The impact of frailty on outcomes following hip and knee arthroplasty

A thesis submitted to the University of Manchester for the degree of Doctor of Philosophy in the Faculty of Biology, Medicine and Health

2022

Michael J Cook

School of Biological Sciences

Division of Musculoskeletal & Dermatological Sciences

Contents

List of tables 5
List of supplementary tables 6
List of figures 6
List of supplementary figures 7
List of abbreviations 7
Abstract 10
Declaration 11
Copyright statement 11
Acknowledgements 12
Preface 12
Role of the candidate in this PhD 13
Rationale for alternative format 13

Chapter 1. Introduction and background 14

1.1. Overview of thesis 14
1.2. Frailty 15
1.2.1. Definition 15
1.2.2. Classification and frailty models 16
1.2.3. Epidemiology of frailty 19
1.2.4. Summary 24

1.3. Osteoarthritis 24
1.3.1. Definition 25
1.3.2. Clinical diagnosis 25
1.3.3. Radiographic assessment 25
1.3.4. Epidemiology of osteoarthritis 25
1.3.5. Impact 28
1.3.6. Management of osteoarthritis 29
1.3.7. Summary 30

1.4. Hip and knee arthroplasty 30
1.4.1. Surgical process, preparation and recovery 30
1.4.2. Occurrence and secular trend 31
1.4.3. Factors affecting the likelihood of receiving hip and knee arthroplasty 32
1.4.4. Outcomes following total hip and knee arthroplasty 35
1.4.5. Factors affecting outcomes following hip and knee arthroplasty 39
1.4.6. Summary 44

1.5. The impact of frailty on outcomes of total hip and knee arthroplasty 44
1.5.1. Search strategy and inclusion and exclusion criteria 44
1.5.2. Overview of studies identified by the literature search 46
1.5.3. Identification of frailty 47
1.5.4. The association between frailty and short-term mortality following hip and knee arthroplasty 50

1.5.5. The association between frailty and patient-reported outcomes following hip and knee arthroplasty 57
1.5.6. The impact of frailty on other outcomes following hip and knee arthroplasty 62
1.5.7. Summary 62

Chapter 2. Aims and objectives 64

2.1. Aim 64
2.2. Specific objectives 64

Chapter 3. Methods 65

3.1. Overview 65
3.2. Study participants and setting 65
3.3. Data sources 65
3.3.1. Overview 65
3.3.2. The Clinical Practice Research Datalink 65
3.3.3. Linked datasets 67
3.3.4. Clinical coding in the clinical practice research datalink 69
3.3.5. Mapping between coding systems 69
3.4. Data access and ethics 69
3.5. Data management 70
3.6. Summary 70
3.7. Exposures and outcomes 71
3.7.1. Overview 71
3.7.2. Assessment of frailty – the electronic frailty index 71
3.7.3. Identification of hip and knee arthroplasty 75
3.7.4. Identification of hip and knee osteoarthritis 75
3.7.5. Patient-reported outcome measures 76
3.7.6. Identification of mortality 77
3.7.7. Identification of neighbourhood deprivation – the index of multiple deprivation 77
3.7.8. Identification of covariates 77
3.8. Statistical analysis 79
3.8.1. Statistical analysis – objective 1 79
3.8.2. Statistical analysis – objective 2 82
3.8.3. Statistical analysis – objective 3 84

Chapter 4. The impact of frailty on short-term mortality following primary total hip and knee arthroplasty due to osteoarthritis 87

4.1. Abstract 87
4.2. Background 88
4.3. Methods 89
4.3.1. Data sources 89
4.3.2. Assessment of frailty 89
4.3.3. Identification of THA and TKA 89
4.3.4. Identification of hip and knee OA 90
4.3.5. Statistical analysis 90

4.4. Results 92
4.4.1. Participants 92
4.4.2. Crude 30-, 60- and 90-day mortality following THA and TKA 93
4.4.3. Influence of frailty on short-term mortality following THA and TKA 95
4.4.4. Influence of total hip and knee arthroplasty on short-term mortality 98

4.5. Discussion 100
4.6. Supplementary data 103

Chapter 5. The impact of frailty on patient-reported outcomes following hip and knee arthroplasty 109

5.1. Abstract 109
5.2. Background 109
5.3. Methods 110
5.3.1. Data 110
5.3.2. Assessment of frailty 111
5.3.3. Assessment of patient-reported outcomes 111
5.3.4. The Oxford hip and knee scores 112
5.3.5. Patient-reported success 112
5.3.6. Covariates 112
5.3.7. Statistical analysis 113

5.4. Results 114
5.4.1. Patient characteristics 114
5.4.2. Association between frailty, preoperative, postoperative and change in Oxford hip and knee scores 115

5.5. Discussion 120
5.6. Supplementary data 123

Chapter 6. The impact of total hip and knee arthroplasty on the trajectory of frailty 129

6.1. Abstract 129
6.2. Background 130
6.3. Methods 131
6.3.1. Data sources 131
6.3.2. Assessment of frailty 131
6.3.3. Identification of THA and TKA 132
6.3.4. Covariates 132
6.3.5. Study cohort and follow up period 132
6.3.6. Statistical analysis 133

6.4. Results 134
6.4.1. Participants 134
6.4.2. Change in electronic frailty index before and after hip and knee arthroplasty 134

6.5. Discussion 138
6.6. Supplementary data 141

Chapter 7.Discussion 146

7.1. Overview 146
7.2. Summary of key findings 146
7.2.1. Short-term mortality 146
7.2.2. Patient-reported outcomes 147
7.2.3. Frailty trajectory 147

7.3. Strengths and limitations 148
7.4. Clinical implications 151
7.5. Future work 151
7.6. Conclusions 153

References 154

Word count: 34,647

List of tables

Table 1.1. Literature search strategy 46

Table 1.2. Studies examining the association between frailty and mortality up to 90 days following hip or knee arthroplasty 54

Table 1.3. Studies examining the association between frailty and patient-reported outcomes 60

Table 3.1. Deficits included in the eFI 74

Table 3.2. Read codes used to identify (A) hip osteoarthritis and (B) knee osteoarthritis 76

Table 4.1. Patient characteristics 92

Table 4.2. Crude mortality at 30, 60, and 90 days following total hip arthroplasty and total knee arthroplasty 94

Table 4.3. Hazard ratio for 30-, 60-, and 90-day mortality by frailty category among people who had a total hip arthroplasty or total knee arthroplasty 96

Table 4.4. Predicted probability of 30-day mortality following hip and knee arthroplasty in men and women, by age and frailty 97

Table 4.5. Hazard ratio for 30-, 60-, and 90-day mortality among cases compared to controls, by frailty category 99

Table 5.1. Participant characteristics 115

Table 5.2. Preoperative, postoperative and absolute change in Oxford hip and knee scores by frailty category 116

Table 5.3. Association between frailty category and postoperative Oxford hip and knee scores 117

Table 5.4. Proportion and odds ratio of achieving minimally important change in Oxford hip and knee scores and reporting a successful outcome, by frailty category 119

