pathway to access joint replacement surgery: An exploratory qualitative study"

See Chapter 4, Pages 52-59

The **second** research paper (objective 2) was a qualitative study exploring the referral and selection of patients with comorbidities for hip and knee replacement surgery. It involved interviews with healthcare professional along the referral pathway to joint replacement surgery. There was an endeavour to recruit a variety of different professionals including both men and women with a range of years of experiences and from both urban and rural settings. This qualitative study and the quantitative investigation of access (RP4) were intended to be complimentary and to inform each other. The qualitative study informed

the interpretation of the quantitative results by providing insight into the health-system factors at the pathway level which may influence access. The output of this study was a published research paper which is presented in chapter 4.

RP3: "The agreement between chronic diseases reported by patients and derived from administrative data in patients undergoing joint arthroplasty"

See Chapter 5, Pages 63-81

The **third** research paper (objective 3) was a methodological study exploring the agreement between patient-reported and hospital administrative-data derived comorbidities. Sensitivity and specificity of 11 patient-reported comorbidities were estimated with hospital administrative data as the reference standard. The challenge was how to best interpret these measures of agreement. This study was essential to develop a measure of comorbidity that would identify the list of comorbidities that would form the basis of the analysis in the subsequent three results chapters. The results of the analysis have been presented as a research paper which has been submitted for publication.

RP4: "Patients with comorbidities have joint replacement surgery later in their joint disease based on patient-reported pain and functional status"

See Chapter 6, Pages 85-109

The **fourth** research paper (objective 4) analysed the impact of comorbidities on access to hip and knee replacement surgery by analysing differences in patient-reported pre-operative functional status, pain and duration of joint problems just before surgery. If there were differences in access, we might expect to see differences in the severity of joint problems and in duration of problems just before surgery. Linear regression analysis was conducted comparing patients with and without comorbidities (adjusted for relevant case-mix criteria). The challenge however, was how to account for the potential influence of comorbidities on the OHS/OKS score. Functional status and pain OHS/OKS scores were therefore investigated separately as pain is less likely to be influenced by comorbidities than functional status. The results of the analysis have been presented as a research paper which is in preparation for its submission.

RP5: "Impact of comorbidities on adverse outcomes after hip or knee arthroplasty: a study of 640 832 patients in England"

See Chapter 7, Pages 113-136

The **fifth** research paper (objective 5) explored the impact of comorbidities on a number of adverse outcomes that reflect safety of hip and knee replacement surgery. The literature on safety measures have predominantly focused on surgical complications and as result the focus was on health service use associated with adverse outcomes after surgery. Outcomes included mortality, emergency readmissions, transfers to another consultant and LOS. Due to a low number of events, and the number of outcomes explored, individual outcomes were combined into a composite measure. The challenge of using a composite measure was then how to draw meaningful conclusions. Logistic regression analysis was conducted comparing patients with and without comorbidities while adjusting for relevant case-mix criteria. The results of the analysis have been presented as a research paper, which is in preparation for submission for publication.

RP6: "The impact of comorbidities on the effectiveness of hip or knee replacement surgery: a national population-based study"

See Chapter 8, Pages 140-161

The **sixth** research paper (objective 6) explored the impact of comorbidities on the effectiveness of hip and knee replacement surgery. The challenge was what outcomes to choose that would reflect effectiveness. Primary outcomes related to effectiveness included severity of joint problems (OHS/OKS) and HRQoL (EQ-5D). Secondary outcomes included patient satisfaction with the results of the operation and overall improvement after hip or knee replacement surgery. Linear and logistic regression analysis was conducted comparing patients with and without comorbidities (adjusted for relevant case-mix criteria). The findings are presented as a research paper, which is in preparation for submission for publication.

2.4 Ethics

2.4.1 Quantitative component

Ethics approval from the Health Research Authority (HRA) Ethics Committee and the Confidentiality Advisory Group (CAG) was sought for the quantitative components. Ethics approval was sought because it was required as part of the data application to NHS Digital. Further approval, directly from ONS for mortality data, was also required because date-of-death data is sensitive and can, potentially, be used to identify an individual. PROMs data access itself did not require further ethics approval because the study population, as part of their participation in the PROMS programme, have explicitly consented for their data to be collected, used for research and linked to other data held by the NHS. All hospital admissions for patients undergoing hip and knee replacement surgery and who were participants in the PROMs programme included the request for consent, and while the data does not allow the patient to be identified, it was important to ensure adherence to confidentiality and data security.

The data were received, managed, stored and analysed at the Clinical Effectiveness Unit (an academic collaboration between the Department of Health Services Research & Policy at LSHTM and the Royal College of Surgeons (RCS) of England). The data were stored in a restricted access folder on a secure server at the RCS. Only the minimum data that was required to carry out the analyses was requested from NHS Digital.

Ethics Approval by the HRA Proportionate Review Sub-committee of the Wales REC 6 was granted on the 3 August 2016 (Reference: 211186). CAG approval was granted on 1 September 2016 (Reference: 16/CAG/0113). Ethics approval was also sought from the London School of Hygiene & Tropical Medicine ethics committee and granted on the 3 October 2016 (Reference: 11628) (see Appendix D for all approvals).

2.4.2 Qualitative component

NHS Ethics approval was also sought for the qualitative study at the same time as the quantitative study. This was because NHS staff might have been interviewed on NHS premises. One NHS Ethics application was submitted for both the quantitative and qualitative components.

All participants of the qualitative study were given all the information on the study and asked to sign a consent form before participating (see Appendix E and F). They were

reminded that they could opt out at any stage if they wished to. In addition, participants were assured that any quotes used from the transcripts would be reported anonymously.

The qualitative data were stored on the secure server at London School of Hygiene & Tropical Medicine (LSHTM). Interview recordings and transcripts were anonymised, given an identification number, were password protected and stored securely on computers at LSHTM. The recording device were wiped clean after transcription, and paper transcripts stored in locked secure boxes at LSHTM which were then destroyed following completion of the study. Consent forms were stored separately and only accessed by the research team.

2.5 Patient and Public Involvement

Prior to commencing this programme of research, the protocol was assessed for relevance and appropriateness by patient representatives on the National Institute for Health Research (NIHR) Collaboration for Leadership in Applied Health Research and Care (CLAHRC) North Thames Patient and Public Involvement committee. Their comments, which specifically related to the approach to recruitment of healthcare professionals to the qualitative study, the selection of outcomes that were relevant to patients as well as the interpretation of access, were incorporated in the protocol and guided further analysis.

3 RESULTS CHAPTER – Systematic Review

The first component of this programme of research was a systematic review and meta-analysis assessing the outcomes of elective hip and knee replacement surgery for patients with different comorbidities. The results have been presented in the form of a published research paper. The supplementary information referred to in the paper is available in Appendix C.

Title: Impact of comorbid conditions on outcomes of hip and knee replacement surgery: a systematic review and meta-analysis

The online PDF version can be accessed at:
https://bmjopen.bmj.com/content/8/7/e021784.info

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RESEARCH PAPER COVER SHEET

Please note that a cover sheet must be completed for each research paper included within a thesis.

SECTION A – Student Details

Student ID Number	LSH342490	**Title**	Ms
First Name(s)	BÉLÈNE		
Surname/Family Name	PODMORE		
Thesis Title	The access to and outcomes of elective hip and knee replacement surgery for patients with comorbidities: a study using PROMs and administrative data		
Primary Supervisor	Professor Jan van der Meulen		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

SECTION B – Paper already published

Where was the work published?	BMJ Open		
When was the work published?	11/07/18		
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion			
Have you retained the copyright for the work?*	**Yes**	Was the work subject to academic peer review?	**Yes**

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Where is the work intended to be published?	
Please list the paper's authors in the intended authorship order:	

Stage of publication	Choose an item.

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	I designed this study, undertook the analyis and wrote the first draft of the manuscript.

SECTION E

Student Signature	[redacted]
Date	23 November 2018

Supervisor Signature	[redacted]
Date	23 November 2018

3.1 Research Paper 1 (RP1)

Open access Research

BMJ Open

Impact of comorbid conditions on outcomes of hip and knee replacement surgery: a systematic review and meta-analysis

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ABSTRACT

Objective To systematically perform a meta-analysis of the association between different comorbid conditions on safety (short-term outcomes) and effectiveness (long-term outcomes) in patients undergoing hip and knee replacement surgery.

Design Systematic review and meta-analysis.

Methods Medline, Embase and CINAHL Plus were searched up to May 2017. We included all studies that reported data to allow the calculation of a pooled OR for the impact of 11 comorbid conditions on 10 outcomes (including surgical complications, readmissions, mortality, function, health-related quality of life, pain and revision surgery). The quality of included studies was assessed using a modified Newcastle-Ottawa Scale. Continuous outcomes were converted to ORs using the Hasselblad and Hedges approach. Results were combined using a random-effects meta-analysis.

Outcomes The primary outcome was the adjusted OR for the impact of each 11 comorbid condition on each of the 10 outcomes compared with patients without the comorbid condition. Where the adjusted OR was not available the secondary outcome was the crude OR.

Results 70 studies were included with 16 (23%) reporting on at least 100 000 patients and 9 (13%) were of high quality. We found that comorbidities increased the short-term risk of hospital readmissions (8 of 11 conditions) and mortality (8 of 11 conditions). The impact on surgical complications was inconsistent across comorbid conditions. In the long term, comorbid conditions increased the risk of revision surgery (6 of 11 conditions) and long-term mortality (7 of 11 conditions). The long-term impact on function, quality of life and pain varied across comorbid conditions.

Conclusions This systematic review shows that comorbidities predominantly have an impact on the safety of hip and knee replacement surgery but little impact on its effectiveness. There is a need for high-quality studies also considering the severity of comorbid conditions.

Strengths and limitations of this study

- This study went beyond published reviews by analysing the relative impact of individual comorbid conditions on multiple outcomes that relate to safety and effectiveness of hip and knee replacement surgery.
- Further to previous studies, to allow for meta-analysis of all outcomes, continuous outcomes were converted to the corresponding OR using the Hasselblad and Hedges approach.
- The search was limited to include specific comorbidities and outcomes so studies may have been missed.
- To enable a meta-analysis of the multiple conditions and outcomes, comorbid conditions and outcomes were grouped together and may have compromised the validity of the conclusions.

INTRODUCTION

Hip and knee replacement surgery, the surgical replacement of a joint, is one of the most successful and cost-effective interventions in medicine.[1] It offers considerable improvement in function and quality of life.[2] It is expected that the demand for hip and knee replacement will increase as the prevalence of hip and knee osteoarthritis rises due to increases in life expectancy.[3]

There has been increasing interest in identifying the risk factors for poor outcomes of elective joint replacement to be able to optimise patients and improve outcomes. Previous research has reported variation in the use of hip and knee replacement according to socioeconomic status,[4] sex,[5] insurance status,[6] ethnicity[7] and geography.[8] This variation may be explained in part by the lack of consensus among clinicians about the clinical indications for joint replacement surgery.[9]

Comorbid conditions, conditions that are present in addition to the index condition but are unrelated to the latter, are on the rise around the world as more people are living with multiple morbidities. In a large US study using administrative data, 83.7% patients who had undergone hip or knee replacement had

at least one comorbid condition.[10] This is higher than in the general population where in 2012 only 49.8% of US adults had at least one comorbid condition.[11] As the prevalence of people living with multiple morbidities increases with age, it is expected that the number of patients undergoing elective hip and knee replacement with at least one comorbid condition will increase.[12]

There have been a number of studies reporting the impact of comorbidity on outcomes after hip and knee replacement.[13–15] There is little evidence, however, to which extent different individual comorbid conditions affect a variety of outcomes that relate not just to the safety of the surgery but also long-term outcomes such as quality of life after hip and knee replacement surgery. Previous systematic reviews on comorbid conditions and outcomes of hip and knee replacement have typically focused on individual comorbidities,[16] specific outcomes,[17] process measures and cost,[18] short-term outcomes following hip and knee replacement or the overall impact of composite comorbidity indices on outcomes.[14]

This study provides evidence of the impact of different individual comorbid conditions on a wide range of surgical outcomes, including short-term outcomes related to the 'safety' of the surgery and long-term outcomes related to the 'effectiveness' of the surgery.

The aim of this systematic review and meta-analysis was to synthesise the literature on the impact of different individual comorbid conditions on short-term and long-term outcomes of hip and knee replacement surgery.

METHODS

Patient and public involvement

This systematic review forms part of a wider piece of work investigating the access to and outcomes of hip and knee replacement surgery for patients with comorbidities. The protocol, including the systematic review, was reviewed by patient representatives on the National Institute for Health Research (NIHR) Collaboration for Leadership in Applied Health Research and Care (CLAHRC) North Thames Patient and Public Involvement committee. Their comments and feedback were incorporated in the protocol.

Literature search

A search of Medline, Embase and CINAHL Plus was conducted up to 31 May 2017 to identify studies written in English. Limitations were not placed on date. Search terms for hip and knee replacement were combined with search terms for health outcomes and search terms for 11 common comorbid conditions: heart disease, high blood pressure, stroke, leg pain due to poor circulation, lung disease, diabetes, kidney disease, diseases of the nervous system, liver disease, cancer and depression (see online supplementary information 1). The conditions were selected because they are the comorbid conditions that are routinely captured in the national Patient-Reported Outcome Measures (PROMs) programme for patients undergoing elective surgery in the English National Health Service and were considered relevant comorbidities in terms of outcome prediction.[19] Where possible MeSH or index terms were used. All the titles, selected abstracts and full-text articles were reviewed for eligibility by two reviewers (BP, AA). Data extraction was conducted by BP and checked by AH. Any disagreements were resolved by two reviewers (JvdM, AH). The reference lists of existing systematic reviews and included studies were also checked for additional eligible articles.

Eligibility criteria and data extraction

We included published full-text observational (either prospective or retrospective) studies in the English language that compared the outcomes of hip or knee replacement in patients with and without any of the 11 comorbid conditions. Studies were ineligible if they used a summary comorbidity index (eg, Charlson Comorbidity Index) or a single count of comorbidities because the aim of our study was to understand the impact of individual comorbid conditions. Studies, including other joint replacements, were only eligible if hip and/or knee replacement represented at least 90% of participants or if results were reported separately. Small studies, those with fewer than 100 participants, were excluded because hip and knee replacement are common procedures and the selected comorbid conditions are relatively common. Studies were ineligible if they failed to include at least one of the following outcomes: surgical complications, mortality, function, pain, health-related quality of life, hospital readmission and revision surgery.

Information on the study design, population and measures of association was extracted for eligible studies. Data were extracted on the participants (type of surgery), source of study data, the specific condition and the definition of the outcome for each reported association between a comorbid condition and outcome in a study (see online supplementary information 2). In addition, data were also extracted on the measure of association and its uncertainty and, for adjusted measures, the variables used in the adjusted analysis. Where possible, data on counts or means were used to calculate measures of association that had not been reported in the original study. Studies that indicated the statistical significance or otherwise of an association without reporting a quantitative metric were also recorded. Data were verified by a third reviewer (JvdM).

Ten categories of outcome were defined. Five short-term outcomes, those occurring closest to 3 months after surgery, were: surgical complications, occurrence of venous thromboembolism (VTE), surgical site infections, readmission to hospital and mortality. Surgical complications were defined as the presence of any surgical complication as reported in a study. Two commonly reported surgical complications, VTE and infection, were also examined separately. Five long-term outcomes closest to 1 year postoperatively were: measures of hip or knee function, patient-reported quality of life, pain, revision

Box 1 Study quality appraisal using a modified Newcastle-Ottawa Scale*

Patient selection

1. Was the cohort of patients undergoing hip or knee replacement surgery with comorbid conditions representative?
2. Was the reference cohort for patients without comorbid conditions drawn from the same community?
3. Was the presence of comorbid conditions adequately verified? (Yes=secure record or structured interview/self-report.)
4. Did the study demonstrate that the outcome of interest was not present at the start of the study?
5. Was the cohort or patients drawn from multiple communities?

Comparability

1. Did the study control for age and sex?
2. Did the study control for socioeconomic status and ethnicity?

Outcome assessment

1. Was the outcome of interest clearly defined? (Yes=study specific/self-report, joint registry, No=administrative data.)
2. Was follow-up long enough for outcomes to occur? (Yes=short term minimum 30 days, long term minimum 6 months.)
3. Was follow-up adequate? (Yes=completed follow up >90%.)

*Studies were graded on an ordinal scoring scale with higher scores indicating studies of higher quality. A study could be awarded a maximum of one point for each numbered item except comparability items and the first item in outcome assessment, which could be awarded a maximum of two points for each numbered item.

surgery and mortality. We defined short-term outcomes as maximum 3 months and long-term outcomes as closest to 1 year after surgery because this reflected the definitions of outcomes used in the included studies and our judgement of events that reflect safety and effectiveness. For function and quality of life, they were only eligible for inclusion if analyses incorporated adjustment for preoperative scores or if similarity of preoperative scores was demonstrated. This was to ensure that the outcome captures the impact of surgery rather than any preoperative difference in score.

Quality assessment

The internal and external validity of the studies was appraised using the Newcastle-Ottawa Scale (NOS)[20] that was modified to meet the requirements of this study (see box 1). Two reviewers (BP, AH) examined three items: patient selection, comparability of exposure and reference groups, and assessment of outcomes. For the comparability between the two groups, we focused on the following variables that previous studies have identified as predictors of various outcomes of hip and knee replacement surgery: age, sex, socioeconomic status and ethnicity. We added an extra item to assess the comparability of the cohorts on the basis of whether the cohort of patients were drawn from multiple centres or a single centre and whether the data sources were from specialist arthroplasty databases. The total possible score was 13. A study with a score of 11 or greater was considered high quality (see online supplementary information 3). This was to ensure we only included the highest quality studies and excluded those where there were concerns with cohort selection, confounding and outcome assessment.

Table 1 Mapping of comorbid conditions

Comorbid condition	No of studies	Included comorbid conditions
Cancer	9	All cancers but if reported separately cancer chosen in preference to metastasis.
Depression	12	All diagnoses of depression
Diabetes	41	Type 2 diabetes in preference to type 1 diabetes. Controlled diabetes in preference to uncontrolled diabetes. Diabetes without complications in preference to diabetes with complications.
Diseases of the nervous system	6	Alzheimer's disease, Parkinson's disease, dementia.
Heart disease	21	Heart disease but if reported separately coronary heart disease, coronary artery disease or heart failure was chosen.
High blood pressure	13	High blood pressure.
Kidney disease	19	Renal disease but if reported separately chosen chronic kidney disease, chronic renal disease or renal failure.
Liver disease	7	Liver disease but if reported separately cirrhosis chosen.
Lung disease	18	Lung disease but if reported separately chronic obstructive pulmonary disorder chosen.
Poor circulation	7	Peripheral vascular disease.
Stroke	12	Stroke or cerebrovascular disease.

Quantitative data synthesis and meta-analysis

An approach to data synthesis was chosen which allowed for a meta-analysis across multiple outcomes and conditions. This meta-synthesis approach has been used by a previous systematic review.[21] The first stage of data synthesis involved selecting each study's measures of association to be included in the meta-analyses for each of the possible combinations of comorbid condition and outcome. Individual studies might have multiple measures for different combinations, for example, studies reporting multiple outcomes or different comorbid conditions. Studies might also have multiple measures for the same combination, for example, unadjusted and adjusted measures, measures for controlled and uncontrolled diabetes, or measures for hip and knee replacement surgery. Separate measures for hip and knee replacement were included

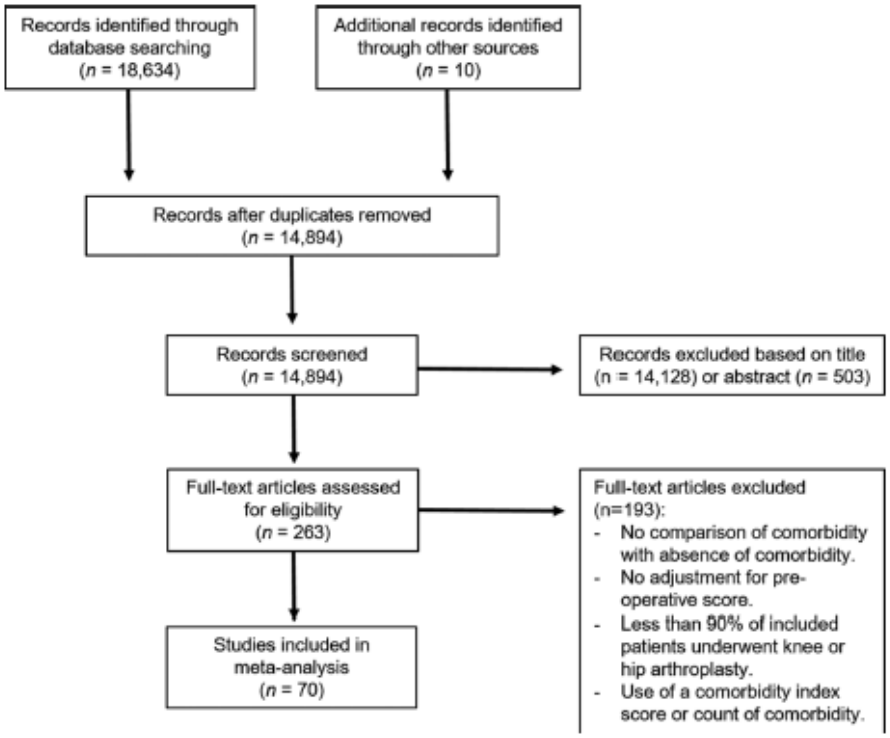

Figure 1 Flow chart.

in a combination's meta-analysis because they comprised different groups of participants. For other multiple measures, a single measure was selected for inclusion in a meta-analysis using the following criteria: adjusted over unadjusted measures, closer matching or more common subcategories of comorbid conditions for inexact mapping to the 11 selected conditions (see table 1), and closer matching to the timing (3 or 12 months) and definition of outcomes.

Most of the studies reported outcomes as ORs or it was possible to derive an OR. For studies reporting continuous outcomes the difference between means divided by the pooled SD (standardised mean difference) was converted to the corresponding OR using the Hasselblad and Hedges approach.[22] If higher scores represented a good outcome then reciprocal values were used to ensure that ORs greater than 1 represented higher odds of a poor outcome. Where zero events precluded the calculation of an OR, each cell in the contingency table was inflated by adding 0.5[23] to allow calculation of an OR.

We estimated the pooled OR for each combination of comorbid condition and outcome comprising two or more measures of association. ORs were computed such that a result greater than 1 indicates a higher odds of a worse outcome in patients with a specified comorbid conditions compared with patients without. We used a random-effects model as results were drawn from different populations.[24] Pooled ORs by condition were plotted for each outcome. A sensitivity analysis was performed to assess the impact of the quality of the studies on the outcomes by comparing higher quality studies with studies of lower quality. The risk of publication bias was assessed using the graphical assessment of the funnel plot[23] on outcomes which were reported on by a greater than six studies. All statistical analyses were carried out using STATA V.14.

RESULTS

Selected studies

Full search results are represented in figure 1. Of the 18644 studies identified in the search, we included 70 studies,[25–94] which produced 314 results for individual comorbid conditions and outcomes of hip and knee replacement surgery. The 70 studies had a range of patients sample sizes from 122 to 8 379 490. Sixteen (23%) studies had at least 100 000 patients. Twenty-six (37%) studies reported combined hip and knee arthroplasties, 12 (17%) studies reported on hip arthroplasties only, 24 (34%) studies on knee arthroplasties and 9 (13%) studies reported hip and knee arthroplasties separately. Forty (70%) studies reported outcomes after primary hip or knee replacement. The 70 studies came from 13 different countries with 37 (53%) coming from the USA. They were published between 1984 and 2017.

Overall, 43 (61%) studies only looked at single comorbid conditions and 35 (50%) only looked at single

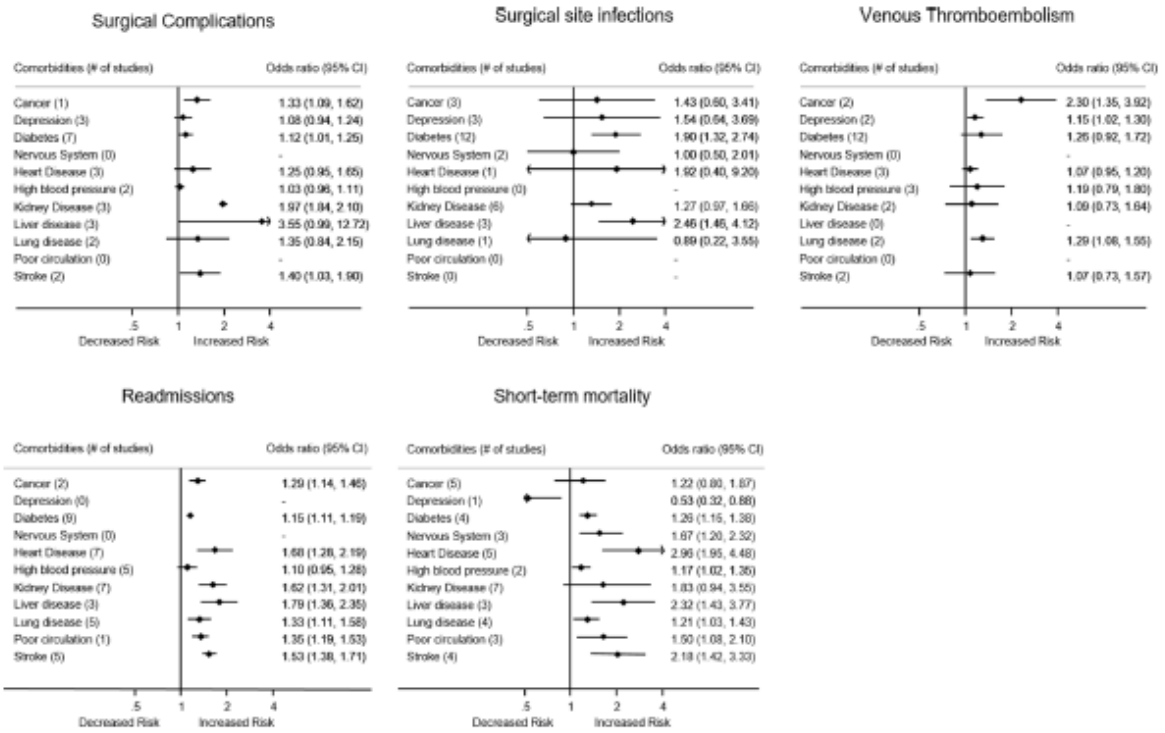

Figure 2 Forest plots of short-term outcomes.

outcomes. Sixty (86%) studies investigated the association between comorbid conditions and surgical complications (including VTE and surgical site infections), and only 5 (7%) quality of life. The comorbid condition that was most frequently studied was diabetes (41 studies), followed by heart disease (21 studies) and kidney disease (19 studies) (see table 1). The least frequently studied comorbid condition was diseases of the nervous system (six studies).

The median NOS score, the measure of study quality, was 10 (6–13). Of the 70, nine (13%) studies met our predefined criteria for high quality of scores of greater than 11. The majority of studies had a representative cohort of patients with a specified comorbid condition (56 studies) and adjusted for potential confounders such as age and gender (41 studies).

Short-term outcomes

Surgical complications

In this meta-analysis, 15 studies reported an OR for surgical complications in patients with comorbid conditions (see figure 2). The risk of surgical complications was significantly higher in patients with cancer (pooled OR 1.33, 95% CI 1.09 to 1.62), diabetes (pooled OR 1.12, 95% CI 1.01 to 1.25), kidney disease (pooled OR 1.97, 95% CI 1.84 to 2.10) and stroke (pooled OR 1.40, 95% CI 1.03 to 1.90). No studies reported surgical complications in patients with nervous system diseases or poor circulation.

Surgical site infections

Twenty-seven studies reported on surgical site infections after surgery. Overall, surgical site infections tended to occur more frequently in patients with comorbid conditions but the likelihood was only significantly higher in patients with diabetes (pooled OR 1.90, 95% CI 1.32, 2.74) and liver disease (pooled OR 2.46, 95% CI 1.46 to 4.12) (see figure 2). No studies reported the likelihood of surgical site infections in patients with high blood pressure, poor circulation or stroke.

Venous thromboembolism

Eighteen studies reported the risk of VTE postoperatively. VTE was more likely in patients with cancer (pooled OR 2.30, 95% CI 1.35 to 3.92), depression (pooled OR 1.15, 95% CI 1.02 to 1.30) and lung disease (pooled OR 1.29, 95% CI 1.08 to 1.55). No studies reported the risk of VTE in patients with nervous system diseases, liver disease or poor circulation.

Readmissions to hospital

Sixteen studies looked at the presence of comorbid conditions and being readmitted to hospital within 90 days after surgery. Overall, the likelihood of readmissions to hospital was significantly higher for patients with comorbid conditions (8 out of 11) with the highest likelihood in patients with liver disease (pooled OR 1.79, 95% CI 1.36 to 2.35) (see figure 2). No studies reported the likelihood of readmissions in patients with nervous system diseases or depression.

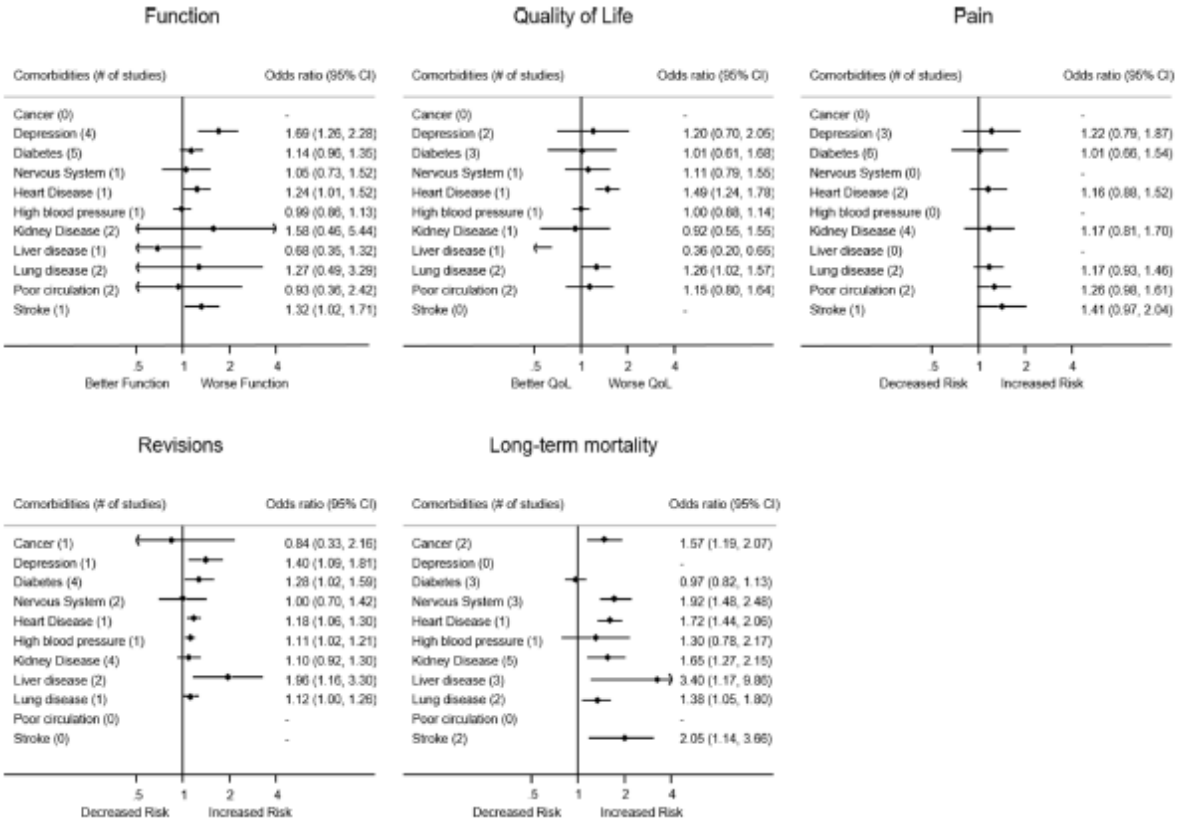

Figure 3 Forest plots of long-term outcomes.

Short-term mortality

Thirteen studies looked at mortality within 90 days after surgery. Overall, the likelihood of short-term mortality tended to be significantly higher in patients with comorbid conditions (8 out of 11) with the highest likelihood in patients with heart disease (pooled OR 2.96, 95% CI 1.95 to 4.48) (see figure 2). In contrast, one study reported a significant lower likelihood of short-term mortality in patients with depression (pooled OR 0.53, 95% CI 0.32 to 0.88).

Long-term outcomes

Hip and knee function

Ten studies look at the impact of comorbid conditions on postoperative hip or knee function (see figure 3). Knee or hip function measures included: The Knee Society Knee Score,[72 78] Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) Score,[28 29 74] Oxford Knee Score[35] and Activities of Daily Living limitation.[83 87 95] The most frequently used measure was the WOMAC Score. Overall, the impact of comorbid conditions on function was variable. Patients with depression (pooled OR 1.69, 95% CI 1.26 to 2.28), heart disease (pooled OR 1.24, 95% CI 1.01 to 1.52) and stroke (pooled OR 1.32, 95% CI 1.02 to 1.71) had worse function after surgery. Postoperative function in patients with heart disease[35] and stroke[87] was each only reported on by one study. No studies investigated the postoperative function in patients with cancer.

Health-related quality of life

Five studies compared the improvement in quality of life 1 year after surgery in patients with comorbid conditions with those patients without comorbidities. Measures of quality of life included the Short Form-12,[35] Short Form-36[29 74 96] and the Health Utilities Index.[28] Overall, across comorbid conditions there was no consistent pattern. Quality of life was significantly worse for patients with heart disease (pooled OR 1.49, 95% CI 1.24 to 1.78) and lung disease (pooled OR 1.26, 95% CI 1.02 to 1.57). For patients with liver disease, quality of life was significantly better after surgery (pooled OR 0.36, 95% CI 0.20 to 0.65).[35] Postoperative quality of life in patients with heart disease and liver disease was each only reported by one study. No studies investigated the postoperative quality of life in patients with cancer or stroke.

Pain

Ten studies reported on the association between comorbid conditions and pain. Five (50%) studies looked at the outcome moderate to severe pain at 2 years and were studied by the same author.[84 85] Other measures of pain included the WOMAC Pain Score[28] and the Knee

Society Pain Score.[68 72] Overall, pain tended to be worse for patients with comorbid conditions but was not statistically significant. No studies investigated the postoperative pain in patients with cancer, nervous system diseases, liver disease or high blood pressure.

Revision surgery

Twelve studies reported on the likelihood of revision surgery in patients with comorbid conditions. Overall, revision surgery tended to be more likely in patients with comorbid conditions (6 out of 11) but the evidence remains weak. The pooled OR ranged from 1.11 (95% CI 1.02 to 1.21) for patients with high blood pressure to 1.96 (95% CI 1.16 to 3.30) for patients with liver disease. No studies reported the risk of revision surgery in patients with poor circulation or stroke.

Long-term mortality

Twelve studies reported the association between comorbid conditions and long-term mortality. Overall, the risk of long-term mortality tended to be higher for patients with comorbid conditions (7 out of 11). The pooled OR ranged from 1.38 (95% CI 1.05 to 1.80) for lung disease to 3.40 (95% CI 1.17 to 9.86) for liver disease (see figure 3). No studies investigated the risks of long-term mortality in patients with depression and poor circulation.

Impact of comorbid conditions

There is a lack of consistency across short-term and long-term outcomes by different comorbid conditions. In the short term, comorbidities had the most impact on readmissions to hospital and short-term mortality, but the impact on surgical complications was variable with most results not statistically significant. In the long term, comorbid conditions had the most impact on risk of revision surgery and long-term mortality. The impact on function and quality of life was inconsistent across comorbid conditions. The evidence for the impact of comorbid conditions on long-term outcomes was weaker than for short-term outcomes. Heart disease of all the included comorbid conditions had the most impact on both short-term and long-term outcomes with an increased likelihood of readmissions, short-term mortality, worse function, worse quality of life, revision surgery and long-term mortality.

Publication bias

We explored the possible impact of publication bias on outcomes: surgical complications, VTE, surgical site infections, readmissions, pain and mortality which had greater than six studies. This included studies in patients with diabetes (see figure 4) and kidney disease (see figure 5). The studies were not evenly distributed across both sides of the funnel plot. This asymmetry suggests that studies publishing negative effects may be missing. The impact of comorbidities on outcomes of hip and knee replacement may therefore be overestimated.

Sensitivity analysis

We performed a sensitivity analysis to estimate the robustness of the results by evaluating the effects of study quality (see online supplementary information 4). Overall, high-quality studies pointed in the same direction as the lower-quality studies, although the latter generally reported larger effects. Higher-quality studies did not include studies reporting on the outcomes function, quality of life and pain, which suggest the evidence on long-term outcomes is poor compared with the evidence of the impact of comorbid condition on short-term outcomes. This may be largely because of the smaller sample size of these studies, the lack of adjustment for confounders and the lack of patient-reported outcomes in joint registries which focus primarily on surgical complications, mortality and revision rates.

DISCUSSION

Main findings

Overall, this meta-analysis demonstrates that patients with comorbid conditions are more likely to have a readmission and a higher short-term mortality in the early follow-up, but there is little evidence that patients benefit significantly less in terms of health-related quality of life, function and pain compared with patients with no comorbid conditions. In the short term, the impact on surgical complications was variable and mostly statistically insignificant. Patients with comorbid conditions tended to have a higher risk of revisions and long-term mortality but the available evidence was weak. There is some evidence of publication bias which may indicate an overestimation of the impact of comorbid conditions on outcomes. Given this, there is a need for high-quality studies in order to get a better understanding of the true impact of comorbidities on both short-term and long-term outcomes of hip and knee replacement.

Our study has implications for future research on clinical indication for joint replacement surgery. Clinicians should take into account prognostic factors that affect treatment effectiveness in their decision-making to refer or select patients for hip or knee replacement[97] but due to the lack of clarity on clinical indication for hip and knee replacement, they are not able to do so effectively.[98] Further research, specifically focusing on the long-term outcomes such as function, quality of life and pain and that stratify individual comorbidities according to severity are needed to provide clinicians with more evidence to guide their decision-making and management of patients with comorbid conditions and to minimise the variation and quality of care provided for this patient group.

Quality of evidence

Only 13% of the studies were graded as being of high quality. Poorer quality studies were typically less clear about the inclusion criteria for study patients and did not adjust for potential confounders such as age and gender. They were also based on either small single-site studies

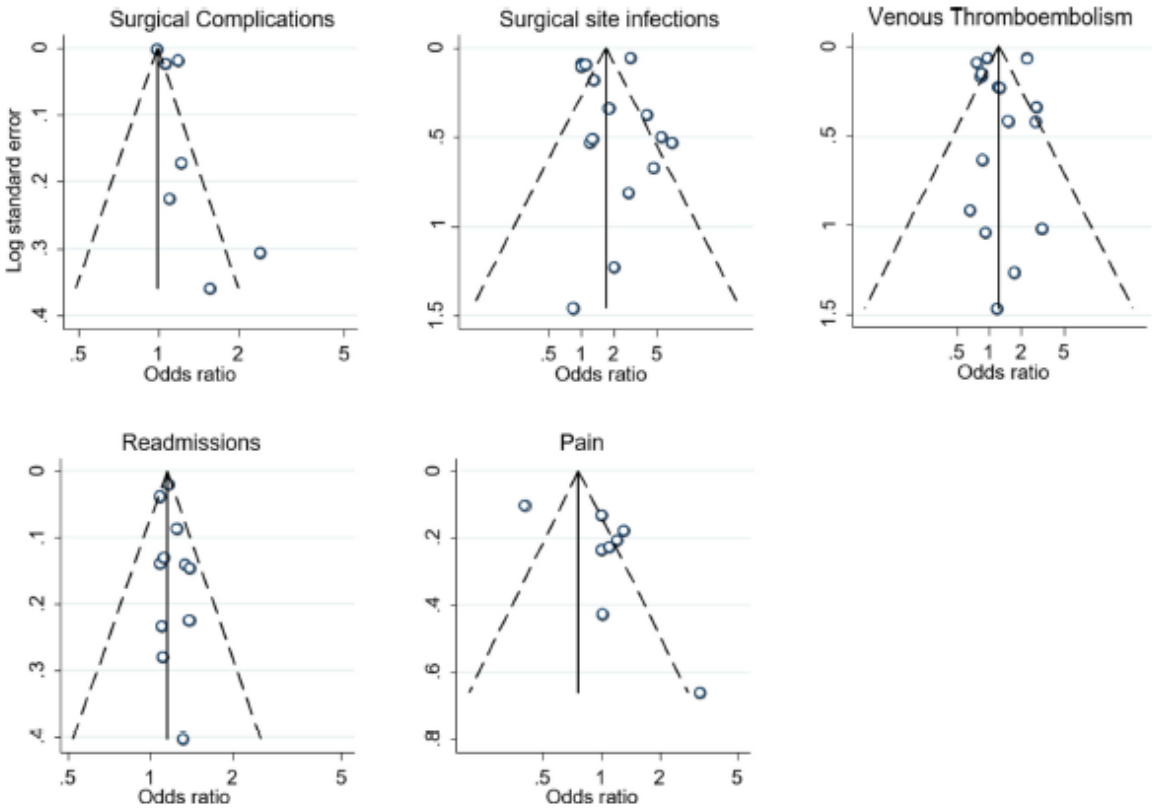

Figure 4 Funnel plot showing 95% confidence limits for any surgical complications, surgical site infections, venous thromboembolism, readmissions to hospital and pain in patients with diabetes.

or large administrative data-based studies that use data sources that were not from specialist arthroplasty databases. Large administrative data-based studies greatly influenced the meta-analysis and thereby the limitations of these studies will therefore have a considerable influence on the validity of this meta-analysis. The higher quality studies primarily used joint registries and did not focus on patient-reported outcomes such as quality of life, function and pain.

Our sensitivity analysis showed that lower quality studies seem to overestimate the risk of short-term outcomes after hip and knee replacement in patients with comorbid conditions. Similarly, the evidence of reporting bias towards reporting positive findings may indicate an overestimation of the impact of comorbid conditions on outcomes of hip and knee replacement surgery. Due to the relatively small number of studies exploring the impact of each comorbid condition, it was not possible to fully explore the impact of publication bias and other factors that might cause heterogeneity.

It is important to consider, that patients included in the reported studies may represent a healthier population. Several studies have shown that patients are not accessing hip and knee replacement because clinicians are excluding complex and severe patients who are deemed too high risk for surgery.[99] This may introduce selection bias which may lead to an underestimation of the true effect on the impact of comorbid conditions on outcomes of hip and knee replacement surgery.

Relation to prior reviews

Our study provides evidence that comorbid conditions have an impact on safety of the surgery but little impact on the effectiveness of the surgery in terms of quality of life, function and pain after hip and knee replacement surgery. There have been a number of earlier systematic reviews reporting the impact of comorbid conditions on outcomes after hip and knee replacement surgery. One systematic review and meta-analysis following elective total hip replacement in patients with diabetes found diabetes to be associated with a twofold increase risk of surgical site infections in line with our findings.[16] Another one looking at the impact of comorbidity and length of stay and costs found limited evidence that comorbidities increase length of stay and costs compared with patients with no or fewer comorbidities.[18] One systematic review looking at health-related quality of life in total hip and knee replacement reported that comorbid conditions was given as a reason for modest improvements in outcomes.[17] This finding was only based on two studies

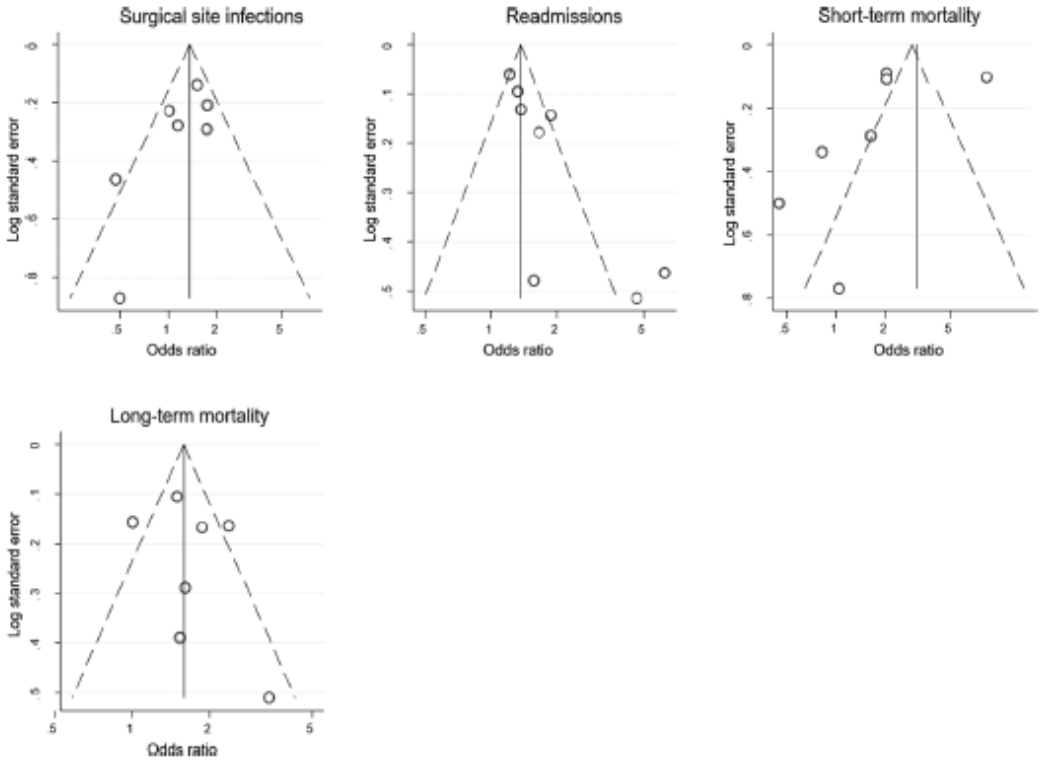

Figure 5 Funnel plot showing 95% confidence limits for any surgical site infections, readmissions to hospital, short-term mortality and long-term mortality in patients with kidney disease.

both using composite comorbidity measures. Another systematic review looking at all preoperative predictors for outcomes for hip and knee replacement, however, demonstrated the inconsistency in study findings with seven studies reported a significant worse association between comorbid conditions and outcomes but six studies reported no significant association.[14]

LIMITATIONS

For some combinations of outcomes and comorbid conditions, there were no studies of impact or impact was only based on a single study. Only six studies focused on patients with diseases of the nervous system whereas over half of the studies we reviewed investigated outcomes in patients with diabetes. Similarly, short-term outcomes, particularly surgical complications, were commonly investigated but only five studies[28 29 35 74 96] reported on quality of life outcomes and the results on pain were from two publications.[84 85] This highlights that evidence on short-term outcomes is stronger than evidence on long-term outcomes. Half of the studies were analyses of data collected in population-based administrative datasets. This may account for the relative scarcity of studies reporting on long-term outcomes such as quality of life or function that need patient-reported results.

We limited our review to studies with at least 100 patients and patients with the 11 comorbid conditions. Comorbid conditions that did not fit into the 11 categories that are captured in the PROMs programme for patients undergoing elective surgery in the English National Health Service were not included in this review. In addition, specific outcomes and patient-reported measures were not specified in the literature search so this may have resulted in the omission of some studies that met the inclusion criteria. We performed manual searches of relevant journals however and checked the references lists of all included studies and other systematic reviews, so we believe that any missed studies would not affect our conclusions significantly.

The scope of this review required the grouping of heterogeneous studies. Across all studies, there were differences in study populations, definitions of comorbid conditions and their severity, definitions of outcomes, particularly for patient-reported outcomes, and the constructs they are measuring and the timing of their measurement. To make the results comparable and to be able to conduct any form of meta-analysis, some comorbid conditions were grouped together, outcomes were categorised as short and long term, and continuous outcomes were converted to OR using the Hasselblad and Hedges approach. In addition, it was not possible to evaluate hip

and knee replacement separately as 27 (38%) studies reported on combined hip and knee arthroplasties.

In addition to variation in definitions of comorbid conditions, few included studies graded comorbid conditions according to severity which would have allowed a better understanding of their impact. For the few studies that reported results according to the severity of a comorbid condition, we included the most common severity subgroup, therefore excluding the most severe patients.

CONCLUSION

Clinicians should be aware of the short-term risks relating to the safety of the surgery in their management of patients with comorbid conditions. There is little evidence that patients with comorbid conditions benefit significantly less from hip and knee replacement in terms of quality of life, function and pain after surgery than patients without comorbid conditions. As a result comorbid conditions have an impact on safety but little impact on effectiveness of hip and knee replacement surgery. Future research should however consider the severity of comorbid conditions to better understand the impact of comorbid conditions on outcomes.

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4 RESULTS CHAPTER – Qualitative Study

The second component of this programme of research was a qualitative study exploring how patients with comorbidities are referred and selected for elective hip and knee replacement surgery. The results have been presented in the form of a published research paper. The supplementary information referred to in the paper is available in Appendix G (Interview Topic Guides).

Title: Comorbidities and the referral pathway to access joint replacement surgery: An exploratory qualitative study

The online PDF version can be accessed at:
https://bmchealthservres.biomedcentral.com/articles/10.1186/s12913-018-3565-0

Further additional information can be found in the appendix:

Appendix D – Ethics approval

Appendix E – Participant Information Sheet

Appendix F – Consent form

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Student ID Number	LSH342490	**Title**	Ms
First Name(s)	BÉLÈNE		
Surname/Family Name	PODMORE		
Thesis Title	The access to and outcomes of elective hip and knee replacement surgery for patients with comorbidities: a study using PROMs and administrative data		
Primary Supervisor	Professor Jan van der Meulen		

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SECTION E

Student Signature	[redacted]
Date	23 November 2018

Supervisor Signature	[redacted]
Date	23 November 2018

4.1 Research Paper 2 (RP2)

RESEARCH ARTICLE Open Access

Comorbidities and the referral pathway to access joint replacement surgery: an exploratory qualitative study

Bélène Podmore[1,2*], Andrew Hutchings[1,2], Mary-Alison Durand[1], John Robson[3], Sujith Konan[4], Jan van der Meulen[1,2] and Rebecca Lynch[1]

Abstract

Background: Variation in access to joint replacement surgery has been widely reported but less attention has been given to the impact of comorbidities on the patient journey to joint replacement surgery. There is a lack of consensus amongst healthcare professionals and commissioners about how patients with comorbidities should be referred or selected for joint replacement surgery. It is therefore important to understand the views of healthcare professionals on the management, referral and selection of patients with comorbidities for joint replacement surgery.

Methods: An exploratory qualitative study involving semi-structured interviews with 20 healthcare professionals in England across the referral pathway to joint replacement surgery. They were asked to talk about their experiences of referring and selecting patients with comorbidities for joint replacement surgery. The interviews were audio-recorded and transcribed verbatim. Data analysis followed a thematic analysis approach based on the principles of grounded theory.

Results: In general, the presence of comorbidities was not seen as a barrier to being referred or selected for joint replacement but was seen as a challenge to manage the patients' journey across the referral pathway. Each professional group, concentrated on different aspects of the patients' condition which appeared to affect how they managed patients with comorbidities. This implied there was a disagreement about roles and responsibilities in the management of patients with comorbidities. None of the professionals believed it was their responsibility to address comorbidities in preparation for surgery. This disagreement was identified as a reason why some patients seem to 'get lost' in the referral system when they were considered to be unprepared for surgery. Patients were then potentially left to manage their own comorbidities before being reconsidered for joint replacement.

Conclusions: At the clinician-level, comorbidities were not perceived as a barrier to accessing joint replacement surgery but at the pathway-level, it may create an implicit barrier such that patients with comorbidities may get 'lost' to the system. Further study is needed to explore the roles and responsibilities of professionals across the current orthopaedic referral pathway which may be less suitable for patients with comorbidities.

Keywords: Comorbidities, Access to surgery, Experiences of healthcare professionals, Qualitative design, In-depth interviews

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Background

Hip and knee joint replacements are two of the most common and effective interventions in the UK [1]. Many patients undergoing joint replacement surgery have at least one comorbid condition (a condition that is present in addition to the joint problem but is an unrelated condition) [2]. As the prevalence of people living with comorbidities increases with age, it is expected that an increasing number of patients with comorbidities will be undergoing hip and knee replacement [3].

In the English National Health Service (NHS), the referral pathway to joint replacement surgery connects primary care, intermediate services and specialist orthopaedic surgeons in secondary care. General practitioners (GPs) are the gatekeepers to secondary care, assessing the patient first in primary care and referring them on to the most appropriate orthopaedic service in secondary care. In certain areas of the country GPs refer patients to intermediate musculoskeletal assessment centres run by physiotherapists or GPs. Introduced in 2006 to reduce waiting times for specialist care, they act as a one-stop-shop for distinguishing patients into those who can benefit from local community services (e.g. physiotherapy, diabetes clinic) and those who need immediate referral to an orthopaedic surgeon [4]. These centres are located in either community or secondary care. In areas without such centres, this triage is undertaken by the surgeons in secondary care.

Evidence suggests that there is wide variation in access to joint replacement surgery in the UK [5–8] which can be partly linked to a lack of consensus about the impact of comorbidities on the risk and benefits of replacement surgery [9, 10]. For example, two studies found that the presence of comorbidities was a reason for some health care professionals to avoid a recommendation for surgery [11, 12]. Studies have also found that different groups of healthcare professionals do not have the same views on who should have joint replacement surgery [5].

In addition, there is also lack of consensus at the commissioning level with some regional commissioners of joint replacement services having sought to limit access to surgery by imposing minimum thresholds for severity of preoperative function [13] and pain [14] and the requirement that a patient's the body mass index is lower than 30 kg/m^2 [15]. There is also disagreement about the impact of comorbidities on suitability for joint replacement. However, there is no evidence to support these arbitrary thresholds [16] and the National Institute for Health and Clinical Excellence (NICE), the health authority that develops clinical guidance and quality standards for the NHS in England and Wales, recommends that patient-level factors, including comorbidities, should not preclude patients from being referred to secondary care for joint replacement surgery [17].

Given this lack of consensus, there is a need to get a better understanding of the referral pathway for patients with comorbidities who are candidates for joint replacement surgery and whether their comorbidities has an impact on the care they receive. Coordination between care providers is essential to delivering good quality care for patients with different chronic diseases [18]. Patients with chronic diseases have reported continuity of care as being important when moving across providers and to give them confidence to express their needs to clinicians [19, 20]. Studies have also found that low continuity of care is associated with higher rates of adverse outcomes for patients with multiple chronic diseases [21, 22]. As such it is important to understand the patient journey for patients with comorbidities towards joint replacement surgery.

This exploratory qualitative study investigated the views of GPs, intermediate care professionals, and orthopaedic surgeons on the management, referral and selection of patients with comorbidities for joint replacement surgery.

Methods

Sampling strategy

The participants were purposively sampled [23] and included orthopaedic surgeons, GPs and professionals working in intermediate musculoskeletal assessment centres - all professionals who are playing a significant role in either referring or selecting patients for joint replacement surgery in the NHS.

There was an endeavour to include both men and women with a range of years of experience. Orthopaedic surgeons were selected from a list of all orthopaedic surgeons specialising in hip or knee replacements in the NIHR CLAHRC North Thames (North Central and East London, Essex and Hertfordshire) area. Consultant orthopaedic surgeons (senior surgeons who have completed all their specialist training) were contacted via email. GPs were recruited through the local teaching networks using snowballing techniques from a sample of GP practices across the NIHR CLAHRC North Thames area. Intermediate care professionals were recruited, using snowballing techniques, from intermediate services used by GPs and surgeons who had been interviewed.

Data collection

A semi-structured interview guide was developed and modified slightly for the different roles that the different professionals might have in managing, referring and selecting patients with comorbidities for joint replacement surgery (see Additional file 1). The interview topic guide was developed in consultation with a GP and an orthopaedic surgeon and informed by a scoping

literature review on the barriers to accessing joint replacement surgery. The topics included the referral process, how decisions are made to refer or select patient, whether or not and how comorbidities influence clinical decision-making and how these comorbidities affect the patient journey through the orthopaedic referral pathway.

Interviews were conducted by BP and took place face-to-face at the professional's workplace except for six interviews which were conducted by telephone for the convenience of busy interviewees. Interviews were conducted until no new themes emerged across all professional groups [24]. Interviews were recorded and transcribed verbatim.

Analysis

Inductive and deductive approaches to data analysis based on the principles of grounded theory were used in order to derive the themes from the responses given by the professionals [25]. The aim was not to generate a theory or a framework. Interview transcripts were initially open-coded to derive broader concepts and to identify major themes based initially on the interview topic guide (deductive coding). Further thematic codes were then drafted inductively and revised regularly through the entire process of analysis through discussion with the members of the research team (BP, RL, MLD, AH and JvdM). This continuous discussion increased coding reliability. The constant comparative method [26] was also used throughout to highlight similarities and differences between healthcare professionals [27]. All data was managed and coded using the qualitative data software program NVIVO. In addition, a first draft of the results section was reviewed by the clinical members of the research team (SK, an orthopaedic surgeon and JR, a GP) and their comments were incorporated.

Ethical considerations

This study forms part of a larger project investigating the access to and outcomes of hip and knee replacement surgery for patients with different comorbidities. This study received approval from the Health Research Authority NHS Research Ethics Committee (Reference: 16/WA/0241). The participants all signed informed consent and all transcripts and recordings were anonymised.

Participants

The total sample of this study comprised of 20 English healthcare professionals. This included eight orthopaedic surgeons, seven GPs, and five intermediate care professionals (ICP). Intermediate care professionals were predominantly physiotherapists by training but a small number were also GPs. 13 were men and they had on average been working in their current role for 7 years (range 2–36).

Results

Regarding the importance of understanding the journey along the referral pathway towards joint replacement surgery for patients with comorbidities, the majority of the professionals reported that the system needed to be improved to better manage patients with comorbidities across the system. As one intermediate care professional explained:

"...it's a hole in the NHS provision, if they could get better at stopping patients with long-term conditions crashing and burning, if they could commission something that would help support them so they stayed on a good functional level, all our jobs would be easier" (ICP, Interview 8).

This quote underlines that while there was an understanding of a need to improve the system for patients with comorbidities the professionals do not know how best to achieve this improvement and whose responsibility it is to make it happen. It also highlights that the professionals perceive managing patients with comorbidities as challenging. This appears to be exemplified in the two major themes that emerged from the data: differences in approaches to managing comorbidities and the professional's view on whose role and responsibility it is to prepare patients for joint replacement surgery.

Managing comorbidities

The presence of comorbidities did not preclude the referral or selection of patients for joint replacement. All the professionals indicated that diabetes, chronic obstructive pulmonary disease (COPD) and heart disease were the most common comorbidities which they often found challenging to manage. Each professional group, however, concentrated on different aspects of comorbidity. This different focus influenced how each group of professionals approached the management of patients with comorbidities. GPs focused on the long-term complex care of the patient's conditions, intermediate care professionals focused on the patients' eligibility for surgical consultation, and orthopaedic surgeons on the short-term risks of the surgical procedure.

GPs spoke about the complexity of the long-term management of patients' comorbidities alongside their hip or knee pain. This is perhaps unsurprising as GPs are responsible for the management of the patients before and after surgery. The majority of GPs described their initial assessment of patients presenting with hip or knee pain as being not just about evaluating the risks of the surgery but also about the impact

of the comorbidities on the patient's daily life and the long-term benefits of the hip or knee replacement in terms of improvements in quality of life, pain and disability. One GP explained that he did not think in terms of specific comorbidity categories as one could assume that patients presenting with hip or knee pain were from an age group in which comorbidities were very common (GP, Interview 1). Similarly, several GPs reported general 'frailty' in elderly patients as a reason to be concerned about 'fitness for surgery' but these GPs seemed to be primarily concerned about the patients' ability to recover from such an invasive surgery (GP, Interview 3).

GPs reported also having to manage the complexity of 'multimorbidity', given the impact different comorbid conditions can have on each other. As one GP described it, core management of joint pain focuses on improving mobility and people with comorbidities struggle even more with mobility. Similarly, the joint pain makes it more difficult for patients to deal with their comorbidities. For some GPs, this complexity did have an impact on the care they believed they could provide in the lead up to joint replacement. For example, as one GP said:

"If someone's got severe COPD then offering them physiotherapy may not be an option, the exercise class may not be good enough so there will be comorbidity that will limit what you can and can't offer in all spectrums, so whether that is medication, exercises, even surgical fitness, you know, all of these come into mind and have to be detailed at the time of consultation." (GP, Interview 9).

In contrast, intermediate care professionals, reported focusing the impact that comorbidity has on the patients' suitability for surgical consultation and the likelihood of patients being selected by surgeons for surgery. Patients, if not sent directly by the GP for orthopaedic consultation, were referred to an intermediate service to be further assessed. The intermediate care professionals reported that, while the presence of comorbidities did not prevent the referral of patients for orthopaedic consultation, a key aspect of their management of patients was the decision about the likely impact that comorbidities have on the risks and benefits of the surgery. As one intermediate care professional explained:

"I had a patient who had osteoarthritis knee but they'd had a coronary artery bypass graft, they'd had a stroke, they had high blood pressure, they actually hadn't tried much physiotherapy so we went down the conservative route first, but looking at all of those things and their age, would a surgeon actually want to put them on the operating table for fear that with all of that they might not wake up again. So that's sort of weighing up the pros and cons of 'are you going to benefit from this or is there no point in us actually doing the surgery'." (ICP, Interview 15).

All intermediate care professionals described risk in terms of the risks of the surgical intervention itself. This may partly reflect the fact that intermediate care professionals reported working more closely with surgeons.

Orthopaedic surgeons focused on the risk comorbidities posed to the surgical procedure itself and the immediate postoperative recovery. Despite this focus on the procedure and postoperative period, they indicated that the presence of comorbidity did not preclude the selection of patients with comorbidities for hip or knee replacement. Orthopaedic surgeons often talked about assessing risks as necessary to avoid the risk of *'death on the table'* (Surgeon, Interview 6). This risk of death was primarily linked to the impact of comorbidities on anaesthetic risk.

Some surgeons also spoke about what they described as needing to assess the benefits, which they defined as the likelihood of a successful surgery without postoperative complications. Surgeons reported that the likelihood of complications such as cardiac complications was important to consider in the effective management of resources for patients with comorbidities. Patients with multiple comorbidities were labelled as 'complex patients' who therefore needed high-dependency beds in case of complications. One surgeon reported that getting a high-dependency bed was challenging. As a result, surgeons explained that in managing patients with comorbidities they had to think not only of the risks of the actual surgical procedure but also the immediate post-operative risks and the logistics of providing care for these 'complex 'patients. As one surgeon describes:

"Last week I did a patient and [...] this patient had been put on a list over a year ago and we'd delayed her on three successive occasions, mainly because they needed high-dependency bed..." (Surgeon, Interview 5).

Roles and responsibilities

Across the professionals, the theme of roles and responsibilities was central to the discussion about referring and selecting patients for replacement surgery. Differences between professionals groups emerged in how professionals perceived their roles and responsibilities in supporting patients in their preparation for surgery.

GPs indicated that it was not their responsibility to support patients in their preparation for joint replacement by addressing their comorbidities prior to surgery, as they were not clinical orthopaedic experts. They explained therefore that they could not make final

decisions on appropriateness for surgery for patients with comorbidities. One GP described the role of GPs more succinctly indicating that it was about *"intervening in modifiable long term risks"* (GP, Interview 11) rather than the short-term risks related to surgery. Another GP reported:

"I don't really feel that I'm referring someone for surgery in that kind of way. I kind of more feel like I'm referring them to a specialist who can help them in a special way which might involve surgery. So I don't, I'm not really in that kind of mindset of this person is going for surgery and I need to be for sure that they're ready for it" (GP, Interview 3).

Some GPs mentioned that it was not their role to make a decision about appropriateness for surgery. Others admitted they were not sufficiently informed about what constitutes appropriateness for surgery and therefore let the surgeons make this decision. In addition, some GPs explained that the complexity of the referral system was a barrier to being confidently able to refer and manage patients with comorbidities in preparation for joint replacement surgery.

Intermediate care professionals did not consider it their responsibility to support patients with comorbidities in their preparation for joint replacement surgery. In general, these professionals all suggested that their role was to triage patients referred to them from GPs and not to give an accurate diagnosis or consider fitness for surgery. Again, like GPs, they assigned the role of 'expert' to the orthopaedic surgeons. One interviewee explained: *"I'm not a surgeon, I'm not the expert"* (ICP, Interview 15). There was an agreement amongst all intermediate care professionals that their role was very technical and was to ensure that surgeons were sent only those patients who were 'appropriate'. An appropriate referral was defined as a patient who had tried all non-surgical treatment options and had undergone all investigative tests. All intermediate care professionals suggested that it was important to achieve high 'conversion rates', that is, the rate of consultations with the surgeon resulting in a surgical intervention, so that they did not waste a surgeon's time. Several intermediate care professionals reported that they worked alongside surgeons to improve this conversion rate with the aim of reducing waiting times. They also believed that their role, and the reason intermediate services were introduced, was to relieve the pressure on GPs who were not 'experts' either. One intermediate care professional stated:

"GPs are fantastic, the 13% of their case load is musculoskeletal (MSK) dysfunction and they're not specialists in MSK, so a lot of the time these patients would be more appropriate to come to us in that we are a cheaper service and our tariff is less but we can give just as good care, but we don't do the surgery." (ICP, Interview 16).

Orthopaedic surgeons defined their role as the 'expert' who made the decision about the most appropriate surgical option but were not responsible for supporting patients in their preparation for surgery. One surgeon explained that ideally surgeons would receive only appropriate referrals of patients who needed surgery and were prepared for surgery. At the pre-assessment clinic, surgeons reported that further investigative tests could be ordered if necessary. The majority of surgeons, however, agreed that it was the GP's main role and responsibility to support patients with comorbidities in their preparation for joint replacement by addressing their comorbidities prior to referral. In order for patients with comorbidities to be prepared for surgery, surgeons explained they needed to be 'optimised' – their comorbidities had to be under control. One surgeon reported it was about *"managing those long-term conditions so they don't delay surgery"* (Surgeon, Interview 5). As he explained, operations were often cancelled due to patients not being 'optimised':

"This week we cancelled a patient on a day surgery, in fact we'd seen her two weeks ago, she had high blood pressure, cancelled her on day surgery, she... hadn't started on blood pressure medication, sent her back to her GP, "Can you start on medication,"..., a month later she comes back her blood pressure's even higher than it was the first time around" (Surgeon, Interview 5).

When patients with comorbidities are assessed by a surgeon and deemed unprepared for surgery the majority of surgeons explained that in most cases they refer patients back to GPs. One surgeon explained there was an incentive to discharge patients as hospitals were penalised if they did not meet the 18-week target from referral to surgery. More than half of the surgeons suggested, however, that GPs may not make re-referrals and patients therefore may be 'lost to the system'. As a result, these surgeons took it upon themselves to refer patients for further investigations or to other secondary care specialists. They described this as a measure to reduce the waiting time for patients. One surgeon said:

"I'll keep them under my review, I won't discharge them, I'll bring them back after a few months because I don't want them getting lost, forgotten about. If I'm not sure, it's borderline then I might refer to my anaesthetist and ask them their opinion and then they can decide,

they may just say yes, that's fine, just order a few more tests or they may say, yes, I think they need to see a cardiologist for example." (Surgeon, Interview 20).

Some GPs and intermediate care professionals reported that patients also had a role in preparing themselves for surgery and this explained why some patients referred back to GPs were not re-referred. They reported that patients were not able to change their lifestyle, to improve their ability to manage their comorbidities, to be prepared for surgery and as a result were never re-referred and never receive the hip or knee replacement. According to one GP:

"I regard that as basically saying you can't have the operation because people like her have got to their weight over the course of their life, ... most people have very high BMIs so you're talking about them having to lose some life-changing amount of weight and they don't do it, so I regard that as just saying no, I'm not going to do your surgery...." (GP, Interview 11).

Discussion

The referral pathway towards joint replacement surgery in England generally involves three professional groups: GPs, intermediate care professionals and orthopaedic surgeons. While all professionals reported managing patients with comorbidities across the system as challenging, each group of professionals viewed comorbidities differently and had different opinions about how patients with comorbidities should be managed. This misalignment had an impact on the perceived role and responsibilities of each professional group and how they relate to each other in managing patients who are candidates for joint replacement surgery along the orthopaedic referral pathway. At the individual clinician-level, comorbidities were not perceived as a barrier to surgery but they had an impact on how patients were managed. At the level of the whole referral pathway, comorbidities may create subtle barriers, for example when patients are referred back to GPs and operations may be delayed or never happen.

Each professional group focused on different aspects of comorbidities, and therefore managed patients with comorbidities differently. GPs focused on the long-term impact of comorbidities on the patient's everyday life and the complexity of multi-morbidity. Intermediate care professionals focused on managing patients with comorbidities through the system and therefore focused on the likelihood of patients being selected by surgeons for surgery. The surgeons focused on the procedure itself and therefore only managed the patients with comorbidity through the surgical intervention but not beyond. Intermediate care professionals and surgeons used similar language when considering comorbidities and describing the management of patients with comorbidities which reflects the close working relationship between the two groups.

Interestingly, while there are differences in focus across all three groups, there is little discussion about comorbidities changing over time [28]. A general assumption appears to be that, once dealt with, the comorbidities will remain constant. This poses a problem in the current system where waiting times for elective joint replacement are long and increasing.

These differences in the way that comorbidities were viewed may point to wider differences between professional groups and how they relate to each other. In addition the different perspectives may lead to fragmented management of patients across the referral pathway to joint replacement surgery indicating the current pathway may be less suitable for patients with comorbidities. This reporting of challenges in coordinating care for patients with comorbidities between primary and secondary care professionals has also been reported in a previous study [29]. Healthcare professionals need to be aware of this potential system failure and more broadly need to consider the impact this has for clinical practice and the care of patients with comorbidities.

GPs and intermediate care professionals did not consider themselves 'experts' and therefore did not see it as their responsibility to support patients with comorbidities in their preparation for surgery. Some GPs mentioned this was due to a lack of knowledge which is in accordance with the findings of a survey of GPs about how they make decision about whether or not they should refer a patient for joint replacement surgery. The results of that survey suggest that, on average, they felt only moderately confident about their decisions about who to refer for joint replacement surgery, which was related to their uncertainty about the risks of the surgery [30]. A previous study has found that GPs felt the need for collaboration with 'specialists' was even more important for patients with chronic illnesses [31]. This highlights the potential benefits of further guidance on referrals for joint replacement surgery for patients with comorbidities in primary care.

In contrast, surgeons believed that it is the role of GPs to support patients in their preparation for surgery. This tension between GPs and 'specialists' in secondary care about their perceived roles and responsibilities has been reported in previous studies [32, 33]. This tension has been reported to be a barrier to delivering coordinated care [29]. Nevertheless, some surgeons, who observed that care was not being provided for patients who were unprepared for surgery, stepped outside the usual clinical pathway and provided the care themselves. These surgeons indicated that they aim to fill a gap in the

continuity of care for the patient. In a study investigating the relationship between GPs and hospital consultants across all specialities, hospital consultants were also reported to be filling the gap in continuity of care [34].

Interspersed through the interviews is the observation that patients with comorbidities were getting 'lost' as a results of the fragmented management of patients across the referral pathway. Patients with comorbidities who were considered unprepared for surgery by intermediate care professionals or surgeons were reported to be referred back to their GP where often the patients themselves were given responsibility to manage their comorbidities. Many patients however, may not be able to improve the management of their comorbidities [35] and therefore may never receive a joint replacement. It has also been reported in the cancer patient journey that patients are being sent back to their GPs who are not given the information to enable them to provide the continuity of care [36].

A study that carried out a qualitative thematic review exploring the perspectives of patients who were advised to manage their multiple chronic conditions themselves highlighted that access to care when needed is a major challenge [35]. Better support and access to care for patients with comorbidities may therefore play an important role in helping patients to be better prepared for joint replacement surgery.

Strengths and limitations

The sampling strategy employed for this study allowed us to explore the views of a range of health care professionals across the referral pathway to joint replacement surgery. The aim of this study was not to be representative but to collect extensive varied information in order to obtain an information-rich sample [27]. The study's limitations in addition to the relative small sample of professionals in each group was its focus on only one region of England which may limit its generalisability to other health systems in other countries. In particular, it is important to note that not every area in England has an intermediate musculoskeletal service within the NHS and therefore the views on the pathway to joint replacement of professionals working in other geographical regions may be different. However, one GP and two surgeons were also recruited from areas where no intermediate musculoskeletal services are operating and their responses to the questions and their understanding of managing comorbidities varied little. We tried to achieve a gender balance but this was not possible as almost all surgeons in our research area were male and almost all intermediate care professionals were female. This might have an impact on the way the participants framed their role. While this study is small in scale, it is unlikely that any of these limitations have affected the results as a diverse set of views were obtained. A larger scale qualitative study, with both patients and healthcare professionals, would be useful however, to further explore the journey along the referral pathway for patients with comorbidities and multimorbidity. Multimorbidity is an area that is underexplored but is an increasing problem for healthcare professionals to manage across the healthcare system [37].

Conclusions

Research on access to joint replacement surgery has predominantly used quantitative methods to compare characteristics of patients who needed a hip replacement with those who received it [38]. Our qualitative study looked directly at the referral pathway. Patients with comorbidities may access specialist care in terms of surgical consultation but then may not receive a hip or knee replacement. Access to joint replacement surgery seems to be complicated by a fragmented management of patients with comorbidities across the system. This may create an implicit barrier and make the current pathway less suitable for patients with comorbidities.

Additional file

Additional file 1: Topic guides. The topic guides for the semi-structured interviews with each group of healthcare professionals: Orthopaedic Surgeons, GPs and Intermediate care professionals. (DOCX 23 kb)

Abbreviations

COPD: Chronic Obstructive Pulmonary Disease; GP: General Practitioner; ICP: Intermediate care professional; MSK: Musculoskeletal

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Authors' contributions

BP designed the study, conducted the main study, analysis and wrote the manuscript. RL helped design the study design, conduct the analysis and with the drafting of the manuscript. JvM helped design the study design, with the analysis and the drafting of the manuscript. AH helped design the study design, analysis and with the drafting of the manuscript. MA helped design the study design, with the analysis and the drafting of the manuscript. SK helped with recruitment of surgeons and revised the manuscript. JR helped with recruitment of GPs and revised the manuscript. All authors have read and approved the manuscript.

Ethics approval and consent to participate

The participants gave written consent based on written and oral information. The study was approved by the Health Research Authority NHS Research Ethics Committee (Reference: 16/WA/0241) as well as the London School of Hygiene & Tropical Medicine ethics committee (Reference: 11628).

Consent for publication
Participants have provided written informed consent for direct anonymised quotes to be used for scientific publication purposes.

Competing interests
The authors declare they have no competing interest.

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5 RESULTS CHAPTER – Identifying comorbidity

The third component of this research programme investigated the agreement between patient-reported and administrative data-derived comorbidities. The results have been presented in the form of the submitted research paper. The supplementary material referenced to in the paper can be found in Appendix I (mapping of comorbidities).

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Thesis Title	The access to and outcomes of elective hip and knee replacement surgery for patients with comorbidities: a study using PROMs and administrative data		
Primary Supervisor	Professor Jan van der Meulen		

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5.1 Research Paper 3 (RP3)

The agreement between chronic diseases reported by patients and derived from administrative data in patients undergoing joint arthroplasty

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5.1.1 Abstract

Background: This study examined the agreement between patient-reported chronic diseases and hospital administrative records in hip or knee arthroplasty patients in England.

Methods: Survey data reported by 676 428 patients for the English Patient Reported Outcome Measures (PROMs) programme was linked to hospital administrative data. Sensitivity and specificity of 11 patient-reported chronic diseases were estimated with hospital administrative data as reference standard.

Results: Specificity was high (>90%) for all 11 chronic diseases. However, sensitivity varied by disease with the highest found for 'diabetes' (87.5%) and 'high blood pressure' (74.3%) and lowest for 'kidney disease' (18.8%) and 'leg pain due to poor circulation' (26.1%). Sensitivity was increased for diseases that were given as specific examples in the questionnaire (e.g. 'parkinson's disease' (65.6%) and 'multiple sclerosis' (69.5%), compared to 'diseases of the nervous system' (20.9%)).

Conclusions: Patients can give accurate information about the presence of chronic diseases if the description in the patient questionnaire is precise and if the disease is familiar to most patients and has significant impact on their life. Such patient questionnaires need to be validated before they are used for research and service evaluation projects.

5.1.2 Background

Patient surveys are often used in epidemiology to collect health data. However, the reliability and accuracy of patient-reported data, including patients' own accounts of whether or not they have been diagnosed with a particular chronic disease, have been questioned [1]. Administrative data – hospital data collected for a range of administrative purposes including managing payments to the healthcare providers for every hospital admission and procedure – offer an alternative source of data [2].

To be able to record accurately chronic diseases is essential. Healthcare providers depend on accurate coding to be reimbursed for the care they provide especially when treating complex patients with multiple chronic diseases. In patients undergoing hip and knee arthroplasty the number of complex patients is likely to rise with more than 60% of patients for these operations reporting at least one comorbid chronic disease [3]. This number is expected to continue to rise as the number of people living with multiple chronic diseases is on the increase [4]. In addition, good quality coding is essential when looking at outcomes of hip and knee arthroplasty which may be affected by chronic diseases and analyses must therefore adjust for this effect.

Few studies have assessed the accuracy of patient-reported chronic diseases compared to chronic diseases derived from administrative data [5-7]. The studies that did were predominantly cohort studies with relatively small sample sizes that reported single measures of agreement, such as the kappa statistic [1, 8]. A few larger scale studies investigated the agreement of a small number of patient-reported chronic diseases, with the most common being high blood pressure, stroke, heart disease and diabetes [5-7]. These studies found results for the agreement between patient-reported chronic diseases and hospital administrative data to vary significantly [1, 9-11].

We used the national Patient-Reported Outcome Measures (PROMs) programme of the English National Health Service (NHS), one of the largest collections of patient-reported data in the world, to assess the agreement of patient-reported chronic diseases against disease condition derived from hospital administrative data in patients undergoing hip or knee arthroplasty.

5.1.3 Methods

Study sample

The study sample of 676 428 patients was drawn from patient-reported data collected by the national PROMs programme in the English NHS [12]. All hospitals providing elective hip or knee arthroplasty funded by the English NHS are required to participate and patients are asked to complete pre-operative and post-operative questionnaires about their hip or knee condition and general health.

The data sample comprised completed pre-operative questionnaires linked with routinely collected administrative hospital data, Hospital Episode Statistics (HES) data, on all patient who had a hip or knee arthroplasty carried out in the English NHS between April 2009 and March 2016. The HES database contains a record of every inpatient hospital admission in the English NHS and is used primarily for reimbursement purposes [13]. A linked pre-operative PROMs questionnaire and HES record is available for 71% of eligible hip and knee arthroplasties [12].

We created a dataset comprising one unique linked patient-reported record for each individual patient. Duplicate records were excluded if more than one pre-operative questionnaire was linked to a procedure or more than one procedure in HES was linked to the same questionnaire. The first linked HES record for each patient was included but linked records for any subsequent procedures were excluded. Patients were also excluded if they reported seven or more comorbidities in the preoperative PROMs questionnaire due to the concerns about the validity of the responses. Patients appeared to report the absence rather than the presence of a chronic disease.

Chronic disease according to the PROMs programme

In the PROMs pre-operative questionnaire patients were asked: 'Have you ever been told by a doctor that you have any of the following conditions? Heart disease (for example angina, heart attack or heart failure), high blood pressure, problems caused by stroke, leg pain when walking due to poor circulation, lung disease (for example asthma, chronic bronchitis or emphysema), diabetes, kidney disease, diseases of the nervous system (for example, Parkinson's disease or multiple sclerosis, liver disease, cancer (within the last 5

years), depression, [or] arthritis'. 'Arthritis' was excluded from our analyses because it is the primary a reason for hip or knee arthroplasty (81% patients reported having arthritis).

Chronic disease according to administrative data

The 11 patient-reported chronic diseases were identified within HES data using International Classification of Disease (ICD-10) codes from the corresponding linked HES record of the hip or knee arthroplasty and from HES records of any other hospital admission within the previous 12 months or five years. Each HES record includes up to 20 ICD-10 diagnosis codes.

The initial set of ICD-10 codes for each of the 11 chronic diseases was derived from three chronic disease indices that have been used to identify chronic diseases in administrative data: The Royal College of Surgeons of England Charlson Comorbidity Index (RCS CCI) [14], the Quan Charlson Comorbidity Index (Quan CCI)[15] and the Elixhauser Comorbidity index [16]. The RCS CCI was chosen because it was designed to predict outcomes in surgical patients and has been validated for total hip arthroplasty using English HES data [14]. The Quan CCI is an adaptation of the Deyo CCI [15], and was chosen because it uses ICD-10 coding and is similar to other CCI adaptations in predicting both short-term and long-term mortality [17]. The Elixhauser Comorbidity Index was chosen because there is evidence that it may predict mortality better than other adaptations of the CCI [18].

The set of ICD-10 codes derived from the three chosen comorbidity indices were then mapped to the 11 diseases included in the PROMs questionnaire (see supplementary material). A further 16 ICD-10 codes were added to the chronic disease mapping through the process of 'backward coding'. 'Backward coding' involved reviewing linked HES records of hospital admissions in patients who had reported a chronic disease but who had no mapped records (ICD-10 codes) of the chronic disease in their HES records. First, relevant ICD-10 chapters were identified for each of the 11 chronic diseases. The most common (>1% of patients reporting the chronic disease) and clinically relevant codes at the ICD-10 three-character category level were then identified. Second, the codes identified at the ICD-10 three-character level were further investigated at the ICD-10 four-character subcategory level. The prevalence of each four-character code in the administrative data were compared between patients who had and those who had not reported a specific chronic disease. The four-character code was added to the mapped ICD-10 codes if the

proportion of patients reporting presence of a chronic disease was at least twice that in patients not reporting the chronic disease. For the main analyses, this final set of codes was used to determine the presence of chronic disease according to administrative data from the corresponding linked hospital record and from records of admissions within the previous 12 months or five years.

Statistical analysis

The patient-reported chronic diseases at the point of surgery were compared with recorded diagnoses in the corresponding administrative record of the linked hospital admission and the records of previous admissions in two ways. First, agreement between patient-reported and administrative records was evaluated using sensitivity and specificity with administrative data as the reference standard. Second, we calculated the kappa statistic as an alternative measure of the agreement between patient-reported and administrative data for each condition. The kappa statistic is an agreement measure that takes into account chance agreement. A value of one indicates perfect agreement and a value of zero indicates no agreement above that expected by chance. Kappa values are often categorised in the following way: < 0.40 'poor agreement', 0.40-0.60 'moderate agreement', 0.61-0.80 'substantial agreement', and 0.81 – 1.00 'near perfect agreement' [19].

The sensitivity of patient-reported chronic disease was also explored further at the chronic disease subcategory level derived from administrative data. We grouped the set of ICD-10 codes for each of the 11 comorbid conditions according to clinically relevant subcategories (see supplementary material). ICD-10 codes were grouped according to whether they reflected a cause (e.g. subarachnoid haemorrhage), a manifestation (e.g. asthma), or a consequences of disease (e.g. renal failure). For each comorbid condition ICD-10 codes that did not fit into any these grouping, the codes were put into an 'other' group. The sensitivity of the patient-reported chronic diseases compared to these chronic disease subcategories derived from administrative data were presented in a forest plot.

Sensitivity analysis

The impact of the length of the look-back period on the performance of the combined chronic disease measure in administrative data was also investigated [20-22]. Some chronic

diseases such as ‘heart disease’ are diseases that can fluctuate and others, such as ‘stroke’ are single events. For that type of chronic diseases, a longer look-back ensures that records of chronic diseases coded in admissions that occurred further in the past are also captured. In the PROMs questionnaire, patients were asked to recall cancer within the last five years which is another reason to use a 5-year look-back period as an alternative to the one-year look-back period.

5.1.4 Results

Study sample

Agreement between chronic disease measures reported by patients and derived from administrative data was examined in 676 428 patients who underwent a hip or knee arthroplasty between 2009 and 2016 in the English NHS and who participated in the PROMs programme from a total 791 369 linked records. Records were excluded for the following reasons: duplicate pre-operative questionnaires (10 762), duplicate HES procedures (140), subsequent procedures for patients included in the analyses (103 395), and patients reporting seven or more chronic diseases on their pre-operative questionnaire (644) (see Figure 1). 50.6% of the patients underwent knee arthroplasty. The average age of the population was 68 years (18-105). The majority of the patients had a white ethnic background (86.3%) and 58.0% of the study cohort were female (see Table 1). Patients living in the most socioeconomically deprived areas were slightly under-represented in the sample: those in the bottom two deprivation groups based on quintiles made up only 34.5% of patients undergoing a primary hip or knee arthroplasty whereas 40% is expected given that the quintiles reflect the national distribution.

Agreement between patient-reported chronic disease and administrative data

Sensitivity, specificity, and the kappa statistic for patient-reported chronic disease against chronic diseases derived from administrative data using a 1-year look-back are reported in Table 1. Patient-reported chronic diseases had high specificity (ranging between 90.3% for ‘high blood pressure’ and 99.7% for ‘disease of the nervous system’ and ‘liver disease’), but sensitivity varied (ranging from 18.8% for ‘kidney disease’ to 87.5% for ‘diabetes’).

According to the kappa statistic, there was 'substantial agreement' between patient-reported and administrative results for 'high blood pressure' (κ =0.65) and 'almost perfect agreement' for 'diabetes' (κ =0.88) (see Table 2). There was 'moderate agreement' for 'heart disease' (κ =0.54) and 'lung disease' (κ =0.55). In contrast, there was 'poor agreement' for 'stroke', 'liver disease', 'leg pain due to poor circulation', 'kidney disease' and 'depression'.

Agreement between patient-reported chronic diseases and chronic disease subcategories derived from administrative data

Further investigation comparing patient-reported chronic disease against chronic disease subcategories derived from administrative data demonstrated that the sensitivity varied if the patient-reported results were compared against subcategories defined according to administrative data (see Figure 2). Sensitivity ranged from 1.3% for patient-reported 'leg pain due to poor circulation' compared against 'gangrene' according to administrative data to 91.6% for patient-reported 'diabetes' compared against 'insulin-dependent diabetes' according to administrative data.

The sensitivity was considerably higher in subgroups of chronic diseases where specific examples of the chronic diseases were given as examples in the questionnaire used for the PROMs survey in the PROMs survey. For example, we saw that the sensitivity of 'diseases of the nervous system (for example Parkinson's disease or multiple sclerosis)' was much higher in subgroups of patients who had these two specific diseases quotes as examples in their administrative data (65.6% and 69.5%, respectively) than in entire group of patients who had the generic term 'diseases of the nervous system' in the administrative data (20.9%). We saw a similar effect for the examples given in 'heart disease (for example angina, heart attack or heart failure)'. The sensitivity in the subgroup of patients with the specific term ischemic heart disease in the administrative data was significantly higher (64.9%) than in all patients who had the generic term 'heart disease' according to administrative data (46.4%).

Impact of length of look-back period on agreement

The impact of the length of look-back period on the chronic diseases derived from administrative data was investigated. Increasing the look-back period for identifying

chronic diseases in administrative data from 12 months to five years had little impact on the sensitivity, specificity and kappa statistic (see Table 3). As expected, sensitivity decreased and specificity increased. The biggest change was the increase of the kappa statistic for 'cancer' from 0.37 with a 12-month look-back period to 0.69 with a 5-year look-back period.

5.1.5 Discussion

In this large study of patients undergoing hip or knee arthroplasty we determined that for 11 patient-reported chronic diseases specificity was high but sensitivity varied greatly when the patient-reported results were compared to administrative data. Specifically, sensitivity was highest for 'diabetes' and 'high blood pressure' and lowest for 'leg pain due to poor circulation' and 'stroke'. The variation in sensitivity also differed further when the patient-reported chronic diseases were compared against chronic diseases subcategories derived from administrative data. Sensitivity is high if the description of the chronic disease in the patient questionnaire is precise and uses language familiar to most patients, if it requires daily treatment or drug administration for the patient, or the chronic diseases has a significant impact on patient's lives.

Sensitivity was high for comorbid conditions that describe a specific disease diagnosis (in terms of a cause, manifestation, or disease consequence) rather than a collection of symptoms. This might explain why 'diabetes' had higher sensitivity than 'leg pain due to poor circulation' and 'problems caused by stroke'. Similarly, when looking at disease subcategories, sensitivity was higher when specific examples of chronic diseases were given in the PROMS questionnaire survey rather than the generic category for the chronic disease. This demonstrated that if a disease has a spectrum of severity, subcategories may be more useful categories to use to ask patients about the presence of any chronic diseases.