Table 6.1. Participant characteristics at study entry 134

Table 6.2. Rate of change in eFI before and after total hip and knee arthroplasty from linear spline model 137

List of supplementary tables

Supplementary Table 4.1. Cause-specific 30-day mortality among cases and controls 103

Supplementary Table 4.2. Mean eFI by frailty strata among cases and controls 104

Supplementary Table 4.3. Hazard ratio for 30-, 60-, and 90-day mortality among cases compared to controls, by frailty category, adjusted for eFI as a continuous variable 104

Supplementary Table 4.4. Hazard ratio for 30-, 60-, and 90-day mortality among cases compared to controls, by frailty category, adjusting for each of the individual eFI deficits 105

Supplementary Table 4.5. Subhazard ratio for 30-, 60-, and 90-day mortality (deaths not due to neoplasms) among cases compared to controls, by frailty category 105

Supplementary Table 5.1. Patient characteristics of those included in the analysis of the Oxford hip and knee scores and those excluded due to missing data 123

Supplementary Table 5.2. Association between frailty category and absolute change in Oxford hip and knee scores 125

Supplementary Table 5.3. Preoperative, postoperative, and absolute change in Oxford hip and knee pain subscore by frailty category 125

Supplementary Table 5.4. Association between frailty category and postoperative Oxford hip and knee pain subscores 126

Supplementary Table 6.1. Rate of change in eFI before and after total hip and knee arthroplasty from linear spline model, including interaction terms between sex and time and fifth of IMD and time . 141

List of figures

Figure 3.1. Illustration of the impact of a ceiling effect on regression modelling 83

Figure 3.2. Linear spline with knots at *a* and *b* 85

Figure 6.1. Linear spline trajectories of the electronic frailty index before and after (A) total hip arthroplasty and (B) total knee arthroplasty 136

List of supplementary figures

Supplementary Figure 4.1. Hazard function in the 90-day period following hip arthroplasty (A) and knee arthroplasty (B) 106

Supplementary Figure 5.1. Patient flow diagram 127

Supplementary Figure 6.1. Follow up period 143

Supplementary Figure 6.2. Participant flow diagram 144

Supplementary Figure 6.3. Cubic spline trajectories of the electronic frailty index before and after (A) total hip arthroplasty and (B) total knee arthroplasty 145

List of abbreviations

ASR	Age-standardised rate
BMI	Body mass index
CGA	Comprehensive geriatric assessment
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
CPRD	Clinical practice research datalink
CSHA	Canadian study of health and ageing
CTV3	Clinical terms version 3
DVT	Deep vein thrombosis
eFI	Electronic frailty index
EMIS	Egton Medical Information Systems
EMR	Electronic medical record
EQ-5D	EuroQol-5 dimension
FI	Frailty index
GDP	Gross domestic product
GFI	Groningen frailty indicator
HES	Hospital episode statistics
HHS	Harris hip score
HKASS	Hip and knee arthroplasty satisfaction scale
HOOS	Hip disability osteoarthritis outcome score
HR	Hazard ratio
ICD	International classification of diseases
IMD	Index of multiple deprivation
IQR	Inter-quartile range

ISAC	Independent scientific advisory committee
KOOS	Knee disability osteoarthritis outcome score
LOAS	Longitudinal orthopaedics outcomes of osteoarthritis study
LP	Linear prediction
MeSH	Medical Subject Headings
mFI	Modified frailty index
mFI-5	Modified frailty index 5 components
mFI-11	Modified frailty index 11 components
MI	Myocardial infarction
MIC	Minimally important change
NHS	National health service
NICE	National institute for health and care excellence
NIHR	National institute for health and care research
NJR	National joint registry
NSQIP	National surgical quality improvement programme
OA	Osteoarthritis
OHS	Oxford hip score
OKS	Oxford knee score
ONS	Office for national statistics
OPCS	Office of population, census and surveys classification
OR	Odds ratio
PROMs	Patient-reported outcome measures
ROC	Receiver operating characteristic
SD	Standard deviation
SF	Short-form
SNOMED-CT	Systematized nomenclature of medicine clinical terms
THA	Total hip arthroplasty
THIN	The health improvement network
TJA	Total joint arthroplasty
TKA	Total knee arthroplasty
TPP	The phoenix partnership
UK	United Kingdom
USA	United States of America
VAS	Visual analogue scale

WOMAC Western Ontario and McMaster Universities

Abstract

Aim: The broad aim of this thesis was to investigate the impact of frailty on outcomes following total hip and knee arthroplasty (THA and TKA). The outcomes considered were short-term mortality, patient-reported outcomes (PROMs) and frailty trajectories.

Methods: Databases of primary and secondary care electronic medical records from England and linked mortality records were used. Frailty was assessed using the validated electronic frailty index (eFI) and categorised as fit (eFI≤0.12), mild (0.12<eFI≤0.24), moderate (0.24<eFI≤0.36), and severe frailty (eFI>0.36). PROMs were assessed using the Oxford hip and knee scores (OHS and OKS) and patient-reported success. The association between frailty and (i) short-term mortality and (ii) PROMs following THA and TKA were assessed using multivariable regression models, with year of birth, sex, year of surgery, and quintile of index of multiple deprivation included as covariates. The rate of change in eFI in the period up to two years before THA and TKA and up to two years after THA and TKA was assessed using random effects models with linear splines.

Results: Increasing frailty was associated with increasing 30-day mortality following THA and TKA in a multivariable model. Crude 30-day mortality following THA and TKA, respectively increased from 0.25% and 0.16% among those who were fit to 0.85% and 0.44% among those with severe frailty. Increasing frailty was also associated with lower postoperative OHS and OKS (indicating worse outcomes) in a multivariable model, which persisted after adjustment for preoperative score. Patient-reported success following hip and knee arthroplasty, respectively decreased from 97% and 93% among fit individuals to 90% and 83% among those with severe frailty. The association between increasing frailty and reduced likelihood of patient-reported success persisted in a multivariable model. In a multivariable random effects model, the rate of increase in the eFI (95% CI) in the period before THA and TKA, respectively was 0.025 (0.024, 0.025) and 0.025 (0.025, 0.025) units per year. The rate of increase in the eFI in the period after THA and TKA, respectively was statistically significantly lower than the preoperative increase, by -0.0036 (-0.0041, -0.0032) and -0.0030 (-0.0034, -0.0026) units per year.

Conclusion: Frailty was associated with higher short-term mortality and poorer PROMs following THA and TKA. However, even among those with severe frailty, crude 30-day mortality following THA and TKA was less than 1% and more than 80% of patients reported a successful outcome. The results are consistent with a modest beneficial impact of THA and TKA on the rate of progression of frailty.

Declaration

No portion of the work referred to in the thesis has been submitted in support of an application for another degree or qualification of this or any other university or other institute of learning.

Copyright statement

Acknowledgements

I am grateful to my PhD supervisors: Professor Terry O'Neill, Dr Mark Lunt, and Professor Tim Board for their advice and mentorship throughout my PhD and for supporting my fellowship application. Thanks to Dr Steve Pye and Professor Andy Clegg for their advice on the implementation of the electronic frailty index. I am grateful to Professor Chris Todd for acting as my PhD advisor and for encouragement and support in preparing for my fellowship application.