While specificity was generally high for all chronic diseases, it did vary by up to 10%. It is important to note that administrative hospital data, HES, is not a perfect reference standard. Certain chronic diseases may not be fully recorded in administrative data because they may not be severe enough to significantly alter the treatment a patient receives in hospital or influence the hospital's resource use related to a patient's care. Further coding errors in hospital administrative data can also occur as coding is often undertaken by administrative staff who depend on medical notes so any errors in the notes

can lead to chronic diseases not being captured. On the other hand, conditions that are single events in time such as stroke and ischemic heart diseases may not be recorded in administrative data due to a limited look-back period [23-25]. Nevertheless, when we increased the look-back period from 12 months to five years there appeared to be little or no impact on sensitivity of patient-reported chronic disease relative to administrative data. An increase of the duration of the look-back period to five years did improve the agreement for cancer but this may just be a reflection of the PROMs question, which asked patients to report ever being diagnosed with cancer in the last five years.

A study comparing patient-reported chronic disease against chart review suggested that low agreement, especially low sensitivity, may be due to the description of the conditions in the patient questionnaire, for example if the wording is based more on symptoms ('leg pain due to poor circulation') than disease ('diabetes) or if the disease has stable or only a few symptoms (e.g. 'kidney disease') [26]. Similarly, previous studies found that conditions requiring ongoing management such as diabetes or hypertension had highest agreements in comparison to poorly defined diseases such as stroke or congestive heart failure [5-7, 27].

With respect to the impact of the length of the look-back period, other studies had similar findings to ours in that they found limited benefits in increasing the look-back period beyond one year [6, 27].

These findings provide support for the use of patient-reported data to identify patients with chronic diseases if administrative data are unavailable. The questionnaire should however be validated beforehand with patients to ensure clarity, comprehension and ease of completion. This is especially important to improve the capture of less common and more complex chronic diseases such as kidney disease or diseases of the nervous system.

There are several limitations to this study. As is the case for any cohort study the generalisability of our conclusions are limited by the characteristics of our population and the quality of the data. The PROMs questionnaires were completed by patients who underwent hip or knee arthroplasty and as a consequence, these patients were likely to have fewer and less severe chronic diseases than a population of older patients with arthritis because more severe cases are less likely to be eligible for surgery [28]. Disease status is often not clear-cut and the recording in hospital administrative data – our reference standard – will often be based on a 'cut-off point' with most misclassification occurring in those patients with a true disease status close to the cut-off point. The

combination of a relatively low prevalence and mild severity may therefore partly explain our finding of relatively low sensitivities and high specificities [29].

5.1.6 Conclusion

This study indicates that patients can give accurate information about the presence of chronic diseases. The sensitivity and specificity of patient-reported chronic disease can be high if the description in the patient questionnaire is precise and familiar to most patients and if the conditions have a specific impact on the patients' lives. These findings may guide the development of questionnaires that can be used to ask patients whether or not they have particular chronic diseases.

5.1.7 Figures and Tables

Figure 1 - Flow chart

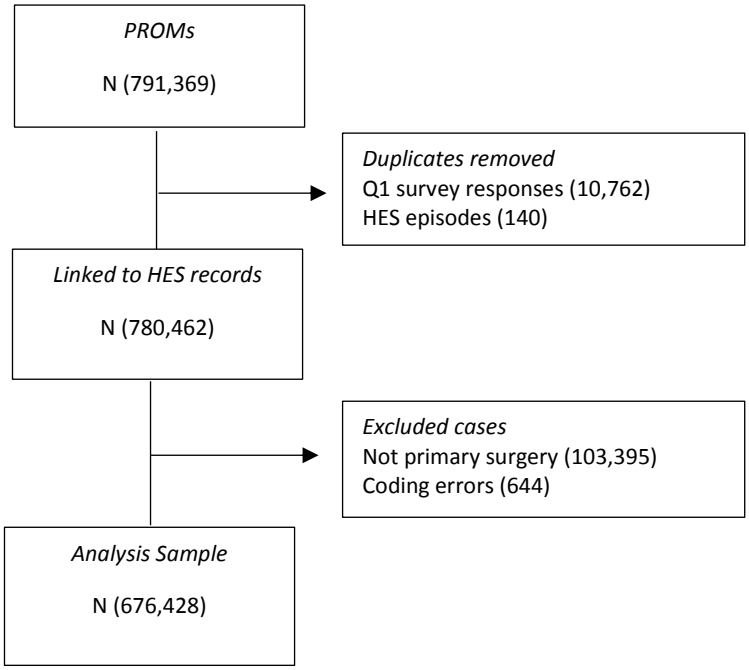


Table 1 - Characteristic of PROMs study population (N=676,428)

	Number (%)
Age (mean, range)	69 (18-105)
Gender	
Male	283 892 (42.0)
Female	392 107 (58.0)
Missing, not stated	429 (0.06)
Socioeconomic status by quintile group	
1 (least deprived)	151 850 (22.5)
2	159 353 (23.6)
3	125 160 (18.5)
4	118 487 (17.5)
5 (most deprived)	114 691 (17.0)
Missing, not stated	6 887 (1.02)
Ethnicity	
White or White British	583 674 (86.3)
Mixed background	1 469 (0.22)
Asian or Asian British	12 126 (1.79)
Black or Black British	5 377 (0.79)
Chinese or other ethnic	2 991 (0.44)
Missing, not stated	70 791 (10.5)

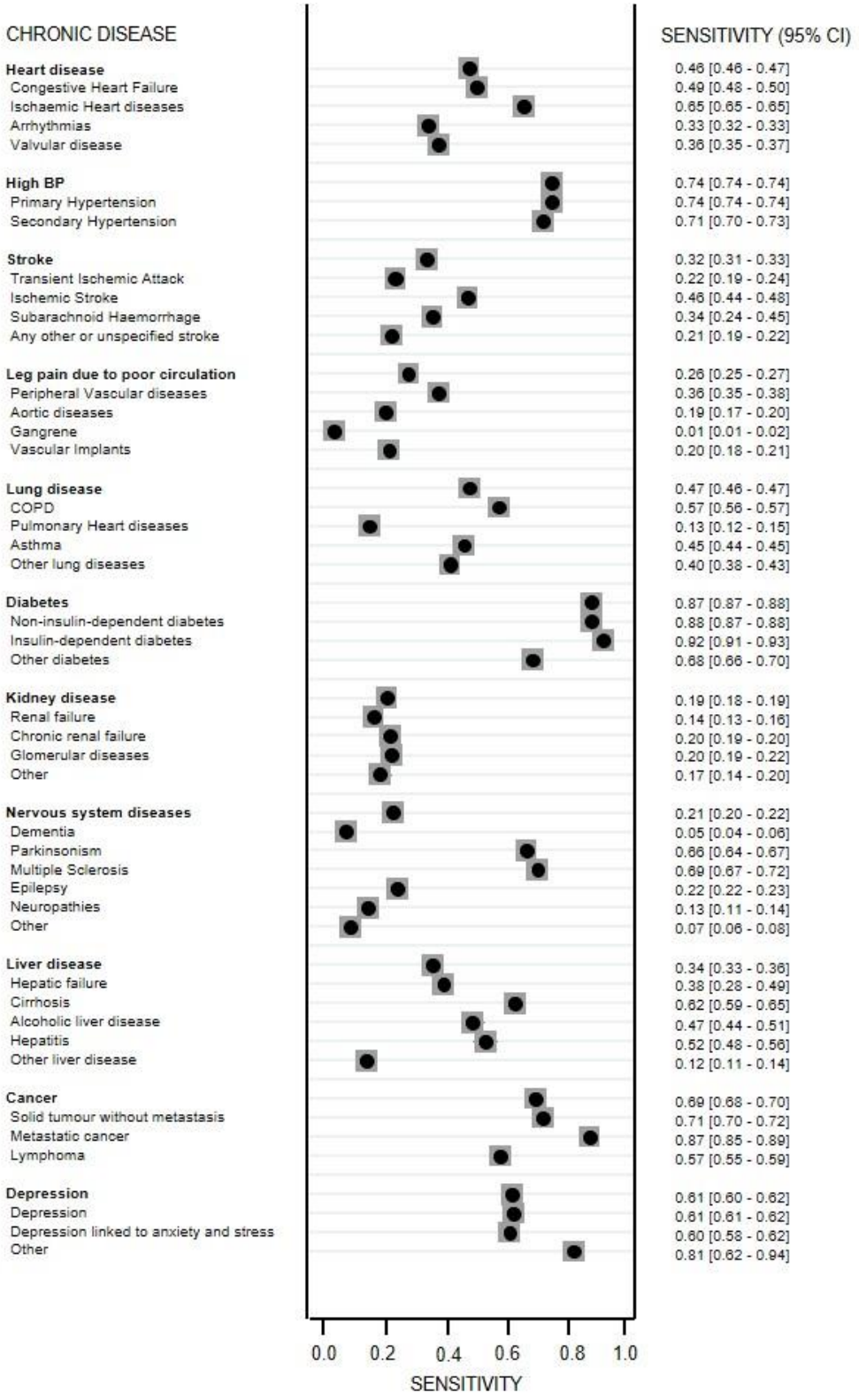
Table 2 – Sensitivity and specificity of patient-reported chronic diseases relative to chronic diseases derived from administrative data (1-year look-back) (N=676,428)

Chronic disease	Patient-reported n (%)	Administrative n (%)	Prevalence in either patient-reported or administrative data, n (%)				Sensitivity (%)	Specificity (%)	Kappa (κ)
			Both	Admin only	Patient-reported only	Neither			
Heart disease	67 425 (9.97)	122 219 (18.1)	56 736 (8.39)	65 460 (9.68)	10 689 (1.58)	543 543 (80.4)	46. 4	98.1	0.54
High blood pressure	282 785 (41.8)	335 958 (49.7)	249 608 (36.9)	86 350 (12.8)	33 177 (4.90)	307 293 (45.4)	74.3	90.3	0.65
Stroke	11 126 (1.64)	7 348 (1.09)	2 367 (0.35)	4 981 (0.74)	8 759 (1.29)	660 321 (97.6)	32.2	98.7	0.25
Leg pain due to poor circulation	48 298 (7.14)	10 917 (1.61)	2 855 (0.42)	8 063 (1.19)	45 444 (6.72)	620 067 (91.7)	26.1	93.2	0.07
Lung disease	55 717 (8.24)	100 260 (14.8)	46 876 (6.93)	53 384 (7.89)	8 841 (1.31)	567 327 (83.9)	46.8	98.5	0.55
Diabetes	75 998 (11.2)	78 816 (11.7)	68 952 (10.2)	9 864 (1.46)	7 046 (1.04)	590 566 (87.3)	87.5	98.8	0.88
Kidney disease	12 435 (1.84)	36 823 (5.44)	6 910 (1.02)	29 913 (4.42)	5 542 (0.82)	634 080 (93.7)	18.8	99.1	0.26
Diseases of the nervous system	5 840 (0.86)	19 550 (2.89)	4 092 (0.60)	15 458 (2.29)	1 748 (0.26)	655 130 (96.9)	20.9	99.7	0.31
Liver disease	3 585 (0.53)	4 120 (0.61)	1 412 (0.21)	2 708 (0.40)	2 173 (0.32)	670 135 (99.1)	34.3	99.7	0.36
Cancer	32 384 (4.79)	12 710 (1.88)	8 740 (1.29)	3 970 (0.59)	23 644 (3.50)	640 074 (94.6)	68.8	96.4	0.37
Depression	61 589 (9.11)	29 923 (4.42)	18 263 (2.70)	11 660 (1.72)	43 326 (6.41)	603 179 (89.2)	61.0	93.3	0.36

Table 3 - Sensitivity and specificity of patient -reported chronic disease relative to chronic disease derived from administrative data using a 5-year look-back period.

Chronic disease	Prevalence n (%)	Sensitivity (%)	Specificity (%)	Kappa (κ)
Heart disease	141 457 (20.9)	43.0	98.8	0.52
High blood pressure	358 699 (53.0)	72.3	92.7	0.64
Stroke	15 783 (2.33)	30.3	99.0	0.34
Leg pain due to poor circulation	17 728 (2.62)	24.1	93.3	0.10
Lung disease	112 774 (16.7)	43.6	98.8	0.53
Diabetes	82 384 (12.2)	85.6	99.1	0.88
Kidney disease	45 172 (6.68)	17.1	99.3	0.25
Diseases of the nervous system	24 727 (3.66)	17.4	99.8	0.27
Liver disease	7 173 (1.06)	24.6	99.7	0.32
Cancer	31 649 (4.68)	71.2	98.5	0.69
Depression	38 503 (5.69)	58.4	93.9	0.41

Figure 2 - Forest plot of sensitivity by chronic disease subcategories derived from administrative data (95% CI)



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6 RESULTS CHAPTER – Access

The fourth component of this research programme investigated the impact of comorbidities on the access to elective hip and knee replacement surgery. Specifically the study looked at severity of joint problems (functional status and pain) and duration of symptoms just before surgery. This study worked with the assumption that if there were differences in access we might expect differences in severity of joint problems and the duration of these joint problems just before surgery. The results have been presented in the form of a research paper. Supplementary information can be found at the end of the section.

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First Name(s)	BÉLÈNE		
Surname/Family Name	PODMORE		
Thesis Title	The access to and outcomes of elective hip and knee replacement surgery for patients with comorbidities: a study using PROMs and administrative data		
Primary Supervisor	Professor Jan van der Meulen		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

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Stage of publication	**Not yet submitted**

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	I designed this study, undertook the analyis and wrote the first draft of the manuscript.

SECTION E

Student Signature	[redacted]
Date	23 November 2018

Supervisor Signature	[redacted]
Date	23 November 2018

6.1 Research Paper 4 (RP4)

Patients with comorbidities have joint replacement surgery later in their joint disease based on patient-reported pain and functional status

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6.1.1 Abstract

Background: An increasing number of patients with comorbidities are undergoing joint replacement surgery. Comorbidities may delay access to surgery. If that is the case, pain, functional status and duration of joint problems just before surgery may vary according to comorbidities.

Methods: We analysed data reported by 640 832 patients who had hip or knee surgery between 2009 and 2016 in England. Multivariable regression was used to estimate impact of 11 comorbidities on symptom severity as measured by the Oxford Hip (OHS) and Knee Score (OKS), ranging from 0 (worst) to 48 (best), just before surgery and on likelihood of having long-standing joint problems.

Results: Patients with comorbidities reported more severe symptoms compared to patients without (OHS differences ranged from 1.1 to 2.5 and OKS differences from 0.5 to 2.6 for the 11 comorbidities). Differences were observed for pain and for functional status when examined. Evidence for increased likelihood of long-standing problems was less consistent and observed in 6 out of 11 comorbidities in hip patients and 2 of 11 in knee patients.

Conclusions: Patients with comorbidities reported more severe joint problems just before surgery which suggests they may have joint replacement later in the course of their joint disease.

6.1.2 Introduction

Hip and knee replacement surgery is one of the most common and effective surgeries, improving quality of life significantly [1]. Previous research has reported inequalities in access to hip and knee replacement surgery according to socioeconomic status [2], sex [3-5], insurance status [6], ethnicity [7], and geography [8], but less attention has been given to the impact that comorbidities might have on access.

Variation in access may be explained in part by the lack of consensus amongst clinicians with respect to the clinical indications for joint replacement surgery [9-12]. In addition, in England as well as in Canada, eligibility criteria restricting access to hip and knee replacement surgery have recently been introduced to limit inappropriate use of joint replacement surgery and reduce healthcare cost [13, 14]. In England, eligibility criteria such as severity of preoperative functional status [15] and pain [13], the requirement that a patient's body mass index is lower than 30kg/m2 [16], and the optimisation of pre-existing comorbid conditions [17-19] have been imposed by some regional commissioners of healthcare. There is no evidence, however, to suggest that limiting access according to any of these criteria is justified and these policies are not supported by National Institute for Health and Care Excellence (NICE) guidelines [20].

Previous research investigating variation in access to joint replacement surgery has used two different approaches to measuring access. Some papers have measured access indirectly from a population perspective by focusing on those not receiving surgery and seek to measure unmet need [21-23]. Others have looked at those who do have surgery, studying variation in utilisation of surgery according to factors such as regional variation [24] or socioeconomic status [25]. The Patient Reported Outcome Measures (PROMs) programme in England has provided a new opportunity to explore access as it provides information on severity of joint problems and duration of joint problems just before surgery. If there were differences in access, we might expect to see differences in severity of joint problems and in duration of problems just before surgery according to the presence of comorbidity. A similar approach has been used before to look at the impact of socioeconomic status [25] in joint replacement patients and patients with heavy menstrual bleeding referred to secondary care [26] and found that patients from a lower

socioeconomic status reported more severe symptoms which suggest delayed access to secondary care.

Severity of joint problems is typically measured using disease-specific measures such as the Oxford Hip (OHS) and Knee (OKS) score. The challenge of these measures, which are designed to only assess the severity of the hip or knee problem, is that they may be capturing the impact of both joint problems and comorbidities [27-29]. To further explore this influence we looked at functional status and pain scores separately. We hypothesised that pain is more 'joint-specific' than functional status and that it is less likely to be influenced by comorbidities. In this paper, we examine associations of the severity of joint problems (pain and functional status), and duration of joint problems in patients with different individual comorbidities just before the hip or knee replacement surgery.

6.1.3 Methods

Data sources

We used data from the England's national Patient Reported Outcome Measures (PROMs) programme for elective hip and knee replacement surgery. All NHS providers are required to participate and patients are asked to report their physical functioning and wellbeing at the preoperative assessment clinic or on admission to hospital and then again six months after surgery. Over 75% of eligible patients complete the preoperative questionnaire and the OHS/OKS [30]. The PROMs data were linked at patient level to data from the Hospital Episode Statistics (HES) database. HES contains administrative records of all admissions to all NHS hospitals in England. Eligibility was restricted to the first primary replacement surgery (see Figure 1).

Defining comorbidities

The 11 comorbidities that were included in the analysis were defined using ICD-10 codes in the linked hospital admissions HES data up to one year prior to the surgery. The 11 comorbidities comprised heart disease; high blood pressure; problems caused by a stroke;

leg pain when walking due to poor circulation; lung disease; diabetes; kidney disease; nervous system disease; liver disease; cancer and depression. These comorbidity categories are used in the PROMs questionnaire and are based on the work of Bayliss et al [31]. These comorbidity categories were used because it allowed for comparison with a combination of already existing ICD-10 diagnosis-based comorbidity indices.

Measures

We used the OHS and the OKS as our measures of severity of joint problems just before surgery. These are derived from patient responses to 12 questions about pain and limits on physical functioning and everyday activities caused by the hip or the knee (see supplementary information). Responses to each question are measured on a five-point scale, and values associated with each response are added up to produce an overall scale from 0 (worst) to 48 (best). The OKS and OHS have been validated and found to correlate with surgeon assessment of symptoms [32, 33].

We also considered the questions related to pain and those related to functional status separately. We hypothesised that any impact of comorbidities was more likely to influence functional status rather than pain. This approach has been used before to predict patient satisfaction after hip and knee replacement surgery [34]. For the OKS, scores for the five questions on pain were added together as were those for the seven on functional status (see supplementary information). For the OHS, there were six questions each on pain and functional status.

A categorical measure of symptom duration was derived from responses to a single question asking patients how long they had experienced problems with the hip or the knee on which they were about to have surgery. The four response categories included ‘Less than 1 year’, ‘1–5 years’, ‘6–10 years’, and ‘More than 10 years’. We defined long-standing hip or knee symptoms as problems with a duration of symptoms of more than 5 years.

Statistical analysis

We estimated adjusted differences in mean preoperative pain and functional status using multivariable linear regression and calculated the mean scores according to the presence or absence of each comorbidity. We also estimated odds ratio (ORs) for having long-standing hip or knee problems for each comorbidity using multivariable logistic regression. The impact of number of comorbidities (1, 2, 3, 4 or more comorbidities) on the severity of joint problems and duration of joint problems was also investigated to explore the effect of having multiple comorbidities.

We adjusted for sociodemographic factors (age, sex, ethnicity and socioeconomic status) and other comorbidities. Information on age, sex, ethnicity and socioeconomic status [35] were derived from the HES records. Missing values for ethnicity, age, sex and socioeconomic status were imputed with chained equations. Analyses were run on each of the 10 imputed data sets and estimated parameters were combined using Rubin's rules. Statistical results are presented with their 95% confidence interval and p-values. All statistical analysis were carried out using STATA V.15.

6.1.4 Results

Patient characteristics

640 832 patients were eligible (see supplementary material 1 and 3). The mean age was 68 and 42% were male. About 3% of patients reported a minority ethnic background with Black or Black British being the largest group but there was a high percentage of missing data.

Just before surgery, the mean score for symptom severity was 17.4 for the OHS and 18.3 for the OKS. Nearly 20% of patients undergoing hip replacement and more than 40% of patients undergoing knee replacement had their joint problems for more than five years. Patients who reported long-standing problems tended to have more severe OHS and OKS scores but the average differences were small (less than one point).

The most common comorbidities were high blood pressure (52.8%), heart disease (17.8%), and lung disease (14.5%). The least common comorbidity was liver disease (0.6%). 35% of patients had one comorbidity and 32% two or more. Of those with two comorbidities, 87% had high blood pressure and 37% had heart disease. Of those patients with three comorbidities, 94% had high blood pressure, 62% had heart disease and 42% had diabetes. Of those patients with four or more comorbidities, 97% had high blood pressure, 80% had diabetes and 58% had lung disease.

Severity of joint problems

Patients with any of the 11 comorbidities for both hip and knee replacement surgery reported more severe joint problems than patients without comorbidities just before surgery (see Table 1). For hip replacement, adjusted differences in severity of joint problems ranged from 1.06 (95% CI 0.93, 1.19) for kidney disease to 2.49 (95% CI 2.31, 2.66) for diseases of the nervous system. For knee replacement surgery, adjusted difference in severity of joint problems ranged from 0.46 (95% CI 0.26, 0.66) for cancer patients to 2.58 (95% CI 2.42, 2.73) for patients with diseases of the nervous system. The largest differences in severity of joint problems for both hip and knee replacement were reported by patients with diseases of the nervous system, depression and liver disease and the smallest differences for high blood pressure, cancer and kidney disease.

We also performed regression modelling to establish the impact of comorbidities on pain and functional status scores separately. Patients with comorbidities reported not only worse functional status but also more pain just before surgery than patients without for each of the 11 comorbidities (see Table 2). Similar to the overall OHS and OKS score, the stronger impact on both functional status and pain scores was found in patients with diseases of the nervous system and depression and the lowest in patients with kidney disease and cancer.

Long-standing joint problems

The likelihood of having long-standing hip or knee problems showed a mixed picture for patients with different comorbidities compared to patients without comorbidities (see Figure 1). For hip replacement surgery, patients with six out of the 11 comorbidities were more likely to have more long-standing problems compared to only two out of 11 comorbidities for knee replacement surgery. In hip patients, the adjusted OR ranged from 0.86 (95% CI 0.80, 0.93) for cancer to 1.17 (95% CI 1.07, 1.29) for stroke. Patients with heart disease (OR 1.08, 95% CI 1.05, 1.11), diabetes (OR 1.14, 95% CI 1.10, 1.17) and stroke (OR 1.17, 95% CI 1.07, 1.29), were more likely to have long-standing problems. In the case of knee replacement surgery only, patients with heart disease (OR 1.06, 95% CI 1.04, 1.08) and diabetes (OR 1.06, 95% CI 1.04, 1.09) were more likely to have long-standing problems. Patients with high blood pressure (OR 0.95, 95% CI 0.94, 0.96) and diseases of the nervous system (OR 0.84, 95% CI 0.81, 0.88) were less likely to have long-standing problems.

Multiple comorbidities

Severity of joint problems increased with the number of comorbidities after adjustment for age, sex, ethnicity and socioeconomic status (see Table 3). In hip replacement surgery, adjusted differences increased (worsened) from 1.45 (95% CI 1.38, 1.52) in patients with one comorbidity to 2.79 (95% CI 2.70, 2.87) for patients with two comorbidities. Patients with four or more comorbidities, with the most common combination being high blood pressure, heart disease, diabetes and lung disease, reported the largest adjusted differences (5.79, 95% CI 5.61, 5.96). In knee replacement surgery, adjusted differences indicated severity increased (worsened) from 1.06 (95% CI 0.99, 1.12) in patients with one comorbidity to 4.79 (95% CI 4.64, 4.94) for patients with four or more comorbidities. The same gradient was observed in knee replacement surgery patients and when looking at pain and functional status separately.

The impact of the number of comorbidities on the likelihood of reporting long-standing problems was inconsistent. In hip patients, only patients with four or more comorbidities were more likely to report long-standing problems (OR 1.15, 95% CI 1.09, 1.23). In knee

patients, an increasing number of comorbidities had no impact on the likelihood to report long-standing problems.

6.1.5 Discussion

Main findings of the study

Patients with comorbidities undergoing hip and knee replacement surgery reported more severe joint problems just before surgery than patients without comorbidities. The largest differences in severity of joint problems were reported by patients with liver disease, depression and diseases of the nervous system. These differences in severity of joint problems persisted even when considering pain and functional status scores separately. Patients with comorbidities reported not only worse functional status but also more pain just before surgery, suggesting patients with comorbidities have truly worse joint symptoms regardless of any direct influence of comorbidities on the validity of the disease-specific measure. When looking at the number of comorbidities, the differences increased (worsened) with an increasing number of comorbidities. Patients with different comorbidities however reported little to no differences in duration of symptoms compared to patients without comorbidities. The differences in the likelihood of having long-standing problems were small and variable across all 11 comorbidities and the two surgical sites. Overall, the findings suggest that some patients with comorbidities may be having surgery later in their course of their joint disease and experience greater joint problems just before surgery than those without comorbidities.

The observed differences in severity of joint problems were small but statistically significant for all of the 11 different comorbidities. To interpret the size of the difference, a possible comparison is with 'minimally important differences (MID)', the smallest important difference in scores that patients report as beneficial. Suggested MID values are five points for both the OHS and OKS [36]. Only hip and knee patients with four or more comorbidities reported a minimally important difference in scores compared to patients without comorbidities.

With regard to the variable impact of comorbidities on duration of symptoms, the inconsistency in results may be due to recall bias. Patients were asked, “How long they had experienced problems with the hip or the knee on which they were about to have surgery?” but patients may have reported the duration of symptoms of a most recent episode with a specific level of severity, rather than the overall duration [37].

What is already known on this topic?

Differences in symptom severity just before surgery have been suggested to reflect inequitable access to healthcare [25]. Little is known about the impact of comorbidities on access to surgery. Drawing on the evidence on the variation in access to joint replacement surgery according to other factors such as socioeconomic status [25] and geography [8], this variation has been explained by delays to surgery due to patient decision-making [38] or clinical decision-making [39-42].

Delays to surgery may be due to patient decision-making such as the patients’ unwillingness to undergo surgery or health-seeking behaviour. A number of studies have reported differences in patient preferences and expectations for joint replacement surgery according to sex, ethnic group and socioeconomic status [38, 43, 44]. For example, some patients with comorbidities may decide not to want major surgery, which requires a long recovery period. Similarly, elderly people may prefer to delay surgery and manage the pain and the limited mobility [45]. Health-seeking behaviour and differences in thresholds for pain may also delay seeking clinical advice or having surgery. There is evidence that more deprived people tend to accept a higher threshold of chronic pain and functional limitation before having surgery [46].

Delays to surgery may also reflect variation in clinical decision-making about the indications for replacement surgery [10, 41]. In two studies with different groups of healthcare professionals, comorbidities were reported to be reasons not to recommend patients for surgery due to the risks of surgery [42, 47]. In our previous work, we explored the views of healthcare professionals along the referral pathway to joint replacement about referring and selecting patients with comorbidities for joint replacement surgery [48]. Healthcare professionals reported that patients with comorbidities were often not ‘prepared’ for surgery due to their comorbidities not being controlled and their surgery were therefore

delayed and the patients sent back to GPs. Patients were then left to manage their own conditions before being reconsidered for surgery. This delayed access to surgery, as a result of the fragmented management of patients with comorbidities across the system, is likely to be reflected in the severity of joint problems and duration of these joint problems at the point of surgery [49].

What this study adds?

This study is the first to examine the relationship between comorbidities and patient-reported functional status, pain and duration of joint problems just before surgery in a routine representative sample of patients undergoing hip or knee replacement surgery. By considering functional status and pain scores separately, it was possible to further distinguish the impact of comorbidities on severity of joint problems. Patients with comorbidities reported not only worse functional status but also more pain suggesting they truly have more severe joint problems before surgery compared to patients without comorbidities. A further analysis of the number of comorbidities demonstrated that the difference between patients with and without comorbidities increases in importance with number of comorbidities.

This study demonstrates there are differences in severity of joint problems just before surgery suggesting some patients with comorbidities are having joint replacement later in their joint disease. Previous research suggests that differences in severity of joint problems just before surgery may be due to delays to surgery [25]. There are several plausible explanations for such delays. These may be related to patient decision-making such as patients' unwillingness to undergo surgery [38] or clinicians' differences in decision-making [42, 47]. The variation in clinical decision-making may also be linked to the eligibility criteria imposed by regional commissioners of healthcare to optimise comorbidities before surgery.

Limitations of this study

Our final sample represents 71% of all patients who had a hip or knee replacement in the NHS. While response rate to the PROMs survey is high, non-recruitment may lead to confounders being unevenly distributed between different groups of patients and hospitals [50]. To account for this, we controlled for hospital variation. This had a minimal impact on

the findings. In addition, there is evidence to suggest that a healthy-surgical patients effect is operating such that patients who are considered too high-risk, many of whom will likely suffer comorbidities, may not be selected for surgery [11]. As a result, our population may represent a healthier hip and knee replacement population with one or more comorbidities than a random sample from the general population with a similar comorbidity profile.

There may also be unmeasured or unobserved confounders that are not accounted for that would make our sample relatively less frail. For example, indication for surgery may lead to the selection of less frail patients for surgery. Due to the limitations of the clinical data available, it was not possible to account for any selection criteria. Such bias may explain the small difference in preoperative severity of joint problems between patients with and without comorbidities. In addition, lack of information on behavioural risk factors such as smoking status and BMI meant it was not possible to ascertain whether any of the variation in severity of joint problems is due to variation in behavioural risk factors. Clinical data on the severity of the 11 comorbidities was also limited.

The OKS and OHS measures are also not completely disease-specific. Previous studies have reported concerns that the OKS and OHS also capture the effects of comorbidity [27-29]. It was therefore important that we also looked at pain and functional status OHS/OKS scores separately as pain is considered to be more joint-specific.

There may also be a risk of recall bias. With regards to duration of symptoms there is very limited literature on the accuracy of the reporting of symptom duration. Drawing on the evidence on the accuracy of retrospective symptom duration in patients presenting with lower back pain, symptom duration reporting is often found to be inconsistent [37, 51]. This may be due to the lack of clarity on the definitions of symptom duration and the use of unreliable questions to elicit information about symptom duration [37, 51]. As such, this may partly explain why the findings about the duration of symptoms were inconsistent.

6.1.6 Conclusion

Patients with comorbidities undergoing hip or knee replacement surgery reported more severe joint problems, and not only worse functional status but also more pain, just before surgery compared to patients without comorbidities. This suggests that patients with comorbidities have truly worse joint problems and it is not simply an effect of comorbidity on the disease-specific measure. The differences in severity of symptoms increased (worsened) with the number of comorbidities. Patients with comorbidities reported little to no difference in the duration of symptoms which is likely due to patients reporting symptoms of a most recent specific level of severity, instead of the overall duration. The findings therefore suggest that patients with comorbidities may on average have surgery slightly later in the course of their joint disease. Some of these differences could be attributable to delays to surgery resulting from variation in patient decision-making or clinical decision-making.

6.1.7 Figures and Tables

Table 1- Pre-operative severity of joint problems (OHS/OKS) according to comorbidity (adjusted according to age, sex, ethnicity, SES, and other comorbidities)

Comorbidity	OHS total (0 worse and 48 best)			OKS total (0 worse and 48 best)		
	Mean score	Adjusted difference (95% CI)	P-value	Mean score	Adjusted difference (95% CI)	P-value
Heart disease						
No	17.7	-		18.4	-	
Yes	16.0	-1.29 (-1.37, -1.21)	<0.001	17.6	-1.05 (-1.12, -0.98)	<0.001
High blood pressure						
No	18.2	-		18.9	-	
Yes	16.5	-1.22 (-1.29, -1.17)	<0.001	17.8	-0.87 (-0.92, -0.81)	<0.001
Stroke						
No	17.4	-		18.3	-	
Yes	14.5	-1.39 (-1.67, -1.10)	<0.001	16.2	-1.15 (-1.40, -0.89)	<0.001
Leg pain due to poor circulation						
No	17.4	-		18.3	-	
Yes	15.3	-1.28 (-1.50, -1.06)	<0.001	17.4	-0.83 (-1.05, -0.62)	<0.001
Lung disease						
No	17.7	-		18.6	-	
Yes	15.6	-1.49 (-1.57, -1.41)	<0.001	16.7	-1.21 (-1.28, -1.14)	<0.001
Diabetes						
No	17.6	-		18.5	-	
Yes	15.7	-1.31 (-1.41, -1.21)	<0.001	16.8	-1.26 (-1.34, -1.18)	<0.001
Kidney disease						
No	17.5	-		18.3	-	
Yes	15.3	-1.06 (-1.19, -0.93)	<0.001	17.1	-0.82 (-0.94, -0.71)	<0.001
Diseases of the nervous system						
No	17.5	-		18.4	-	
Yes	14.4	-2.49 (-2.66, -2.31)	<0.001	15.5	-2.58 (-2.73, -2.42)	<0.001
Liver disease						
No	17.4	-		18.3	-	
Yes	14.0	-2.29 (-2.65, -1.93)	<0.001	16.9	-1.30 (-1.64, -0.97)	<0.001
Cancer						
No	17.4	-		18.3	-	
Yes	16.4	-1.22 (-1.42, -1.03)	<0.001	18.6	-0.46 (-0.66, -0.26)	<0.001
Depression						
No	17.5	-		18.4	-	
Yes	14.6	-2.07 (-2.21, -1.93)	<0.001	15.3	-1.98 (-2.10, -1.85)	<0.001

Table 2 – Pre-operative severity of joint problems (OHS/OKS) separated by functional status and pain (adjusted according to age, sex, ethnicity, SES and other comorbidities)

Comorbidity	OHS				OKS			
	Functional status (0 worst 24 best)		Pain (0 worst 24 best)		Functional status (0 worse and 28 best)		Pain (0 worse 20 best)	
	Adjusted difference (95% CI)	P-value	Adjusted difference (95% CI)	P-value	Adjusted difference (95% CI)	P-value	Adjusted difference (95% CI)	P-value
Heart disease								
No	-		-		-		-	
Yes	-0.68 (-0.72, -0.64)	<0.001	-0.61 (-0.65, -0.57)	<0.001	-0.70 (-0.74, -0.66)	<0.001	-0.35 (-0.38, -0.32)	<0.001
High blood pressure								
No	-		-		-		-	
Yes	-0.69 (-0.73, -0.66)	<0.001	-0.54 (-0.57, -0.50)	<0.001	-0.59 (-0.62, -0.55)	<0.001	-0.28 (-0.31, -0.26)	<0.001
Stroke								
No	-		-		-		-	
Yes	-0.81 (-0.96, -0.66)	<0.001	-0.57 (-0.72, -0.43)	<0.001	-0.84 (-1.00, -0.68)	<0.001	-0.30 (-0.41, -0.19)	<0.001
Leg pain due to poor circulation								
No	-		-		-		-	
Yes	-0.62 (-0.74, -0.50)	<0.001	-0.66 (-0.78, -0.55)	<0.001	-0.59 (-0.73, -0.46)	<0.001	-0.24 (-0.33, -0.15)	<0.001
Lung disease								
No	-		-		-		-	
Yes	-0.70, (-0.75, -0.66)	<0.001	-0.79 (-0.83, -0.75)	<0.001	-0.78 (-0.83, -0.74)	<0.001	-0.43 (-0.46, -0.40)	<0.001
Diabetes								
No	-		-		-		-	
Yes	-0.72 (-0.77, -0.67)	<0.001	-0.59 (-0.64, -0.53)	<0.001	-0.84 (-0.89, -0.79)	<0.001	-0.42 (-0.45, -0.38)	<0.001
Kidney disease								
No	-		-		-		-	
Yes	-0.60 (-0.67, -0.53)	<0.001	-0.46 (-0.53, -0.39)	<0.001	-0.57 (-0.65, -0.50)	<0.001	-0.25 (-0.30, -0.20)	<0.001
Diseases of the nervous system								
No	-		-		-		-	
Yes	-1.48 (-1.57, -1.39)	<0.001	-1.01 (-1.10, -0.91)	<0.001	-1.87 (-1.96, -1.77)	<0.001	-0.71 (-0.78, -0.65)	<0.001
Liver disease								
No	-		-		-		-	
Yes	-1.28 (-1.48, -1.08)	<0.001	-1.01 (-1.20, -0.82)	<0.001	-0.90 (-1.11, -0.69)	<0.001	-0.41 (-0.55, -0.26)	<0.001
Cancer								
No	-		-		-		-	
Yes	-0.72 (-0.83, -0.61)	<0.001	-0.50 (-0.61, -0.40)	<0.001	-0.35 (-0.48, -0.22)	<0.001	-0.11 (-0.20, -0.03)	<0.001
Depression								
No	-		-		-		-	
Yes	-1.12 (-1.19, -1.04)	<0.001	-0.95 (-1.03, -0.88)	<0.001	-1.31 (-1.38, -1.23)	<0.001	-0.67 (-0.73, -0.62)	<0.001

Figure 1 - Impact of comorbidities on long-standing joint problems (duration> 5 years) (95% CI) (adjusted according to age, sex, ethnicity, SES and other comorbidities)

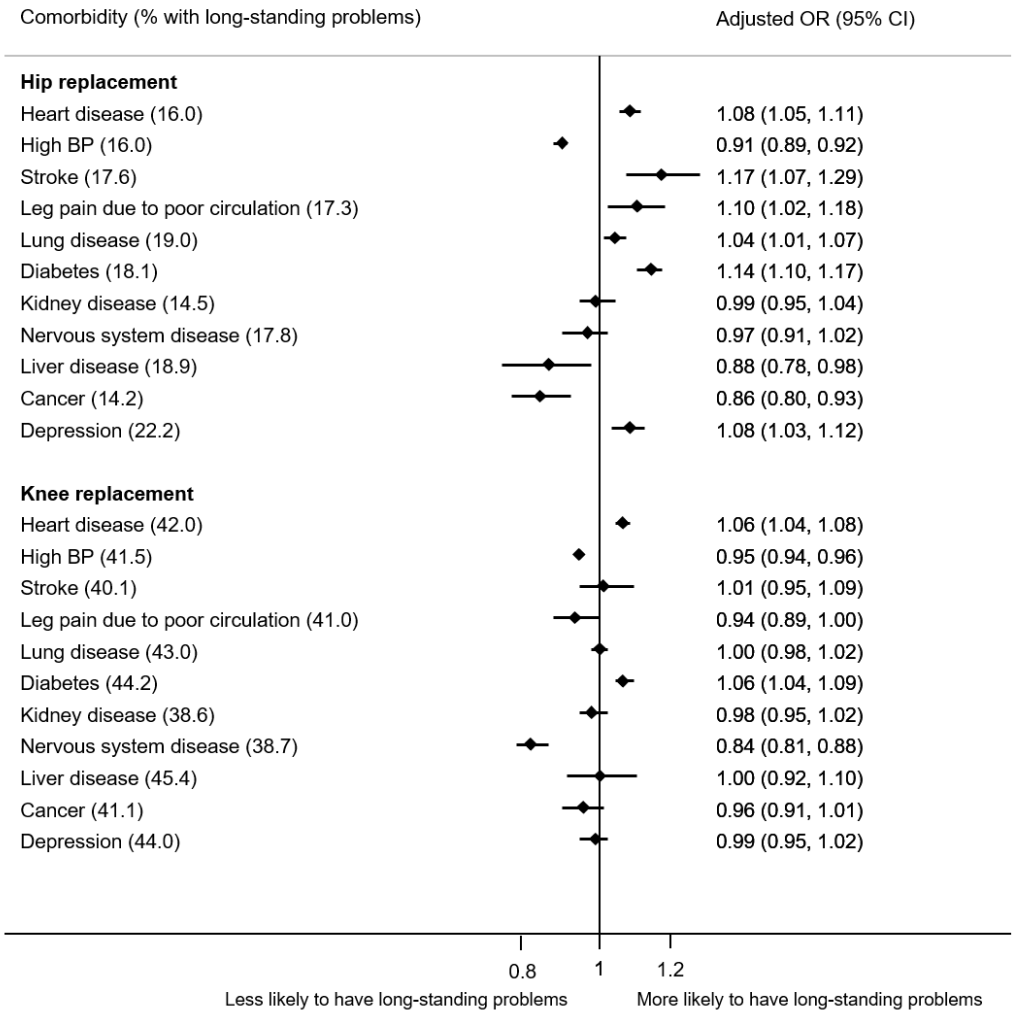

Table 3 – Pre-operative severity of joint problems (OHS/OKS) and likelihood of long-standing problems by number of comorbidities (95% CI, P-value for trend) (adjusted according to age, sex, ethnicity and SES)

Number of comorbidities	Severity of joint problems (OHS or OKS) (0 worse and 48 best)			Functional status (OHS or OKS) (0 worst 24 best)			Pain (OHS or OKS) (0 worst 24 best)			Long-standing joint problems (duration > 5 years)		
	Mean score	Adjusted difference (95% CI)	P-value	Mean score	Adjusted difference (95% CI)	P-value	Mean score	Adjusted difference (95% CI)	P-value	%	Adjusted OR (95% CI)	P-value
Hip replacement												
0	18.8	Reference		10.6	Reference		8.21	Reference		21.3	Reference	
1	17.4	-1.45 (-1.52, -1.38)	<0.001	9.73	-0.79 (-0.83, -0.76)	<0.001	7.67	-0.66 (-0.69, -0.62)	<0.001	17.3	0.93 (0.91, 0.95)	0.076
2	16.2	-2.79 (-2.87,-2.70)		9.03	-1.52 (-1.56, -1.47)		7.17	-1.28 (-1.32, -1.23)		16.5	0.98 (0.95, 1.00)	
3	14.9	-4.15 (-4.27, -4.04)		8.31	-2.23 (-2.30, -2.17)		6.58	-1.92 (-1.98, -1.86)		16.1	1.02 (0.98, 1.06)	
4+	13.3	-5.79 (-5.96, -5.61)		7.42	-3.13 (-3.23, -3.03)		5.89	-2.66 (-2.75, -2.56)		17.5	1.15 (1.09, 1.23)	
Knee replacement												
0	19.5	Reference		12.5	Reference		7.01	Reference		45.7	Reference	
1	18.5	-1.06 (-1.12, -0.99)	<0.001	11.7	-0.72 (-0.76, -0.68)	<0.001	6.77	-0.34 (-0.37, -0.31)	<0.001	42.2	0.95 (0.93, 0.97)	0.663
2	17.6	-2.16 (-2.24, -2.09)		11.0	-1.50 (-1.51,-1.42)		6.51	-0.70 (-0.73, -0.67)		41.9	0.97 (0.95, 0.99)	
3	16.5	-3.38 (-3.48, -3.28)		10.3	-2.28 (-2.34, -2.22)		6.17	-1.10 (-1.15, -1.06)		41.8	0.98 (0.96, 1.01)	
4+	15.1	-4.79 (-4.94, -4.64)		9.39	-3.21 (-3.31, -3.11)		5.75	-1.58 (-1.64, -1.51)		41.9	0.99 (0.95, 1.04)	

6.1.8 References

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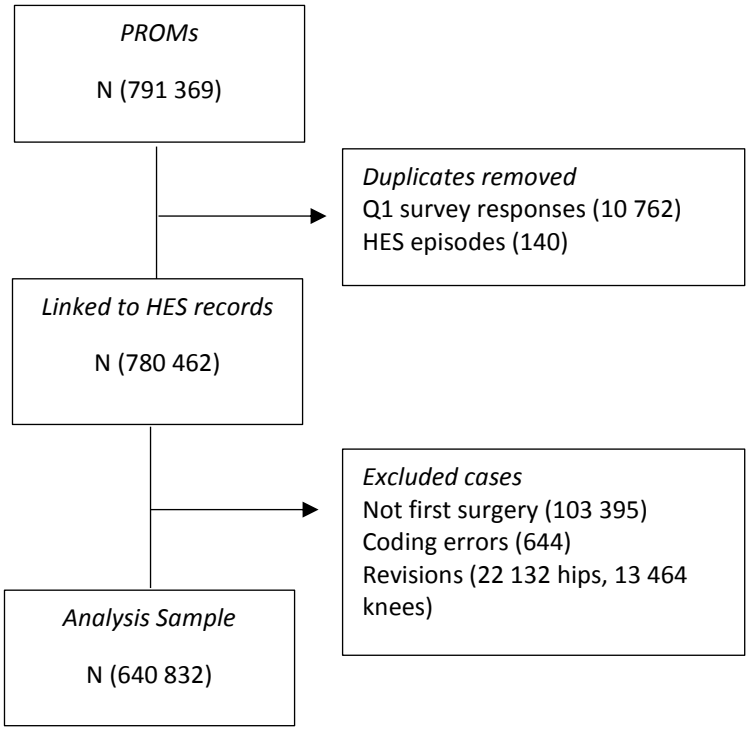
6.1.9 Supplementary Information

Supplementary Information 1 – Flow chart



Supplementary Information 2– Breakdown of OKS and OHS by pain and function questions (P=pain, F=function)

	OHS	OKS
1	How would you describe the pain you usually have in your hip? (P)	Describe the pain you usually have from your knee? (P)
2	Have you been troubled by pain from your hip in bed at night? (P)	How much trouble do you have washing and drying yourself? (F)
3	Have you had any sudden, severe pain-' shooting ', 'stabbing', or 'spasms' from your affected hip? (P)	How much trouble do you have getting in/out car or using public transport? (F)
4	Have you been limping when walking because of your hip? (F)	How long can you walk before pain becomes severe? (P)
5	For how long have you been able to walk before the pain in your hip becomes severe (with or without a walking aid)? (P)	After a meal how painful has it been to stand up from a chair? (P)
6	Have you been able to climb a flight of stairs? (F)	Have you been limping when walking? (F)
7	Have you been able to put on a pair of socks, stockings or tights? (F)	Could you kneel down and get up again? (F)
8	After a meal (sat at a table), how painful has it been for you to stand up from a chair because of your hip? (P)	Have you been troubled by pain in bed at night? (P)
9	Have you had any trouble getting in and out of a car or using public transportation because of your hip? (F)	How much has pain from your knee interfered with your normal work? (P)
10	Have you had any trouble with washing and drying yourself (all over) because of your hip? (F)	Have you felt your knee might suddenly give way or let you down? (F)
11	Could you do the household shopping on your own? (F)	Could you do the shopping on your own? (F)
12	How much has pain from your hip interfered with your usual work, including housework? (P)	Could you walk down a flight of stairs? (F)

Supplementary information 3 - Study population characteristics

Characteristic	Hip replacement	Knee replacement
No. of patients	312 079 (48.7)	328 753 (51.3)
Mean (SD) OHS or OKS	17.4 (8.25)	18.3 (7.87)
Mean (SD) EQ-5D	0.33 (0.33)	0.39 (0.32)
Problem for more than five years, n (%)	57 827 (18.5)	141 559 (43.1)
Age (mean, range)	68 (18-105)	69 (18-102)
Gender, n (%)		
Male	126 925 (40.7)	140 971 (42.9)
Female	184 982 (59.3)	187 525 (57.0)
Missing, not stated	172	257
Socioeconomic status by quintile group, n (%)		
1 (least deprived)	74 380 (23.4)	69 582 (21.2)
2	76 164 (24.4)	74 799 (22.8)
3	55 793 (17.9)	62 851 (19.1)
4	52 194 (16.7)	60 177 (18.3)
5 (most deprived)	50 408 (16.2)	58 327 (17.7)
Missing	3 140	3 017
Ethnicity, n (%)		
White or White British	271 959 (98.3)	279 159 (94.5)
Mixed background	546 (0.19)	836 (0.28)
Asian or Asian British	1 239 (0.45)	10 445 (3.53)
Black or Black British	1 703 (0.62)	3 347 (1.13)
Chinese or other ethnic	1 150 (0.42)	1 706 (0.58)
Missing	35 482	33 260
Prevalence of comorbidities, n (%)		
Heart disease	53 277 (17.1)	60 755 (18.5)
High blood pressure	151 163 (48.4)	187 815 (57.1)
Stroke	3 227 (1.03)	3 530 (1.07)
Leg pain due to poor circulation	5 140 (1.65)	4 955 (1.51)
Lung disease	43 481 (13.9)	51 176 (15.6)
Diabetes	29 535 (9.46)	44 813 (13.6)
Kidney disease	16 428 (5.26)	18 000 (5.48)
Diseases of the nervous system	8 483 (2.72)	9 741 (2.96)
Liver disease	1 888 (0.60)	1 931 (0.59)
Cancer	6 354 (2.04)	5 545 (1.69)
Depression	13 367 (4.28)	14 814 (4.51)
Count of comorbidity, n (%)		
0	113 479 (36.4)	94 290 (28.7)
1	107 139 (34.3)	119 012 (36.2)
2	59 976 (19.2)	75 202 (22.9)
3	22 929 (7.35)	29 761 (9.05)
4+	8 556 (2.74)	10 488 (3.19)

7 RESULTS CHAPTER – Safety

The fifth component of the research programme investigated the impact of comorbidities on safety outcomes after hip and knee replacement surgery. The research is presented in the form of a research paper. Supplementary information can be found at the end of this section.