I am grateful for the training and opportunities that were available to me during my time at the Versus Arthritis Centre for Epidemiology. Thank you to Professor Suzanne Verstappen and Professor Deborah Symmons for their mentorship and advice during my time at the Centre for Epidemiology and for guiding me through my first research projects.

Thank you to the friends that I have met over the years at the Centre for Epidemiology, in particular Ruth Costello, Therese Sheppard, Kamilla Kopec-Harding, and Roze Witkam.

I am grateful to the National Institute for Health and Care Research for funding my doctoral fellowship.

Thank you to my family for their love and support, and for looking after me during difficult times.

Preface

I graduated from the University of Manchester with a BSc (Hons.) in mathematics in 2005. I then worked in a number of roles at Warrington Borough Council, including as a data analyst supporting the adult social care division. My interest in health research led me to pursue an academic career and in 2014, I was appointed as a research assistant in the Centre for Epidemiology Versus Arthritis at the University of Manchester (formerly the Arthritis Research UK Centre for Epidemiology). In 2015, I graduated with an MSc in computing from Liverpool John Moores University, which I had studied for on a part-time basis around my employment. While working as a research assistant, I was involved in a number of research projects, including a project looking at frailty and bone health in the European Male Ageing study. This led me to develop an interest in ageing, frailty and musculoskeletal health. My ambition to progress in an academic research career and to

pursue my interests motivated me to apply for a National Institute for Health and Care Research (NIHR) doctoral research fellowship, which commenced in 2019. This thesis is the product of my NIHR doctoral research fellowship.

Role of the candidate in this PhD

I was responsible or the following aspects of this PhD:

- Development of research ideas, research methods and statistical analysis plan
- Writing an NIHR Doctoral Fellowship application
- Writing the application to the Independent Scientific Advisory Committee (ISAC) to access data from the Clinical Practice Research Datalink (CPRD)
- Obtaining data from the CPRD and preparing the data for analysis
- Statistical analysis
- Interpretation of results
- Presenting work at national and international scientific meetings
- Writing research papers for publication
- Writing this PhD thesis

Rationale for alternative format

This thesis is presented in the alternative format, with self-contained journal style papers making up each of the results chapters. The rationale for this choice of format is that the three objectives of this thesis correspond to three related but distinct research questions which were suitable for presentation as self-contained research papers. In addition, two of the results chapters have been accepted for publication in the Journal Age and Ageing and it is anticipated that the third results chapter will be submitted to a journal for publication.

Chapter 1. Introduction and background

1.1. Overview of thesis

The broad aim of this thesis is to determine the impact of frailty on outcomes following total hip arthroplasty (THA) and total knee arthroplasty (TKA). THA and TKA are surgical procedures which involve the construction of a new prosthetic moveable hip/knee joint and are most commonly carried out to treat the joint disease osteoarthritis. This thesis presents a summary of the existing literature relevant to this aim, outlines the methodology used to address the aim; presents the results of the original research; and discusses the interpretation of the results in the context of previous research and implications for clinical practice. The contents of the chapters are briefly described below.

The following sections of Chapter 1 provide a background to the thesis, including an introduction to the concept of frailty; a brief overview of osteoarthritis (OA) (the primary indication for THA and TKA), including a definition, overview of the epidemiology of OA, and management of OA; and an introduction to THA and TKA, including occurrence, factors affecting the likelihood of receiving THA and TKA and outcomes of THA and TKA. A summary of the previous literature relating to the impact of frailty on outcomes following THA and TKA is also included and gaps in the literature are highlighted.

Chapter 2 sets out the broad aim and specific objectives of the thesis.

Chapter 3 describes the methods and data used in the analysis, including a description of the data sources, definitions of exposures, outcomes, and covariates, as well as an overview of the statistical methods used.

Chapter 4, Chapter 5, and Chapter 6 contain the results of original research, each relating to one of the thesis objectives. This thesis is presented in a journal format, with each of the three results chapters presented as stand-alone research papers, including background, methods, results, and discussion sections.

Finally, Chapter 7 summarises the main findings, discusses the strengths and limitations of the analysis, and also the relevance of the research to clinical practice. Potential areas for future research are also discussed.

The broad aim of this thesis was to determine the impact of frailty on outcomes following THA and TKA. This chapter introduces key concepts central to this aim, including a definition of frailty, an overview of the epidemiology of frailty, and a description of commonly used frailty models. A definition of OA (the primary indication for THA and TKA) is provided and brief descriptions of the epidemiology, impact, and management of OA are included. This is followed by an overview of THA and TKA, and a review of data on the occurrence of THA and TKA and factors affecting the likelihood of THA and TKA. Following this, the literature looking at the impact of frailty on outcomes of THA and TKA is reviewed, with a focus on short-term mortality and patient-reported function and gaps in the literature highlighted.

1.2. Frailty

This section provides an overview of clinical frailty including a definition, operational classification, and models of frailty. The epidemiology of frailty, including occurrence, determinants, and outcomes is also reviewed.

1.2.1. Definition

Frailty is a widely recognised clinical syndrome, particularly affecting older adults, and is linked with a variety of adverse health outcomes. Although widely recognised, there is, however, currently no universally accepted definition of frailty. A number of definitions have been proposed and are in widespread use (1). An international consensus group proposed that frailty is "a medical syndrome with multiple causes and contributors that is characterised by diminished strength, endurance, and reduced physiologic function that increases an individual's vulnerability for developing increased dependency and/or death" (2). Frailty has been described also by Fried and colleagues, as an accumulation of deficits affecting multiple physiologic systems leading to reduced physiologic reserve and reduced ability to maintain homeostasis following a biological stressor (3). Both

definitions convey a core feature of the frailty syndrome, which is vulnerability, or susceptibility, to adverse outcomes.

1.2.2. Classification and frailty models

1.2.2.1. The phenotypic model of frailty

The physical frailty phenotype model developed by Fried and colleagues operationalises frailty as a biological syndrome (4) and captures key domains of the frail state: unintentional weight loss, weakness, low activity, exhaustion and slowness. It was developed as a classification tool using data from the Cardiovascular Health Study; a prospective, observational study of men and women aged 65 years and older in the United States (4). Threshold values for each of the five components of the Fried phenotype have been defined: unintentional weight loss (>10 lbs in the prior year by direct measurement of weight, though some subsequent studies have used self-reported unintentional weight loss), weakness (hand grip strength in lowest 20% of the cohort by gender and body mass index), self-reported exhaustion, slowness (time to walk 15 feet in slowest 20% of the cohort by gender and height), and low activity (Kcals/week in lowest 20% of the cohort, determined based on self-reported activity in the Minnesota Leisure Time Activities Questionnaire) (4). Individuals are categorised as “not frail” if no criteria are present, “intermediate” or “pre-frail” if 1-2 criteria are present, and “frail” if 3 or more criteria are present. The frailty phenotype has been shown to have the characteristics of a clinical syndrome; there are no distinct subsets of the criteria that cluster together, rather the presence of any three (to five) of the criteria predict adverse health outcomes more than any one or two criteria (5, 6). Early manifestations of frailty are declines in muscle strength, walking speed and/or physical activity (6, 7). The frailty phenotype has been validated and is widely used in research (8).

Many studies have applied modifications of the frailty phenotype to different datasets. The frailty phenotype appears to be robust to small modifications to definitions of its components, though modifications do have an impact on the properties of the phenotype, including its ability to predict adverse outcomes (9).

1.2.2.2. Frailty indices

A frailty index (FI) is based on a deficit accumulation model of frailty; deficits are accumulated with increasing age and the greater the number of deficits accumulated, the

higher the likelihood of frailty (10). The cumulative deficit model views frailty as a dynamic, stochastic process in complex organisms with interdependent systems and high physiological redundancy (11). As deficits are accumulated, physiological redundancy reduces and the complex biological, interdependent systems become more vulnerable to stressors. The model was developed by Rockwood and colleagues who operationalised frailty using 38 binary variables that measured health or disability in the National Population Health Survey of Canada (12). The model is robust, however, and not dependent on individual health deficits included in the index, allowing for widespread application. Unlike the frailty phenotype, frailty indices do not comprise fixed components. Rockwood and colleagues have provided details of a standard procedure for the identification of variables suitable for inclusion in a frailty index (13). To be included as a deficit in a frailty index, a variable must satisfy key criteria: (i) be associated with health status, (ii) to increase in prevalence with age, and (iii) must not saturate too early (i.e. must not become common before older age, such as age-related changes in the lens of the eye (presbyopia) (13). In addition, the resulting FI must cover a range of physiological systems and if the FI is to be applied serially on the same people, the deficits included in the FI must be the same at each assessment. The FI is calculated by dividing the total number of deficits present in an individual, by the total number of deficits considered. For example if 40 deficits were assessed in total and 10 deficits are present in an individual, their FI would be 10/40 = 0.25. Since the original description a number of frailty indices have been developed in different settings and different studies. Although theoretically the FI ranges from 0 to 1, based on research from a large number of studies a sub-maximal limit of around 0.7 has been observed (14).

Previous studies confirm that the specific deficits included in a frailty index do not appear to be important, provided they meet the inclusion criteria outlined earlier (15). The aggregate expression of health deficits across multiple systems represent a reduced physiological reserve and increased risk of adverse outcomes. One study randomly selected 37 variables for inclusion in a FI, taken from a set of 70 possible deficits and used Cox regression to estimate the association between the FI and mortality up to 5-years (15). The analysis was repeated up to 1,000 times, selecting a random subset of 37 deficits each time. From these analyses, it was estimated that the hazard ratio (HR) for 5-year mortality that would be estimated if 10 different FIs were used would range from 1.25 (95% confidence interval (CI), 1.20, 1.30) to 1.31 (1.25, 1.37). The HR for 5-year mortality using all 70 deficits in the FI was 1.29 (1.23, 1.35). Although the specific deficits included

in a FI are not important, it has been suggested that a sufficient number of deficits is needed. A minimum of 30 deficits has been shown to produce a FI with good ability to predict adverse outcomes (16).

Unlike the frailty phenotype, the FI provides a continuous measure, which may be more sensitive to measuring change in frailty state. Population-based studies suggest that individuals accumulate an average of 0.03 deficits per year beyond the age of 70 years (17).

1.2.2.3. Electronic frailty indices

Although frailty indices were developed primarily for use in a research setting, using data collected as part of a research study, the cumulative deficit approach has been used to derive frailty indices in both primary and secondary care clinical databases using a standard procedure, allowing for widespread use in both research and clinical practice (13).

In the UK, an electronic FI (eFI) has been developed using routinely collected primary care electronic medical records (EMRs) and is described in more detail in section 3.7.2 (18).

There are important factors to consider, however, when using primary and also secondary care EMRs to assess for frailty using a FI. Unlike studies that have collected data specifically for research purposes, frailty indices constructed from EMR data are based on routine interactions with primary care and therefore may be influenced by variation in clinical practice, coding practice, and by individual patient healthcare utilisation. Notwithstanding these potential limitations, it has been demonstrated that a FI based on EMRs in both primary and secondary care settings have utility in predicting adverse health outcomes (18-20).

1.2.2.4. Clinical frailty tools

While the frailty phenotype and frailty index have proved useful models of frailty in research studies, they may have limited utility in clinical practice due to the data and time required to implement them. A number of simple and rapidly applicable clinical frailty screening tools have been developed and validated, including the FRAIL questionnaire (21), the Gérontopôle Frailty Screening Tool (22), and the Clinical Frailty Scale (23). Each of these tools is designed to be easy to use and applicable in a clinical setting within a few

minutes. The FRAIL questionnaire and the Gérontopôle Frailty Screening Tool, respectively identify frailty based on 5 and 6 simple questions. The Clinical Frailty Scale comprises pictorial representations and short descriptions of nine degrees of frailty.

1.2.3. Epidemiology of frailty

1.2.3.1. Prevalence

A systematic review, which included studies from Europe, the US, Australia, Canada, and Taiwan, estimated the weighted prevalence of frailty in community-dwelling adults aged 65 or older to be 10.7% (95% CI), 10.5%, 10.9%) (24). Studies included in the review used different instruments to identify frailty, the most commonly used was the Fried frailty phenotype. There was evidence of variation in the occurrence of frailty in different regions and populations, which was thought in part to be due to technical artefacts including differences in study samples and also definitions of frailty used (24).

In a cohort study of 638 men and women aged 64 to 74 years in Hertfordshire, UK, which used a modified Fried phenotype definition, the prevalence of frailty was 8.5% among women and 4.1% in men (25). In another UK cohort of 5,450 men and women aged 60 and over, the English Longitudinal Study of Ageing, frailty was assessed using a modified Fried phenotype. The weighted prevalence of frailty was 14%, rising from 6.5% among those aged 60-69 to 65% among those aged 90 years or older (26).

The prevalence of frailty increases sharply with age beyond the age of 65 years and is higher among women compared to men at all ages (27-29).

1.2.3.2. Incidence and secular change

Longitudinal studies have suggested that frailty can improve within individuals, though that progression to a higher level of frailty is more likely (30-32). In a meta-analysis of 16 population based cohorts (33) which assessed frailty using the frailty phenotype, it was reported that 13.7% of individuals improved in their frailty status over a mean follow up of 3.9 years, 29.1% deteriorated, and 56.5% maintained the same frailty status.

Data from another systematic review and meta-analysis looked at the incidence of frailty, assessed using the frailty phenotype, with incidence defined as becoming frail from a non-frail or pre-frail state (34). In total, 46 studies, which included men and women aged 60 years or older at baseline from North America, Asia, Europe, Australia, and South America

were analysed. Among 120,805 people without frailty at baseline who survived a median follow up of 3.0 years (range 1.0 to 11.7 years), 13.6% became frail, resulting in a pooled incidence rate of frailty of 43.4 (95% CI, 37.3, 50.4) cases per 1,000 person-years (34).