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RESEARCH PAPER COVER SHEET

Please note that a cover sheet must be completed for each research paper included within a thesis.

SECTION A – Student Details

Student ID Number	LSH342490	**Title**	Ms
First Name(s)	BÉLÈNE		
Surname/Family Name	PODMORE		
Thesis Title	The access to and outcomes of elective hip and knee replacement surgery for patients with comorbidities: a study using PROMs and administrative data		
Primary Supervisor	Professor Jan van der Meulen		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

SECTION B – Paper already published

Where was the work published?			
When was the work published?			
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion			
Have you retained the copyright for the work?*	Choose an item.	Was the work subject to academic peer review?	Choose an item.

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SECTION C – Prepared for publication, but not yet published

Where is the work intended to be published?	The Bone & Joint Journal
Please list the paper's authors in the intended authorship order:	Podmore, B; Hutchings, A; Konan, S; van der Meulen, J

Stage of publication	**Not yet submitted**

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	I designed this study, undertook the analyis and wrote the first draft of the manuscript.

SECTION E

Student Signature	[redacted]
Date	23 November 2018

Supervisor Signature	[redacted]
Date	23 November 2018

7.1 Research Paper 5 (RP5)

Impact of comorbidities on adverse outcomes after hip and knee arthroplasty: a study of 640 832 patients in England

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7.1.1 Abstract

Aims

Increasing numbers of patients with comorbidities are undergoing hip and knee arthroplasty. We assessed the impact of different comorbidities on a number of adverse outcomes that reflect the safety of hip and knee arthroplasty.

Patients and Methods

We included 640 832 patients who underwent elective primary hip or knee arthroplasty patients between 2009 and 2016. Multivariable logistic analysis was used to estimate the impact of 11 different comorbidities on the likelihood of an adverse outcome (minimum of one of the following: in-hospital transfers to another consultant, mortality and emergency readmissions 30 days after surgery) and on the likelihood of a prolonged hospital length of stay (LOS)(> 8 days) after hip or knee arthroplasty adjusted for age, sex, socioeconomic status, ethnicity and other comorbidities.

Results

A total of 28 273 (4.4%) patients had an adverse outcome and 35 334 (5.5%) patients had a prolonged LOS. Presence of heart disease, stroke, diseases of the nervous system and liver disease had the largest impact on these outcomes. In hip arthroplasty, the relative odds ratio for an adverse outcome ranged from 1.15 (95% CI 1.10, 1.19) for high blood pressure to 1.86 (95% CI, 1.67, 2.08) for patients with stroke. The relative odds ratio for a prolonged LOS ranged from 1.24 (95% CI 1.20, 1.29) for high blood pressure to 3.05 (95% CI 2.86, 3.26) for patients with disease of the nervous system. In knee arthroplasty, the increased risk for an adverse outcome ranged from 1.14 (95% CI 1.10, 1.19) for patients with high blood pressure to 1.89 (95% CI 1.70, 2.10) for patients with stroke. The relative odds ratio for a prolonged LOS ranged from 1.20 (95% CI 1.16, 1.24) for patients with high blood pressure to 2.90 (95% CI 2.73, 3.08) for patients with diseases of the nervous system. The impact of comorbidities on adverse outcomes was most pronounced with increasing number of comorbidities: patients with three or more comorbidities had a 3 to 4-fold increase in risk of adverse outcomes.

Conclusion

The risk of adverse outcomes and a prolonged hospital stay is moderate for patients with single comorbidities but if number of comorbidities increases, the risk becomes substantial. This finding demonstrates that safety is a key issue in patients with multiple comorbidities.

7.1.2 Introduction

Increasingly more patients with comorbidities are undergoing hip and knee arthroplasty [1]. As populations age, the number of patients with multiple comorbidities will only continue to increase. Hip and knee arthroplasty is one of the most effective surgeries and its use continues to increase [2-4] but the impact of a variety of individual comorbidities on adverse outcomes that reflect the safety of hip and knee arthroplasty has not been fully explored.

Patient safety is a critical issue in elective total joint arthroplasty. Orthopaedic surgery patients continue to develop complications and management of these complications requires a thorough understanding of the impact of preoperative comorbidities [5]. Identification of these risk factors for complications and adequate critical care intervention have proven to be instrumental in reducing mortality and morbidity after surgery [6].

In a previous meta-analysis of 70 papers published up until May 2017, looking at the impact of comorbidities on outcomes of hip and knee arthroplasty, comorbidities predominantly had an impact on the safety of joint arthroplasty but little impact on its effectiveness. The impact on outcomes related to safety (surgical complications, short-term mortality and readmissions) however presented an inconsistent picture [7]. The most common measure of safety across all 70 studies was surgical complications (85% of studies). While commonly investigated, the validity and reliability of the coding of these surgical complications in administrative data has been called into question [8-10]. Furthermore, there is a lack of consensus on how to best measure surgical complications [11]. Studies investigating safety have therefore resorted to looking at other safety outcomes that measure health service use [12] and that can act as surrogates for surgical complications, such as short-term mortality and readmissions to hospital after surgery.

The aim of this nationwide study was to investigate the impact of comorbidities on a variety of adverse outcomes that reflect safety of hip and knee arthroplasty, using large datasets from Hospital Episode Statistics (HES) and the Office for National Statistics (ONS). We studied multiple adverse outcomes that reflect the safety of joint arthroplasty such as a transfer to another consultant during the admission for the joint arthroplasty, emergency readmissions and 30-day mortality, which we presented as a single composite adverse outcome as well as looking separately at prolonged length of stay in hospital.

7.1.3 Patients and Methods

Ethics approval was obtained from the NHS Health Research Authority Ethics committee (Ref: 211186). We used outcome data on patients undergoing hip and knee arthroplasty between 2009 and 2016 in the English NHS and who participated in the Patient Reported Outcome Measures (PROMs) programme. The PROMs programme includes patients undergoing elective hip or knee arthroplasty who complete a questionnaire before surgery and then again six months after surgery. Patients' PROMs data were linked with hospital records from Hospital Episodes Statistics (HES), the national dataset for all hospital admissions in England, and the Office for National Statistics (ONS) death registry data, the national registry for all deaths in England. NHS Digital, the national information and technology partner to the health system, linked the HES data to ONS death registry data for all PROMS eligible procedures.

Patients who completed more than one pre-operative questionnaire for the same procedure were identified and the closest questionnaire to the date of procedure was retained. The final analysis sample was restricted to the first primary procedure for each patient. Subsequent primary procedures and all revision procedures were excluded. This left a final sample of 640 832 hip and knee arthroplasty patients.

Eleven comorbidities were identified from the list of 12 self-reported comorbidities from the pre-operative PROMs questionnaires which, in turn, represented a simplified version of the 13-item Self-Administered Comorbidity Questionnaire by Katz et al. [13]. Arthritis was excluded because it was the reason for surgery rather than a comorbidity. The 11 comorbidities comprised: heart disease; high blood pressure; problems caused by a stroke; leg pain when walking due to poor circulation; lung disease; diabetes; kidney disease; nervous system disease; liver disease; cancer and depression. Each comorbidity was mapped to its relevant, International Classification of Diseases, Tenth Revision, (ICD-10) diagnosis codes in HES data as described in a previous study [14]. The presence of a comorbidity was indicated if a mapped code appeared in any HES diagnosis field in any hospital admission up to one year prior to a patient's surgery.

Measures

The primary outcome for the analysis was a composite measure of safety following hip or knee arthroplasty to increase the statistical power and to simplify the reporting of multiple outcome measures that relate to safety of joint arthroplasty. Composite measures have

also been found to give a more comprehensive view of quality of care [15] and better explain hospital-level variation in serious complications and mortality compared to individual measures [16]. The primary outcome was defined as a binary variable indicating the presence of one or more of the following three indicators of safety: a transfer to another consultant during the same hospital admission, mortality and an emergency readmission to hospital within 30 days of the procedure. Patients transferred for care under a different consultant in the same admission as their hip or knee arthroplasty were identified by examining subsequent episodes of care within their hospital admission (see supplementary material 2). In HES the unit of care is a single consultant episode of care - the total time a patient spends under the care of an individual consultant. Mortality was captured using linked ONS death registry data. Emergency readmissions were identified by checking for any emergency hospital admission within 30 days of surgery using linked HES records for each patient.

Length of stay (LOS) following surgery was examined as a secondary outcome. A prolonged LOS was defined as a LOS greater than eight days as measured from the date of operation to the date of hospital discharge or, if available, the date the patient was ready for discharge. The threshold of eight days was based on the median LOS for patients whose hospital admission included any additional episode of care following the episode of the primary procedure. The date the patient was ready for discharge was used in the LOS calculation to avoid delays in discharge outside the control of the hospital contributing to a prolonged LOS. Further validation work was conducted to ascertain that patients with our definition of prolonged LOS were more likely to have complications (OR 4.07, 95% CI 3.94, 4.20) and that they had higher number of procedures conducted than patients with a shorter LOS. Complications were identified using ICD-10 diagnosis codes (Y40-Y84) – coded complications associated with adverse incidents of medical care.

Statistical analysis

We conducted multivariable logistic regression for the primary (adverse outcomes) and secondary outcomes (prolonged LOS) for hip and knee arthroplasty comparing those patients with and without each comorbidity. The analyses were adjusted for sociodemographic factors (age, sex, ethnicity and socioeconomic status as measured by the Index of Multiple Deprivation [17]) and the other comorbidities. Missing values for ethnicity, age, sex, and socioeconomic status were imputed with chained equations [18].

Analyses were run for each of the 10 imputed data sets and estimated parameters were combined using Rubin's rules and reported as odds ratios (OR) with 95% confidence intervals. The results are presented in forest plots of the 11 comorbidities for hip and knee arthroplasty. The impact of multiple comorbidities was examined by repeating the analyses using the number of comorbidities.

We conducted an array of sensitivity analyses. We looked at the impact of changing the definition of prolonged LOS. We also repeated our analyses adjusting for hospital variation and preoperative severity of symptoms. All p-values were two-tailed and p-values less than 0.05 were considered statistically significant. A test-for-trend was conducted for all p-values (multiple comorbidities). All statistical analysis were carried out using STATA V.15.

7.1.4 Results

We included 640 832 patients undergoing a primary hip or knee arthroplasty (312 079 hip operations and 328 753 knee operations) between April 2009 and March 2016 in the analyses. Patients were on average 68 years of age, female (58%) and were from a White ethnic background (>95%) (see Figure 1). Over 65% had at least one comorbidity and high blood pressure, heart disease and lung disease were the comorbidities with the highest prevalence. High blood pressure and heart disease were the most common comorbidity combinations across all groups of patients with multiple comorbidities (2, 3 or 4 comorbidities) (see supplementary information 1).

Of these patient populations, 13 374 (4.29%) hip patients and 14 899 (4.53%) knee patients had adverse outcomes (i.e. minimum of one or more of transfers to another consultant, mortality in 30 days, emergency readmissions in 30 days) (see Table 2). The majority of patients who had an adverse outcome, had an emergency readmission in 30 day (57.9%) followed by a transfer to another consultant (37.0%). Only 9 (0.03%) patients had all three adverse outcomes (see Table 3).

Adverse outcome

Multivariable analysis of the adverse outcome showed that patients with single comorbidities, especially patients with heart disease, stroke, diseases of the nervous system and liver disease, were more likely to have adverse outcomes compared to patients without comorbidities (see Figure 2). In hip arthroplasty, patients with stroke (OR 1.86, 95%

CI 1.67, 2.08), liver disease (OR 1.83, 95% CI 1.55, 2.16), heart disease (OR 1.77, 95% CI 1.70, 1.84) and diseases of the nervous system (OR 1.69 95% CI 1.56, 1.84) of all 11 comorbidities were most likely to have an adverse outcome. The least likely to have an adverse outcome among those with comorbidities, but still statistically significant, was observed in patients with high blood pressure (OR 1.15, 95% CI 1.10, 1.19), and diabetes (OR 1.17, 95% CI 1.11, 1.23). In knee arthroplasty, we found patients with stroke (OR 1.89, 95% CI 1.70, 2.10); diseases of the nervous system (OR 1.79, 95% CI 1.66, 1.93), liver disease (OR 1.78, 95% CI 1.51, 2.09) and heart disease (OR 1.64, 95% CI 1.57, 1.70) had the highest likelihood among those with comorbidities of an adverse outcome. Similar to hip arthroplasty, patients with high blood pressure (OR 1.14, 95% CI 1.10, 1.19), and diabetes (OR 1.22, 95% CI 1.17, 1.27) were the least likely among those with comorbidities to have an adverse outcome.

Prolonged LOS

Multivariable analysis of prolonged LOS in hospital after hip or knee arthroplasty showed that all patients with the 11 comorbidities were more likely to have a prolonged LOS than patients without comorbidities (see Figure 3). In hip arthroplasty, patients with diseases of the nervous system (OR 3.05, 95% CI 2.86, 3.26), liver disease (OR 2.43, 95% CI 2.10, 2.83) stroke (OR 2.15, 95% CI 1.96, 2.37) and heart disease (OR 2.13, 95% CI 2.06, 2.21) were most likely among patients with comorbidities to have a prolonged LOS. The lowest likelihood was seen in patients with high blood pressure (OR 1.24, 95% CI 1.20, 1.29). In knee arthroplasty, the highest likelihood of a prolonged LOS among patients with comorbidities was seen in patients with diseases of the nervous system (OR 2.90, 95% CI 2.73, 3.08), stroke (OR 2.21, 95% CI 2.01, 2.41), liver disease (OR 1.95, 95% CI 1.67, 2.27) and heart disease (OR 1.94, 95% CI 1.88, 2.01). Similar to hip arthroplasty, patients with high blood pressure (OR 1.20, 95% CI 1.16, 1.24) were the least likely among patients with comorbidities to have a prolonged LOS.

Impact of multiple comorbidities

The risk of adverse outcomes and likelihood of a prolonged LOS increased with the number of comorbidities (see Table 4). In hip arthroplasty, patients with four or more comorbidities were five-times as likely (OR 4.63, 95% CI 4.30, 4.99) to have an adverse

outcome and were also eight times (OR 8.35, 95% CI 7.80, 8.95) more likely to have a prolonged LOS than patients without comorbidities. In knee arthroplasty, patients with four or more comorbidities were four-times as likely (OR 4.09, 95% CI 3.80, 4.39) to have an adverse outcome and were also seven times (OR 6.82, 95% CI 6.39, 7.28) more likely to have a prolonged LOS.

7.1.5 Discussion

This study demonstrates that the presence of a comorbidity in patients undergoing hip or knee arthroplasty was associated with a moderately higher risk of adverse outcomes and a prolonged hospital stay. This risk increased with the number of comorbidities and was considerably higher in patients with three or more comorbidities. Heart disease, stroke, diseases of the nervous system and liver disease were the comorbidities associated with the highest relative increase in risk of an adverse outcome and prolonged LOS whereas patients with high blood pressure, diabetes and cancer had the lowest relative increased risk.

To our knowledge, this is the first study to focus on the impact of a range of different comorbidities and the number of comorbidities on multiple adverse outcomes that reflect the safety of hip and knee arthroplasty in a large national sample of patients in England. Previous research has predominantly focused on determining the impact of single risk factors for surgical complications [19-21]. In this study, we have explored outcomes that are associated with adverse outcomes as well as developing a new outcome, the need for a transfer to another consultant, in the same admission as the joint arthroplasty.

Orthopaedic surgeons have to operate on increasingly more complex patients [1]. Often these patients have more than one comorbidity [22]. This study suggests that for individual comorbidities the increase in the risk of adverse outcomes is relatively small. Only in patients with multiple comorbidities does the increased risk become considerable. These findings can assist healthcare professionals in the discussion with patients with comorbidities and especially patients with multiple comorbidities about the risks of surgery as well as predict the possibility of an adverse outcome and to allocate appropriate resources to manage these adverse outcomes. Determining what is an acceptable risk level is beyond the scope of this study but any increased risk should be interpreted in the context of whether patients benefit overall.

Our findings are consistent with other studies looking at short-term outcomes in patients with comorbidities undergoing total joint arthroplasty. From our previous systematic review the impact of comorbidities on readmissions within 90 days [21, 23-25] and mortality within 90 days [26, 27] was highest for patients with liver disease, heart disease, stroke and diseases of the nervous system [7]. Similarly, a small study of 802 patients in the USA, looking at complications and LOS in patients undergoing elective primary hip and knee arthroplasty, reported that patients with congestive heart failure, chronic kidney disease, and cirrhosis experienced the majority of the documented major complications following joint arthroplasty and were also more likely to have an increased LOS beyond 3 days [28]. Prolonged hospital LOS can have a negative impact on health service use after elective surgery and our findings are consistent with previous studies that have implicated comorbidities in high LOS [29, 30]. The finding that adverse outcomes are more likely with increasing number of comorbidities corroborates a recent large US study of 516,745 patients undergoing knee arthroplasty that showed that increasing number of comorbidities were associated with longer LOS [30].

This study has several limitations. The first relates to the use of a composite measure of adverse outcomes. While there are advantages of using composite measures such as increasing statistical power and simplifying the reporting of many outcome measures, the validity and the interpretability of a measure may be compromised as a result [31]. In addition, a composite outcome will not capture the impact of changes in one outcome on the other outcomes in the composite measure, for example a reduction in mortality may lead to an increase in emergency readmission and as a result the two effects will be cancelled out. It has been suggested that methodological transparency can address some of the challenges of using composite measures [32]. Following this guidance, the logic of choosing the measure, the aim the measure is trying to achieve, the individual effects on each outcome, and risk adjustment of individual measures were all reported.

The second limitation relates to the observational nature of the study. It is not possible to account for all unobserved patient characteristics and it was not possible to explore any selection bias. There is likely to be a 'healthy-surgical patient' effect such that high-risk patients, who are likely to have many comorbidities, are excluded from elective surgery. Evidence has suggested that patients with comorbidities are being selected out by healthcare professionals along the referral pathways to joint arthroplasty [33]. This has been used to explain why patients undergoing knee arthroplasty have lower than expected mortality for their age and sex [26]. Due to selection criteria, not being fully available in our

dataset we could not account for selection in our analysis. Furthermore, the data did not allow us to stratify comorbidities by severity of disease.

7.1.6 Conclusion

In conclusion, our results show that patients with single comorbidities have a moderately increased risk of adverse outcomes and a prolonged hospital stay than patients without comorbidities. The risk was considerably higher in patients with multiple comorbidities. A surgeon must assess the risks and benefits of conducting hip and knee arthroplasty especially for more complex patients. These findings can guide this discussion but should be interpreted in the context of whether patients with comorbidities benefit overall.

7.1.7 Figures and Tables

Figure 1- Flow chart

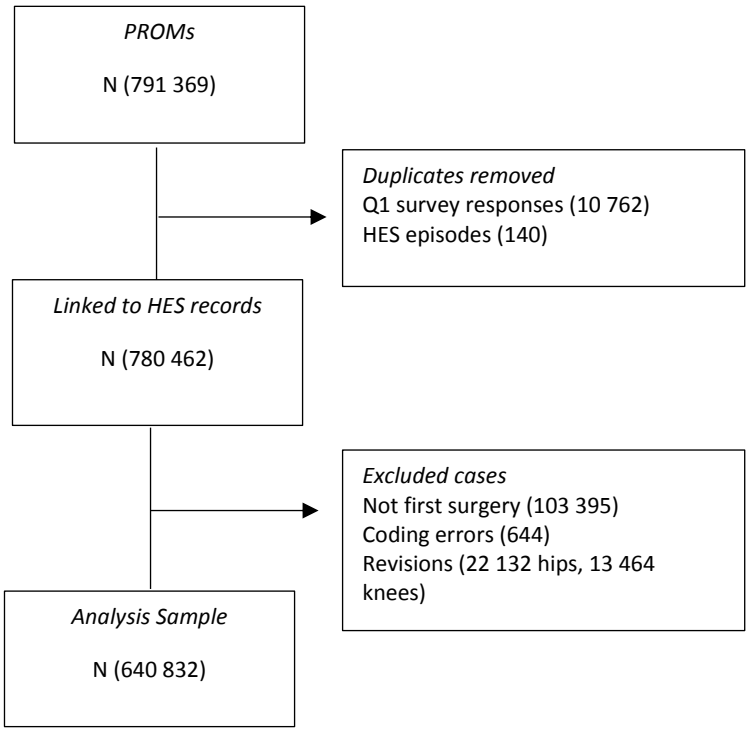

Table 1 - Patient characteristics

	Hip arthroplasty	Knee arthroplasty
No. of patients, n (%)	312 079 (48.7)	328 753 (51.3)
Age (mean, range)	68 (18-105)	69 (18-102)
Gender, n (%)		
Male	126 925 (40.7)	140 971 (43.0)
Female	184 982 (59.3)	187 525 (57.0)
Missing, not stated	172	257
Socioeconomic status by quintile group, n (%)		
1 (least deprived)	74 380 (23.4)	69 582 (21.2)
2	76 164 (24.4)	74 799 (22.8)
3	55 793 (17.9)	62 851 (19.1)
4	52 194 (16.7)	60 177 (18.3)
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Missing	3 140	3 017
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White or White British	271 959 (98.3)	279 159 (94.5)
Mixed background	546 (0.19)	836 (0.28)
Asian or Asian British	1 239 (0.45)	10 445 (3.53)
Black or Black British	1 703 (0.62)	3 347 (1.13)
Chinese or other ethnic	1 150 (0.42)	1 706 (0.58)
Missing	35 482	33 260
Prevalence of comorbidities, n (%)		
Heart disease	53 277 (17.1)	60 755 (18.5)
High blood pressure	151 163 (48.4)	187 815 (57.1)
Stroke	3 227 (1.03)	3 530 (1.07)
Leg pain due to poor circulation	5 140 (1.65)	4 955 (1.51)
Lung disease	43 481 (13.9)	51 176 (15.6)
Diabetes	29 535 (9.5)	44 813 (13.6)
Kidney disease	16 428 (5.26)	18 000 (5.48)
Diseases of the nervous system	8 483 (2.72)	9 741 (2.96)
Liver disease	1 888 (0.60)	1 931 (0.59)
Cancer	6 354 (2.04)	5 545 (1.69)
Depression	13 367 (4.28)	14 814 (4.51)
Count of comorbidity, n (%)		
0	113 479 (36.4)	94 290 (28.7)
1	107 139 (34.3)	119 012 (36.2)
2	59 976 (19.2)	75 202 (22.9)
3	22 929 (7.35)	29 761 (9.05)
4+	8 556 (2.74)	10 488 (3.19)

Table 2 – Number of patients with adverse outcomes and a prolonged LOS by comorbidity (n(%))

Comorbidity	Hip arthroplasty		Knee arthroplasty	
	Adverse outcomes	**Prolonged LOS**	**Adverse outcomes**	**Prolonged LOS**
Heart disease				
No	8967 (3.46)	9859 (3.81)	10 165 (3.79)	11 526 (4.30)
Yes	4407 (8.27)	6850 (12.9)	4734 (7.79)	7099 (11.7)
High blood pressure				
No	5214 (3.24)	5159 (3.21)	4978 (3.53)	5267 (3.74)
Yes	8160 (5.40)	11 550 (7.64)	9921 (5.28)	13358 (7.11)
Stroke				
No	12 962 (4.20)	16 000 (5.18)	14 453 (4.44)	17 880 (5.50)
Yes	412 (12.8)	709 (22.0)	446 (12.6)	745 (21.1)
Leg pain due to poor circulation				
No	12 884 (4.20)	16 005 (5.21)	14 468 (4.47)	18 034 (5.57)
Yes	490 (9.53)	704 (13.7)	431 (8.70)	591 (11.9)
Lung disease				
No	10 583 (3.94)	12 947 (4.82)	11 701 (4.22)	14 253 (5.13)
Yes	2791 (6.42)	3762 (8.65)	3198 (6.25)	4372 (8.54)
Diabetes				
No	11 517 (4.08)	13 869 (4.91)	12 188 (4.27)	14 560 (5.13)
Yes	1857 (6.29)	2840 (9.62)	2781 (6.21)	4065 (9.07)
Kidney disease				
No	11 854 (4.01)	14 125 (4.78)	13 321 (4.29)	16 005 (5.15)
Yes	1520 (9.25)	2584 (15.7)	1578 (8.77)	2620 (14.6)
Diseases of the nervous system				
No	12 638 (4.16)	15 269 (5.03)	14 004 (4.39	17 013 (5.33)
Yes	736 (8.68)	1440 (17.0)	895 (9.19)	1612 (16.6)
Liver disease				
No	13 206 (4.26)	16 470 (5.31)	14 730 (4.51)	18 411 (5.63)
Yes	168 (8.90)	239 (12.7)	169 (8.75)	214 (11.1)
Cancer				
No	12 925 (4.23)	16 086 (5.26)	14 510 (4.49)	18 078 (5.59)
Yes	449 (7.07)	623 (9.80)	389 (7.02)	547 (9.86)
Depression				
No	12 554 (4.20)	15 787 (5.29)	13 952 (4.44)	17 634 (5.62)
Yes	820 (6.13)	922 (6.90)	947 (6.39)	991 (6.69)

Table 3 – Composite outcome breakdown (and proportion of patients who also have a prolonged LOS> 8 days)

Outcome combinations	n (%)	Outcome combination + LOS > 8 days
Total number with a composite outcome	28,273	
One outcome only		
1. Transfer to another consultant	10 449 (37.0)	4 187/10 449 (40.1)
2. Death in 30 days only	634 (2.24)	151/634 (23.8)
3. Emergency readmission in 30 days only	16 366 (57.9)	1 331/16 366 (8.13)
Two outcomes only		
1. Transfer to another consultant + Emergency readmission in 30 days only	461 (1.63)	271/461 (58.8)
2. Transfer to another consultant + death in 30 days only	247 (0.87)	168/247 (68.0)
3. Emergency readmission in 30 days + death in 30 days only	107 (0.38)	18/107 (16.8)
All three outcomes	9 (0.03)	8/9 (88.9)

Figure 2- Forest plot for composite adverse outcomes comparing patients with and without comorbidity (adjusted according to age, sex, ethnicity, SES, and other comorbidities)

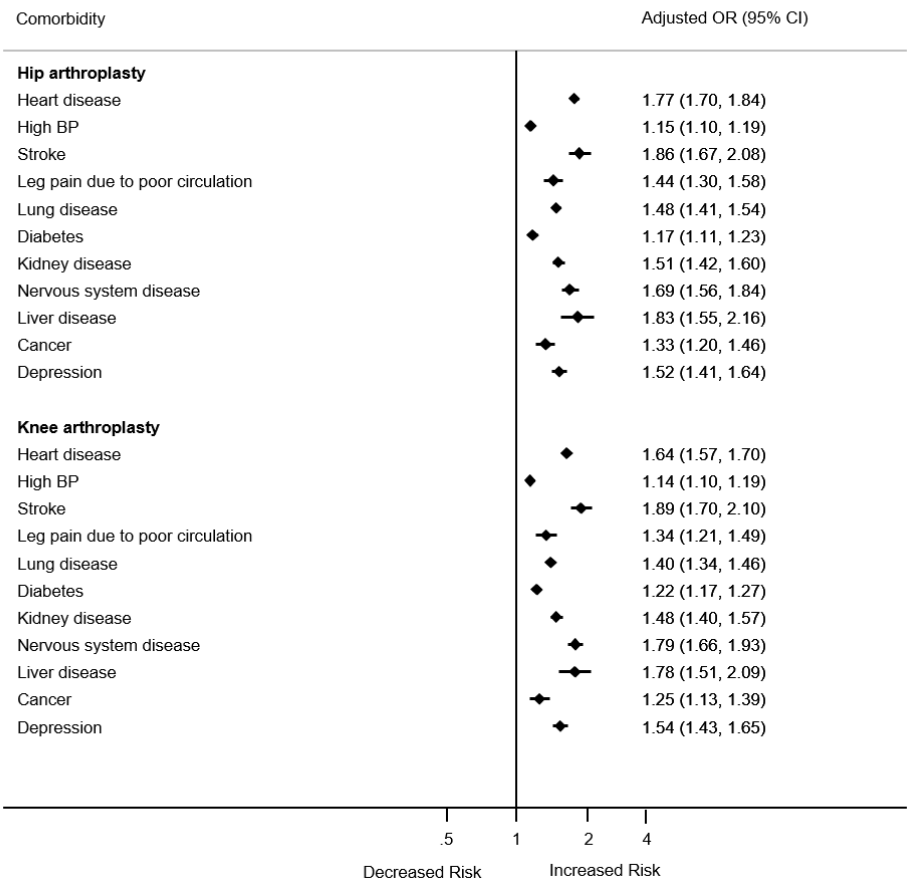

Figure 3 - Forest plot for prolonged LOS comparing patients with and without comorbidities (95% CI) (adjusted according to age, sex, ethnicity, SES, and other comorbidities)

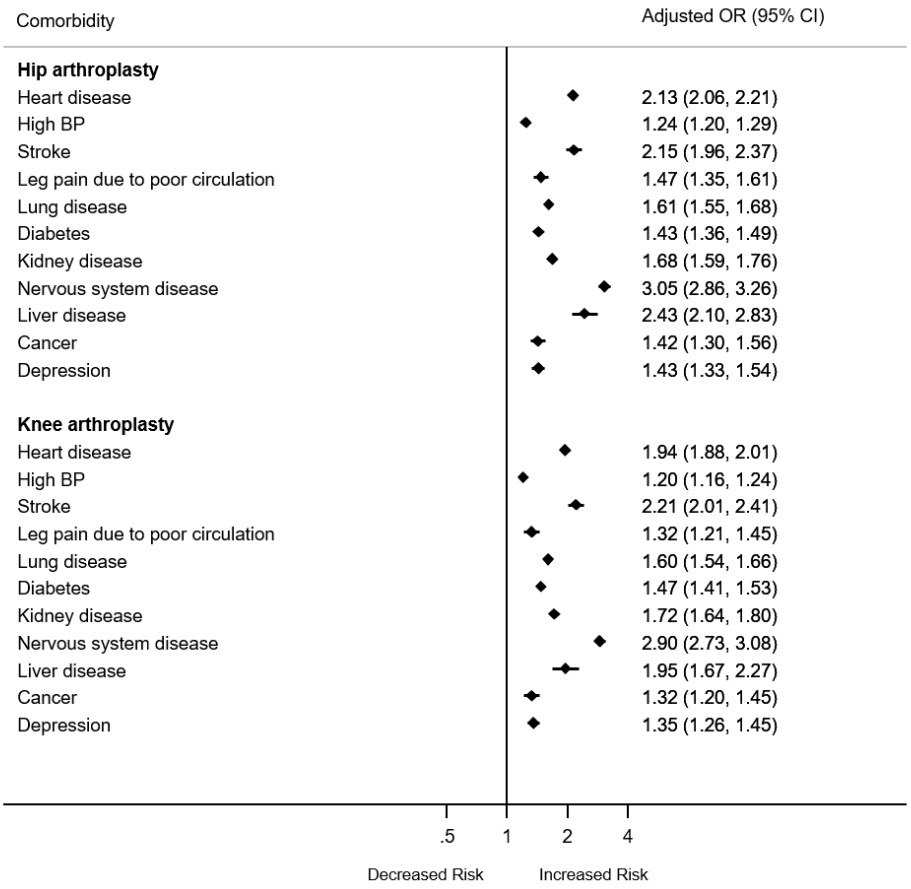

Table 4 – Impact of multiple comorbidities on safety outcomes after hip and knee arthroplasty (95% CI) (adjusted according to age, sex, ethnicity, and SES)

Number of comorbidities	Adverse outcomes			Prolonged LOS		
	%	Adjusted OR (95% CI)	P-value for trend	%	Adjusted OR (95% CI)	P-value for trend
Hip arthroplasty						
0	2.46	Reference		1.94	Reference	
1	3.75	1.36 (1.30,1.43)	<0.001	4.19	1.62 (1.54,1.71)	<0.001
2	5.69	1.95 (1.85, 2.06)		8.17	2.84 (2.69, 2.99)	
3	8.73	2.95 (2.77, 2.13)		14.0	4.79 (4.52, 5.08)	
4+	13.4	4.63 (4.30, 4.99)		22.4	8.35 (7.80, 8.95)	
Knee arthroplasty						
0	2.73	Reference		2.49	Reference	
1	3.78	1.30 (1.24, 1.37)	<0.001	4.06	1.39 (1.32,1.46)	<0.001
2	5.49	1.83 (1.74, 1.93)		7.54	2.33 (2.08, 2.53)	
3	8.15	2.69 (2.53, 2.85)		12.5	4.02 (3.81, 4.25)	
4+	12.2	4.09 (3.80, 4.39)		19.8	6.82 (6.39, 7.28)	

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7.1.9 Supplementary information

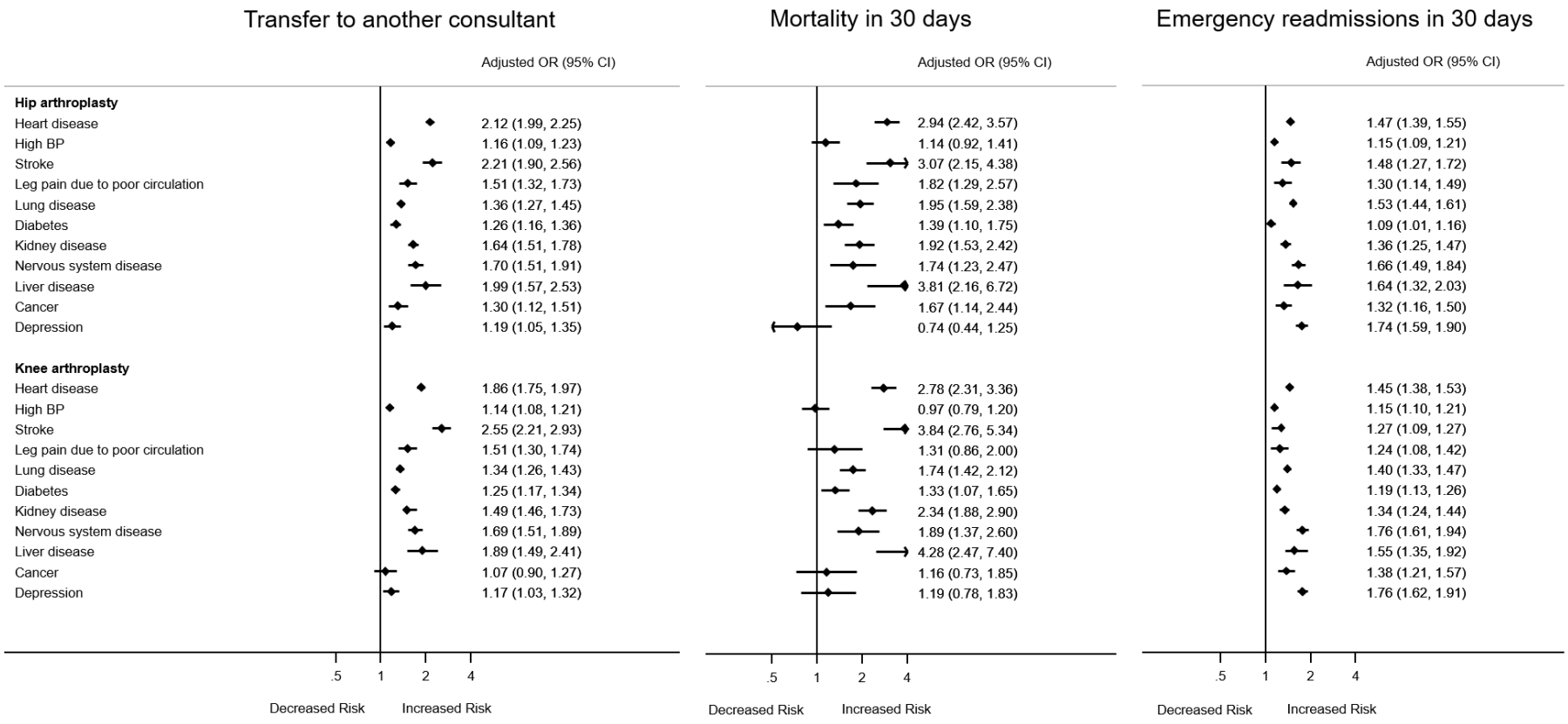
Supplementary information 1- Comorbidity profile by number of comorbidities (n (%))

# of Comorbidities	Heart disease	High BP	Stroke	Circulation	Lung disease	Diabetes	Kidney disease	Nervous system disease	Liver disease	Cancer	Depression
1	16 310	152 508	504	1 075	28 060	8 552	2 470	4 597	693	2 938	8 444
	(7.21)	(67.4)	(0.22)	(0.48)	(12.4)	(3.78)	(1.09)	(2.03)	(0.30)	(1.30)	(3.73)
2	49 510	118 334	1 696	2 482	34 107	32 470	11 120	5 758	1 130	3 948	9 801
	(36.6)	(87.5)	(1.25)	(1.84)	(25.2)	(24.0)	(8.23)	(4.26)	(0.80)	(2.92)	(7.25)
3	32 909	49 607	2 151	3 338	21 476	22 134	12 175	4 289	1 012	2 925	6 054
	(62.5)	(94.1)	(4.08)	(6.34)	(40.8)	(42.0)	(23.1)	(8.14)	(1.92)	(5.55)	(11.5)
4	15 303	18 529	2 406	3 200	11 014	11 192	8 663	3 580	984	2 088	3 881
	(80.4)	(97.3)	(12.6)	(16,8)	(57.8)	(58.8)	(45.5)	(18.8)	(5.17)	(11.0)	(20.4)

Supplementary information 2 – Treatment specialty of consultants that patients are transferred to (n= 11,128)

Treatment specialty	**Transfer to another consultant n (%)**
Trauma or & Orthopaedics	4 151 (37.3)
Rehabilitation	1 768 (15.9)
General Medicine	1 163 (10.4)
Critical care medicine	1 005 (9.02)
Geriatric medicine	922 (8.27)
Cardiology	744 (6.68)
Gastroenterology	366 (3.28)
General surgery	253 (2.27)
Intermediate Care	163 (1.46)
Respiratory Medicine	141 (1.27)
Other	452 (4.18)

Supplementary information 3 - Forest plot of individual outcomes in the composite measure comparing patients with and without comorbidities (adjusted OR, 95% CI) (adjusted according to age, sex, ethnicity, SES, and other comorbidities)



Supplementary information 4 – Adjusted OR for individual outcomes in the composite adverse outcome by number of comorbidities (95% CI) (adjusted according to age, sex, ethnicity and SES)

Number of comorbidities	Transfer to another consultant		Mortality in 30 days		Emergency Readmissions in 30 days	
	%	Adjusted OR (95% CI)	%	Adjusted OR (95% CI)	%	Adjusted OR (95% CI)
Hip arthroplasty						
0	0.85	Reference	0.03	Reference	1.62	Reference
1	1.38	1.37 (1.26, 1.49)	0.10	2.11 (1.46, 3.08)	2.34	1.35 (1.27, 1.43)
2	2.46	2.22 (1.05, 2.42)	0.22	3.94 (2.74, 5.68)	3.20	1.76 (1.65, 1.88)
3	3.97	3.42 (3.11, 3.76)	0.52	8.25 (5.69, 12.0)	4.78	2.58 (2.38, 2.79)
4+	6.77	5.76 (5.17, 6.42)	1.10	16.2 (11.0, 23.8)	6.51	3.50 (3.16, 3.86)
Knee arthroplasty						
0	0.97	Reference	0.05	Reference	1.73	Reference
1	1.35	1.28 (1.18,1.39)	0.08	1.30 (0.92, 1.83)	2.39	1.31 (1.24, 1.40)
2	2.20	1.97 (1.81, 2.14)	0.18	2.41 (1.73, 3.35)	3.27	1.74 (1.64, 2.45)
3	3.42	2.95 (1.70, 3.24)	0.42	5.04 (3.61, 7.04)	4.68	2.45 (2.27, 2.63)
4+	5.40	4.62 (4.14, 5.14)	0.96	10.9 (7.68, 15.4)	6.55	3.42 (3.11, 3.75)

8 RESULTS CHAPTER– Effectiveness

The fifth component of the research programme investigated the impact of comorbidities on the effectiveness of hip and knee replacement surgery. The research is presented in the form of a research paper. Supplementary information can be found at the end of this section.