Most studies looking at the progression of frailty have a relatively short follow up and data on the longer-term progression of frailty is limited. In a study from the Netherlands men and women aged 65 years and older were followed for a period of 17 years. Frailty was assessed using a FI (35). Mean FI score at baseline was 0.17, rising to 0.39 after 17 years, representing a doubling in the FI score after 12.6 years. The doubling time was similar among participants aged 65-74 years at baseline and those aged 75 years and older at baseline.

A few cohort studies have also assessed secular trends in the prevalence of frailty, with most (from the UK (36, 37), the US and Hong Kong (38)), showing a higher level of frailty in later birth cohorts compared to earlier birth cohorts. One study from Sweden, however, showed no difference in the mean value of frailty index in cohorts recruited 30 years apart (39). Data from England (36) and the UK (37) suggest a higher level of frailty among people of the same age in more recent cohorts compared to earlier cohorts, however, differences were apparent only among people aged ≥70 years (36).

1.2.3.3. Risk factors

Demographic and social factors

As noted previously, both increasing age and female sex are associated with the occurrence of frailty.

Socioeconomic factors, including lower income, have also been associated with a higher prevalence of frailty (28). Data from the US suggest that frailty is more prevalent among people of African-American ethnicity compared to White ethnicity (4, 5, 40), though it is not clear whether other factors, including socioeconomic status, may partially explain the increased risk among African-Americans.

Social factors, including social support, loneliness, and living alone have also been associated with increased frailty (41). Data from the English Longitudinal Study of Ageing, showed that higher (vs lower) levels of loneliness (assessed using the University of California, Los Angeles (UCLA) loneliness scale) were associated with an increased risk of

becoming pre-frail, relative risk ratio (95% CI), 1.74 (1.29, 2.34), or frail, relative risk ratio 1.85 (1.14, 2.99), according to the frailty phenotype during a 4 year follow up (42). A high level of loneliness was not, however, associated with change in FI. High social isolation (assessed based on data on living alone, frequency of contact with friends, family and children, and participation in social organisations) was associated with an increased risk of becoming frail in men, RRR (95% CI) 2.01 (1.00, 4.05), but not in the cohort overall (men and women) (42). Social isolation was not associated with change in frailty index (42).

Some studies have shown that a lower level of education may be associated with an increased risk of frailty, though other studies have found no association between education level and frailty (28).

Clinical factors

Multisystem physiological dysregulation, or allostatic load, and also comorbidity, are linked with an increased risk of incident frailty (43). In a cohort of 803 non-frail men and women aged 70-79, a summary score of allostatic load was calculated based on assessment of 13 biomarkers of cardiovascular, metabolic, and endocrine stress regulatory systems. For each participant, allostatic load summary score was calculated as the sum of biomarkers falling in the highest risk quartile of biomarker distribution. In a multivariable model, each 1-unit increase in allostatic load was associated with a 10% (95% CI, 3%. 19%) increased risk of incident frailty (assessed using the Fried frailty phenotype) during follow up (43).

Increased allostatic load is linked also with multimorbidity (the coexistence of multiple diseases and medical conditions in an individual) (44). The relationship between multimorbidity and frailty may be bi-directional, with multimorbidity increasing the risk of incident frailty and also frailty increasing the risk of multimorbidity (44).

Depressive symptoms have also been linked with an increased risk of incident or worsening frailty in longitudinal studies (28). In a systematic review and meta-analysis, the pooled odds ratio (95% CI) for incident frailty among those with depression, over a mean follow up of 2.9 years, was 3.72 (1.95, 7.08) (45).

Cross-sectional analysis of the UK Biobank also found a graded association between increasing number of morbidities in an individual and increasing risk of frailty (46).

Compared to individuals with no long-term conditions, individuals with one long-term condition had an increased risk of being frail (vs non-frail), according to a modified frailty phenotype, (OR (95% CI), 2.27 (2.12, 2.42)), rising to 27.1 (25.3, 29.1) among participants with 4 or more long term conditions. Specific morbidities, including multiple sclerosis, chronic fatigue syndrome, chronic obstructive pulmonary disease, diabetes, cardiovascular disease, and depression were also linked with an increased risk of pre-frailty and frailty in cross-sectional analysis (46). Depressive symptoms have also been linked with an increased risk of incident or worsening frailty in longitudinal studies (28).

Body mass index (BMI) has been linked with an increased risk of frailty, with being underweight (BMI<18.5 kg/m^2), overweight (25 kg/m^2≤BMI<30 kg/m^2), or obese (BMI>30 kg/m^2) associated with an increased risk, compared to BMI in the normal range (18.5 kg/m^2≤BMI<25 kg/m^2) (28). One longitudinal study of 40,657 women aged 65-79 at baseline found that a BMI of < 18.5 kg/m^2 (vs BMI 18.5 kg/m^2-24.9 kg/m^2) at baseline was associated with an increased risk of pre-frailty and frailty (assessed using a modified frailty phenotype), respectively 3 years later (OR (95% CI), 1.36 (1.03, 1.81) and 1.65 (1.11, 2.45)) (40). Similarly, a BMI of 25.0 kg/m^2- 29.9 kg/m^2 (vs BMI 18.5 kg/m^2-24.9 kg/m^2) at baseline was associated with an increased risk of incident pre-frailty and frailty, respectively, 1.36 (1.26, 1.46) and 1.92 (1.73, 2.13). Participants with a BMI ≥30 kg/m^2 (vs BMI 18.5 kg/m^2-24.9 kg/m^2) had the highest risk of incident pre-frailty and frailty, respectively, 2.04 (1.85, 2.24) and 3.95 (3.50, 4.47) (40).

The association between polypharmacy and frailty has been assessed in a systematic review (47). Sixteen out of the 18 cross-sectional studies included reported a significant positive association between increasing number of medications and increasing risk of frailty. Of the 7 longitudinal studies included, 5 reported a significant positive association between increasing number of medications and incident frailty (47). Whether an association between polypharmacy and frailty is causal, however, remains unclear. As has been shown in some studies looking at the association between multimorbidity and frailty, the association between polypharmacy and frailty appears to be bi-directional (47).

Other clinical risk factors for frailty have been identified, including nutritional factors and cognition. Both undernutrition and obesity have been linked with an increased risk of frailty, as well as specific dietary nutrients (48). Reduced protein intake among older

people may contribute to an imbalance between muscle protein synthesis and degradation (48), and contribute to an increased risk of frailty.

Micronutrients, including vitamins D, E, C and folate, have been associated with an increased risk of frailty in cross-sectional studies (49). One longitudinal study of community-dwelling women aged 65 years and older found that, compared to women in the upper three quartiles, those in the lowest quartile of serum carotenoids (HR (95%CI), 1.39 (1.01, 1.92)), α-tocopherol (HR (95% CI), 1.39 (1.02, 1.92)) and 25-hydroxyvitamin D (HR (95% CI), 1.34 (0.94, 1.90)) had an increased risk of becoming frail, according to the frailty phenotype, during a 3 year follow up (50).