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RESEARCH PAPER COVER SHEET

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SECTION A – Student Details

Student ID Number	LSH342490	**Title**	Ms
First Name(s)	BÉLÈNE		
Surname/Family Name	PODMORE		
Thesis Title	The access to and outcomes of elective hip and knee replacement surgery for patients with comorbidities: a study using PROMs and administrative data		
Primary Supervisor	Professor Jan van der Meulen		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

SECTION B – Paper already published

Where was the work published?			
When was the work published?			
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SECTION C – Prepared for publication, but not yet published

Where is the work intended to be published?	Arthritis Care & Research
Please list the paper's authors in the intended authorship order:	Podmore, B; Hutchings, A; van der Meulen, J

Stage of publication	**Not yet submitted**

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	I designed this study, undertook the analyis and wrote the first draft of the manuscript.

SECTION E

Student Signature	[redacted]
Date	23 November 2018

Supervisor Signature	[redacted]
Date	23 November 2018

8.1 Research Paper 6 (RP6)

The impact of comorbidities on the effectiveness of hip or knee replacement surgery: a national population-based study

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8.1.1 Abstract

Background: In some areas of the UK access to hip and knee replacement surgery has been restricted to reduce costs. Eligibility criteria has included body mass index and the optimisation of pre-existing comorbidities. It is important to therefore understand the impact of comorbidities on the effectiveness of hip and knee replacement surgery.

Methods: Our sample included 640 832 patients in England who had an operation between 2009 and 2016. Eleven different comorbidities were identified from hospital admissions data based on ICD-10 diagnosis coding. Primary outcomes were change in the Oxford Hip or Knee Score (OHS/OKS) which measures severity of joint problems (pain and function) on a scale from 0 (worst) to 48 (best) and EQ-5D a health-related quality of life (HRQoL) measure. Linear regression analysis was used with adjustment for age, sex, ethnicity, socioeconomic status and other comorbidities.

Findings: Overall, patients with comorbidities reported large improvements in severity of joint problems and HRQoL after hip and knee replacement surgery. Patients with comorbidities reported slightly smaller improvements in OKS/OHS (adjusted differences in OHS ranged from 0·39 (95% CI 0·27, 0·51) to 0·74 (95% CI 0·31, 1·17) and OKS ranged from 0·32 (95% CI 0·07, 0·57) to 1.15 (95% CI 0·58, 1·72)) compared to patients without comorbidities, except for patients where a comorbidity was high blood pressure, kidney disease or cancer who had little to no improvement. There was limited to no impact of comorbidities on HRQoL. The adjusted differences increased with the number of comorbidities but remained small.

Conclusions: Patients with comorbidities do benefit from hip and knee replacement surgery and the improvements in function are only slightly less than patients without comorbidities. This suggests that the negative impact of comorbidities on the outcome of hip or knee replacement surgery is small compared to the positive impact of the surgery itself. Our findings therefore indicate that restricting access based on the presence of comorbidities alone is unjustified.

8.1.2 Introduction

Since the first hip replacement in 1962 and knee replacement in the early 1970s [1], joint replacement surgery has become one of the most successful interventions in medicine [2-4]. It offers substantial improvement in function and HRQoL in patients suffering with osteoarthritis or inflammatory arthritis [5-8]. Despite the success of joint replacement surgery, a small number of patients continue to report no improvement in function [9]. A European collaborative study of 1327 patients with total hip and knee replacement, found that, despite hip and knee replacement being effective in the majority of cases, between 14% and 36% of patients were found not to have improved or even to be worse 12 months after surgery [9].

In England, some commissioners of healthcare services have recently introduced arbitrary eligibility criteria to access hip and knee replacement surgery in a bid to cut spending despite their being no clinical or economic justification for any of these criteria [10] and not being supported by national clinical guidelines [11]. Examples of eligibility criteria include that a patient's body mass index is lower than 30kg/m2 [12, 13] and that any pre-existing medical conditions are optimised [14-16]. Obesity and high body mass index (BMI) are rarely an isolated diagnosis and are strongly associated with comorbid conditions (e.g. diabetes and heart disease) that are considered to increase the risk of surgical complications after joint replacement surgery [17, 18]. An increasing number of patients undergoing hip and knee replacement surgery have at least one comorbidity [19]. It is therefore important to understand the impact of comorbidities on the effectiveness of replacement surgery.

Increasingly, researchers have measured effectiveness of hip and knee replacement surgery by using patient-reported measures such as function, health-related quality of life (HRQoL) and patient's perceptions of the success or failure of their joint replacement. The Patient Reported Outcome Measures (PROMs) programme in patients undergoing elective surgery in England routinely collects information on disease severity and HRQoL, from patients just before surgeryand six months after surgery and provides new opportunities to explore and monitor outcomes after joint replacement.

Our previous work, a systematic review and meta-analysis of 70 studies published up until May 2017, found that individual comorbidities had a greater impact on short-term outcomes related to safety of joint replacement surgery such as short-term mortality and readmission [20]. The impact on longer-term outcomes relating to effectiveness was smaller for revision surgery but less clear for patient-reported outcomes such as function

and HRQoL. The fifteen studies (five reporting HRQoL) that examined PROMs were generally small (<2000 patients) single-centre studies. The availability of national PROMs data provides an opportunity to examine the impact of comorbidities on patient-reported outcomes that reflect the effectiveness of hip and knee replacement surgery in a large national representative group of patients undergoing elective hip or knee replacement surgery in the English National Health Service (NHS).

8.1.3 Methods

Study design and population

We used data from the National PROMs Programme for elective surgery in England for patients undergoing hip or knee replacement surgery between April 2009 and November 2016. All NHS patients participating in the PROMS programme were given a questionnaire to complete before surgery either on admission or at preoperative assessment and then sent a follow-up questionnaire 6 months after surgery asking the same questions on the severity of their joint problems and HRQoL as well as their general views on the outcome of their operation.

PROMs data were linked at a patient level to data about their hospital admission extracted from the Hospital Episode Statistics (HES) for patients treated in NHS providers, and NHS-funded patients treated in private hospitals and independent sector treatment centres. To ensure we only had one record per patient we only included the first primary hip or knee surgery and excluded revision surgeries. We also excluded patients who had not returned a postoperative questionnaire with complete information on the main outcome and patients who had a second primary operation before they completed their postoperative questionnaire (see Figure 1).

Instruments and data collection

Our primary outcomes were the improvement in the Oxford Hip (OHS), Oxford Knee (OKS) and EQ-5D scores. The OHS and OKS produce disease-specific scores that are derived from patient responses to 12 questions about pain and limits on physical functioning and everyday activities. Responses to each question are measured on a 5-point scale, and values associated with each response are added up to produce an overall score with the

range 0 (worst) to 48 (best). Both scales have been shown to be internally consistent, reliable and to correlate with surgeon-assessed measures of symptoms and disability in patients undergoing hip or knee replacement [21, 22]. The EQ-5D was used to measure HRQoL and is derived from the EQ-5D profiles. The score ranges from -0.594 (worst) to 1 (best) with 0 reflecting 'death'.

Our secondary outcomes were overall improvement in the hip or knee problem and satisfaction with the results of the operation. These outcomes were derived from responses to the question: "overall, how are the problems now in the (hip/knee) on which you had surgery, compared with before your operation?" and "How would you describe the results of your operation?". Five categories of response for the first question were 'much better', 'a little better', 'about the same', 'a little worse' and 'much worse'. Responses were grouped to form a binary outcome, taking the value 1 for patients that reported no improvement in problems (i.e. same or worse) and 0 for those that reported them to be a little or much better. Five categories of responses for describing the results of the operation were 'excellent', 'very good', 'good', 'fair' and 'poor'. A binary outcome was derived grouping patients into a group who were dissatisfied (described their results as 'fair' or 'poor') and ones who were satisfied (described their results as 'good', 'very good', 'excellent').

Eleven common comorbidities were defined from HES using an algorithm described in a previous study that correspond to the comorbidity categories in the PROMs pre-operative questionnaire which included: heart disease; high blood pressure; problems caused by a stroke; leg pain when walking due to poor circulation; lung disease; diabetes; kidney disease; nervous system disease; liver disease; cancer and depression [23]. HES derived comorbidities were used in preference to patient-reported comorbidities to ensure comorbidities were consistent with clinical records.

Statistical analysis

We used multivariable linear regression to explore the relationship between the 11 different comorbidities and improvement (change scores) in severity of joint problems (OHS and OKS) and HRQoL (EQ-5D). In nonrandomised studies of pre-existing group (e.g. patients with and without comorbidities), change scores (postoperative-preoperative) have been shown to be less biased than the ANCOVA approach (postoperative scores adjusted

for preoperative scores) [24]. This assumes however that without treatment the groups have equal change over time [25]. This is plausible in the case of deterioration of joint problems over time between patients with and without comorbidities. Regression analysis included all 11 comorbidities and adjusted for other confounders such as age, sex, ethnicity and socioeconomic status (Index of Multiple Deprivation [25]) and other comorbidities. We used multivariable logistic regression to explore the relationship between comorbidities and the odds of reporting no improvement in hip or knee problems and being dissatisfied with the results of the operation. We also investigated the association between number of comorbidities and all outcomes to explore the effect of having multiple comorbidities. Descriptive results are presented as means and percentages. Multiple imputation using chained equations [26] was used to deal with missing values for ethnicity, age, sex and socioeconomic status. Analyses were run on each of the 10 imputed data sets and estimated parameters were combined using Rubin's rules [27]. Regression results are presented as adjusted differences and odds ratios (ORs), both with their 95% confidence intervals and graphically presented in forest plots. All statistical analysis were carried out using STATA V.15.

8.1.4 Results

Sample characteristics

Our final sample included 234 432 patients who had a hip replacement and 245 200 patients who had a knee replacement. The majority of patients were female (60% hips and 57% knees) with an average age of 69. The majority of patients were of White ethnicity (98.7% for hip and 95.7% for the knee). Population characteristics are shown in Table 1.

The most common comorbidities were high blood pressure, heart disease and lung disease for both knee and hip patients. 31% of patients had two or more comorbidities. Of those patients with two comorbidities, 88% of patients had high blood pressure and 37% had heart disease. Of those patients with three comorbidities, 95% had high blood pressure, 64% had heart disease and 42% had diabetes. Of those patients with four or more comorbidities, 98% had high blood pressure, 81% had heart disease, 59% had diabetes and 57% had lung disease (see supplementary information 2).

The impact of comorbidities on the improvement in the OHS and OKS and HRQoL

On average, hip patients reported a 20-point improvement in the OHS and knee patients reported a 15-point improvement in the OKS after their hip or knee replacement surgery. Similarly, hip patients reported a 0·43-point and knee patients a 0·31-point improvement in the EQ-5D score (see Table 2).

Six months after surgery, patients with comorbidities tended to have slightly less improvement in pain and mobility issues in their hip or knee than patients without comorbidities. The mean OHS score for patients after surgery was 38·9 and 34·5 for the OKS. In hip patients, all comorbidities were associated with a slightly smaller improvement in OHS score except for patients with high blood pressure, kidney disease and cancer (see Figure 2). For hip replacement, the adjusted differences in the OHS score ranged from 0·40 (95% CI 0·21, 0·60) for kidney disease to -0·74 (95% CI -1·17, -0·31) for stroke. For knee replacement surgery, all patients with comorbidities except high blood pressure, kidney disease and cancer were more likely to report a smaller improvement in OKS score. The adjusted differences in the OKS score ranged from 0·32 (95% CI 0·14, 0·51) for kidney disease to -1·15 (95% CI -1·72, -0·58) for liver disease.

Six months after surgery, improvement in general HRQoL scores did not vary significantly between patients with and without comorbidities (see Figure 2). For hip replacement surgery, only patients with high blood pressure (0·02, 95% CI 0·01, 0·02) and kidney disease (0·02, 95% CI 0·01, 0·02) had more improvement in HRQoL than patients without comorbidities but the difference was very small. Similarly, for knee replacement surgery, only patients with high blood pressure (0·01, 95% CI 0·00, 0·01), kidney disease (0·01, 95% CI 0·00, 0·01) and disease of the nervous system (0·01, 95% CI 0·00, 0·01) had more improvement in HRQoL than patients without comorbidities but again the difference was marginal.

The impact of comorbidities on satisfaction with the results of the operation

Patients with comorbidities were more likely to report being less satisfied with the results of their operation compared to patients without comorbidities (see Figure 3). The percentages describing their results as ‘fair’ or ‘poor’ were 7·35% for hip patients and 15·6% for knee patients. In hip patients, all patients with comorbidities, except patients

with kidney disease and liver disease, were more likely to report being less satisfied with the results of their operation. The adjusted OR in hip patients ranged from 0·69 (95% CI 0·65, 0·75) for depression to 1·02 (95% CI 0·95, 1·09) for kidney disease. In knee patients, all patients with comorbidities, except for patients with kidney disease and cancer were more likely to be less satisfied with the results of their operation. In knee patients the adjusted OR ranged from 0·75 (95% CI 0·65, 0·85) for liver disease to 1·01 (95% CI 0·95, 1·05) for kidney disease.

The impact of comorbidities and reporting overall improvement in hip or knee problem

Patients with comorbidities were less likely to report overall improvement in their hip or knee problems compared to patients without comorbidities (see Figure 2). The percentages reporting no overall improvement after their operation was 4·52% for hip patients and 11·3% for knee patients. In hip replacement, all patients with comorbidities, except for patients with liver disease and cancer, were more likely to report no improvement after surgery. The adjusted OR in hip patients ranged from 0·65 (95% CI 0·59, 0·70) for patients with depression to 1·05 (95% CI 0·97, 1·15) for kidney disease. Similar to reports of dissatisfaction, the highest likelihood was reported in patients with depression and disease of the nervous system (OR 0·67, 95% CI 0·60, 0·74). In knee replacement, patients with comorbidities, except high blood pressure, kidney disease and cancer, were more likely to report no improvement after surgery. The adjusted OR in knee patients ranged from 0·66 (95% CI 0·57, 0·76) for liver disease to 1·02 (95% CI 0·92, 1·12) for cancer with the highest reports in patients with liver disease and depression (OR 0·73, 95% CI 0·69, 0·77). In both hip and knee patients, kidney disease patients were less likely to report no overall improvement in their hip or knee problem after their operation.

Multiple comorbidities

Patients with multiple comorbidities were more likely to report a smaller improvement in OHS and OKS than patients with no comorbidities (see Figure 4). The likelihood of reporting satisfaction with the results of the operation and no overall improvement in the hip or knee problems also decreased (worsened) considerably with increasing number of comorbidities (see Figure 5). Hip patients with four or more comorbidities had a smaller improvement in the OHS (adjusted difference -0·91, 95% CI -1·19, -0·64), a slightly larger

improvement in HRQoL (0·01, 95% CI 0·00, 0·02) and were more than twice less likely to be satisfied (OR 0·41, 95% CI 0·38, 0·45) and report overall improvement (OR 0·41, 95% CI 0·37, 0·45) in their hip compared to patients with no comorbidities. Knee patients with four or more comorbidities had a smaller improvement in OHS (adjusted difference -1·42, 95% CI -1·67, -1·17), no difference in HRQoL (0·00, 95% CI -0·01, 0·01) and were twice less likely to be satisfied (OR 0·48, 95% CI 0·45, 0·51) and to report overall improvement (OR 0·47, 95% CI 0·44, 0·51) in their hip compared to patients with no comorbidities.

8.1.5 Discussion

In our study, substantial improvements in severity of joint problems and HRQoL after hip or knee replacement surgery were reported regardless of comorbidity. When examining differences between patients with and without comorbidities, patients with comorbidities reported slightly smaller improvements in joint problems but a similar HRQoL after hip or knee replacement surgery than patients without comorbidities. Patients with comorbidity also reported less satisfaction and less overall improvement in hip or knee severity of joint problems after surgery. These differences in improvement in severity of joint problems were more pronounced in patients with multiple comorbidities.

While there is a small impact of comorbidities on improvement in severity of joint problems six months after the joint replacement, the differences need to be interpreted within the context of the change in the overall scores. If we compare against the 'Minimal Important Change', the minimum change in health status in a single patient that is perceived by patients as beneficial, the overall change in both the OKS and OHS and EQ-5D in both patients with or without comorbidities was much higher than the minimum change [28, 29].

In contrast, when we investigated differences between patients with and without comorbidities and compared against the 'Minimal Important Difference (MID)', the difference in health gain between two independent groups that a patient perceives as beneficial, the differences are much smaller than the suggested MID values of five points for the OHS and OKS [28], and 0.08 for the EQ-5D [30]. Even in patients with multiple comorbidities, the differences are much smaller than the MID. It is important to note however, that the number of patients with multiple comorbidities is relatively small as the current practice of selecting patients for joint replacement would make patients with multiple comorbidities ineligible for surgery [31]. As a result, the findings suggest patients

with comorbidities do benefit significantly from hip and knee replacement surgery and only slightly less compared to patients without comorbidities.

Previous research on the impact of comorbidities on severity of joint problems and HRQoL after hip and knee replacement surgery has been inconclusive and relied on single-centre studies with small sample sizes [32, 33]. These smaller studies with fewer than 500 patients predominantly found no significant differences [32, 33] but studies with larger samples (>1000 patients) with longer follow-up times (>2 years) reported an impact of comorbidities on improvement in functional impairment [34, 35]. Our study of almost half a million patients from a nationwide representative sample of patients demonstrates that comorbidities have a marginal impact on the improvement in severity of joint problems and no impact on the improvement in HRQoL after joint problems compared to patients without comorbidities.

Even if the differences in improvement between patients with and without comorbidities in severity of joint problems and HRQoL at the individual comorbidity level were marginal, patients with comorbidities were less likely to report overall improvement and satisfaction with the results of their operation. A previous study investigating the use of single-item questions on patient satisfaction demonstrates that single transitional items such as questions about the satisfaction with the results of the operation and the extent of the overall improvement had low correlations with disease-specific severity measures and generic HRQoL suggesting such questions may be offering different insights [36]. Furthermore, previous studies have reported contradictory findings and reported no evidence of an impact of comorbidities on patient satisfaction [37-39]. This study therefore highlights the importance of also measuring severity of symptom and HRQoL to examine differences rather than relying only on single item questions such as patient satisfaction with the outcome of the surgery.

This study has several limitations. The first relates to potential selection bias. Firstly, patients undergoing hip and knee replacement surgery are more likely to be healthy than in the general population as patients considered too high risk such as patients with comorbidities may not be selected for hip or knee replacement surgery [31]. Selection for surgery is likely to be based on risk factors that we have no data for or that we capture very poorly. Due to clinical data being limited it was not possible to account for any selection criteria. Similarly, only patients that returned a postoperative questionnaire were included and a previous study found that non-responders were more likely to be severe cases and

have more comorbidities [40]. These selection biases may lead to an underestimation of the differences in outcomes between patients with and without comorbidities.

The second limitation relates to the availability of data on potential confounders. There was a lack of information on other risk factors such as BMI, smoking status and on the severity of the comorbidities. We did however have information about comorbidities that are associated with obesity such as diabetes, heart disease and high blood pressure. Furthermore, a previous study of 2180 patients, which compared patients with normal weight against patients with a BMI>25kg/m2, reported that functional outcomes after knee replacement surgery were not influenced by BMI [41].

8.1.6 Conclusion

In summary, our findings suggest that the impact of comorbidities on outcomes is very small compared to the overall benefits of the hip or knee replacement surgery itself. Patients with comorbidities reported on average large improvements in joint problems and HRQoL. When compared to patients without comorbidities, patients with comorbidities reported slightly smaller improvements in their joint problems but no difference in HRQoL. Patients with comorbidities were less likely to report overall improvement and to be satisfied with the results of their operation compared to patients without. This study suggests that patient with comorbidities benefit greatly from hip and knee replacement surgery and therefore any restriction of access to hip and knee replacement surgery based on the presence of comorbidity alone is unjustified.

8.1.7 Figures and Tables

Figure 1 - Flow chart

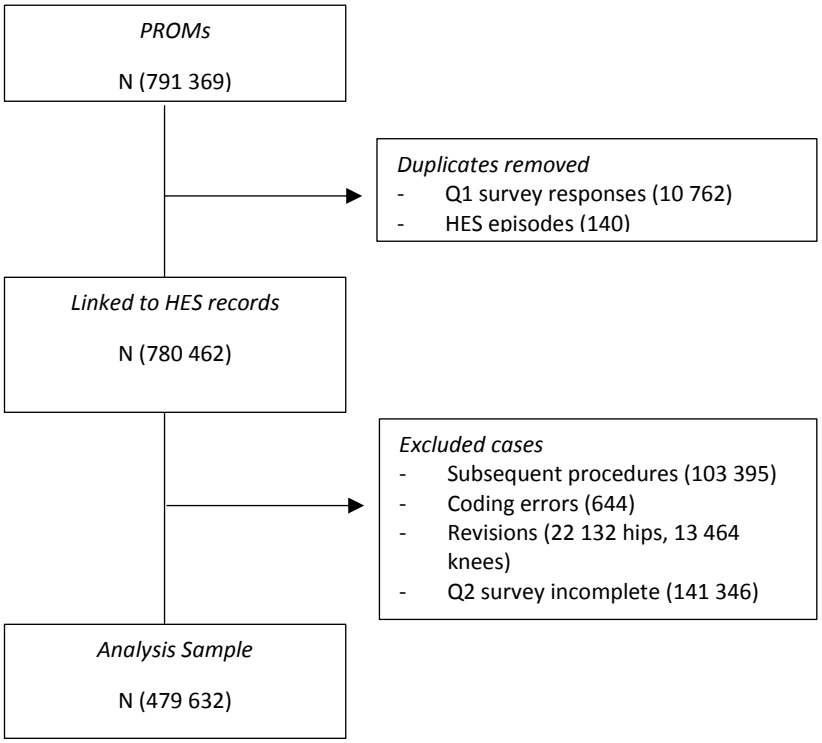


Table 1 - Study population characteristics

Characteristic	Hip replacement	Knee replacement
No. of patients	234 432	245 200
Age (mean, range)	69 (18-101)	70 (18-102)
Gender, n (%)		
Male	94 545 (40·3)	105 150 (42·9)
Female	139 734 (59·7)	139 821 (57·1)
Missing, not stated	153	229
Socioeconomic status by quintile group, n (%)		
1 (least deprived)	58 162 (24·8)	54 117 (22·1)
2	58 824 (25·1)	57 572 (23·5)
3	40 769 (17·4)	45 840 (18·7)
4	37 903 (16·2)	43 397 (17·7)
5 (most deprived)	36 331 (15·5)	41 880 (17·1)
Missing	2 443	2 394
Ethnicity, n (%)		
White or White British	205 512 (98·7)	211 737 (95·7)
Mixed background	304 (0·15)	532 (0·24)
Asian or Asian British	653 (0·31)	5 764 (2·61)
Black or Black British	966 (0·46)	2 102 (0·95)
Chinese or other ethnic	745 (0·36)	1 071 (0·48)
Missing	26 252	23 994
Prevalence of comorbidities, n (%)		
Heart disease	39 594 (16·9)	44 914 (18·3)
High blood pressure	114 373 (48·8)	139 931 (57·1)
Stroke	2 423 (0·99)	3 723 (1·59)
Leg pain due to poor circulation	3 723 (1·59)	3 686 (1·50)
Lung disease	30 989 (13·2)	36 672 (15·0)
Diabetes	21 621 (9·22)	32 247 (13·5)
Kidney disease	11 916 (5·08)	12 992 (5·30)
Diseases of the nervous system	5 723 (2·44)	6 735 (2·75)
Liver disease	1 147 (0·49)	1 219 (0·50)
Cancer	4 633 (1·98)	4 167 (1·70)
Depression	8 288 (3·54)	9 549 (3·89)
Count of comorbidity, n (%)		
0	86 104 (36·7)	71 472 (29·2)
1	81 505 (34·8)	89 798 (36·6)
2	44 789 (19·1)	55 636 (22·7)
3	16 352 (6·98)	21 225 (8·66)
4+	5 682 (2·42)	7 069 (2·88)

Table 2 – Unadjusted net change (Post-Pre) for OHS, OKS and EQ-5D and number of patients reporting being satisfied and an overall improvement in their joint problem.

	Improvement in OHS/OKS Mean (SD)		Improvement in EQ-5D Mean (SD)		Patients reporting being satisfied n (%)		Patients reporting overall improvement n (%)	
	Hips	**Knees**	**Hips**	**Knees**	**Hips**	**Knees**	**Hips**	**Knees**
Comorbidity								
Heart disease	20·4 (10·6)	15·1 (10·4)	0·433 (0·346)	0·303 (0·334)	35 088 (90·5)	36 137 (81·7)	37 279 (94·2)	39 011 (86·9)
High blood pressure	20·9 (10·4)	15·7 (10·1)	0·441 (0·342)	0·314 (0·331)	102 969 (91·7)	115 353 (83·7)	108 676 (95·0)	123 832 (88·5)
Stroke	19·8 (11·1)	14·4 (10·8)	0·434 (0·353)	0·305 (0·351)	1898 (87·3)	1902 (80·2)	2051 (91·9)	2064 (85·2)
Leg pain due to poor circulation	20·1 (10·9)	14·9 (10·5)	0·422 (0·360)	0·293 (0·333)	3228 (88·6)	2946 (81·2)	3464 (93·0)	3185 (86·4)
Lung disease	20·6 (10·9)	15·2 (10·4)	0·435 (0·350)	0·309 (0·340)	27 398 (90·1)	29 158 (80·7)	29 073 (93·8)	31 594 (89·1)
Diabetes	20·4 (10·7)	14·7 (10·6)	0·437 (0·348)	0·309 (0·342)	19 214 (90·6)	25 347 (79·8)	20 278 (93·8)	27 460 (85·2)
Kidney disease	21·0 (10·5)	15·8 (10·4)	0·432 (0·355)	0·322 (0·334)	10 648 (91·3)	10715 (83·8)	11 304 (94·9)	11 527 (88·7)
Diseases of the nervous system	20·2 (10·9)	15·2 (10·8)	0·433 (0·351)	0·317 (0·350)	5325 (80·6)	5000 (89·1)	5311 (92·8)	5740 (85·2)
Liver disease	20·8 (11·1)	14·2 (10·4)	0·445 (0·358)	0·286 (0·347)	1010 (89·6)	920 (76·3)	1072 (93·5)	986 (80·9)
Cancer	20·9 (10·4)	15·6 (10·1)	0·431 (0·337)	0·303 (0·327)	4156 (91·5)	3453 (84·4)	4411 (95·2)	3714 (89·3)
Depression	20·6 (11·1)	14·9 (10·6)	0·434 (0·367)	0·313 (0·361)	7221 (88·5)	7353 (77·9)	7696 (92·9)	7950 (83·3)
Number of comorbidities								
0	21·3 (9·91)	15·9 (10·0)	0·424 (0·327)	0·306 (0·320)	79 672 (92·7)	60 714 (86·2)	83 024 (96·4)	64 197 (89·8)
1	21·1 (10·2)	15·8 (10·1)	0·436 (0·338)	0·314 (0·326)	74 267 (92·7)	75 268 (85·1)	77 965 (95·7)	80 410 (89·6)
2	20·7 (10·5)	15·4 (10·3)	0·439 (0·346)	0·310 (0·334)	40 010 (91·0)	45 376 (82·7)	42 389 (94·6)	48 800 (87·7)
3	20·3 (10·9)	15·0 (10·6)	0·441 (0·351)	0·311 (0·342)	14 322 (89·6)	16 659 (79·8)	15 258 (93·3)	18 152 (85·5)
4+	19·9 (11·3)	14·4 (10·9)	0·434 (0·362)	0·307 (0·357)	4855 (87·3)	5369 (77·3)	5211 (91·7)	5837 (82·6)

Figure 2 – Severity of joint problems and HRQoL for patients with and without comorbidities after hip and knee replacement (adjusted for age, sex, ethnicity, SES and other comorbidities)

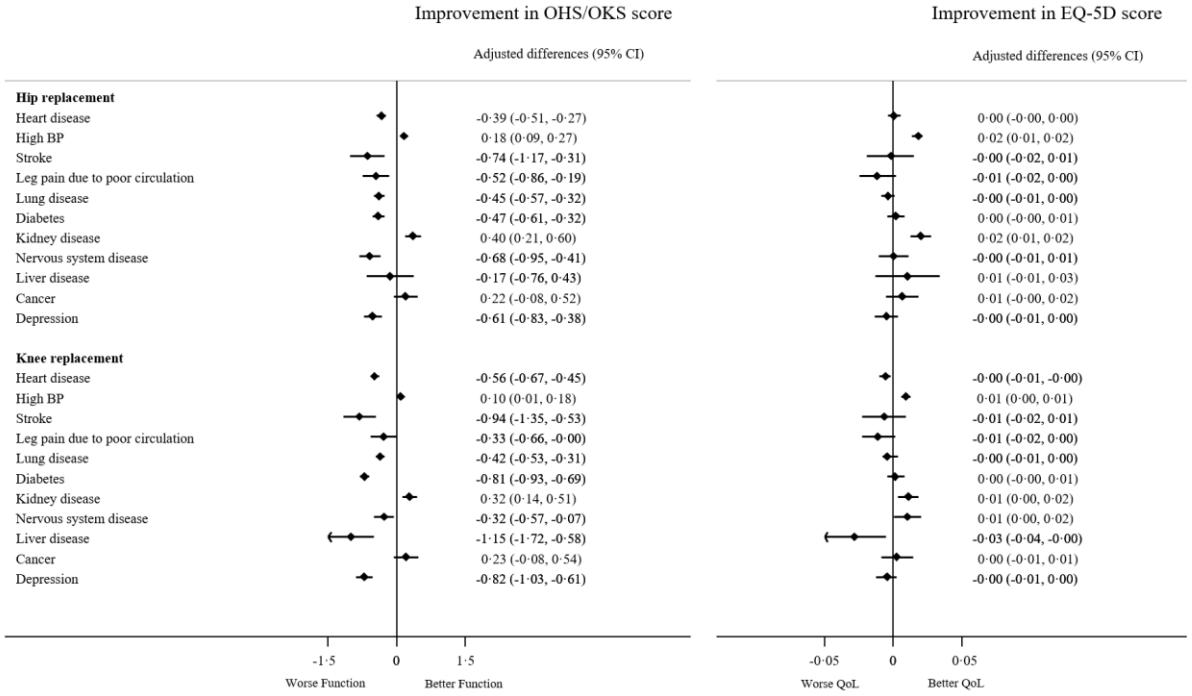


Figure 3 – Adjusted OR for satisfaction and improvement comparing patients with and without comorbidities after hip and knee replacement (adjusted for age, sex, ethnicity, SES and other comorbidities)

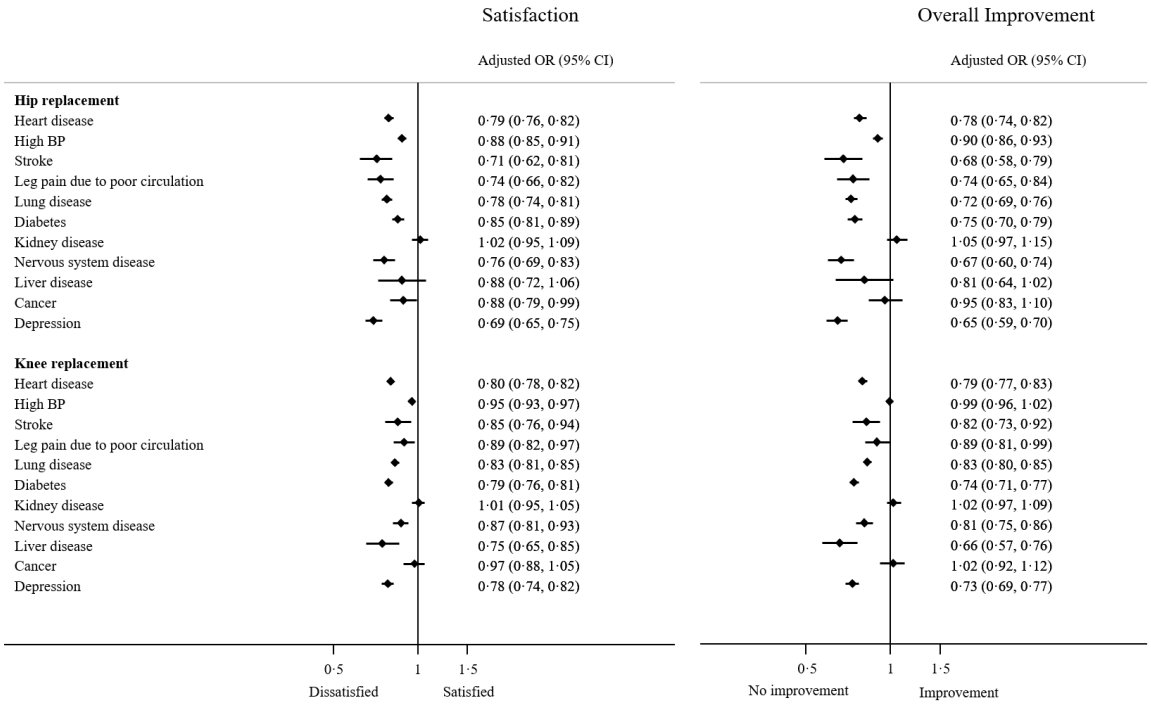


Figure 4 - Severity of joint problems and HRQoL by number of comorbidities (95% CI) (adjusted for age, sex, ethnicity, SES and other comorbidities)

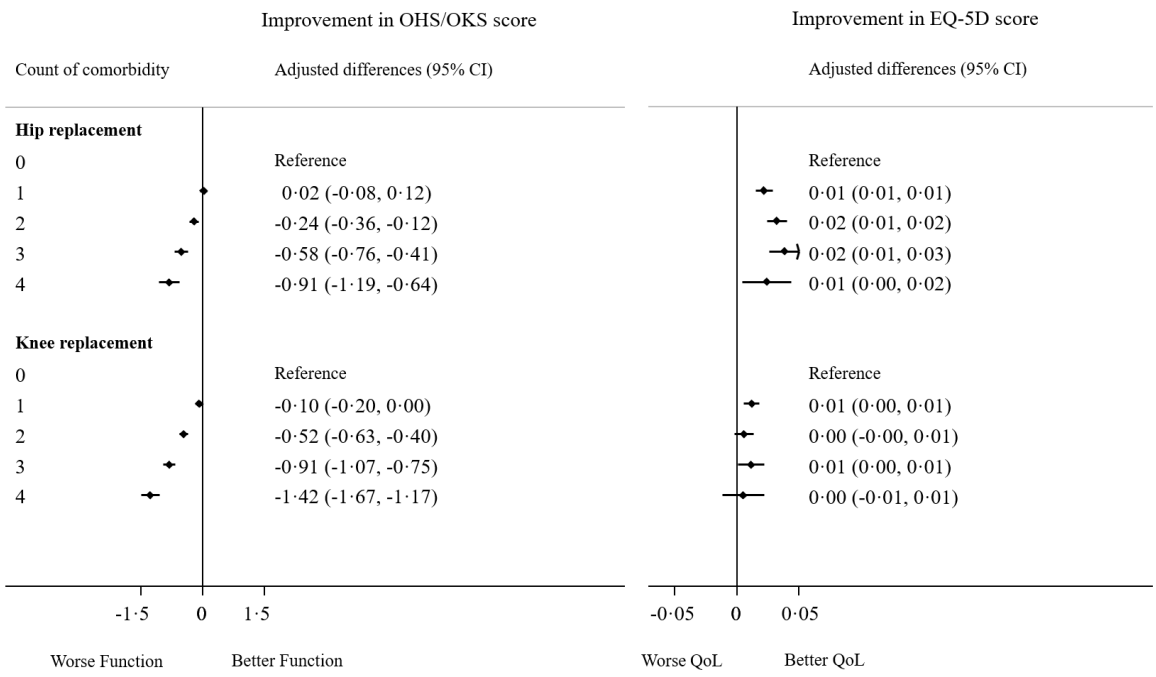
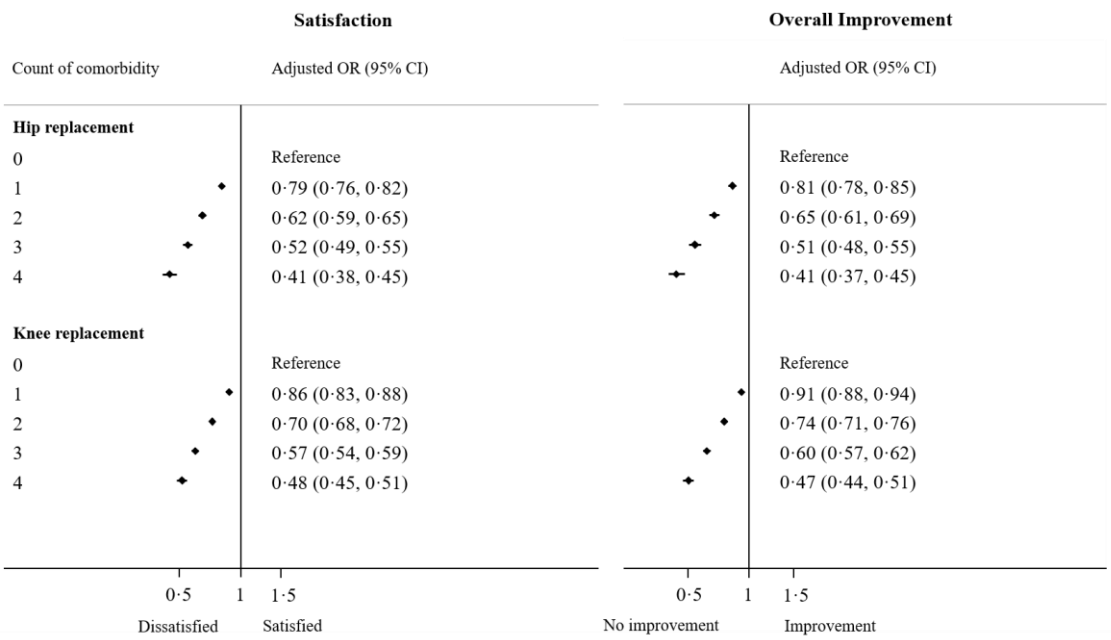


Figure 52- Satisfaction and overall improvement by number of comorbidities (95% CI) (adjusted for age, sex, ethnicity, SES and other comorbidities)



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8.1.9 Supplementary Information

Supplementary information 1- Comorbidity profile

Comorbidity	Comorbidity sub-category	n (%)
Heart disease	Ischemic heart disease	48 555 (57.0)
	Cardiac arrhythmias	38 492 (45.5)
	Valvular disease	9 377 (11.0)
	Congestive heart failure	7 566 (8.91)
Stroke	Ischemic stroke	2 156 (46.3)
	Transient Ischemic Attack	745 (16.0)
	Subarachnoid haemorrhage	52 (1.10)
	Other Stroke	1 806 (38.8)
Leg pain due to poor circulation	Peripheral vascular diseases	3 861 (52.1)
	Vascular implants	2 214 (29.9)
	Aortic diseases	1 844 (24.9)
	Gangrene	105 (1.4)
High BP	Primary hypertension	235 890 (92.7)
	Secondary hypertension	4 323 (1.7)
Diseases of the nervous system	Epilepsy	4 912 (39.4)
	Parkinsonism	2 779 (22.3)
	Dementia	1 713 (13.7)
	Neuropathies	1 004 (8.10)
	Demyelinating diseases	790 (6.31)
	Other nervous system (e.g. paralysis, huntington's disease)	1 534 (12.3)
Lung disease	Asthma	47 728 (70.5)
	COPD	20 574 (30.4)
	Pulmonary heart diseases	1 661 (2.50)
	Other lung disease (e.g. due to external agents)	1 024 (1.51)
Diabetes	Non-insulin-dependent diabetes	51 787 (96.1)
	Insulin-dependent diabetes	2 290 (4.20)
	Other	597 (1.10)
Kidney disease	Chronic renal failure	21 122 (84.8)
	Glomerular disease	3 177 (12.7)
	Acute renal failure	1 191 (4.71)
Liver disease	Cirrhosis	583 (24.6)
	Alcoholic liver disease	401 (16.9)
	Hepatitis	361 (15.2)
	Hepatic failure	37 (1.60)
	Any other liver disease	1 123 (47.4)
Cancer	Cancer without metastasis	6 934 (78.8)
	Lymphoma	1 708 (19.4)
	Metastatic cancer	921 (10.5)
Depression	Depression	16 322 (91.5)
	Depression linked to anxiety and stress	1 721 (9.60)
	Other depression (linked to schizophrenia and BAD)	15 (0.10)

Supplementary information 2- Comorbidity profile by number of comorbidities n (%)

# of Comorbidities	Heart disease	High BP	Stroke	Circulation	Lung disease	Diabetes	Kidney disease	Nervous system disease	Liver disease	Cancer	Depression
1	12 575	117 710	371	805	20 291	6 331	1 871	3 296	437	2 235	5 380
	(7.30)	(68.7)	(0.20)	(0.46)	(11.8)	(3.70)	(1.09)	(1.92)	(0.20)	(1.30)	(3.10)
2	37 623	88 589	1 248	1 889	24 850	24 166	8 394	4 024	716	2 991	6 360
	(37.5)	(88.2)	(1.20)	(1.80)	(24.70)	(24.1)	(8.36)	(4.01)	(0.70)	(2.90)	(6.30)
3	23 933	35 564	1 482	296	15 220	15 840	8 753	2 883	636	2 144	3 780
	(63.7)	(94.6)	(3.90)	(6.60)	(40.5)	(42.1)	(23.3)	(7.67)	(1.69)	(5.70)	(10.1)
4	10 377	12 441	1 555	2 219	7 299	7 531	5 890	2 255	577	1 430	2 317
	(81.4)	(97.6)	(12.1)	(17.4)	(57.2)	(59.1)	(46.2)	(17.7)	(4.53)	(11.2)	(18.2)

9 DISCUSSION

This programme of research seeks to investigate the access to and safety and effectiveness of hip and knee replacement surgery for patients with a variety of comorbidities. In the following section, I summarise the main findings of my PhD research, move on to discuss the policy implications of the findings for the health system and the overall strengths and limitations of the programme. Finally, I consider the future research opportunities.

9.1 Summary of main findings

In the UK, there are indications that access to elective hip and knee replacement surgery is being restricted by commissioners of health services in a bid to cut spending budgets. Restrictions have included eligibility criteria such as the optimisation of comorbidities before surgery. This programme of research set out to determine if there are any inequalities in access to hip and knee replacement as well as the safety and effectiveness of hip and knee replacement for patients with comorbidities. There were three main components to this programme of research: a literature review, methodological work and empirical work.

9.1.1 Literature review: existing literature on access and outcomes

Before analysing the data, I sought to understand the literature on the relationship between comorbidities and access to and outcomes of, hip and knee replacement surgery. My systematic review and meta-analysis (RP1) focused on the impact on outcomes of surgery rather than access to surgery. This was because the literature on access was limited and heterogeneous. This is likely due to the lack of consensus on what constitutes access to healthcare and on how to measure it. Under any useful definition, access is difficult to quantify [133]. The literature identified in the systematic search on access was incorporated into the research paper on access (RP4).

My systematic review demonstrates that patients with comorbidities are more likely to be readmitted and to suffer a higher short-term mortality but there is little evidence that patients benefit significantly less in terms of HRQoL, function and pain compared to patients without comorbidities. Furthermore, it highlighted two gaps in the literature. First, the more common and familiar comorbidities are widely investigated - only six studies

focused on patients with diseases of the nervous system whereas over 30 studies I reviewed investigated outcomes in patients with diabetes. Second, the majority of the literature on outcomes after hip and knee replacement surgery measured the risk of surgical complications (85% of studies) but very few measured patient-reported outcomes - only five studies reported on HRQoL outcomes and only two studies reported on pain.

9.1.2 Methodological work

I then undertook an innovative piece of methodological work to explore the agreement between the two sources of data on comorbidity: patient-reported and administrative-data derived comorbidities (RP3). This is the first study to investigate the agreement between these two datasets. I demonstrated that patients can give accurate information about the presence of comorbidities, if the description in the patient questionnaire is precise, if the disease is familiar to most patients, and if the disease has a significant impact on their life. These results highlight the importance of validating patient questionnaires that ask patients about the presence of comorbidities before they are used for research and service evaluation projects.

Based on this work, I had to decide what measure I would use to identify comorbidities. The decision was to use the PROMs comorbidity categories to group together the individual comorbidities, but to identify the individual comorbidities using a combination of comorbidity indices in administrative data. This was because it allowed for a comparison with a combination of already existing ICD-10 diagnosis based comorbidity indices in administrative data and ensured that I captured as many comorbidities as possible including those that were not captured accurately by patient-report.

9.1.3 Empirical Work

9.1.3.1 Access

Before embarking on the quantitative examination of inequalities in access to joint replacement surgery, I sought to understand the referral pathway for patients with comorbidities (RP2). My qualitative study found that different types of professionals across the system managed patients with comorbidities differently and that there are disagreements about whose role and responsibility it is to prepare patients with comorbidities for surgery. As a result, when patients with comorbidities were considered

unfit for surgery, patients were referred back to their GP where they were left to learn how to improve the self-management of their conditions. A barrier may therefore be operating at the referral pathway level such that patients with comorbidities are getting 'lost in the system' and their surgery delayed.

To explore inequalities in access quantitatively, I compared the severity and duration of joint problems just before surgery between patients with and without comorbidities (RP4). If there were differences in access, we might expect to see differences in the severity of joint problems and in the duration of problems between patients with and without comorbidities just before surgery. The exploration of severity of joint problems just before surgery showed a consistent picture. Patients with comorbidities reported more severe preoperative hip or knee symptoms compared to patients without comorbidities. To further explore the severity of joint problems and to account for the possibility that comorbidities directly influence joint disease-specific measures, pain and functional status scores were investigated separately. I hypothesised that pain is more 'joint-specific' than functional status and is therefore less likely to be linked to comorbidities. Patients with comorbidities reported more severe pain suggesting that they truly have worse joint problems. In addition, the more comorbidities a patient had, the worse the reported severity of joint problems just before surgery. These results support the findings of the qualitative study (RP2) that patients with comorbidities may be having surgery later in the course of their joint disease.

With regards to duration of joint problems, the impact of different comorbidities was less consistent across hip and knee patients and being observed in 6 out of 11 comorbidities in hip patients and 2 out of 11 in knee patients. This inconsistency may be due to patients having reported the duration of symptoms of the most recent episode of a specific level of severity rather than the overall duration suggesting questions about duration of symptoms may be unclear and therefore unreliable.

9.1.3.2 Outcomes

The investigation of outcomes focused on measuring safety (RP5) and effectiveness (RP6) of hip and knee replacement surgery. Healthcare professionals need to consider both the safety risks and the benefits of joint replacement surgery before referring or selecting patients for surgery. Compared to patients without comorbidities, patients with single comorbidities had a slightly increased risk of adverse outcomes and a prolonged hospital

stay, but for patients with three or more comorbidities the study showed that the risk was considerably higher (RP5). In contrast, the study of the impact of comorbidities on effectiveness of hip and knee replacement surgery, in line with the findings from my systematic review, found that patients with comorbidities, measured by improvement in severity of joint problems and HRQoL, did benefit overall from hip and knee replacement surgery, and only slightly less than patients without comorbidities. Together these two papers on safety and effectiveness (RP5 and RP6) suggest that the impact of comorbidities is small compared to the overall benefit of hip and knee replacement surgery.

9.1.3.3 Multiple comorbidities

I also explored the impact of having multiple comorbidities on access to and safety and effectiveness of hip and knee replacements surgery. Increasingly more patients are presenting with multiple comorbidities and little is known about the impact of multiple comorbidities on access to and outcomes of joint replacement surgery. The most common conditions in patients with multiple comorbidities were high blood pressure, heart disease, diabetes and lung disease. The preoperative severity of joint problems decreased (worsened) with increasing number of comorbidities. The risk of adverse outcomes and less improvement in severity of joint problems and HRQoL increased (worsened) with increasing number of comorbidities. Specifically, patients with three or more comorbidities appear to have a clinically important increased risk in adverse outcomes. Nevertheless, despite this increase risk of adverse outcomes, patients with multiple comorbidities continued to report large improvements in severity of joint problems and quality of life after surgery.

9.2 Policy implications for clinical practice and the health system

The next section discusses the policy implications for clinical practice and the NHS derived from the findings of this research.

9.2.1 Before surgery: access and the referral pathway

One of the aims of this thesis was to investigate whether there were any inequalities in access for patients with LTCs. The quantitative and qualitative empirical work on access suggested there are. Compared to patients without comorbidities, patients with comorbidities reported more severe preoperative joint problems, suggesting patients with comorbidities may be having surgery later in their joint disease. The qualitative study revealed that there may be inequalities in access due to patients being considered ineligible for surgery because of their comorbidities. Patients with comorbidities whose conditions were not 'optimised' for surgery had their operations delayed and were sent back to their GPs. Patients were then left to learn how to improve the self-management of their comorbidities before being reconsidered for surgery. This finding suggested that patients with comorbidities may therefore be receiving their hip or knee replacement surgery later (or not at all, if they fail to improve their conditions themselves). Together these findings demonstrate that inequalities in access do exist for patients with comorbidities.

The current approach to resolving these inequalities has been to develop guidelines and procedures to prepare patients with comorbidities for surgery [134, 135]. This assumes, however, that all comorbidities can be 'optimised' or controlled as is the case with conditions such as diabetes or hypertension. This is not the case for comorbidities such as Parkinson's disease, heart failure or COPD. Comorbidities should therefore not be considered as a homogenous group.

In the UK and the USA, enhanced recovery protocols have been introduced (consisting of a multimodal programme before, during and after surgery) to improve outcomes for patients undergoing joint replacement surgery. Before surgery, this programme involves patient education about what to expect from the surgery, preoperative fasting and carbohydrate loading, detecting and correcting anaemia and pre-emptive analgesia [136]. Very little of this programme directly addresses the optimisation of patients with comorbidities. In the USA, orthopaedic surgeons have also developed a programme called *Strong for Surgery* that addresses the care provided to maximise patients' health before elective surgery by

working with surgeons in the clinics. This programme includes a review of nutrition, smoking cessation, glycaemic control and medication use [134]. This relates to the management of comorbidities such as diabetes, high blood pressure, heart disease and stroke. Further research however is needed to evaluate these programmes and determine which interventions work best to optimise patients' health before surgery [135].

Currently, guidelines on how to prepare patients with comorbidities for surgery in the UK are limited [137]. The few guidelines that exist focus on the immediate perioperative period rather than the period between consultation and the procedure. Guidelines specifically relate to the management of anaesthetic risk related to comorbidities in preparation for surgery. Guidelines are also predominantly based on single diseases with a focus on comorbidities that can be controlled such as diabetes and hypertension [138-141]. There is very little literature on preparing patients with multiple comorbidities for surgery. This may be due to the small number of studies examining the impact of multiple comorbidities on surgical risks and other outcomes [137].

9.2.2 After surgery: short-term (safety) and long-term (effectiveness) outcomes

The focus on better preparing patients with comorbidities for surgery, however, is based on the belief that patients with comorbidities will have poorer outcomes after surgery. My research shows that even if patients with comorbidities have an increased risk of short-term adverse outcomes they benefit significantly from hip and knee replacement surgery. Even patients with multiple comorbidities who have a substantial increased risk of adverse outcomes in the short-term benefitted considerably on average.

Healthcare professionals need to consider the risks and benefits of surgery so they can make an informed decision about recommending patients for surgery [142]. The appropriate balance between avoiding complications and providing access to care, however, is difficult to determine. This research shows that a decision to operate on patients with comorbidities is a commitment to managing complications should they arise. Managing complications requires additional time and resources leading to the introduction of eligibility criteria for total joint arthroplasty which then have the effect of delaying or denying the operation to patients. In England, commissioners of healthcare have imposed eligibility criteria such as BMI of less than 30kg/m^2 and the optimisation of comorbidities before surgery with the aim of reducing costs [143]. The concerns about high BMI relate to its association with comorbidities such as diabetes, high blood pressure and heart disease.

My research has also demonstrated however, that compared to patients without comorbidities, patients with comorbidities benefit just as much in terms of improvements in function, pain and HRQoL. Limiting access to joint replacement surgery would be therefore denying pain relief and functional improvement to patients as well as indirectly increasing costs of care associated with advanced hip or knee arthritis.

A study exploring the balance of risk of complications and benefits of joint replacement surgery compared the impact of BMI-based eligibility criteria on avoiding complications or death against how many patients would have been denied access to a complication-free joint replacement. The study reported that the blanket eligibility criterion of having a BMI of less than 30kg/m^2 was only marginally better than flipping a coin and should not determine surgical eligibility. On a population-level, this policy would therefore reduce the overall number of complications but would also deny access to join replacement to a much larger number of patients who would not have suffered complications [144].

The question of whether any blanket criteria on the presence of comorbidities is acceptable or equitable is difficult to answer. Patients might prefer to have the choice to assume any risk whereas surgeons may consider such a trade-off acceptable if they do not have the resources or support to handle any potential complications. NICE clinical guidelines on osteoarthritis have recommended that "patient-specific factors (including age, sex, smoking, obesity and comorbidities) should not be barriers to referral for joint surgery". My findings add to the evidence supporting the NICE guidelines that such restrictive eligibility criteria for patients with comorbidities are unjustified and may be creating inequities in access to joint replacement surgery [19]. Further study however is needed to explore the appropriate balance between the risks and benefits of undertaking joint replacement surgery in patients with comorbidities and therefore whether these inequalities are inequitable.

As part of its Elective Care Transformation Programme (2017-2019), the NHS is currently considering the revision and creation of new standardised eligibility criteria for hip and knee replacement surgery across England in order to reduce the variation in access [145]. This programme aims to support local commissioners and clinicians in changing how patients are referred to secondary care, to make better use of resources, and to reduce the wait for hospital treatment (the 18-week target). The findings of my research could inform this discussion about standardised eligibility criteria for patients in need of hip or knee

replacement surgery and provide the evidence that any restrictions on the basis of the presence of comorbidities alone is unjustified.

9.3 Strengths and Limitations

The strengths and limitations of specific methods and analytical approaches have been discussed in each chapter but this section will focus on overarching strengths and limitations.

9.3.1 Strengths

9.3.1.1 Methodological approach

One of the key strengths of this thesis was the use of both qualitative and quantitative (RP4) research methods (RP2). The qualitative study allowed for an in-depth exploration of the complexity of the health system and to capture the perspectives of providers and organisations [146]. Specifically, the qualitative study gave a better understanding of the patient journey through the health system for a hip or knee replacement and the roles of healthcare professionals in this system. This insight was essential to explore the possible reasons for any differences in access for patients with comorbidities. The quantitative study did not have data on selection criteria and could not account for unobserved confounders such as indication for surgery so the insight from the qualitative interviews with healthcare professionals on the referral and selection of patients with comorbidities was invaluable. The finding that some patients with comorbidities may be getting 'lost in the system' and their operations delayed was supported by the quantitative findings on access. Much of the discussion around the impact of comorbidities on access and the possible explanation for any inequalities in access would have been lost if only a quantitative approach was used.

9.3.1.2 Linked patient-level data

Another major strength of this thesis was the use of linked national patient-level data. The NHS itself is an ideal forum to explore inequalities in health and access due to the available patient-level data. I used both patient-reported (PROMs) data to include the patient

perspective as well as routine administrative hospital data. Data linkage provided an opportunity to study outcomes other than survival, complications and readmissions and to look at outcomes which are a reflection of how patients experience their outcomes. The PROMs survey has a response rate of over 70%, meaning that I did not have access to data on all hip or knee replacement surgeries in England, but I did have a large (>500,000 patients) representative nationwide sample (see further details in Appendix J).

9.3.2 Limitations

There were three main limitations to this thesis: the approach to measuring access, the healthy-surgical patient effect and the assumption that comorbidities have no impact on disease-specific measures.

9.3.2.1 Measuring Access

As discussed in the introduction, it is not possible to directly observe access to joint replacement surgery. I therefore measured access indirectly using a population standard approach which measures variation in 'realised access'. The main limitation of this approach, however is that it cannot explain all the variation. It is not possible to determine whether the rest of the variation is due to random variation or unmeasured or unobserved demand or supply factors [32].

Access to health services as discussed in the introduction is multifaceted and the complexity of what constitutes access was demonstrated in my qualitative study. Access goes further than the utilisation of healthcare services and limiting the definition of access to the use of health services will therefore not fully account for the variation in access. Future research on access to joint replacement surgery should therefore attempt to simultaneously consider other factors that influence 'potential access' such as the structural features of the health system (e.g. availability of service) and features of the individuals (e.g. ability to seek, ability to pay and patient willingness to undergo surgery) [147]. This comprehensive approach will make it possible to truly judge whether there are inequities in access and whether the demand is aligned with supply. This more comprehensive view of access has been called for especially due to the increasing prevalence of patients with more than one LTC. The emphasis currently is on patients to

self-manage their LTCs. Any future concept of access should therefore incorporate patient-centred perspectives into population-level approaches [148].

In addition, to explore the determinants of 'realised access' I hypothesised that if there were differences in access, we might expect to see differences in severity of joint problems and duration of these just before the joint replacement surgery. This assumes that osteoarthritis is a progressive disorder – the longer you have the disorder the more severe the symptoms are. However, there may be other explanations for having more severe joint problems just before surgery such as simply having a more severe form of joint disease such that the disease progresses more rapidly.

My approach to access however is also a strength of this study as it demonstrates what can be inferred about access from PROMs data. In the wider literature, quantitative studies using similar methods to understand access have been limited about what they can conclude from using a population standard approach to measuring access. It is for this reason that I also used qualitative methods to understand the complexity of the pathway to accessing joint replacement surgery.

9.3.2.2 The healthy-surgical patient effect

Whilst the data used in this research were of a representative sample of patients undergoing hip and knee replacement surgery in England, there is still evidence of selection bias. The literature suggests that there is a 'healthy-surgical patient effect' such that the most severe patients, many of whom will likely suffer comorbidities, are unlikely to be eligible for hip and knee replacement surgery and are therefore not selected for surgery [50]. As such, the hip and knee replacement patient population with one or more comorbidities is likely to represent a healthier population than a random sample from the general population with a similar comorbidity profile.

In addition, this study, similar to other observational studies has the limitation of not being able to account for all unmeasured or unobserved confounders such as indication for surgery. Skilled clinicians use their expert judgement to decide whether to select a patient for surgery and this judgement includes an assessment of the severity of the condition or the frailty of the patient. In addition, patients may have other unmeasured characteristics that would make them relatively less frail. This would lead to an underestimation of the difference between patients with and without comorbidities [149]. Due to clinical data

being unavailable and the lack of consensus on indication for surgery, such confounding was not accounted for. A randomised trial would be required to address this limitation.

The limited clinical data on any selection criteria and severity of comorbidities prevented any exploration of this 'healthy-surgical patient' effect. Clinical data on severity of comorbidities would have allowed the stratification of the impact of comorbidities on outcomes according to the severity of the comorbidity. Understanding comorbidity severity is key to understanding the difference between suitability for surgery and unjustifiably restricting access on the basis of concerns about adverse outcomes and decreased benefit [150].

9.3.2.3 Disease-specific measures and comorbidity

One of the challenges of interpreting disease-specific measures was disentangling the impact of comorbidity on the disease-specific measure itself (RP4). Previous research in both hip and knee patients have reported concerns that comorbidities do influence the OHS and OKS, which provides evidence that the OHS/OKS may not be fully 'joint-specific' [151, 152]. This concern has also been reported in studies of patients with COPD, asthma, heartburn and ulcers aiming to measure the extent to which comorbidity influences disease-specific quality of life measures and generic quality of life instruments. These studies demonstrated that comorbidities had a direct impact on the disease-specific measures albeit to a smaller degree than on the generic measure [153-155]. This has significant impact on the estimation of true effects of hip and knee replacement surgery and should be considered in the design of studies looking at comorbidities and using disease-specific as well as generic quality of life measures.

To account for this direct influence of comorbidities on the OHS/OKS I investigated the impact of comorbidities on the two dimensions of severity of joint problems, functional status and pain, separately. I hypothesised that pain is more joint-specific compared to mobility. For example, questions such as "Have you been able to climb a flight of stairs?" or "Could you do the household shopping on your own?" could also elicit a negative response in patients with respiratory problems or who are frail. I therefore investigated the impact of the 11 comorbidities on the OHS/OKS functional status and pain scores separately. This analysis demonstrated that compared to patients without comorbidities, patients with comorbidities reported not only worse functional status but also more severe pain. This

suggests that any direct influence of comorbidities on the OHS/OKS is small compared to the overall impact of comorbidities on the severity of the joint problems.

9.3.3 Further limitations

9.3.3.1 Data

Data limitations prevented further explorations of known important confounders and outcomes. Ideally, I would have wanted to include BMI as a confounder but BMI data was not available in HES. I could have used a proxy measure of patients with a reported diagnosis of obesity (ICD-10 code: E669) but this has only recently started to be coded reliably in HES. This would not have greatly altered the results however as BMI is on the causal pathway of several comorbidities included in this programme of work (e.g. diabetes, high blood pressure, heart disease).

Several large national studies in the UK using National Joint Registry (NJR) and Clinical Practice Research Datalink (CPRD) data have looked at the impact of high BMI [18, 156] and demonstrated that despite slightly increased risks of complications, large improvements in outcomes were observed irrespective of BMI [18, 157]. Similarly, a meta-analysis of 17 studies published before January 2017 found only a small impact of obesity on postoperative pain and surgical complications [158].

It would have been helpful also to have had access to the HES *Accident & Emergency (A&E)* and the *Adult Critical Care* HES datasets in addition to the *Inpatient Admissions* data. *Accident & Emergency* data would have allowed me to look more closely at emergency visits after surgery and the reason for the emergency visit. The quality of the A&E dataset has been questioned however [159]. *Adult Critical Care* data would have allowed for an exploration of patients needing different levels of critical care such as intensive care (unplanned) and high dependency care (planned). It was possible to derive an indicator for entering critical care from the *Inpatient Admissions* data but there were too few critical care admissions (N=732/0.15%) compared to expected figures reported by ICNARC suggesting coding of critical care may be unreliable [160].

I also did not look at specific surgical complications after hip or knee replacement surgery because of the coding limitations of secondary diagnoses (ICD-10) and procedure codes in HES (RP5). There is a lack of consensus on how to measure surgical complications and

adverse events in administrative data. In the USA, the Agency for Healthcare Research and Quality (AHRQ) developed Patient Safety Indicators (PSIs) to screen for problems that patients experience as a result of their care (e.g. postoperative sepsis, respiratory failure, sepsis, infections, haemorrhage) in administrative data [161]. The reliability of the coding of these PSIs have however, been called into question [162-164]. In the UK the accuracy of the coding of secondary diagnoses (comorbidities) and procedure codes (complications) have been found to be unreliable and therefore the rates of complications based on these codes are likely to be underestimated [165]. As a result, like most studies, I measured adverse outcomes that reflect health service use such as 30-day readmission, 30-day mortality and transfers to another consultant, as surrogates for surgical complications.

9.3.3.2 Identifying comorbidities

After analysing the agreement between PROMs and HES-derived comorbidities (RP3), I had to decide which measure of comorbidities to use in the subsequent results chapters (RP 4-6). I decided on using a combination of comorbidity indices to identify the presence of comorbidities in HES rather than just using one comorbidity index (e.g. Charlson Comorbidity Index or the Elixhauser) because I wanted to include as many ICD-10 codes to capture as many comorbidities as possible. Individual comorbidity indices are only designed to calculate a final score for comorbidity adjustment.

The PROMs comorbidity categories were used to group together the individual types of comorbidities. The PROMs survey comorbidity categories were originally chosen based on the work of Bayliss et al [44]. Bayliss et al searched the literature to determine the health conditions that were most frequently assessed in measuring comorbidity, were important to patients and then subsequently pre-tested the instrument for clarity with patients.

It was therefore decided to use the list of 11 PROMS comorbidity categories but to identify the presence of the comorbidity in HES. Each comorbidity was mapped to its relevant ICD-10 codes as described in RP3 (see also Appendix I). The impact of using different definitions of comorbidities is beyond the scope of this thesis but further work needs to be conducted to understand the impact of using different definitions on the likelihood of having adverse outcomes or reporting improvement in severity of joint problems and HRQoL after surgery.

9.4 Opportunities for future research

In this section I describe areas which I believe are opportunities for future research based on the findings here and on the literature in other disease areas and health systems.

9.4.1.1 Future research on access to hip or knee replacement surgery

Due to the limitations of this programme of work on access, further work is needed to understand the profile of patients who are in need of a hip or knee replacement but who do not end up receiving a hip or knee replacement. Future work could study patients with osteoarthritis in primary care and investigate who does or does not receive a hip or knee replacement surgery. This would require the use of GP data (e.g. CPRD data) to identify patients with osteoarthritis in primary care and follow them through to secondary care by linking the GP data to PROMs or NJR data. This data linkage could also allow further investigation of duration of symptoms and validate the patient-reported duration of symptoms by looking at the time from the osteoarthritis diagnosis to the date of the surgery.

Such work would also benefit from a larger qualitative study in multiple areas of England with not only healthcare professionals but also patients to further explore the impact of comorbidities on the referral pathways to joint replacement surgery. Further understanding and the added perspective from patients will help describe the specific barriers at the system level that may lead to patients with comorbidities getting 'lost in the system'.

9.4.1.2 Future research on the impact of comorbidities on disease-specific measures

One of the limitations of this thesis was the impact of comorbidities on joint-specific measures which made interpretation of such measures challenging. Comorbidities may compromise the specificity of such measures, including the OHS/OKS and the WOMAC [166], which were originally designed to exclude the effects of comorbidities. Further work is needed to ascertain the extent to which comorbidities influence these measures, such as the OHS/OKS score, and how to interpret their influence.

9.4.1.3 Future research on patient safety after hip or knee replacement surgery

In the PROMs dataset, patients were also asked to report any postoperative adverse events such as wound complications. I did not investigate these outcomes as further work is needed to ascertain the reliability of using patient-reported adverse events as opposed to adverse events derived from administrative or clinical data. A systematic review of 55 studies exploring the links between patient experience, clinical safety and effectiveness outcomes has found that, in general, there is less evidence available on safety compared to effectiveness in research using patient reports of their care [167]. There is evidence to suggest that patients could be used as partners in identifying poor and unsafe practice and that they could help enhance effectiveness and safety of surgery [168, 169]. Previous studies exploring patients' ability to identify medical errors or adverse events in hospital have shown positive associations between patient-reported adverse events and records of events in medical records [168, 169]. The reliability of patient-reported adverse events has also been explored in oncology [170].

A previous study in England in hip and knee replacement surgery has looked at the impact of BMI on the PROMS patient-reported complications and readmissions but these outcomes have not been validated against hospital records [156]. Further work using patient-reported complications could elucidate whether these outcomes could be used as indicators of unsafe practices after hip or knee replacement surgery.

9.4.1.4 Future research on the impact of multimorbidity on access to and outcomes of hip and knee replacement surgery

Multimorbidity, the presence of one or more comorbidities, is one of the major challenges facing our health system [171]. There is a lack of research on delivering healthcare for patients with multimorbidity and thus guidance is primarily on single comorbidities as is the case for hip and knee replacement surgery [172]. There is evidence that care for patients with multimorbidity is fragmented as the healthcare system is geared towards the single-disease paradigm and super-specialism [173]. Managing resources to provide care for patients with multimorbidity is therefore challenging for healthcare professionals [174, 175].

My research, while focusing on individual comorbidities, has found that a significant number of patients have more than one comorbidity - 29% (91 461) of patients undergoing a hip replacement and 35% (115 451) of patients undergoing a knee replacement. This

highlights the challenges posed to the NHS by the increasing burden of multimorbidity. My research has started to explore the effects of having more than one comorbidity and has demonstrated that with increasing number of comorbidities, pre-operative severity of joint problems increased (worsens) (RP4), improvement in severity of joint problems after surgery decreased (worsens) (RP6) and the likelihood of adverse outcomes (RP5) increased. The qualitative study (RP2) also highlighted the challenge for healthcare professionals to provide care for patients with more than one comorbidity. Further study is needed however, to explore how often specific combinations of comorbidities occur compared with what can be expected based on chance alone. It would also be important to consider how to classify severity of disease with single comorbidities and multiple conditions. Current approaches to severity classification are not adequate to address multimorbidity [150]. Once this is determined, it would be useful to evaluate the impact of the most common combinations of comorbidities on access to and outcomes of hip and knee replacement surgery.

10 CONCLUSION

An increasing number of patients undergoing hip and knee replacement surgery have one or more comorbidities. This thesis demonstrates that there is variation in access to and safety and effectiveness of hip and knee replacement surgery when comorbidity is present. Access for patients with comorbidities appears to be complicated by the fragmented management of patients with comorbidities along the orthopaedic referral pathway and leads to patients being 'lost in the system'. This was supported by the finding that compared to patients without comorbidities, patients with comorbidities reported worse functional status and more severe pain just before surgery, and that they are therefore likely to have had surgery later in the development of their joint disease. With respect to outcomes, patients with comorbidities had a moderately increased risk of adverse outcomes after surgery but continued to benefit from the hip and knee replacement almost as much as patients without comorbidity. A single comorbidity has a small impact but multiple comorbidities have an impact that may be clinically important. The findings from this programme of research therefore suggest that the restriction of access to joint replacement surgery based on the presence of comorbidities alone is unjustified.

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12 APPENDICES

12.1 Appendix A – Conference presentations

As part of my PhD I have attended and presented (oral and poster presentations) at several conferences as outlined below.

Research Paper	Conference
RP1 – Systematic Review	- PROMs Conference 2017 (Oral) - Health Service Research UK Conference 2017 (Oral)
RP2 – Qualitative Study	- Health Service Research UK Conference 2018 (Poster) - Society for Social Medicine & Population Health 2018 (Poster walk)
RP3 –Methodological piece	- PROMs Conference 2018 (Oral)
RP4 - Access	- American Public Health Association Conference 2018 (Poster walk) - European Public Health Conference 2018 (Poster walk)

12.2 Appendix B – Training

As part of the PhD studentship funded by the NIHR CLAHRC North Thames, I have undertaken training in research methods relevant to my PhD study as outlined below.

Research Paper	Training
RP1 – Systematic Review	- Reviewing the Literature course at LSHTM
RP2 – Qualitative Study	- Qualitative Methodologies course at LSHTM - Qualitative interviewing and analysis course at Oxford University - NViVo course at LSHTM
RP3-6	- Statistical Methods in Epidemiology course at LSHTM - Introduction to Hospital Episode Statistics at UCL - Introduction to Quality of Life and Other Patient Reported Outcomes Theory, Measurement, and Applications

12.3 Appendix C – Supplementary Information RP1

Supplementary Information 1 – Search string

1 knee replacement.mp. or exp knee arthroplasty/
2 hip replacement.mp. or exp hip arthroplasty/
3 knee arthroplasty.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
4 hip arthroplasty.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
5 exp Arthroplasty, replacement/
6 exp hip surgery/ or hip surgery.mp.
7 exp knee surgery/ or knee surgery.mp.
8 1 or 3 or 7
9 2 or 4 or 6
10 8 and 9
11 8 or 9 or 10
12 11 or 5
13 Humans/
14 exp Comorbidity/
15 charlson comorbidity index.mp.
16 elixhauser comorbidity index.mp.
17 exp Cardiovascular Diseases/
18 exp Hypertension/
19 exp Stroke/
20 exp Peripheral Vascular Diseases/
21 exp Lung Diseases/
22 exp Diabetes Mellitus/
23 exp Kidney Diseases/
24 exp Nervous System Diseases/
25 exp Liver Diseases/
26 exp Neoplasms/
27 exp Depression/
28 exp Diabetes Complications/
31 underlying diagnosis.mp.
32 comorbidit*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
33 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32
34 exp Postoperative Complications/
35 exp Treatment Outcome/
36 exp "Quality of Life"/

Supplementary Information 2 – Description of selected studies (n = 70)

Study	Data			Patient Sample			Comorbid Conditions	Outcomes
	Country	Years of data	Data source	Type of surgery	Primary or Revision surgery	Sample Size		
Ackland (2011)	UK	2004-2005	Single-site	THA and TKA	Primary & Revision	526	Chronic Kidney disease	Infection, Pain, Postoperative morbidity
Adams (2013)	USA	2001-2009	Joint registry	TKA	Primary	40,491	Controlled diabetes	All-cause rehospitalizations, Deep Infection, Deep vein thrombosis, Revisions
Aggarwal (2013)	USA	2007-2011	Single-site	THA and TKA	Primary & Revision	323	Atrial Fibrillation	Readmission rate
Amusat (2014)	Canada	NS	Multi-site	TKA	Primary	405	Diabetes without impact on routine activities, Kidney Disease	Overall health (HUI3) -6m post-operative, WOMAC function, WOMAC pain
Ayers (2005)	USA	NS	Single-site	TKA	Primary	165	Lower extremity (PVD, venous insufficiency)	Mean change in Physical Function (SF-36) 12mths post surgery, Mean change in Physical Function (WOMAC) 12mths post surgery
Belmont (2016)	USA	2011-2012	Multi-site	TKA	Revision	1754	Cardiac disease, COPD, CVA/Stroke, Diabetes, Hypertension	Readmissions within 30 days
Bolognesi (2008)	USA	1988-2003	Administrative data	THA and TKA	Primary & Revision	2,249,427	Diabetes	DVT, Died, Infection
Browne (2014)	USA	2006-2008	Administrative data	THA and TKA	Primary	497,222	Depression	Infection, Pulmonary embolism
Buller (2015)	USA	1990-2007	Administrative data	THA and TKA	Primary	8,379,490	Chronic pulmonary disease, CAD, Depression, Diabetes, Hypertension	Adverse Events (wound complication , postoperative shock, postoperative bleeding, acute postoperative infection, acute postoperative anemia, acute renal failure, acute myocardial infarction, pulmonary embolism, induced mental disorder, pneumonia, pulmonary insufficiency, DVT, intubation and transfusion of blood)

Chan (2005)	UK	2000-2003	Single-site	THA	NS	1,297	Diabetes	Deep Infection, Deep vein thrombosis
Clement (2013)	UK	NS	Single-site	TKA	Primary	2,389	Depression, Diabetes, Heart disease, High blood pressure, Kidney disease, Lung disease, Neurological diseases, Vascular disease	Post-operative OKS at 12mths, post-operative SF-12 at 12mths
Cohen (2005)	USA	1986-2002	Single-site	THA and TKA	Primary	122	Liver cirrhosis	Death, Major complications
Courtney (2017)	USA	2011-2014	Multi-site	THA and TKA	Primary	169,406	Cardiac disease, Diabetes, History of stroke, Preoperative creatinine >1.5mg/dL	30 day complications (SSI, pneumonia, respiratory, pulmonary embolism, DVT, stroke, cardiac arrest, renal failure, UTI, sepsis, septic shock), 30 day readmissions
Deegan (2014)	USA	2004-2011	Single-site	THA and TKA	NS	779	Chronic Kidney Disease	Death, Infections, Revisions
Deleuran (2015)	Denmark	1995-2001	Administrative data	THA and TKA	Primary	109,522	Liver cirrhosis	Deep prosthetic infection, Intraoperative complications, Mortality within 30 days Readmission within 30 days, Revision in one year
Dowsey (2009)	Australia	1998-2005	Single-site	TKA	Primary	1,214	Cardiovascular disease, Diabetes, Respiratory diseases	Deep Infection
Erkocak (2016)	USA	2000-2012	Single-site	THA and TKA	NS	1077	Chronic Renal failure	Surgical site infections, In-hospital mortality
Gandhi (2009)	Canada	1998-2006	Single-site	TKA	NS	1,460	Diabetes, Hypertension	DVT within 3 months
Gaston (2007)	UK	1998-2006	Single-site	THA	Primary	1,744	Cerebrovascular disease, CHF, COPD, Diabetes	Mortality within 3mths after admission
Huddleston (2009)	USA	2002-2004	Multi-site	TKA	NS	2,033	Diabetes	Adverse events (deep infections, necrosis, nerve injury, dislocation, cardiovascular complication, periprosthetic fracture, Revision, UTI, DVT, Pneumonia, Death)
Hunt (2013)	UK	2003-2011	Joint registry	THA	NS	409,096	CHF, PVD, CVD, Chronic Pulmonary disease, Diabetes without	90-day mortality

							complications, Renal disease, Cancer, Dementia	
Hunt (2014)	UK	2003-2011	Joint registry	TKA	NS	467,779	CHF, PVD, CVD, Chronic Pulmonary disease, Diabetes without complications, Renal disease, Cancer, Dementia	45-day mortality
Inacio (2016)	Australia	2001-2012	Administrative data	THA	NS	30820	Liver disease, CHF, Renal disease, Parkinson's disease, Dementia, Chronic airway disease, Solid tumour without metastasis	90-day mortality, 1-year mortality
Iorio (2012)	USA	2004-2009	Single-site	THA and TKA	Primary	1,529	Diabetes	Infection
Jain (2005)	USA	1988-2000	Administrative data	THA and TKA and shoulder arthroplasty	Primary	959,839	Diabetes, Hypertension	Complications (infections, wound infections, pulmonary embolism, thromophlebitis, vascular complications, other)
Jamsen (2013)	Finland	1998-2008	Joint registry	THA and TKA	Primary	96,754	Cancer, CHD, Depression, Diabetes, Hypertension (without CVD), Pulmonary disease	Risk of Revision surgery
Jamsen (2014)	Finland	1998-2009	Administrative data + Joint registry	THA and TKA	Primary	3,428	Parkinson's disease	Infection at 1 year, Mortality > 1 year Revisions in 0-2 years postoperative
Jamsen (2015)	Finland	1998-2009	Administrative data + Joint registry	THA and TKA	Primary	4,526	Alzheimer's disease	Mortality after 10 years, Rate of surgical site infection, Risk of Revision
Jorgensen (2015a)	Denmark	2010-2012	Multi-site	THA and TKA	Primary	8,757	Cardiovascular disease, Pulmonary disease	90-day readmission
Jorgensen (2015b)	Denmark	2010-2012	Multi-site	THA and TKA	Primary	8,055	Diabetes Type II	"Diabetes-related morbidity" (cardiac arrhythmias, acute congestive heart failure, MI, prosthetic or wound infections, renal insufficiency, cerebral attacks, pneumonia, UTI>4days, dysregulated blood glucose, other infections), 90-day readmission
Judge (2012)	UK	1993-1995	Multisite	THA	NS	282	Diabetes	SF-36 Physical functioning

Kapoor (2010)	USA	2003-2006	Administrative data	THA and TKA	Primary	316,671	COPD, CAD, Cerebrovascular disease, Diabetes	Venous Thromboembolism
Kapoor (2013)	USA	2002-2009	Administrative data	THA and TKA	Primary & Revision	24,051	COPD, CAD, Cerebrovascular disease, Diabetes	Venous Thromboembolism
Karam (2015)	USA	2000-2011	Single-site	THA and TKA	Primary & Revision	26,415	Cancer	Deep vein thrombosis, Mortality Overall in-hospital complications, Periprosthetic joint infection
Keswani (2016)	USA	2011-2013	Multi-site	THA and TKA	Revision	10,112	Disseminated cancer, Cardiac disease, Diabetes, Renal disease, Stroke, Hypertension, Pulmonary disease	30-day readmissions
Kildow (2017)	USA	2005-2012	Multi-site	THA	NS	61,778	Diabetes	DVT- 30 days, Prosthetic Joint infection - 90 days, THA Revision - 2-years
Kuo (2017)	Taiwan	2009-2012	Single-site	TKA	Primary	615	Chronic Kidney Disease	30-day readmissions
Lee (2017)	Korea	2004-2013	Single-site	TKA	Primary	3,049	Diabetes, Hypertension	90-day readmission
Liao (2016)	Taiwan	2004-2008	Administrative data	THA	NS	2,426	Cardiovascular disease, CVA, Chronic Kidney disease, COPD, Hypertension	1-year mortality, 30-day readmissions
Marchant (2009)	USA	1988-2005	Administrative data	THA and TKA	Primary & Revision	1,030,013	Controlled diabetes	DVT, Died, Infection
Martinez (2013)	Spain	2001-2008	Administrative data	THA and TKA	Primary	373,131	Diabetes	In-hospital mortality
Mazoch (2009)	USA	2004-2012	Single-site	THA and TKA	Revision	130	Diabetes	All complications, Infection
McCleery (2010)	UK	1985-2008	Joint registry	TKA	NS	59,288	Renal failure	Early infection (<90 days), Late Revision
Meding (2003)	USA	1987-1999	Single-site	TKA	Primary	5,220	Diabetes	Deep Infection, DVT, Knee Society Pain score - 1yr
Menendez (2016)	USA	2002-2011	Multi-site	THA and TKA	Primary	6,054,344	Multiple Myeloma	In-hospital mortality, SSI, Thromboembolic events
Miric (2014a)	USA	2005-2010	Joint registry	TKA	Primary	41,852	Chronic Renal Disease	DVT, Mortality (anytime), Mortality within 90 days, Readmission within 90 days, Revision, SSI deep

Miric (2014b)	USA	2006-2010	Joint registry	THA	Primary	20,720	Chronic Kidney Disease	DVT, Mortality (anytime), Mortality within 90 days, Readmission within 90 days, Revision (any), SSI (any)
Moon (2008)	Korea	1995-2004	Single-site	TKA	Primary	1,581	Diabetes	Deep joint infection, DVT, Knee Society Score – function, Knee Society Score – Pain, Overall complications
Pedersen (2010)	Denmark	1996-2005	Joint registry	THA	Primary	57,575	Diabetes	Overall Revisions
Perez (2014)	Spain	NS	Single-site	TKA	NS	736	Depression	SF-36 Physical component scores, WOMAC score
Radkte (2016)	Germany	2011-2012	Single-site	THA	Primary	498	Cancer, Depression, Diabetes	Periprosthetic joint infection
Rajamaki (2015)	Finland	2009-2011	Single-site	THA and TKA	Primary	134	Glucose metabolism abnormalities	Persistent Pain
Rasouli (2016)	USA	2009-2009	Single-site	THA and TKA	Primary & Revision	1,969	Depression	Surgical complications
Robertson (2012)	UK	1989-2002	Single-site	TKA	NS	734	Diabetes	Knee Society knee score year 1
Sanders (2012)	UK	2006-2010	Administrative data	THA and TKA	Primary	414,985	Cancer, Diabetes, Heart Failure, Hypertension, Liver disease, PVD, Renal failure, Respiratory disease, Stroke	In-hospital mortality, Readmission
Seol (2017)	South Korea	2007-2015	Multi-site	THA and TKA	Primary	143	Liver Cirrhosis	Infections, Medical complications
Sikora-Klak (2017)	USA	2012-2014	Single-site	THA and TKA	Primary	2,914	Diabetes	90-day readmission
Singh (2014a)	USA	1993-2005	Joint registry	TKA	Primary and Revision	8,672	Depression	Knee status: much better 2- years
Singh (2009)	USA	1993-2005	Joint registry	THA	Revision	2,687	Depression	Moderate-Severe ADL limitation - 2 years Moderate-severe pain - 2 years
Singh (2014b)	USA	1993-2005	Joint registry	TKA	Primary & Revision	7,139	Cerebrovascular disease	Moderate-Severe ADL limitation - 2 years Moderate-severe pain - 2 years

Singh (2013a)	USA	1993-2005	Joint registry	THA	Primary & Revision	8,394	COPD, Diabetes, Heart disease, PVD, Renal disease	Moderate-severe pain at 2 years
Singh (2013b)	USA	1993-2005	Joint registry	TKA	Primary	7,139	Diabetes without complications	Moderate-severe ADL limitation 2 -years
Singh (2013c)	USA	1993-2005	Joint registry	TKA	Primary	8,672	COPD, Depression, Diabetes, Heart disease, PVD, Renal disease	Moderate-severe pain at 2 years
Singh (2014)	USA	1993-2005	Joint registry	TKA	Revision	1,533	Depression	Moderate-severe pain at 2 years
Stundner (2013)	USA	2000-2008	Administrative data	THA and TKA	Primary	1,212,493	Depression	In-hospital mortality, Major complications, Sepsis, Venous Thromboembolism
Tiberi (2014)	USA	2000-2012	Single-site	THA and TKA	NS	230	Liver cirrhosis	Infections within 90 days, Mortality most recent follow-up, Mortality within 90 days, Readmissions 90 days, Revision surgery during follow up
Vannini (1984)	Italy	1969-1979	Single-site	THA	NS	1,227	Diabetes	Post-surgery infections
Wang (2013)	China	2003-2011	Single-site	TKA	NS	245	CHD, Diabetes, Hypertension	DVT
Warth (2015)	USA	2006-2012	Administrative data	THA and TKA	Primary	74,300	Chronic Renal disease	Overall complications
Zhao (2014)	China	2011-2013	Single-site	TKA	NS	358	Diabetes, Hypertension	DVT within 14 days

Note. NS = not stated; THA = Total Hip Arthroplasty; TKA = Total Knee Arthroplasty; PVD = Peripheral Vascular Disease; COPD = Chronic Obstructive Pulmonary Disorder; CAD = Coronary Artery Disease ; CHD = Coronary Heart Disease ; CHF = Coronary Heart Failure; CVA/CVD = Cerebrovascular Accident/Disease; SF-36= Short-form 36; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index; OKS = Oxford Knee Score; SF-12 = Short-form 12; SSI = Surgical Site Infection; DVT = Deep Vein Thrombosis; UTI = Uterine Infection; MI = Myocardial Infarction.