Reduced cognitive function has also been positively associated with an increased risk of physical frailty (28). In one study, a mini mental state examination score of ≤23 was associated with increased odds of developing frailty in longitudinal analysis, with a follow up of up to 13 years in a multivariable model, OR (95% CI), 1.48 (1.06, 2.07) (51).

Biological factors

Inflammation

Ageing is associated with increased circulating inflammatory markers, even in the absence of clinical disease (52), a phenomenon that has been termed “inflammaging” (53). The association between circulating inflammatory markers and frailty have been assessed in cross-sectional and longitudinal cohort studies (54). A systematic review and meta-analysis of 32 cross-sectional studies (total of 23,800 participants) and 3 longitudinal studies with a median follow up of 3 years (total of 3,402 participants who were not frail at baseline), assessed the association between circulating inflammatory markers and frailty (54). A meta-analysis of cross-sectional studies showed that frail (vs robust) and pre-frail (vs robust) participants, respectively had higher levels of CRP (standardised mean difference (SMD) (95% CI), 1.00 (0.40, 1.61) and 0.33 (0.04, 0.62)), and also IL-6 (SMD (95% CI), 1.12 (0.27, 2.13) and 0.56 (0.00, 1.11)). In a meta-regression of the cross-sectional studies, age and BMI appeared to partially explain the association between CRP and frailty. However, in a meta-analysis of the three longitudinal studies identified, higher levels of serum CRP and IL-6, respectively were not statistically significantly associated with incident frailty after confounder adjustment, (OR (95% CI), 1.06 (0.78, 1.44)) and 1.19 (0.87, 1.62) (54).

Endocrine factors

Low bioavailable testosterone has been associated with an increased risk of prevalent frailty in cross-sectional studies among men and also women (55). Longitudinal studies have also assessed the association between testosterone and the risk of incident frailty (55). One study in men found that each standard deviation decrease in free testosterone was associated with increased odds of incident frailty, assessed using the FRAIL scale, during a mean follow up 5.3 years, OR (95% CI), 1.22 (1.05, 1.42) (56). Total testosterone, sex hormone binding globulin, and luteinising hormone was not associated with incident frailty (56).

Insulin-like growth factor 1 (IGF-1), a hormone which has anabolic effects in adults, has also been associated with worsening frailty. In one multicentre study of men in Europe, each 1 standard deviation increase in IGF-1 was associated with worsening frailty assessed using the frailty phenotype (OR (95% CI), 0.82 (0.73, 0.93)), and also a FI, percent change in FI (95%), -3.7% (-6.0%, -1.5%)), over a median follow up of 4.3 years (57).

1.2.4. Summary

Frailty is a widely recognised clinical syndrome primarily affecting older adults. Around 11% of adults over the age of 65 have evidence of frailty with the proportion affected increasing with age. A number of models of frailty have been proposed for use in research and clinical practice. Frailty indices, based on a deficit accumulation model of frailty, are one of the most commonly used models of frailty in research. Recently, frailty indices using routinely collected data from EMRs have been developed and are increasingly being used in research.

1.3. Osteoarthritis

The focus of this thesis is to determine the impact of frailty on outcomes following THA and TKA. Most of these procedures are undertaken for people with osteoarthritis (OA) in whom symptoms have persisted despite medical care. This section provides a brief overview of OA, including the definition, diagnosis, occurrence, risk factors, and management.

1.3.1. Definition

OA has been described by the Osteoarthritis Research Society International, as “a disorder involving moveable joints characterised by cell stress and extracellular matrix degradation initiated by micro- and macro-injury that activates maladaptive repair responses including pro-inflammatory pathways of innate immunity” (58).

1.3.2. Clinical diagnosis

A clinical diagnosis of OA is generally based on clinical examination and symptoms. Typical symptoms include pain, stiffness and loss of function. Signs of OA include bony swelling, tenderness and crepitus – a grating sensation on movement of the affected joint. A number of classification criteria have been developed which include combinations of symptoms, signs and also radiological changes. The European League Against Rheumatism (EULAR) and the American College of Rheumatology (ACR) have both published diagnostic criteria for knee OA (59).

1.3.3. Radiographic assessment

Osteoarthritis is characterised radiologically by the presence of joint space narrowing, new bone formation at the periphery of the joint (osteophytes) and also thickening of the subchondral bone (sclerosis). Radiologically, joints can be classified based on the severity of these features. The most widely used classification is the Kellgren-Lawrence scale, which provides a grading from 0 (no presence of OA) to 4 (severe OA), based on the radiographic features present in an individual (60).

1.3.4. Epidemiology of osteoarthritis

1.3.4.1. Prevalence and incidence

OA is the most common joint disorder worldwide. The most frequently affected joints are the hip, knee, hand, foot and spine, although OA can affect any joint. Estimates of prevalence vary depending on the definition of OA used, study setting, and composition of the study cohort. A systematic review of 63 studies reported that prevalence estimates of OA were significantly higher for radiographic OA (OA based on assessment of structural changes seen in imaging data), compared to symptomatic OA (OA based on symptoms, including pain and functional limitation). The prevalence of OA is higher among women

than men, particularly at the knee (59). One large study calculated the incidence of knee and hip OA during the period 2006-2010 among men and women aged 40 years or older using primary care data from Catalonia (61). The incidence of OA at both sites was higher among women than men, and increased sharply between the ages of 50-75 years, particularly for knee OA (61).

A study from the UK estimated the prevalence and incidence of OA (any site) among people aged 20 years or older during the period 1997 to 2017 using diagnostic codes recorded in primary care electronic medical records (the Clinical Practice Research Datalink) (62). The overall estimated prevalence of OA in 2017 was 12.8% (95% CI, 12.8, 12.9%) in women and 8.6% (8.5, 8.7%) in men. The prevalence of OA was higher in women than men at all age groups and peaked at age 85-89 (62).

The overall incidence (95% CI) of OA was 6.8 (6.7, 6.9) per 1,000 person-years (62). The overall incidence was higher in women 8.1 (7.9, 8.3) per 1,000 person-years than men 5.5 (5.3, 5.7), and also in each age group. The incidence increased with age in both sexes and peaked at 75-79 years. The incidence of OA at 75-79 years among women was 27.0 (23.5, 29.8) per 1,000 person-years and was 18.0 (15.4, 20.6) among men (62). The joint-specific incidence in 2017 was highest at the knee, 2.3 (2.2, 2.4) per 1,000 person-years (62).

The Framingham study in the US looked at the prevalence of hip and knee OA. The prevalence of radiographic and symptomatic knee OA, respectively, was reported to be 33% and 9.5% among people aged 63 to 94 years (63). The age-standardised prevalence of radiographic and symptomatic hip OA, respectively, was reported to be 19.6% and 4.2% among people aged over 50 years. Another study from the US reported that the age-standardised incidence of hip and knee OA, respectively among people aged 20-89 years was 88/100,000 person-years and 240/100,000 person-years (64).