Supplementary Information 3 - Quality appraisal of included 70 studies

Study	Patient Selection					Comparability		Outcome Assessment			Overall quality score
	Cohort Representative?	Patients drawn from same community?	Presence of comorbidities verified?	Outcome not present at the start?	Cohort drawn from multiple communities?	Controlled for age and sex?	Controlled for SES and Ethnicity?	Outcome of interest clearly defined?	Follow-up long enough?	Follow-up adequate?	
Ackland (2011)	Yes	Yes	Yes	Yes	No	No	No	Yes	NS	No	6
Adams (2013)	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	11
Aggarwal (2013)	Yes	Yes	Yes	Yes	No	Yes	No	Yes	NS	No	8
Amusat (2014)	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	No	10
Ayers (2005)	No	Yes	Yes	Yes	No	Yes	No	Yes	Yes	No	8
Belmont (2016)	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Yes	9
Bolognesi (2008)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	NS	No	9
Browne (2014)	Yes	Yes	Yes	Yes	Yes	Yes	Yes (ethnicity)	No	NS	No	8
Bulle (2015)	Yes	Yes	Yes	Yes	Yes	Yes	No	No	NS	No	7
Chan (2004)	Yes	Yes	Yes	Yes	No	Yes	No	Yes	Yes	Yes	10
Clement (2013)	Yes	Yes	Yes	Yes	No	No	No	Yes	Yes	Yes	8
Cohen (2005)	Yes	Yes	Yes	Yes	No	No	No	Yes	Yes	No	7
Courtney (2017)	Yes	Yes	Yes	Yes	Yes	Yes	Yes (ethnicity)	No	Yes	Yes	10
Deegan (2014)	Yes	Yes	Yes	Yes	No	Yes	No	Yes	Yes	Yes	10
Deleuran (2015)	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Yes	9
Dowsey (2009)	Yes	Yes	Yes	Yes	No	Yes	No	Yes	Yes	Yes	10
Ekocak (2016)	Yes	Yes	Yes	Yes	No	No	No	No	Yes	Yes	6
Gandhi (2009)	Yes	Yes	Yes	Yes	No	Yes	No	Yes	Yes	No	9
Gaston (2007)	Yes	Yes	Yes	Yes	No	Yes	No	Yes	Yes	Yes	10
Huddleston (2009)	Yes	Yes	Yes	Yes	Yes	Yes	Yes (ethnicity)	No	Yes	Yes	10
Hunt (2013)	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	11
Hunt (2014)	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	11

Inacio (2016)	No	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Yes	8
Iorio (2012)	Yes	Yes	Yes	Yes	No	No	No	Yes	NS	No	6
Jain (2005)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	NS	No	9
Jamsen (2013)	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	11
Jamsen (2014)	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	11
Jamsen (2015)	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	11
Jorgensen (2015a)	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	9
Jorgensen (2015b)	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	9
Judge (2012)	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	No	10
Kapoor (2010)	No	Yes	Yes	Yes	Yes	Yes	No	No	NS	Yes	7
Kapoor (2013)	No	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	10
Karam (2015)	Yes	Yes	Yes	Yes	No	No	No	Yes	Yes	Yes	8
Keswani (2016)	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Yes	9
Kildow (2017)	No	Yes	Yes	Yes	Yes	No	No	No	Yes	Yes	6
Kuo (2017)	No	Yes	Yes	Yes	No	Yes	No	Yes	Yes	Yes	9
Lee (2017)	No	Yes	Yes	Yes	No	Yes	No	Yes	Yes	Yes	9
Liao (2016)	No	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Yes	8
Marchant (2009)	No	Yes	Yes	Yes	Yes	Yes	Yes (SES)	No	Yes	Yes	9
Martinez (2013)	No	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Yes	8
Mazoch (2009)	Yes	Yes	Yes	Yes	No	1	No	Yes	NS	Yes	8
McCleery (2010)	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Yes	9
Meding (2003)	Yes	Yes	Yes	Yes	No	No	No	Yes	Yes	No	7
Menendez (2016)	Yes	Yes	Yes	Yes	Yes	Yes	Yes (ethnicity)	No	Yes	Yes	10
Miric (2014a)	Yes	Yes	Yes	Yes	Yes	Yes	Yes (ethnicity)	Yes	Yes	Yes	12
Miric (2014b)	Yes	Yes	Yes	Yes	Yes	Yes	Yes (ethnicity)	Yes	Yes	Yes	12
Moon (2008)	Yes	Yes	Yes	Yes	No	No	No	Yes	Yes	Yes	8
Pedersen (2010)	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	11
Perez (2014)	Yes	Yes	Yes	Yes	No	No	No	Yes	Yes	Yes	8

Radkte (2016)	No	Yes	Yes	Yes	No	No	No	Yes	Yes	Yes	7
Rajamaki (2015)	Yes	Yes	Yes	Yes	No	Yes	No	Yes	Yes	No	9
Rasouli (2016)	Yes	Yes	Yes	Yes	No	Yes	No	Yes	Yes	Yes	10
Robertson (2012)	Yes	Yes	Yes	Yes	No	Yes	No	Yes	Yes	Yes	10
Sanders (2012)	Yes	Yes	Yes	Yes	Yes	Yes	Yes (SES)	No	Yes	Yes	10
Seol (2017)	Yes	Yes	Yes	Yes	Yes	No	No	Yes	NS	Yes	8
Sikora-Klak (2017)	No	Yes	Yes	Yes	No	No	No	Yes	Yes	No	6
Singh (2014a)	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	No	10
Singh (2009)	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	No	10
Singh (2014b)	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	No	10
Singh (2013a)	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	No	10
Singh (2013b)	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	No	10
Singh (2013c)	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	No	10
Singh (2014)	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	No	10
Stundner (2013)	Yes	Yes	Yes	Yes	Yes	Yes	Yes (ethnicity)	No	Yes	Yes	10
Tiberi (2014)	Yes	Yes	Yes	Yes	No	No	No	Yes	Yes	Yes	8
Vannini (1984)	Yes	Yes	Yes	Yes	No	No	No	Yes	Yes	Yes	8
Wang (2013)	No	Yes	Yes	Yes	No	Yes	No	Yes	No	Yes	8
Warth (2015)	Yes	Yes	Yes	Yes	Yes	No	No	No	Yes	Yes	7
Zhao (2014)	No	Yes	Yes	Yes	No	Yes	No	Yes	No	Yes	8

Note: SES = Socioeconomic Status

Supplementary Information 4 – Sensitivity Analysis

Comorbidities	All Studies					High Quality Studies (Quality score ≥11)				
	# of studies	# of patients	OR	95% lower CI	95% upper CI	# of studies	# of patients	OR	95% lower CI	95% upper CI
Surgical Complications										
Cancer	1	<100,000	1.33	1.09	1.62	0				
Depression	3	>1M	1.08	0.94	1.24	0				
Diabetes	7	>1M	1.12	1.01	1.25	0				
Diseases of the Nervous System	0					0				
Heart Disease	3	>1M	1.25	0.95	1.65	0				
High blood pressure	2	>1M	1.03	0.96	1.11	0				
Kidney Disease	3	<1M	1.97	1.84	2.10	0				
Liver disease	3	<1M	3.55	0.99	12.72	0				
Lung disease	2	>1M	1.35	0.84	2.15	0				
Poor circulation	0					0				
Stroke	2	<1M	1.40	1.03	1.90	0				
Venous Thromboembolism										
Cancer	2	>1M	2.30	1.35	3.92	0				
Depression	2	>1M	1.15	1.02	1.30	0				
Diabetes	12	>1M	1.26	0.92	1.72	1	<100,000	0.84	0.60	1.17
Diseases of the Nervous System	0					0				
Heart Disease	3	<1M	1.07	0.95	1.20	0				
High blood pressure	3	<10,000	1.19	0.79	1.80	0				
Kidney Disease	2	<100,000	1.09	0.73	1.64	2	<100,000	1.09	0.73	1.64
Liver disease	0					0				
Lung disease	2	<1M	1.29	1.08	1.55	0				
Poor circulation	0					0				
Stroke	2	<1M	1.07	0.73	1.57	0				
Surgical site infections										
Cancer	3	>1M	1.43	0.60	3.41	0				
Depression	3	>1M	1.54	0.64	3.69	0				
Diabetes	12	>1M	1.90	1.32	2.74	1	<100,000	1.31	0.92	1.86
Diseases of the Nervous System	2	<10,000	1.00	0.50	2.01	2	<10,000	1.00	0.50	2.01
Heart Disease	1	<10,000	1.92	0.40	9.20	0				
High blood pressure	0					0				
Kidney Disease	6	<1M	1.27	0.97	1.66	2	<100,000	1.06	0.75	1.50
Liver disease	3	<1M	2.46	1.46	4.12	0				
Lung disease	1	<10,000	0.89	0.22	3.55	0				
Poor circulation	0					0				
Stroke	0					0				
Readmissions										
Cancer	2	<1M	1.29	1.14	1.46	0				

Depression	0					0				
Diabetes	9	<1M	1.15	1.11	1.19	1	<100,000	1.08	1.00	1.16
Diseases of the Nervous System	0					0				
Heart Disease	7	<1M	1.68	1.28	2.19	0				
High blood pressure	5	<1M	1.10	0.95	1.28	0				
Kidney Disease	7	<1M	1.62	1.31	2.01	2	<100,000	1.34	1.16	1.56
Liver disease	3	<1M	1.79	1.36	2.35	0				
Lung disease	5	<1M	1.33	1.11	1.58	0				
Poor circulation	1	<1M	1.35	1.19	1.53	0				
Stroke	5	<1M	1.53	1.38	1.71	0				
Short-term mortality										
Cancer	5	>1M	1.22	0.80	1.87	0				
Depression	1	>1M	0.53	0.32	0.88	0				
Diabetes	4	>1M	1.26	1.15	1.38	0				
Diseases of the Nervous System	3	<1M	1.67	1.20	2.32	0				
Heart Disease	5	>1M	2.96	1.95	4.48	0				
High blood pressure	2	<1M	1.17	1.02	1.35	0				
Kidney Disease	7	>1M	1.83	0.94	3.55	2	<100,000	0.73	0.42	1.26
Liver disease	3	<1M	2.32	1.43	3.77	0				
Lung disease	4	>1M	1.21	1.03	1.43	0				
Poor circulation	3	>1M	1.50	1.08	2.10	0				
Stroke	4	>1M	2.18	1.42	3.33	0				
Function										
Cancer	0					0				
Depression	4	<100,000	1.69	1.26	2.28	0				
Diabetes	5	<100,000	1.14	0.96	1.35	0				
Diseases of the Nervous System	1	<10,000	1.05	0.73	1.52	0				
Heart Disease	1	<10,000	1.24	1.01	1.52	0				
High blood pressure	1	<10,000	0.99	0.86	1.13	0				
Kidney Disease	2	<10,001	1.58	0.46	5.44	0				
Liver disease	1	<10,000	0.68	0.35	1.32	0				
Lung disease	2	<10,000	1.27	0.49	3.29	0				
Poor circulation	2	<10,000	0.93	0.36	2.42	0				
Stroke	1	<10,000	1.32	1.02	1.71	0				
Quality of Life										
Cancer	0					0				
Depression	2	<10,000	1.20	0.70	2.05	0				
Diabetes	3	<10,000	1.01	0.61	1.68	0				
Diseases of the Nervous System	1	<10,000	1.11	0.79	1.55	0				
Heart Disease	1	<10,000	1.49	1.24	1.78	0				
High blood pressure	1	<10,000	1.00	0.88	1.14	0				

Kidney Disease	1	<10,000	0.92	0.55	1.55	0				
Liver disease	1	<10,000	0.36	0.20	0.65	0				
Lung disease	2	<10,000	1.26	1.02	1.57	0				
Poor circulation	2	<10,000	1.15	0.80	1.64	0				
Stroke	0					0				
Pain										
Cancer	0					0				
Depression	3	<100,000	1.22	0.79	1.87	0				
Diabetes	6	<100,000	1.01	0.66	1.54	0				
Diseases of the Nervous System	0					0				
Heart Disease	2	<100,000	1.16	0.88	1.52	0				
High blood pressure	0					0				
Kidney Disease	4	<100,000	1.17	0.81	1.70	0				
Liver disease	0					0				
Lung disease	2	<100,000	1.17	0.93	1.46	0				
Poor circulation	2	<100,000	1.26	0.98	1.61	0				
Stroke	1	<10,000	1.41	0.97	2.04	0				
Revisions										
Cancer	1	<100,000	0.84	0.33	2.16	1	<100,000	0.84	0.33	2.16
Depression	1	<100,000	1.40	1.09	1.81	1	<100,000	1.40	1.09	1.81
Diabetes	4	>1M	1.28	1.02	1.59	3	<1M	1.17	1.06	1.30
Diseases of the Nervous System	2	<100,000	1.00	0.70	1.42	2	<100,000	1.00	0.70	1.42
Heart Disease	1	<100,000	1.18	1.06	1.30	1	<100,000	1.18	1.06	1.30
High blood pressure	1	<100,000	1.11	1.02	1.21	1	<100,000	1.11	1.02	1.21
Kidney Disease	4	<1M	1.10	0.92	1.30	2	<100,000	0.99	0.77	1.28
Liver disease	2	<1M	1.96	1.16	3.30	0				
Lung disease	1	<100,000	1.12	1.00	1.26	2	<100,000	1.12	1.00	1.26
Poor circulation	0					0				
Stroke	0					0				
Long-term mortality										
Cancer	2	<100,000	1.57	1.19	2.07	0				
Depression	0					0				
Diabetes	3	>1M	0.97	0.82	1.13	0				
Diseases of the Nervous System	3	<100,000	1.92	1.48	2.48	2	<10,000	1.67	1.24	2.25
Heart Disease	1	<100,000	1.72	1.44	2.06	0				
High blood pressure	1	<10,000	1.30	0.78	2.17	0				
Kidney Disease	5	<100,000	1.65	1.27	2.15	2	<100,000	1.24	0.84	1.83
Liver disease	3	<100,000	3.40	1.17	9.86	0				
Lung disease	2	<10,000	1.38	1.05	1.80	0				
Poor circulation	0					0				
Stroke	2	<100,000	2.05	1.14	3.66	0				

12.4 Appendix D – Ethics approval

12.4.1 Ethics approval

Ymchwil Iechyd a Gofal Cymru
Health and Care Research Wales

Gwasanaeth Moeseg Ymchwil
Research Ethics Service

Ariennir gan Lywodraeth Cymru
Funded by Welsh Government

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03 August 2016

Ms Belene Podmore
PhD student/Research Fellow
London School of Hygiene and Tropical Medicine/ Royal College of Surgeons of England
15-17 Tavistock Place
London
WC1H 9SH

Dear Ms Podmore

Study title:	**The access to and outcomes of elective joint replacement surgery for patients with long-term conditions: a study using PROMs and administrative data**
REC reference:	**16/WA/0241**
Protocol number:	**N/A**
IRAS project ID:	**211186**

The Proportionate Review Sub-committee of the Wales REC 6 reviewed the above application on 03 August 2016.

We plan to publish your research summary wording for the above study on the HRA website, together with your contact details. Publication will be no earlier than three months from the date of this favourable opinion letter. The expectation is that this information will be published for all studies that receive an ethical opinion but should you wish to provide a substitute contact point, wish to make a request to defer, or require further information, please contact the REC Manager Ms Penny Beresford, penny.beresford@wales.nhs.uk. Under very limited circumstances (e.g. for student research which has received an unfavourable opinion), it may be possible to grant an exemption to the publication of the study.

Ethical opinion

On behalf of the Committee, the sub-committee gave a favourable ethical opinion of the above research on the basis described in the application form, protocol and supporting documentation, subject to the conditions specified below.

Conditions of the favourable opinion

The REC favourable opinion is subject to the following conditions being met prior to the start of the study.

London School of Hygiene & Tropical Medicine
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United Kingdom
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www.lshtm.ac.uk

Observational / Interventions Research Ethics Committee

Miss Belene Podmore
LSHTM

3 October 2016

Dear Belene

Study Title: The access to and the outcomes of elective joint replacement surgery for patients with long-term conditions: a study using PROMs and administrative data

LSHTM Ethics Ref: 11628

Thank you for your application for the above research project which has now been considered by the Observational Committee via Chair's Action.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation, subject to the conditions specified below.

Conditions of the favourable opinion

Approval is dependent on local ethical approval having been received, where relevant.

Approved documents

The final list of documents reviewed and approved is as follows:

Document Type	File Name	Date	Version
Protocol / Proposal	Protocol-200716	20/07/2016	1
Investigator CV	CV-BP-July2016	25/07/2016	1
Investigator CV	CV-JVM-July2016	25/07/2016	1
Investigator CV	CV-AH-July2016	25/07/2016	1
Local Approval	211186 16WA0241 FAV OPINION LETTER 3-8-16	03/08/2016	1
Protocol / Proposal	211186-Information Sheet-V1-240816	24/08/2016	1
Protocol / Proposal	211186-Consent form-V1-240816	24/08/2016	1
Local Approval	16 CAG 0113 conditional support letter	01/09/2016	1
Protocol / Proposal	Podmore Upgrading Report	12/09/2016	1

After ethical review

The Chief Investigator (CI) or delegate is responsible for informing the ethics committee of any subsequent changes to the application. These must be submitted to the committee for review using an Amendment form. Amendments must not be initiated before receipt of written favourable opinion from the committee.

The CI or delegate is also required to notify the ethics committee of any protocol violations and/or Suspected Unexpected Serious Adverse Reactions (SUSARs) which occur during the project by submitting a Serious Adverse Event form.

At the end of the study, the CI or delegate must notify the committee using the End of Study form.

All aforementioned forms are available on the ethics online applications website and can only be submitted to the committee via the website at: http://leo.lshtm.ac.uk.

Further information is available at: www.lshtm.ac.uk/ethics.

Yours sincerely,

[redacted]

Professor John DH Porter
Chair

12.4.2 Confidentiality Advisory Group (CAG) approval

NHS
Health Research Authority

Skipton House
80 London Road
London
SE1 6LH

06 October 2016

Ms Belene Podmore
Phd Student/ Research Fellow
15-17 Tavistock Place
London
WC19SH

Dear Ms Podmore

Application title:	**The access to and outcomes of elective joint replacement surgery for patients with long-term conditions: a study using PROMs and administrative data**
CAG reference:	**16/CAG/0113**
IRAS project ID:	**211186**
REC reference:	**16/WA/0241**

Thank you for your research application, submitted for approval under Regulation 5 of the Health Service (Control of Patient Information) Regulations 2002 to process patient identifiable information without consent. Approved applications enable the data controller to provide specified information to the applicant for the purposes of the relevant activity, without being in breach of the common law duty of confidentiality, although other relevant legislative provisions will still be applicable.

The role of the Confidentiality Advisory Group (CAG) is to review applications submitted under these Regulations and to provide advice to the Health Research Authority on whether an application should be approved, and if so, any relevant conditions. This application was considered at the precedent set CAG meeting held on 12 August 2016. The application was considered via the Precedent Set process under criteria category 12 – where applicants are requesting access to mortality, cancer or GP registration data from the Health and Social Care Information Centre – (otherwise referred to as a "class support study")

Health Research Authority approval decision

The Health Research Authority, having considered the advice from the Confidentiality Advisory Group as set out below, has determined the following:

1. The application is approved, subject to compliance with the standard and specific conditions of approval.

This letter should be read in conjunction with the outcome letter dated 1 September 2016.

12.4.3 Health Research Authority approval

NHS
Health Research Authority

Ms Belene Podmore
PhD student/Research Fellow
London School of Hygiene and Tropical Medicine/ Royal College of Surgeons of England
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7 October 2016

Dear Belene

Letter of HRA Approval

Study title:	**The access to and outcomes of elective joint replacement surgery for patients with long-term conditions: a study using PROMs and administrative data**
IRAS project ID:	**211186**
Protocol number:	**N/A**
REC reference:	**16/WA/0241**
Sponsor	**London School of Hygiene and Tropical Medicine**

I am pleased to confirm that **HRA Approval** has been given for the above referenced study, on the basis described in the application form, protocol, supporting documentation and any clarifications noted in this letter.

Participation of NHS Organisations in England

The sponsor should now provide a copy of this letter to all participating NHS organisations in England.

Appendix B provides important information for sponsors and participating NHS organisations in England for arranging and confirming capacity and capability. **Please read *Appendix B* carefully**, in particular the following sections:

- *Participating NHS organisations in England* – this clarifies the types of participating organisations in the study and whether or not all organisations will be undertaking the same activities
- *Confirmation of capacity and capability* - this confirms whether or not each type of participating NHS organisation in England is expected to give formal confirmation of capacity and capability. Where formal confirmation is not expected, the section also provides details on the time limit given to participating organisations to opt out of the study, or request additional time, before their participation is assumed.
- *Allocation of responsibilities and rights are agreed and documented (4.1 of HRA assessment criteria)* - this provides detail on the form of agreement to be used in the study to confirm capacity and capability, where applicable.

12.5 Appendix E – Participant Information Sheet

Participant Information Sheet

We would like to invite you to take part in our research study. Before you decide whether you would like to, please read this information so you know what the study is about and what taking part would involve.

Study Title

The access to and outcomes of elective joint replacement surgery for patients with long-term conditions: a study using Patient Reported Outcomes Measures data and administrative data

What is the study about?

One of the biggest challenges currently facing the NHS is the increase in the number of patients living with long- term conditions. The latest estimates from 2010 suggest that around 15 million people in England have a long-term condition. Long-term conditions, such as diabetes or heart disease, are conditions that are of long duration and are incurable. Patients with long-term conditions tend to use health services often. They account for at least 50% of General Practitioner appointments, outpatient appointments and inpatient stays.

Studies have shown that factors such as age, gender, ethnicity and socioeconomic status have an impact on the likelihood of accessing healthcare interventions such as surgery and on the outcomes, post-surgery. Less attention however, has been given to understanding the impact of long-term conditions on access to and outcomes of surgery.

What does the study involve?

This study aims to investigate the access to, and outcomes of, hip and knee replacement surgery for patients with long-term conditions using data that is already collected on patients in the NHS in England (Patient Reported Outcome Measures data and administrative data such as Hospital Episodes Statistics) and will include conducting interviews with healthcare professionals. Healthcare professionals, who have the responsibility of referring and selecting patients for hip and knee replacement surgery, will

be interviewed in order to understand their views on selecting and referring patients with long-term conditions. This study seeks to understand the process by which patients are referred or selected for surgery and what influences this decision and how this might differ for patients with long-term conditions. The findings of this study will inform the analysis of the data on access to hip and knee replacement surgery and will be published.

Who is carrying out this study?

The study is part of a PhD project, led by Belene Podmore, based at the London School of Hygiene and Tropical Medicine and at the Royal College of Surgeons of England. She will be supported by a team of researchers who specialise in joint replacement surgery and in healthcare quality improvement. The study is funded by the NIHR CLAHRC North Thames.

What would taking part involve?

We would like you to take part in a one-to-one interview with the lead researcher. Interviews will take place at a time and place that suits you and we anticipate that they will last a minimum of 30 minutes. The interview will involve discussing your views, opinions and experiences of referring and selecting patients for hip and knee replacement surgery and how this decision is made. With your permission, I will audiotape your views to ensure I have recorded them accurately. If you do take part, you don't have to answer all the questions and you can end the interview at any time. Your participation is voluntary, so you can opt out at any time.

What are the possible benefits of taking part?

This study will help health professionals to improve the care provided to patients with long-term conditions. It's an opportunity to talk about your views on an important aspect of policy, namely access to healthcare services. At the same time you will be contributing to research of national importance which will have an impact on how services are provided, in the future, to patients with long-term conditions to optimise patient outcomes.

What are the possible disadvantages and risks of taking part?

The possible disadvantages of taking part relate to issues of confidentiality but anything you tell me will remain strictly confidential and any views or comments we use in writing-up the study will remain anonymous. All the audio recordings will be transcribed by a

professional transcribing company which has experience of working with confidential information. The recordings once transcribed will be destroyed and the data will be anonymised. All transcriptions will be securely stored for the period of the project (December 2018) and only the research team will have access to the data.

What do I do if I am interested in taking part?

If you are interested in taking part we would be grateful if you could reply to the introductory email that has been sent indicating you would be happy to be contacted about the study. Following this, one of the research team will phone you to talk to you about whether you would like to take part in an interview and answer any questions you may have about the study.

If you have any questions or would like to know more, please contact:

Belene Podmore

London School of Hygiene and Tropical Medicine

15-17 Tavistock Place

London WC1H 9SH

Phone: 07881596310

E-mail: Belene.Podmore@lshtm.ac.uk

12.6 Appendix F – Consent Form

Study Title: The access to and outcomes of elective joint replacement surgery for patients with long-term conditions: a study using Patient Reported Outcomes Measures data and administrative data

Please read all the following statements and initial those you agree with in the box to the right and then sign your name at the end.

1. I confirm that I have read the information sheet dated 25/07/2016 (version 1) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason. ☐
3. I agree to the interview being audio recorded and I understand that this audio recording will be transcribed by a professional transcribing company and then destroyed. ☐
4. I understand that all information I give during the interview will be strictly confidential and that all the results will be anonymised and nothing will be attributed directly to me. ☐
5. I am willing for other members of the project research team to have access to my responses. ☐
6. I agree to take part in the above study. ☐

_____	_____	_____
Name of Participant	Date	Signature
_____	_____	_____
Name of Person taking consent	Date	Signature

12.7 Appendix G – Interview topic guides

Topic Guide – Orthopaedic Surgeons

Clarification of details

- NHS grade
- Number of years practicing/Years of experience
- Type of hospital
- Specialty

Contextual Factors

1. Can you tell me who the patients are that are typically referred to you?
    a. E.g. elderly, young with sports injuries, gender, socioeconomic status
    b. How severe are their symptoms?
2. Where are the patients typically referred from?
    a. E.g. musculoskeletal services, GPs, other?
    b. How long have they been waiting to see you?
3. In your opinion what percentage of patients are inappropriately referred and why?
    a. What would you regard as an appropriate referral? What is your conversion rate?

Assessment/Selection

1. When a patient is referred to you for hip surgery run me through what you do next.
    a. assessment, diagnosis, selection for surgery
    b. Is it any different for patients with knee patients?
2. What factors do you take into account in your assessment of the patient before selecting them for surgery?
    a. severity of symptoms, duration of symptoms, quality of life
    b. Can you talk through a couple of typical hip and knee patients?
    c. Is it different for hip and knee patients? Do you take into account different factors?

Long-term Conditions

1. Do you take into account any Long-term conditions (for example diabetes, Heart disease) that patients may have when selecting patients for surgery? If so, why?
    a. Are LTCS important to take into account?
    b. Hip vs knee patients
2. What the most common LTCs/comorbidities you see?
    a. Can you talk through the last patient you had who had a comorbidity?
3. Are there specific LTCs that you think are especially important to take into account?
    a. controlled vs. uncontrolled LTCs, severity of LTCs

Other Factors

1. At what point do you give the go ahead for the patient to undergo surgery?
2. Are there any other factors that influence your decision to go ahead with surgery?
    a. E.g. hospital pressures, financial pressures, other healthcare professionals, social environment of the patient.
3. How do patients respond when they get selected for surgery?

Topic Guide – GPs

Clarification of details

- Profession – Partner or salaried
- Number of years practicing/Years of experience
- What type of GP practice (size of GP practice)

Contextual Factors

1. How often do you see new patients with hip or knee pain?
    a. E.g. daily, weekly, monthly
    b. prevalence of hip vs. knee pain
2. What kind of patients are they usually? What is a typical patient?
    a. E.g. elderly, young with sports injuries, gender, socioeconomic status
3. Do they come specifically for their hip and knee pain or is it a secondary to another issue?

Referral Process

1. When a patient presents with hip or knee pain run me through what you do next.
    a. Assessment
    b. Diagnosis
    c. Referral: where do you send the patients in the first instance?
    d. At what point do you refer patients to be considered for surgery?
    e. Do you do things differently if it is a problem of the Hip vs. the knee?
2. What factors do you take into account in your assessment of the patient before referring them?
    a. Can you talk through a couple of typical hip or knee patients?
    b. severity of symptoms, duration of symptoms, quality of life
    c. Is it different for hip vs knee patients?
    d. In your opinion what are the most important factors?

Long-term Conditions

1. Do you take into account any Long-term conditions (for example diabetes, Heart disease) that patients may have in your referral for assessment to surgery? If so, why?
    a. Hip vs knee patients
    b. Are LTCS important to take into account?

2. Are there specific LTCs that you think are especially important to take into account?
    a. controlled vs. uncontrolled LTCs, severity of LTCs

Other factors

1. Are there any other factors that influence your decision to refer?
    a. E.g. practice pressures, financial pressures
2. How do patients respond when they get referred for assessment for surgery?

Topic Guide – Intermediate care professionals

Clarification of details

- Profession
- Number of years practicing/Years of experience

Contextual Factors

1. How often do you see new patients with hip or knee pain?
    a. E.g. daily, weekly, monthly
    b. prevalence of hip vs. knee pain
2. What kind of patients are they usually? What is a typical patient?
    a. E.g. elderly, young with sports injuries, gender, socioeconomic status

Referral Process

1. When a patient presents with hip or knee pain run me through what you do next.
    a. Assessment
    b. Diagnosis
    c. Referral: where do you send the patients?
    d. At what point do you refer patients to be considered for surgery?
    e. Do you do things differently if it is a problem of the Hip vs. the knee?
2. What factors do you take into account in your assessment of the patient before referring them?
    a. severity of symptoms, duration of symptoms, quality of life
    b. Is it different for hip vs knee patients?
    c. In your opinion what are the most important factors?

Long-term Conditions

1. Do you take into account any Long-term conditions (for example diabetes, Heart disease) that patients may have in your referral for assessment to surgery? If so, why?
    a. Hip vs knee patients
    b. Are LTCS important to take into account?
2. What are the most common LTCs/Comorbidities do you see?

    a. Can you talk through the last patient you had who had a comorbidity?
3. Are there specific LTCs that you think are especially important to take into account?
    a. controlled vs. uncontrolled LTCs, severity of LTCs

Other factors

1. Are there any other factors that influence your decision to refer?
    a. E.g. service pressures, financial pressures
2. How do patients respond when they get referred to orthopaedic surgeons for assessment for surgery?

12.8 Appendix H – Identifying comorbidities in administrative datasets

12.8.1 Introduction

Comorbidity, is the presence of additional diseases in relation to an index disease in one individual, and needs to be measured, as the additional diseases will have an impact on the index disease or any health intervention. This is why, in epidemiology, comorbidity needs to be measured to account for confounding and to understand how it interacts with the outcome and the natural history of the outcome [1].

Administrative datasets are large datasets used in health services for administrative purposes such as reimbursement for health service or insurance payments. Due to the complexity of these large databases, comorbidity indices have been developed to identify comorbidities and quantify their impact on the outcome. This is why these comorbidity Indices are used widely for risk adjustment and risk prediction modelling in administrative datasets.

The most common comorbidity indices are the Charlson and the Elixhauser comorbidity indices. Each comorbidity index includes different comorbidities but they usually include conditions that cannot also be complications of care. Each index or set of indices was also originally developed to predict a certain outcome such as to predict 1-year mortality (Charlson) or length of stay, hospital charges and in-hospital mortality (Elixhauser). The comorbidities included are defined using the International Classification of Disease (ICD) codes that are used in administrative data to record diagnoses. The majority of the indices have been developed for use in version 9 of the ICD and not for the most recent version 10. The majority of the studies comparing indices were carried out in the United States and in Canada using Medicare and Medicaid data [2].

Due to the variability in the comorbidities included in the indices and in the outcomes that they were developed to predict, researchers have been forced to modify them so that they are more suitable to the study population in which they are interested. As a result, there are many modifications of the Charlson and Elixhauser comorbidity indices and it is important to understand how they all differ and what their limitations are.

12.8.2 Assessing the properties of comorbidity indices

Validity

As there is no gold standard for 'true comorbidity', researchers use the assumption that 'true comorbidity' is correlated with worse health outcomes, healthcare utilisation and costs. Therefore, to test the validity of comorbidity indices, the index is assessed by how well it predicts those outcomes which indirectly determine how well the comorbidity index can control for confounding.

There are several measures of validity but the most common is the improvement in the variance, R2. For dichotomous outcomes, there are measures of discrimination and calibration. Measures of discrimination compare the predicted outcome with the actual outcome (e.g. the C statistic) which goes from 0 to 1. [3].

Reliability

Reliability relies on the ability to be able to reproduce the same results in the same set of data. In that sense computerised indices are reliable in the sense that they come from administrative datasets, but reliability also depends on the accuracy of the information stored in the dataset. Accuracy, in turn, depends on how accurately the coded information was gathered from medical or pharmacy records. The reliability of the code-based comorbidity indices are often not measured directly but inferred from other research studies addressing coding accuracy [3].

12.8.3 Types of Diagnosis-based Indices

The Charlson Comorbidity Index (CCI)

The CCI was created by Charlson et al. in 1987 and was developed using chart review to predict 1-year mortality in a cohort of 604 patients admitted to a medical service at New York during 1 month in the year 1984 [4]. The index includes a list of 19 conditions with each condition assigned a weight of 1, 2, 3 or 6 based on adjusted hazard ratios for each comorbid conditions. A total score is then calculated from the sum of the weighted scores [4]. The CCI is the most widely used comorbidity index and has been validated in a variety of patient populations and used to predict a variety of outcomes [5-11]. Many adaptations of the CCI have been developed for use with ICD-9 or ICD-10 codes in administrative databases.

Deyo CCI

The Deyo CCI is an adaptation of the CCI which is the most commonly used adaptation of the CCI [2]. This adaptation uses the ICD-9 codes corresponding to 17 comorbid conditions [12]. Several studies have specifically evaluated the ability of the Deyo CCI to predict outcomes such as 1-year mortality, length of stay or costs [11, 13, 14]. A systematic review in 2012 found that the Deyo CCI showed low abilities to predict short-term mortality but behaved very similarly to other adaptations for long-term mortality [2]. In 2004, the Deyo CCI was adapted for the use with ICD-10 codes and this adaptation performed similarly to the original ICD-9 version in predicting in-hospital mortality [14].

Romano CCI

Another adaptation of the CCI is the Romano CC which was formerly known as the Dartmouth-Manitoba CCI. Compared to the Deyo CCI the Romano adaptation includes broader definitions encompassing more ICD-9-CM codes for peripheral vascular diseases, complicated diabetes and malignancy [15, 16].

Several studies have compared the Romano and Deyo adaptations of the CCI and found them to be very similar [8, 17, 18]. The Romano adaptation of the Charlson index however had better predictive performance than the majority of the indices for long-term mortality [2].

D'Hoore CCI

D'Hoore et al. created a CCI adaptation using only the first three digits of ICD-9 coding without clinical modification (CM) (which includes procedural codes and additional morbidity details) as many institutions outside the US use ICD-9 codes without CM [5]. D'Hoore claims that the CM digits of the ICD-9 codes can lead to inconsistencies, so they have created a simpler and more reliable adaptation. The D'Hoore index has been found to have a high ability to predict in-hospital mortality in populations with a principle diagnosis of myocardial infarction, ischemic heart disease and bacterial pneumonia, but does not have the same ability to predict for stroke and congestive heart failure [19].

Ghali CCI

The Ghali adaptation built further on the Deyo's adaptation to create a shorter study-specific index which includes only five comorbidities. The comorbidities included have been selected based on whether they have been found to be associated with in-hospital mortality. The study-specific weights for each comorbidity were then derived from multiple logistic regression analyses on the study sample used for the development of the index [7]. The Ghali CCI performs better than the Deyo CCI in predicting in-hospital mortality but when compared to the original CCI it did not perform well [20].

Quan CCI

The Quan adaptation was developed in 2006 by adapting the Deyo CCI coding to the ICD-10 coding and adding to the selection of codes for each comorbidity, by using experts' knowledge to assess the validity of the ICD-10 codes [21]. In 2011 the Quan index was updated and used study-specific weights in a similar method to Ghali's and demonstrated a better ability to predict in-hospital mortality and 1-year mortality than the original Quan CCI [22].

In comparison to other CCI adaptations, the Quan index is similar to the Romano adaptation in predicting short-term and long-term mortality [2]

Elixhauser (El)

The original Elixhauser comorbidity index is an index made up of 30 comorbidities defined using ICD-9-CM codes. The comorbidities were included because they were significant predictors of LOS and hospital charges and were explicitly not complications of care. Many of the comorbidities were associated with in-hospital mortality but as a group, they were not significant. The disadvantage of the original EI is there is no weighting system to provide a single score [23].

Several studies have validated the EI and many have then gone on to modify the EI [21, 24, 25]. In predicting in-hospital mortality, all EI versions demonstrated acceptable to excellent predictive ability. Another study found that the ICD-9-CM version performed better than the ICD-10 version. Another EI version using study-derived regression coefficients had

similar results to models using the EI which included all comorbidities. An EI version with only 21 comorbidities was significantly associated with mortality [25].

A number of studies have compared EI to other comorbidity indices and have demonstrated that various versions of the EI predicted mortality outcomes better than the various adaptations of the CCI [20]. Some studies however, found no difference between the two. Several studies demonstrated that combining data sources such as inpatient and outpatient data resulted in even better predictive ability.

12.8.4 Other sources of data

Medications-based Indices

Other sources of administrative data are pharmacy databases. As a result, comorbidity indices have been developed for use in these datasets; it has been claimed that they are more accurate and complete than diagnosis-based databases. One of the indices developed is the Chronic Disease Scores (CDS) which was developed in 1992 using medications data to identify comorbidities. Using a population-based pharmacy database a panel of experts, starting from a selected base of medications, created disease categories and then assigned weights [26]. The original CDS included 17 diseases but was subsequently expanded to 28 and weighting was applied based on regression models [27].

The RxRisk and RxRisk-V is a risk assessment instrument which was developed using outpatient pharmacy data to identify chronic diseases and predict future healthcare costs. The score includes 57 adult and paediatric weighted disease categories and drug classes [28].

The Medication-based Disease Burden Index (MDBI) was developed as an alternative to the chronic disease score. This score had a weak correlation with the CCI and CDS and has only a moderate ability to predict readmission and 6-month mortality [29].

Overall medication-based indices demonstrated a better ability than diagnosis-based indices to predict health utilization outcomes such as prescription medication use, total costs, disease burden and hospital utilisation. EI, however, demonstrated better ability to predict physician visits. Medication and diagnosis-based indices demonstrated similar abilities to predict hospital readmission and length of stay, hospitalisation, spending and costs [20].

Self-report vs. administrative data

Comorbidity indices calculated from administrative data have also been validated against scores derived from self-reported data. Several studies have specifically compared the performance of a CCI adaptation derived from self-reported data with the same index derived from administrative data or chart review. They found that self-reported data and administrative data adaptations had similar ability to predict various outcomes [30, 31]. One study found that the levels of agreement varied according to comorbid conditions and varied from poor to substantial agreement [32].

Chart review vs. administrative data

Comorbidity indices calculated from administrative data have also been validated against scores derived from chart review. A systematic review in 2010 compared chart-review and CCI adaptations derived from administrative data [33]. They found that CCI scores calculated from administrative data were consistently lower than those derived from chart review, and agreement between the two sources was poor to fair. Further studies have found that agreement varied greatly according to the comorbidity [34]. Another found that the two comorbidities correlated well [35].

12.8.5 Application of Comorbidity Indices

Approaches to selecting comorbidities

Studies using comorbidity indices have selected comorbidities based on a mix of looking at the prevalence of the diagnoses, comparisons to existing indices and the seeking of expert opinion [2]. For example Desai et al. [36] reviewed the medical literature, expert opinion and then looked at the preliminary analysis of the data and considered conditions which had a prevalence of >2%. Fleming et al. looked at the prevalence of disease and compared it with the Charlson index and was influenced by the desire to focus on chronic rather than acute conditions [37]. Others simply combined the conditions listed in the Elixhauser and the Deyo adaptation of the Charlson index excepting those conditions thought to be related to the main diagnosis [38, 39]

Look back periods

The length of the look back period to identify comorbidities has been found to influence the performance of both the Charlson and Elixhauser [34]. A study found that by adding inpatient and outpatients claims in the 12 months before the index hospitalisation the Charlson and Elixhauser performed better [40]. In another study looking at 1-year mortality and readmissions, a 1 year lookback period gave the best fit for 1-year mortality and a longer lookback period gave the best fit for readmissions [41].

12.8.6 Limitations of comorbidity indices

One of the clear advantages to using comorbidity indices is that it allows us to use administrative datasets for population-based research. Population-based research provides us with more accurate estimates of prevalence or incidence and may be more generalizable and relevant to policy decision making. Administrative datasets are also less subject to patient-related recall bias and selection and nonresponse bias [42]. Practically, administrative datasets are also much cheaper than primary data collection. Finally, linkage of administrative databases allows for long-term follow-up of the patient journey and its outcomes which is increasingly important in integrated care research [43].

While there are clear advantages of using, comorbidity indices there are also clear disadvantages, which need to be considered of using comorbidity indices, in particular, diagnosis-based indices. These also include variable coding practices and the accuracy and completeness of the data.

One of the disadvantages of diagnosis-based indices includes a variability in ICD coding practices which can lead to under-reporting of chronic conditions in secondary diagnosis [33]. A study has found that acute clinical conditions are more accurately documented than comorbidities and this varies across different types of hospitals [44]. Some researchers argue therefore that chart review is a better source of data on comorbidities than administrative dataset, but research has shown that chart review focuses more on the history of comorbid conditions rather than more active conditions [45].

Another problem with coding is that there is often not a clear difference between diagnoses of comorbidities at the point of admission to hospital and complications arising during the hospital stay. Treating complications as comorbidities can overestimate the performance of the comorbidity index at predicting a worse outcome [46]. In addition, if

you want to adjust for hospital outcome than you cannot adjust for complications as they are partly a result of hospital care [2]. However, a study found that the impact of misinterpreting complications as comorbidities in surgical procedures is minor [47]. There is also the possibility that diagnoses are sometimes recorded as present when in actual fact they are recorded in a bid to rule them out (they are negative). Such misinterpretation is only possible to identify if it is possible to look at admissions before and after that index admission. The use of diagnostic-type codes which allow for the distinction between primary diagnoses and post-admission comorbidities may prevent any misinterpretation [33].

Another limitation is the completeness of the data as this can lead to more inaccuracies. A study found that sensitivity in capturing specific diagnoses in administrative datasets with five diagnosis fields reduced by an average 13% compared to a record with 25 fields [48].

Another disadvantage is that certain CCI adaptations can only be used with specific ICD versions (e.g. Deyo CCI with ICD-9-CM and the Quan CCI with ICD-10). In addition, there is a lot of variation in ICD-10 versions than ICD-9 versions which further limits the applications of these diagnosis-based indices. It is therefore important to consider the ICD version used in the administrative data before selecting the CCI index. [20]

Schneeweiss et al. also argue that comorbidity scores only modestly improve on age adjustment despite comorbidity indices being more comprehensive. This may be because in summarising a complex construct such as comorbidity in one summary score, numerous assumptions are made and therefore inevitability underestimates the magnitude of confounding. Having one summary score however is very useful in adjusting for confounders but it does depend on the accuracy and completeness of the data. Unfortunately, the completeness depends on the accuracy in the data collection and recording processes. [3].

It is also important to note that the prognoses of many comorbidities (such as AIDS) have dramatically changed in the last decade. This will have an impact on the current weights assigned to certain comorbidities which is why studies recommend, if possible, to derive study-based weights rather than relying on the weights derived by the original comorbidity indices [43].

12.8.7 Conclusion

In conclusion, of the diagnosis-based measures, the Elixhauser seems to be better than the CCI in predicting both short and long-term mortality. Of the CCI adaptations it seems the Romano adaptation has been demonstrated to be better at predicting various outcomes compared to other adaptations of the CCI index [2, 20]. Overall comorbidity indices are better at predicting long-term mortality compared to short-term mortality and this may be because in patients with serious acute conditions comorbidities are usually underreported [2].

Evidence suggests that other factors can further improve the performance of these indices. For example using a combination of both inpatient and outpatient, data improves the performance of the comorbidity indices. Similarly, the length of the look back period also influences the performance of comorbidity indices. Almost all studies found that deriving study-specific weights for both the EI and the CCI adaptations greatly improved their performance at predicting outcomes [20].

While pharmacy data is considered to be of better quality and more reliable it is often not very accessible as is the case in this study. There is also a big disadvantage of using pharmacy data in that the comorbidities included are limited to those which are treated with medications [20].

Overall, while there are clearly indicators which have been shown to perform better than others it is important to consider the source of the data being used, the study population and the outcomes of interest before selecting the most appropriate comorbidity indices.