A meta-analysis of 12 studies that looked at sex differences in the prevalence of knee OA and 9 studies that looked at hip OA showed that prevalent knee OA was less common in men compared to women (risk ratio (95% CI), 0.63 (0.53, 0.75)), though there was no statistically significant difference in prevalent hip OA in men compared to women (1.18 (0.91, 1.52)) (65). All studies included in the meta-analysis looking at sex differences in the prevalence of *hip* OA used radiographic assessment to ascertain OA. Of the twelve studies included in the analysis of sex differences in the prevalence of *knee* OA, ten used radiographic assessment, while two studies used clinical assessment to ascertain OA. The

incidence of both knee (four studies) and hip OA (two studies), respectively were lower among men compared to women, incidence rate ratio (95% CI), 0.55 (0.32, 0.94) and 0.64 (0.48, 0.86) (65).

1.3.4.2. Secular change

Data from the Global Burden of Disease 2017 study show that the overall global age-standardised incidence rate (ASR) for OA increased from 167.42 (149.20, 188.38) per 100,000 in 1990 to 181.19 (162.63, 202.40) in 2017 (66). The overall estimated annual percentage change in ASR for OA was 0.32(0.28, 0.36).

A study of primary and secondary care data from Sweden estimated the prevalence of OA at any site (except the spine) among people aged 45 years or older to increase from 26.6% in 2012 to 29.5% by 2032 (67).

However, not all studies have confirmed an increasing incidence of OA over time. Two recent studies using primary care data from the UK showed a slight decrease in the incidence of OA between 1992 and 2017 (62, 68). One study reported that the overall age-sex- and length of data contribution-standardised prevalence of OA (any site) increased from 8.23% (8.06%, 8.40%) in 1997 to 10.77% (10.72%, 10.82%) in 2017 (62). However, the incidence of OA decreased slightly, from 9.50 (7.43, 12.67) per 1,000 person-years in 1997 to 6.78 (6.67, 6.93) per 1,000 person-years in 2017 (62).

1.3.4.3. Risk factors

In addition to age and gender, a number of risk factors for OA have been identified. Participation in high-impact sport (69, 70) and joint trauma (71) have been identified as risk factors for knee OA. Muscle weakness, in particular knee extensor muscle weakness, has also been identified as a risk factor for knee OA (72). Obesity has been identified as a risk factor for both hip and knee OA, though the association between BMI and knee OA is stronger than the association between BMI and hip OA (73, 74). A systematic review and meta-analysis of 14 prospective and case-control studies found that a 5kg/m^2 increase in BMI was associated with an increased risk of hip OA, risk ratio (95% CI), 1.11 (1.07, 1.16), with similar effects among men and women (73). A systematic review and meta-analysis of 21 prospective and case-control studies found that a 5-unit increase in BMI was associated with an increased risk of knee OA, risk ratio (95% CI), 1.35 (1.21, 1.51). The

association between BMI and knee OA was significantly stronger among women (1.38 (1.23, 1.54) than men (1.22 (1.19, 1.25) (74).

Genetic factors appear to be significant in OA, contributing 40-80% of the risk of disease, with genetic factors more significant in hip OA than knee OA (59).

1.3.5. Impact

1.3.5.1. Morbidity

Pain and Disability

Osteoarthritis is a leading cause of pain and disability worldwide (75). Data from the Framingham study looked at disability among people with 10 prevalent medical conditions (knee OA, hip fracture, diabetes, stroke, heart disease, congestive heart failure, intermittent claudication, chronic obstructive pulmonary disease (COPD), depressive symptoms, and cognitive impairment) (76). Of the 10 conditions considered, the largest proportions of disability were attributable to knee OA, heart disease, depressive symptoms, and stroke. Knee OA was associated with an increased risk of dependence in a number of activities: stair climbing, (odds ratio (OR) (95% CI)), 1.98 (1.14, 3.43), walking a mile, 1.91 (1.38, 2.63), housekeeping 2.09 (1.29, 3.39), and "carrying bundles weighing 10 pounds", 2.02 (1.15, 3.54) (76).

Comorbidity

People with OA have an increased risk of comorbidity compared to people without OA. A study from the Netherlands looked at the prevalence of comorbidity among people with one or more of the following chronic conditions: hypertension, coronary heart disease, diabetes mellitus, chronic nonspecific lung disease and hip/knee OA, using primary care data. Of the chronic conditions considered hip/knee OA were the conditions most commonly associated with comorbidity (77). Another study from Denmark found that 62% of people with hip or knee OA treated in primary care had at least one comorbidity, with hypertension (37%), heart disease (8%), and diabetes (7%) being the most common (78).

1.3.5.2. Mortality

There is evidence that OA is associated with increased mortality. In a study of 1,163 participants aged 35 years or older with symptoms and radiological confirmation of OA of the hip or knee in the southwest of England, the standardised mortality ratio for all-cause mortality was estimated to be 1.55 (95% CI, 1.41–1.70) (79). Excess mortality was observed for all disease-specific causes of death, but was particularly pronounced for cardiovascular (standardised mortality ratio, 1.71 (1.49, 1.98)) and dementia-associated mortality (1.99 (1.22, 3.25)). Factors explaining the increased mortality rate are not fully understood, though restriction in walking ability was strongly related to increased mortality (79). A systematic review and meta-analysis of seven longitudinal studies (median follow up 12 years) reported no significant increased hazard ratio for mortality among people with OA at any site (vs no OA), HR (95% CI), 1.10 (0.97, 1.2)), however when data on OA of the hand was excluded from the analysis, a significantly increased mortality risk was observed (1.18 (1.08–1.28)) (80).

1.3.5.3. Health care costs

OA is associated with significant economic costs. One systematic review of 39 international studies, with the majority from the US, estimated the economic cost of OA to be between 0.25% and 0.50% of a country's gross domestic product (GDP) (81). In this review, the total annual mean healthcare costs of OA of the knee and hip, respectively, was €4,257 and €6,525 (81). The review highlighted that a significant proportion of the economic cost of OA was related to joint replacement surgery (81). The national health service (NHS) tariff for an uncomplicated total hip and knee replacement, respectively was set at £5,552 and £5,198 in 2010, leading to a total annual cost for primary hip and knee replacement of around £426 million each (82).

1.3.6. Management of osteoarthritis

Management of OA focuses on controlling symptoms, in particular pain, and also maintaining function. There are currently no disease-modifying therapies licensed for use in OA. Pharmacological therapies to reduce pain and stiffness, including paracetamol and anti-inflammatory therapies are limited either by lack of efficacy or adverse side effects (83). A number of non-pharmacological therapies are available for the management of lower-limb OA, including orthotics and modified footwear (84). For end-stage hip and

knee OA which cannot be managed by conservative therapies, joint replacement surgery is considered to be the definitive treatment. Total joint arthroplasty for hip and knee OA are reviewed in more detail in the next section.

1.3.7. Summary

Osteoarthritis is a common disease, and the prevalence appears to be increasing. Osteoarthritis is associated with substantial disability, morbidity, and early mortality. A range of options are available for the management of OA, focusing on controlling symptoms and maintaining function. For advanced disease not well managed by conservative therapies, total joint replacement is considered to be the definitive treatment.