12.8.8 References

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12.9 Appendix I – Supplementary Information RP3 - Mapping of comorbidities

PROMs chronic disease category	Chronic disease Subcategories	ICD-10 Code	ICD-10 definition	RCS CI	Quan CCI	Elixhauser*	Backward coding
Cancer	Lymphoma	C81.x-C85.x	Malignant neoplasms	x	x	x	
		C88	Malignant neoplasms	x	x	x	
		C90.0	Malignant neoplasms	x	x	x	
		C90.2	Malignant neoplasms	x	x	x	
		C90-C97	Malignant neoplasms	x	x		
		C96.x	Malignant neoplasms	x	x	x	
	Metastatic cancer	C77–C80	Malignant neoplasms	x	x	x	
	Solid Tumour without metastasis	C00.x-C26.x	Malignant neoplasms	x	x	x	
		C30.x-C34.x	Malignant neoplasms	x	x	x	
		C37.x-C41.x	Malignant neoplasms	x	x	x	
		C43	Malignant neoplasms	x	x	x	
		C45.x-C58.x	Malignant neoplasms	x	x	x	
		C60.x-C76.x	Malignant neoplasms	x	x	x	
		C97.x	Malignant neoplasms	x	x	x	
Depression	Depression	F32.x	Depressive episode			x	
		F33	Recurrent depressive disorder			x	
		F34.1	Dysthymia			x	
	Depression linked to anxiety and stress	F41.2	Mixed anxiety and depressive disorder			x	
		F43.2	Adjustment disorders			x	
	Other depression	F20.4	Post-schizophrenic depression			x	
		F31.3-F31.5	Bipolar affective disorder, current episode mild or moderate depression, severe depression without psychotic symptoms, severe depression with psychotic symptoms			x	
Diabetes	Insulin-dependent diabetes	E10	Insulin-dependent diabetes mellitus	x			
	Non-insulin-dependent diabetes	E11	Non-insulin-dependent diabetes mellitus	x	x	x	
	Other	E12	Malnutrition-related diabetes mellitus	x	x	x	
		E13	Other specified diabetes mellitus	x	x	x	
		E14	Unspecified diabetes mellitus	x	x	x	
Heart disease	Cardiac arrhythmias	I441-I443	Atrioventricular block, second degree, Atrioventricular block, complete, Other and unspecified atrioventricular block			x	
		I456	Pre-excitation syndrome			x	
		I459	Conduction disorder, unspecified			x	
		I47-I49	Paroxysmal tachycardia, Atrial fibrillation and flutter, Other cardiac arrhythmias			x	
		R00.1	Bradycardia, unspecified			x	
		R00.8	Other and unspecified abnormalities of heart beat			x	

PROMs chronic disease category	Chronic disease Subcategories	ICD-10 Code	ICD-10 definition	RCS CI	Quan CCI	Elixhauser*	Backward coding
		R000	Tachycardia, unspecified			x	
		T82.1	Mechanical complication of cardiac electronic device			x	
		Z45.0	Adjustment and management of cardiac pacemaker			x	
		Z95.0	Presence of cardiac pacemaker			x	
	Congestive heart failure	I09.9	Rheumatic heart disease, unspecified		x	x	
		I11.0	Hypertensive heart disease with (congestive) heart failure		x	x	
		I13.0	Hypertensive heart and renal disease with (congestive) heart failure	x	x	x	
		I13.2	Hypertensive heart and renal disease with both (congestive) heart failure and renal failure		x	x	
		I255	Ischaemic cardiomyopathy	x	x	x	
		I42	Cardiomyopathy	x			
		I42.0	Dilated cardiomyopathy	x	x	x	
		I42.5-I42.9	Other restrictive cardiomyopathy, Alcoholic cardiomyopathy, Cardiomyopathy due to drugs and other external agents, Other cardiomyopathies, Cardiomyopathy, unspecified	x	x	x	
		I42.6	Alcoholic cardiomyopathy	x		x	
		I43	Cardiomyopathy in diseases classified elsewhere	x	x	x	
		I50	Heart failure	x	x	x	
		I517	Cardiomegaly	x			
	Ischemic heart diseases	I21	Acute myocardial infarction	x	x		
		I22	Subsequent myocardial infarction	x	x		
		I23	Certain current complications following acute myocardial infarction	x	x		
		I252	Old myocardial infarction	x			
		I258	Other forms of chronic ischaemic heart disease				x
		I259	Chronic ischaemic heart disease, unspecified				x
		I20	Angina Pectoris				x
		I251	Atherosclerotic heart disease				x
	Valvular disease	Q23.O-Q23.3	Congenital stenosis of aortic valve, Congenital insufficiency of aortic valve, Congenital mitral stenosis, Congenital mitral insufficiency		x	x	
		Z95.2	Presence of prosthetic heart valve		x	x	
		Z95.4	Presence of other heart-valve replacement		x	x	
		A52.0	Cardiovascular syphilis		x	x	
		I05.x-I08.x	Rheumatic mitral valve diseases, Rheumatic aortic valve diseases, Rheumatic tricuspid valve diseases, Multiple valve diseases		x	x	
		I09.1	Rheumatic diseases of endocardium, valve unspecified		x	x	
		I09.8	Other specified rheumatic heart diseases		x	x	
		I34-I39	Nonrheumatic mitral valve disorders, Nonrheumatic aortic valve disorders, Nonrheumatic tricuspid valve disorders, Pulmonary valve disorders, Endocarditis,		x	x	

PROMs chronic disease category	Chronic disease Subcategories	ICD-10 Code	ICD-10 definition	RCS CI	Quan CCI	Elixhauser*	Backward coding
			valve unspecified, Endocarditis and heart valve disorders in diseases classified elsewhere				
High BP	Primary hypertension	I10.x	Essential (primary) hypertension			x	
	Secondary hypertension	I11	Hypertensive heart disease	x		x	
		I15	Secondary hypertension			x	
Kidney disease	Acute renal failure	N171*	Acute renal failure with acute cortical necrosis	x			
		N172*	Acute renal failure with medullary necrosis	x			
		N179*	Acute renal failure, unspecified				x
	Chronic renal failure	I12.0	Hypertensive renal disease with renal failure		x	x	
		I13.1	Hypertensive heart and renal disease with renal failure		x	x	
		N18	Chronic kidney disease	x	x	x	
		N19	Unspecified kidney failure	x	x	x	
		Z49	Care involving dialysis	x			
		Z49.0-Z49.2	Preparatory care for dialysis, Extracorporeal dialysis, Other dialysis	x	x	x	
		Z94.0	Kidney transplant status	x	x	x	
		Z99.2	Dependence on renal dialysis	x	x	x	
		N19	Unspecified Kidney failure				x
	Glomerular diseases	N01	Rapidly progressive nephritic syndrome	x			
		N03	Chronic nephritic syndrome	x			
		N03.2–N03.7	Rapidly progressive nephritic syndrome	x	x		
		N05	Unspecified nephritic syndrome	x			
		N05.2–N05.7	Unspecified nephritic syndrome Diffuse membranous glomerulonephritis , Diffuse mesangial proliferative glomerulonephritis, Diffuse endocapillary proliferative glomerulonephritis, Diffuse mesangiocapillary glomerulonephritis	x	x		
		N07	Hereditary nephropathy, not elsewhere classified	x			
		N08	Glomerular disorders in diseases classified elsewhere	x			
	Other renal disease	N25	Disorders resulting from impaired renal tubular function	x			
		N289	Disorder of kidney and ureter, unspecified				x
	Secondary hypertension	I12	Hypertensive renal disease	x		x	
		I13	Hypertensive heart and renal disease	x		x	
Leg pain due to poor circulation	Aortic diseases	I70	Atherosclerosis	x	x	x	
		I71	Aortic aneurysm and dissection	x	x	x	
		I72	Other aneurysm and dissection	x			
		I790	Aneurysm of aorta in diseases classified elsewhere		x	x	
	Gangrene	R02	Gangrene, not elsewhere classified	x			
	Peripheral vascular diseases	I73	Other peripheral vascular diseases				
		I731	Thromboangitis obliterans [Buerger]	x	x	x	
		I738	Other specified peripheral vascular diseases	x	x	x	

PROMs chronic disease category	Chronic disease Subcategories	ICD-10 Code	ICD-10 definition	RCS CI	Quan CCI	Elixhauser*	Backward coding
		I739	Peripheral vascular disease, unspecified	x	x	x	
		I770	Arteriovenous fistula, acquired	x			
		I771	Stricture of artery	x	x	x	
		I792	Peripheral angiopathy in diseases classified elsewhere		x	x	
	Vascular implants	Z95.8	Presence of other cardiac and vascular implants and grafts	x	x	x	
		Z95.9	Presence of cardiac and vascular implant and graft, unspecified	x	x	x	
Liver disease	Alcoholic liver disease	K70	Alcoholic liver disease	x		x	
		K70.0	Alcoholic fatty liver	x	x	x	
		K70.1	Alcoholic hepatitis	x	x		
		K70.2	Alcoholic fibrosis and sclerosis of liver	x	x		
		K70.3	Alcoholic cirrhosis of liver	x	x	x	
		K70.4	Alcoholic hepatic failure	x	x		
		K70.9	Alcoholic liver disease, unspecified	x	x	x	
	Cirrhosis	I85.9	Oesophageal varices without bleeding	x	x	x	
		I85.0	Oesophageal varices with bleeding	x	x	x	
		I86.4	Gastric varices	x	x	x	
		I98.2	Oesophageal varices without bleeding in diseases classified elsewhere	x	x	x	
		K71.7	Toxic liver disease with fibrosis and cirrhosis of liver	x	x	x	
		K74	Fibrosis and cirrhosis of liver		x	x	
	Hepatic failure	K71.1	Toxic liver disease with hepatic necrosis	x	x	x	
		K72.0*	Acute hepatic failure				
		K72.1	Chronic hepatic failure	x	x	x	
		K72.9	Hepatic failure, unspecified	x	x	x	
		K72.x	Hepatic failure, not elsewhere classified			x	
	Hepatitis	B18	Chronic viral hepatitis	x	x	x	
		K71.3-K71.6	Toxic liver disease with chronic persistent hepatitis, chronic lobular hepatitis, chronic active hepatitis	x	x	x	
		K73	Chronic hepatitis, not elsewhere classified		x	x	
		K754	Autoimmune hepatitis				x
	Other	K76	Other diseases of liver	x			
		R162	Hepatomegaly with splenomegaly, not elsewhere classified	x			
		Z94.4	Liver transplant status	x	x	x	
Lung disease	Asthma	J45-46	Asthma	x	x	x	
	COPD	J40-42	Bronchitis	x	x	x	
		J43	Emphysema	x	x	x	
		J44	COPD	x	x	x	
	Pulmonary heart diseases	I26	Pulmonary embolism	x		x	

PROMs chronic disease category	Chronic disease Subcategories	ICD-10 Code	ICD-10 definition	RCS CI	Quan CCI	Elixhauser*	Backward coding
		I278	Other specified pulmonary heart diseases	x	x	x	
		I279	Pulmonary heart disease, unspecified	x	x	x	
	Other lung disease (e.g. due to external agents)	J47	Bronchiectasis				
		J60-J67	Lung diseases due to external agents	x	x	x	
		J684	Chronic respiratory conditions due to chemicals, gases, fumes and vapours	x	x	x	
		J701	Chronic and other pulmonary manifestations due to radiation	x	x	x	
		J703	Chronic drug-induced interstitial lung disorders	x	x	x	
		J841	Other interstitial pulmonary diseases with fibrosis				x
		J920	Pleural plaque with presence of asbestos				x
Nervous System	Dementia	F00.x–F03.x	Dementia in Alzheimer disease, Vascular dementia, Dementia in other diseases classified elsewhere, Unspecified dementia	x	x		
		F051	Delirium superimposed on dementia	x	x		
		G30	Alzheimer disease	x	x		
		G31	Other degenerative diseases of nervous system, not elsewhere classified	x			
		G31.1	Senile degeneration of brain, not elsewhere classified	x	x		
		G31.2	Degeneration of nervous system due to alcohol	x		x	
		G31.8	Other specified degenerative diseases of nervous system	x		x	
		G31.9	Degenerative disease of nervous system, unspecified	x		x	
		G32.x	Other degenerative disorders of nervous system in diseases classified elsewhere			x	
	Demyelinating disease	G35	Multiple sclerosis			x	
		G36	Other acute disseminated demyelination			x	
		G37	Other demyelinating diseases of central nervous system			x	
	Epilepsy	G40	Epilepsy			x	
		G41	Status epilepticus			x	
		R56	Convulsions, not elsewhere classified			x	
	Neuropathies	G600	Hereditary motor and sensory neuropathy				x
		G629	Polyneuropathy				x
		G610	Guillain-Barré syndrome				x
		G618	Other inflammatory polyneuropathies				x
		G619	Inflammatory polyneuropathy, unspecified				x
	Parkinsonism	G20.x-G22.x	Parkinson disease, secondary parkinsonism, parkinsonism in diseases classified elsewhere			x	
		G25.4	Drug-induced chorea			x	
		G25.5	Other chorea			x	
		G249	Dystonia, unspecified				x
		G250	Essential tremor				x
		A810	Creutzfeldt-Jakob disease	x			
		G04.1	Tropical spastic paraplegia			x	

PROMs chronic disease category	Chronic disease Subcategories	ICD-10 Code	ICD-10 definition	RCS CI	Quan CCI	Elixhauser*	Backward coding
	Other nervous system (e.g. paralysis, huntington's disease)	G10.x-G13	Huntingdon disease, Hereditary ataxia, spinal muscular atrophy and related syndromes, Systemic atrophies primarily affecting central nervous system in diseases classified elsewhere			x	
		G11.4	Hereditary spastic paraplegia	x		x	
		G80.1	Spastic diplegic cerebral palsy			x	
		G80.2	Spastic hemiplegic cerebral palsy			x	
		G82.x	Paraplegia and tetraplegia	x		x	
		G83	Other paralytic syndromes	x			
		G83.0-G83.4	Diplegia of upper limbs, Monoplegia of lower limb, Monoplegia of upper limb, Monoplegia, unspecified, Cauda equina syndrome	x		x	
		G83.9	Paralytic syndrome, unspecified			x	
		G93.1	Anoxic brain damage, not elsewhere classified			x	
		G93.4	Encephalopathy, unspecified			x	
		R47.0	Dysphasia and aphasia			x	
		G700	Myasthenia				x
		G933	Postviral fatigue syndrome				x
Stroke	Transient Ischemic Attack	G45	Transient cerebral ischaemic attacks and related syndromes	x	x		
	Ischemic stroke	I69.2	Sequelae of other nontraumatic intracranial haemorrhage	x	x		
		G46	Vascular syndromes of brain in cerebrovascular diseases (I60-I67+)	x	x		
		H34.0	Transient retinal artery occlusion		x		
		I61	Intracerebral haemorrhage	x	x		
		I62	Other nontraumatic intracranial haemorrhage	x	x		
		I63	Cerebral infarction	x	x		
		I64	Stroke, not specified as haemorrhage or infarction	x	x		
		I65	Occlusion and stenosis of precerebral arteries, not resulting in cerebral infarction	x	x		
		I66	Occlusion and stenosis of cerebral arteries, not resulting in cerebral infarction	x	x		
		I69.1	Sequalae of intracerebral haemorrhage	x	x		
		I69.3	Sequelae of cerebral infarction	x	x		
		I69.4	Sequelae of stroke, not specified as haemorrhage or infarction	x	x		
		G81.x	Hemiplegia	x		x	
	Subarachnoid Haemorrhage	I60	Subarachnoid haemorrhage	x	x		
		I69.0	Sequalae of subarachnoid haemorrhage	x	x		
	Other stroke	I67	Other cerebrovascular diseases	x	x		
		I68	Cerebrovascular disorders in diseases classified elsewhere	x	x		
		I69.8	Sequelae of other and unspecified cerebrovascular diseases	x	x		

Note : * ICD-10 codes not mapped from the Elixhauser Comorbidity Index: AIDS/HIV , Peptic Ulcer Disease, Pulmonary Circulation disorders, Hypothyroidism, Coagulopathy, Obesity, Weight loss, Fluid and electrolyte disorders, Blood loss anaemia, Deficiency Anaemia, Alcohol abuse, Drug abuse, Psychoses.

12.10 Appendix J – Data application, linkage, cleaning, and derivation of indicators

The following section describes the process of applying for data from NHS Digital and the data linkage process conducted by NHS Digital. Detail about the data cleaning process such as the removal of duplications is also described as well as the derivation of indicators.

12.10.1 Data application process

The data application process was long and arduous (see table 1). The data application was submitted at the end of April 2016 and data was not received until May 2017.

An application was submitted to NHS Digital as well as the Office for National Statistics (ONS) via NHS Digital. Due to the data being potentially patient-identifiable ethics approval from the Health Research Authority (HRA) was requested. Approvals were needed from the HRA Research Ethics Service (RES) and the HRA Confidentiality Advisory Group (CAG). The applications to the HRA were submitted in July 2016. Meanwhile, to access ONS data every researcher needed to be an *ONS Approved Researcher.* A separate application was submitted to ONS for approved researcher status, which involved training. All approvals were received by October 2016. Further queries regarding the fair processing statement, the role of the funder and the storage of the data at the Royal College of Surgeons of England and other NHS Digital delays led to data not being received until May 2017.

Table 3 – Data application process

Steps	Application	Date submitted
1	NHS digital data application - Further approvals needed: HRA approval, Ethics approval, CAG approval, ONS approval, ONS approved researcher status	May 2016
2	HRA Research Ethics and CAG application	July 2016
3	ONS Approved Researcher (involved training)	October 2016
4	Queries: - Fair processing statement - Role of funder - Agreement between the RCS and LSHTM	October 2016 – May 2017

12.10.2 Data sources

The data set available to the study consisted of:

- PROMs records for Hip and Knee replacement – 2009-2017
- HES inpatient records for patients in PROMs survey – 2003-2017
- ONS-HES linked mortality statistics 2009-2017

PROMs

This dataset included 791 474 number of PROMS procedures, of which:

- 385 332 were hip replacements
- 406 142 were knee replacements

HES inpatient records

This dataset included 6 104 484 HES episodes between 2003 and 2017 for the 791 474 PROMs patients.

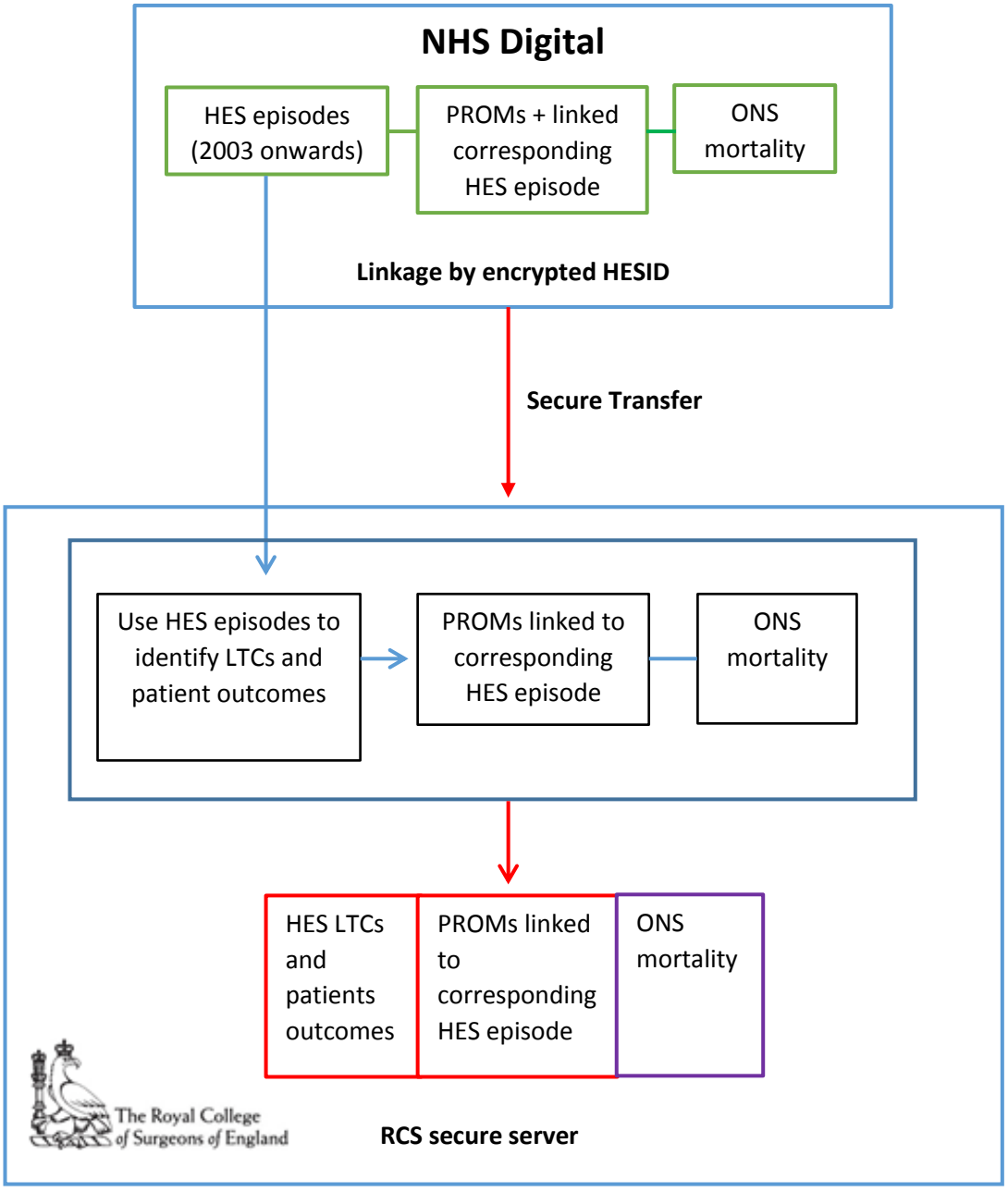
Office for National Statistics mortality data

This dataset included 45 854 registered number of deaths for this population for the 791 474 PROMs patients.

These data derived from death certification give the cause of death of an individual. The record is linked to the HES data set, enabling the individual's previous medical history to be examined.

12.10.3 Data linkage

Below is a diagram of the data linkage processes that NHS Digital undertook and was subsequently undertaken to produce a dataset that was ready for analysis.



12.10.4 Data cleaning

The information which follows provides an account of full data cleaning conducted for the study, prior to data analysis. The project restricted the records to NHS hospital hip and knee replacement. Duplicate episodes of the index hip and knee replacement were removed.

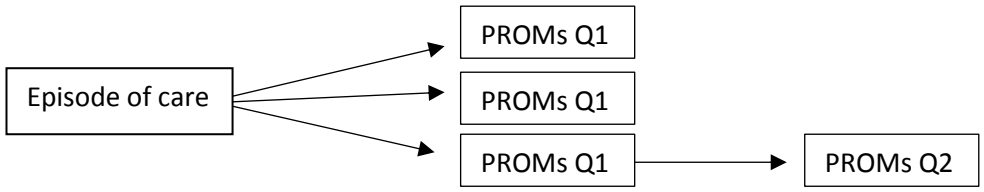
12.10.4.1 Duplicate records

Duplicate PROMs Q1

Some hip and knee replacement had several survey records associated with them that are not necessarily identical. Out of the many alternatives, one record has to be chosen to represent the hip or knee replacement.

Duplicate records might have been created because a surgery was delayed and then reissued again at the operation. This may explain why a matched episode with a lower match rank has a complete record.

Figure 3- Selecting the one record to represent the hip or knee replacement



Duplicate records were chosen using the following algorithm in order of priority:

Algorithm

1. Had a complete Q2
2. Highest match score
3. Latest completed Q1 date
4. Most recent scan date

For the group of records that all relate to one hip or knee replacement, a single record was chosen using the above algorithm. Episode matches with a complete Q1 and Q2 were prioritised and chosen. A match score was derived using the episode match rank (a rank

score which has been calculated by NHS Digital which evaluates the matching quality of a HES episode to a Q1 questionnaire). It uses a four-stage process that looks at a combination of patient identifiable fields, provider codes, operation codes and dates. As the match rank is a combination of three different scores the actual scores in each combination were calculated to derive an overall PROMS match score. This avoids the problem of some matches being ranked better matched in certain fields than others. A higher overall score signifies a higher quality match. The duplicate record with the highest matching scoring was chosen. For the remainder if match score and record completeness was identical the record with the latest completed Q1 date or most recent scan date were chosen. In the cases where there are duplicate records and all above fields are identical, a random number was generated to distinguish records and the lowest random number was chosen.

Duplicate episodes of care

After linkage with HES records a further 280 episodes of care were found to be duplicate records, but for the hospital treatment code. The majority of these duplicate records were recorded in both a private and an NHS trust hospital. The records were chosen in the following order of priority: PROMs Q2 completeness and then scan date. The duplicate record with a complete Q2 was chosen (n=115) and if both were complete or non-complete the duplicate with the latest scan date (n=25) was chosen. This is because the later scan date was closer in proximity to the admission date. As a result, 140 duplicate records were removed.

12.10.4.2 Patients with multiple interventions

There were some patients who had multiple hip and knee surgeries. As we are comparing the presence of comorbidities in PROMs and HES only the first surgery was included in the analysis to ensure there was only one record per patient.

The further episodes while not included in the main analysis were analysed separately to test patient-reported coding consistency between the first and second intervention. This further validates the reliability of patient-reported comorbidity.

Table 4 – Number of surgeries per patient for both hip and knee replacement surgery.

Number of surgeries	Frequency	Percent
1	677 185	86.8
2	97 386	12.5
3	5 460	0.70
4	508	0.07
5	32	0.00
6	4	0.00

A number of patients had multiple surgeries including both primary and revision surgeries. Patients with hip replacement had up to five primary and revision surgeries whereas there were a maximum of six for knee replacement surgeries. For the purposes of the analysis, only the first primary surgery was included. However, a further piece of analysis will be conducted to explore the consistency of coding across subsequent surgeries and whether there were any differences in recording of comorbidities between the first and second surgery.

12.10.4.3 Investigating miscoding and response errors

Previous research has identified a potential issue with the responses to the question in PROMS asking about comorbidities. There may be patients who misinterpreted the question about whether a doctor had ever told them whether they had any of the following comorbidities. Patients may have checked off the comorbidities, which were absent rather than present.

This was investigated by comparing the number of patient-reported comorbidities against the number of HES reported comorbidities, mean reported quality of life and the number of discordant comorbidities.

When looking at the number of reported PROMs comorbidities it was found that more patients reported having 10 rather than 9 comorbidities and more reported having 11 comorbidities than 10. When looking at the HES recorded data in a similar way, the average number of HES comorbidities decreases rather than increases from greater than 6 PROMs reported comorbidities.

Table 5 – Agreement between PROMs and HES number of comorbidities in number of comorbidities reported in both HIP and knee replacement patients.

PROMS # of comorbidities	HES # of comorbidities									Total
	0	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	
0	182566	57 815	16 216	3 854	679	93	13	0	0	261236
1	47 505	139 645	46 416	9 611	1 446	151	11	3	0	244788
2	10 511	35 077	52 379	15 896	2 930	351	32	2	2	117180
3	2 246	6 562	15 187	11 602	3 054	448	54	3	0	39 156
4	523	1 125	3 183	3 897	1 764	372	52	3	0	10 919
5	121	206	563	886	639	207	25	1	0	2 648
6	33	56	95	189	149	69	21	2	0	614
7	10	16	29	32	16	21	2	0	0	**126**
8	13	15	11	10	4	0	3	0	0	**56**
9	18	24	6	4	2	0	0	0	0	**54**
10	63	41	22	9	4	0	0	0	0	**139**
11	137	68	38	18	8	0	0	0	0	**269**
Total	243746	240 650	134145	46008	10695	1712	213	14	2	677185

When also looking at mean quality of life scores (EQ-5D) patients with six or greater number of reported PROMs comorbidities had better reported quality of life compared to patients with only six comorbidities. The quality of life reported appeared to improve as patients had more comorbidities.

Table 6 – The Q2 postoperative mean EQ-5D score and number of HES comorbidities by number of reported PROMS comorbidities for both hip and knee replacement surgery.

PROMs # of comorbidities	Mean number of HES comorbidities	Postoperative mean EQ-5D score
0	0.40	0.79
1	1.09	0.76
2	1.72	0.70
3	2.21	0.63
4	2.60	0.57
5	2.92	0.50
6	3.09	0.48
7	**2.79**	**0.51**
8	**1.80**	**0.53**
9	**1.04**	**0.67**
10	**0.92**	**0.78**
11	**0.86**	**0.75**

Similarly, when looking at the level of agreement between PROMS reported comorbidities and HES recorded comorbidities patients reporting they had greater than 6 comorbidities had greater than 25% disagreement on at least three of the most common comorbidities.

As a result, patients reporting more than six comorbidities were removed as a substantial proportion of patients were incorrectly recording their comorbidities.

Table 7- The percentage of patients undergoing hip and knee replacement surgery who had greater than 25% disagreement on at least three of the most common comorbidities (i.e. diabetes, heart disease, high BP, lung disease and arthritis)

PROMs # of comorbidities	Sum of agreement (HES and PROMs for diabetes, heart disease, high BP and lung disease and whether arthritis is present)							% that have less than 3 in agreement
	0	1	2	3	4	5	Total	
0	86	1 248	6 913	26 908	94 113	131 968	261 236	13.5
1	13	309	3 504	25 231	91 460	124 271	244 788	11.9
2	5	173	2 345	14 120	42 951	57 586	117 180	14.2
3	7	112	1 014	4 913	14 144	18 966	39 156	15.4
4	4	61	396	1 417	3 919	5 122	10 919	17.2
5	2	24	128	353	944	1 197	2 648	19.2
6	4	20	39	70	232	249	614	21.7
7	2	4	11	22	41	46	126	**31.0**
8	7	8	14	13	7	7	56	**75.0**
9	7	22	14	6	4	1	54	**90.7**
10	26	55	37	18	3	0	139	**97.8**
11	17	135	68	34	13	2	269	**94.4**
Total	180	2 171	14483	73 105	247 831	339 415	677 185	

12.10.4.4 Removal of revision surgeries

PROMs field: Proc_revision_flag

Revision surgeries were removed from the analysis cohort as patients undergoing revision surgery are likely to have more severe symptoms and are likely to constitute a different cohort of patients. As the interest of this study was patients accessing their primary surgery, operations tagged as a revision in PROMs were excluded from the analysis. 22 132 hip operations and 13 464 knee operations were excluded.

12.10.4.5 Removal of incomplete postoperative (Q2) questionnaires

PROMs field: Q2_complete

Q2 survey responses that were incomplete were removed. 68 478 hip operations and 72 868 knee operations were removed.

12.10.4.6 Removal of second primary operations

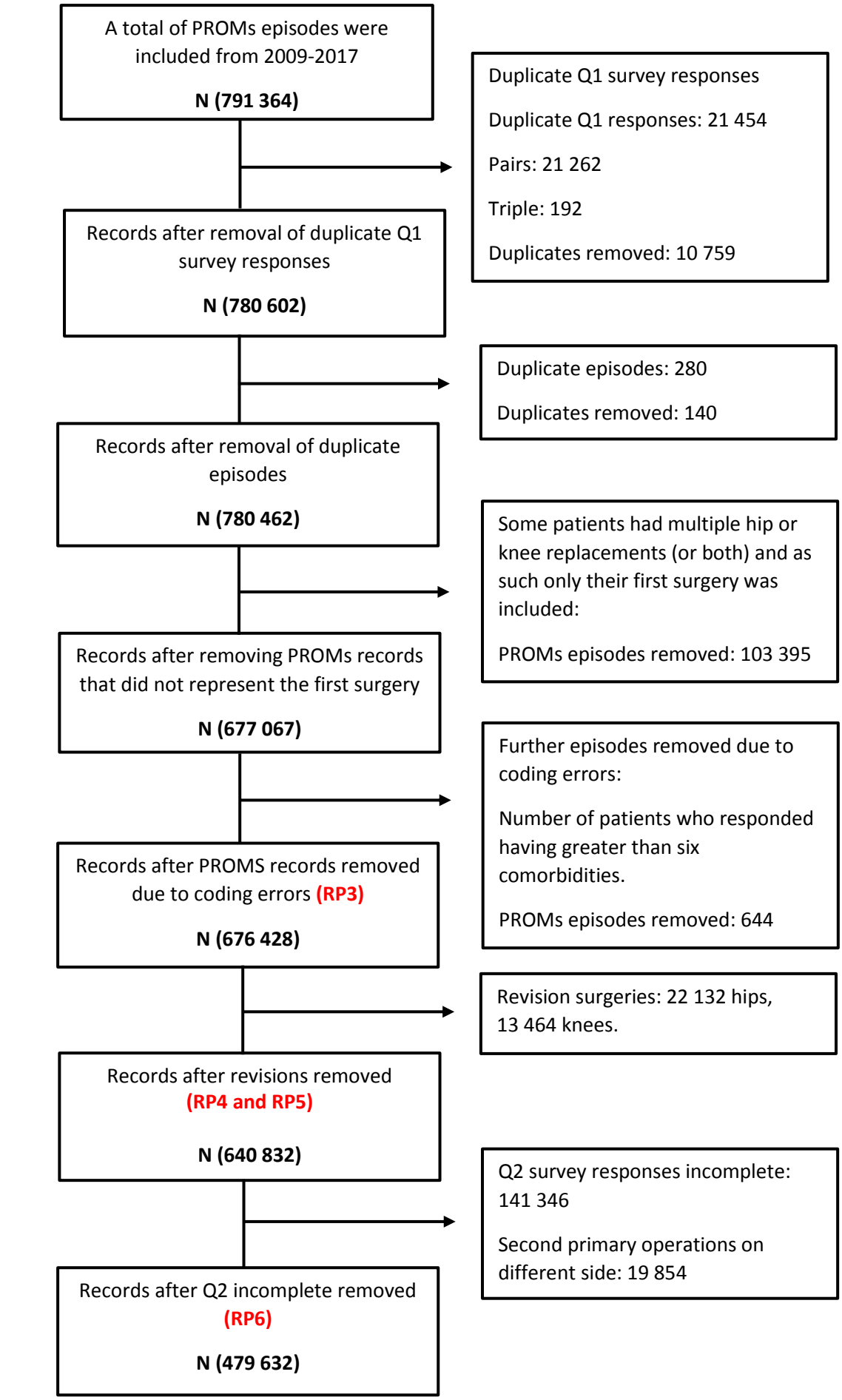
We investigated the number of second primary operations that occurred within the timeframe of index admission discharge and the Q2 questionnaire completion date. Second primary operations on a different joint or side might impact on the Q2 reports of severity of symptoms and quality of life so we wanted to remove any patients who had a second primary operation in this timeframe.

Second primary on same joint and side were not removed as they were suspected to be miscoded primary surgeries that may be revision surgeries. Similarly, revisions were not removed as they are an outcome of interest.

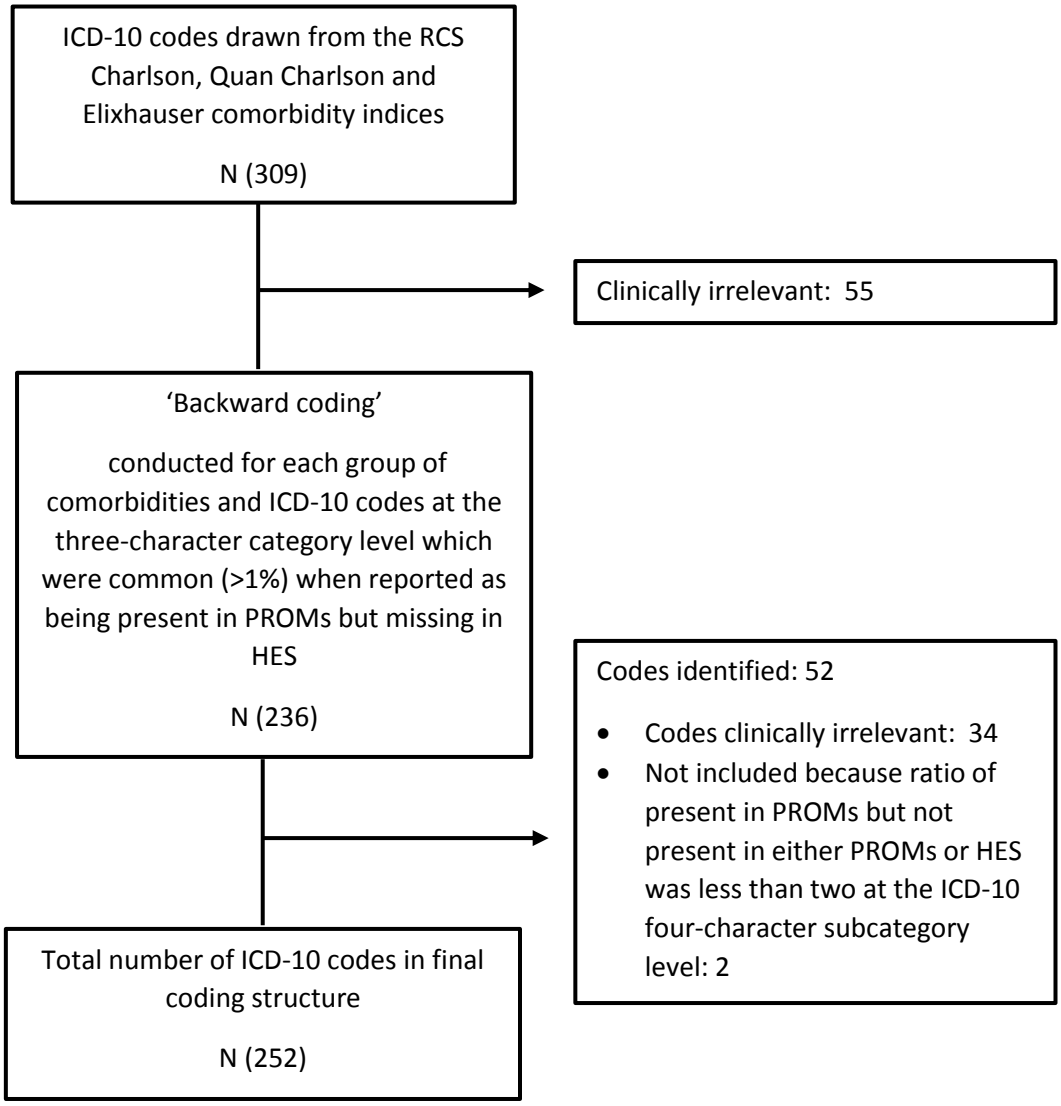
Table 8 – The number of second primary procedures before the Q2 questionnaire completion date for both hip and knee replacement surgery.

Type	**Number (%)**
Second Primary on same joint and side	1 246 (0.25)
Second Primary on different joint or side	**19 854 (3.97)**
Revision on the same joint and side	641 (0.13)
Revisions on different joint or side	3 695 (0.74)

12.10.4.7 Flow chart of overall data cleaning



12.10.5 Derivation of the comorbidity categories in HES



12.10.6 Derivation of Indicators

12.10.6.1 PROMs

Patient-reported comorbidities

Patients are asked if they "Have you ever been told by a doctor that you have any of the following?"

- Cancer in the last five years
- Leg pain when walking due to poor circulation
- Depression
- Diabetes
- Heart Disease (for example angina, heart attack or heart failure)
- High Blood Pressure
- Kidney Disease
- Liver Disease
- Lung Disease (for example asthma, chronic bronchitis or emphysema)
- Diseases of the Nervous System (for example Parkinson's disease or multiple sclerosis)
- Problems caused by stroke

Severity of joint problems

PROMs fields: hr_q1/q2 and kr_q1/q2

We used a previously validated approach by Neuburger et al. to measure disease severity. We used the Oxford Hip Score (OHS) and the Oxford Knee Score (OKS) as our measures of severity of joint problems just before surgery. These are derived from patient responses to 12 questions about pain and limits on physical functioning and everyday activities caused by the hip or the knee (Box 1 and 2). Responses to each question are measured on a five-point scale, and values associated with each response are added up to produce an overall scale from 0 (worst) to 48 (best). Both instruments have been shown to be internally consistent, reliable and to correlate with surgeon assessed measures of symptoms.

OHS	
During the past 4 weeks…	**PROMs field**
1. How would you describe the pain you usually have from your hip?	hr_q1_pain
2. Have you had any trouble washing and drying yourself (all over) because of your hip?	hr_q1_washing
3. Have you had any trouble getting in or out of care or using public transport because of your hip?	hr_q1_transport
4. Have you been able to put on a pair of socks, stockings or tights?	hr_q1_dressing
5. Could you do the household shopping on our own?	hr_q1_shopping
6. For how long have you been able to walk before pain from your hip becomes severe? (with or without a stick)	hr_q1_walking
7. Have you been able to climb a flight of stairs?	hr_q1_stairs
8. After a meal how painful has it been for our to stand up from a chair because of your hip?	hr_q1_standing
9. Have you been limping when walking, because of your hip?	hr_q1_limping
10. Have you had any sudden, severe pain –'shooting, 'stabbing' or 'spasms' – from the affected hip?	hr_q1_sudden_pain
11. How much has pain from your hip interfered with your usual work (including housework)?	hr_q1_work
12. Have you been troubled by pain from your hip in bed at night?	hr_q1_night_pain

OKS	
During the past 4 weeks…	**PROMs field**
1. How would you describe the pain you usually have from your knee?	kr_q1_pain
2. Have you had any trouble washing and drying yourself (all over) because of your knee?	kr_q1_washing
3. Have you had any trouble getting in or out of care or using public transport because of your knee?	kr_q1_transport
4. For how long have you been able to walk before pain from your knee becomes severe? (with or without a stick)	kr_q1_walking
5. After a meal how painful has it been for our to stand up from a chair because of your knee?	kr_q1_standing
6. Have you been limping when walking, because of your hip?	kr_q1_limping
7. Could you kneel down and get up again afterwards?	kr_q1_kneeling
8. Have you been troubled by pain from your knee in bed at night?	kr_q1_night_pain
9. How much has pain from your knee interfered with your usual work (including housework)?	kr_q1_work
10. Have you felt that your knee might suddenly 'give way' or let you down?	kr_q1_confidence
11. Could you do the household shopping on your own?	kr_q1_shopping
12. Could you walk down one flight of stairs?	kr_q1_stairs

Duration of symptoms

PROMs field: q1_symptom_period

A categorical measure of symptom duration was derived from responses to a single question asking patients how long they had experienced problems with the hip or the knee on which they were about to have surgery. Four response categories included: 'Less than 1 year'; '1–5 years'; '6–10 years' and 'More than 10 years'. We defined longstanding problems as durations of symptoms of more than 5 years, but our results were robust to an alternative cut-off of 10 years

EQ-5D score

PROMs field: q1/q2_eq5d_index

The EQ-5D Index score derived from the EQ-5D profile. For every '2' or '3' present a fraction is deducted, the lower the score the worse the patient reported on the EQ-5D questions. The value is between -0.594 and 1 with 0 representing 'death'.

No overall improvement

PROMs field: q2_success

Patients are asked if overall, 'how are your problems now, compared to before your operation?'. Five response categories included: 'Much better', ' A little better', 'About the same', 'A little worse', 'Much worse'. No improvement was defined as responses of 'about the same' or worse.

Patient satisfaction

PROMs field: q2_satisfaction

Patients are asked 'How would you describe the results of your operation?'. Five categories of responses for describing the results of the operation were 'Excellent', 'Very Good', 'Good', 'Fair' and 'Poor'. A binary variable was derived, giving a '1' if patients described their results as only 'Fair' or 'Poor'.

Patient-reported complications

PROMs field: q2_wound, q2_bleeding

Patients are asked: 'Did you experience any of the following problems after your operation: Wound problems? Bleeding?' A binary variable was derived whereby '1' indicates a wound problem or bleeding after hip or knee replacement.

Readmissions

PRO*Ms field:* q2_readmitted

Patients are asked: 'Have you been readmitted to hospital since your operation?' A binary variable was derived whereby '1' indicate a readmission in six months after the hip or knee replacement.

12.10.6.2 HES

Ethnicity

HES field: Ethnos

Ethnicity was recoded into six groups

- White/White British
- Mixed background
- Asian/British Asian
- Black/Black British
- Chinese and Other
- Not stated or missing

Sex

HES field: sex/ PROMs field: Gender

The HES field was more complete than the PROMs field and therefore the HES field was chosen as the primary variable. If a patient's sex was recorded as either 'Unknown' or 'Not stated' in HES then their PROMs record was searched to see if a gender was reported.

IMD deprivation

HES field: imd04_decile

The HES field was recoded into five deprivation groups based on the IMD deciles.

- IMD group 1 = Least deprived 10% + less deprived 10-20%
- IMD group 2 = Least deprived 20-30% + less deprived 30-40%
- IMD group 3 = Less deprived 40-50% + more deprived 10-20%
- IMD group 4 = More deprived 20-30% + more deprived 30-40%
- IMD group 5 = More deprived 40-50% + Most deprived 10%

Emergency readmissions in 30 days

HES field: admimeth

All emergency readmissions in 30 days (readmissions after the index discharge date and 30 days later) were identified. Emergency readmissions were then tagged if the admission method started with a "2" (any emergency admission).

Critical Care

HES field: tretspef

The treatment speciality variable (available since 1989-90 onwards) identifies critical care or also known as Intensive Care Medicine as a treatment specialty. Any patients with a critical care episode in their index admission were tagged as having entered critical care.

Length of stay

HES field: disdate, disreadydate

Length of stay was derived from originally calculating the time between the index operation date and the index discharge date or if available to the discharge ready date. A binary variable was derived for patients with a length of stay greater than the 50th percentile (>8 days) of patients who need further care.

Second episodes of care

HES field: epiorder, tretspef

Second episodes of care was derived from the whether a patient had a second episode of care in the index admission. Half the patients had a second episode of care in the same specialty and others transferred to other specialties.

12.10.6.3 ONS

30-day/90-day mortality

ONS field: date of death (dod)

30-day and 90-day mortality was derived from the difference between the date of death and index procedure date. 12 death dates were a day before the index date but this may be due to recording error and were therefore included in the analysis. 90 dates of death were excluded as they were several years before the index procedure date.