1.4. Hip and knee arthroplasty

This section includes a brief description of THA and TKA, the occurrence of THA and TKA, as well as secular trends in occurrence. Factors affecting the likelihood of, and also outcomes following, THA and TKA discussed. The focus of this section is on outcomes of THA and TKA relevant to the objectives of this thesis (mortality and patient-reported outcomes). The impact of THA and TKA on the progression of frailty is also briefly discussed. The literature relating to the impact of frailty on short-term mortality and patient-reported outcomes following hip and knee arthroplasty is discussed in more detail in section 1.5.

1.4.1. Surgical process, preparation and recovery

Arthroplasty involves the construction of a new prosthetic moveable joint. Total joint arthroplasty was pioneered by Professor Sir John Charnley at Wrightington Hospital, Lancashire in the 1960s (104).

Different surgical options are available which replace different parts of the affected joint with prosthetics. In hip arthroplasty, possible alternatives include hemiarthroplasty, where the femoral head is replaced with a prosthesis, or total joint replacement, where both the femoral head and also the opposed articulating surface are replaced. In knee arthroplasty, most commonly the whole of the knee joint is replaced, though partial

replacement of the most affected parts of the joint (medial, lateral, or patella-femoral) is also possible.

Preparation for surgery may include preoperative rehabilitation, including exercises that may aid recovery, advice about lifestyle and weight management, and advice about maximising independence and quality of life, as outlined in The National Institute for Health and Care Excellence (NICE) Quality Standard (85).

Postoperatively, patients are also offered rehabilitation by a physiotherapist and/or occupational therapist, which should include advice on managing activities of daily living, home exercises, and increasing mobilisation (85).

1.4.2. Occurrence and secular trend

Hip and knee arthroplasty have revolutionised the treatment of hip and knee OA for patients who do not respond to more conservative therapies. Hip and knee arthroplasty are among the most commonly carried out surgical procedures in people aged over 65 years in the US (86). In England, Wales, Northern Ireland, and the Isle of Man, just under 100,000 THAs and just over 100,000 TKAs are carried out each year (87). The demand for THA and TKA is increasing; data from the Clinical Practice Research Datalink (CPRD (formerly General Practice Research Database) in the UK, showed that the age-standardised rates for THA, per 100,000 person-years, increased from 60.3 (95% CI, 53.7, 67.0) in 1991 to 144.6 (138.1, 151.1) in 2006 for women and from 35.8 (30.4, 41.3) to 88.6 (83.4, 93.7) for men over the same period (88). Rates for TKA, per 100,000 person-years, increased from 42.5 (37.0, 48.0) in 1991 to 138.7 (132.3, 145.0) in 2006 for women and from 28.7 (23.9, 33.6) to 99.4 (93.9, 104.8) for men over the same period (88).

The increasing demand for THA/TKA is thought in part to be due to a demographic shift towards an older population with increased number of older people with hip and knee OA, and increase also in the age standardised incidence of OA thought in part related to an increase in obesity (66, 67). A study from the UK projected substantial increases in the incidence of THA and TKA during the period 2015 to 2035 based on projected distributions of age, sex, and BMI under different modelling assumptions (89). Other data from Australia (90) and the US have also predicted substantial increases in the incidence of THA and TKA (91).

1.4.3. Factors affecting the likelihood of receiving hip and knee arthroplasty

The likelihood of receiving hip and knee arthroplasty due to osteoarthritis is driven by symptoms including predominantly pain and disability. However, a number of other factors have been linked with joint replacement surgery including BMI, comorbidity, frailty, sex, socioeconomic status, and ethnicity, which are discussed briefly below.

1.4.3.1. Age

Advanced age is risk factor for hip and knee OA with the incidence of hip and knee OA increasing with increasing age up to 80 years (61). Consequently, since hip and knee OA are the primary indications for THA and TKA, age is a determinant also of THA and TKA and the demographic shift towards an older population is partly driving the increasing demand for THA and TKA (89-91).

1.4.3.2. Sex

Hip and knee OA are more common among women than men (61). However, among individuals with hip and knee OA, women are less likely than men to undergo THA and TKA (92-94). One population-based survey of 22,204 respondents from the UK asked individuals about whether they had experienced pain in or around their hip in the past 12 months (93). After adjusting for the presence of hip pain and age, women were less likely than men to be on a waiting list for hip replacement (OR (95% CI), 0.59 (0.34, 1.01)) (93).

Factors driving the lower rates of THA and TKA among women with OA compared to men with OA are not fully understood, though one study from the USA suggested that women are not less willing to undergo THA and TKA than men (95). Health consultation may be one potential factor; data from a UK study suggested that women with hip pain were less likely than men with hip pain to have consulted their general practitioner about their pain (93).

1.4.3.3. Socioeconomic deprivation

A number of studies have indicated that increasing socioeconomic deprivation is associated with reduced likelihood of receiving THA and TKA among individuals with hip and knee OA (96-100).

One study from the UK looking at the association between deprivation and likelihood of receiving THA or TKA, relative to need, used data from the Somerset and Avon Survey of Health and the English Longitudinal Study of Ageing (98). Deprivation was assessed based on fifths of the 2004 index of multiple deprivation (IMD). Need for THA and TKA was assessed based on a simplified New Zealand score and receipt of THA and TKA was identified using linked hospital episode statistics (HES) data. The authors calculated "equality rate ratios" for the provision of THA, relative to need, based on multilevel Poisson regression models. Increasing quintile of IMD was associated with reduced provision of THA, relative to need, in a multivariable model. Compared to those in the least deprived quintile, those in the 2nd, 3rd, 4th, and 5th (most deprived) quintile of IMD, respectively, the equity rate ratio (provision of THA relative to need) (95% CI), was 0.73 (0.71, 0.76), 0.55 (0.53, 0.57), 0.44 (0.42, 0.46), and 0.31 (0.30, 0.33). The corresponding results for TKA were 0.74 (0.72, 0.77), 0.65 (0.63, 0.68), 0.43 (0.41, 0.45), and 0.33(0.31, 0.34) (98).

A more recent study from the UK, based on a postal survey of 15,000 randomly selected individuals aged 65 years and older (response rate 78%), found that the level of need for TKA (assessed using an adapted version of the index of severity of osteoarthritis of the knee) was higher among those in receipt of means-tested benefits (14% needed TKA) compared to those who did not receive means-tested benefits (6% needed TKA) (96). After accounting though for comorbidity that may preclude TKA, the proportion of individuals who had received a TKA was similar among those in receipt of means-tested benefits and those not in receipt of means-tested benefits (3% in both groups).

1.4.3.4. Ethnicity

A recent review article summarised the literature on racial and ethnic disparities in total joint arthroplasty (TJA) (101). The review found evidence of racial and ethnic disparities in access to and utilisation of TJA. The authors reported that higher levels of morbidity among ethnic minority groups, as well as higher levels of socioeconomic deprivation, may contribute to the ethnic disparities in access to TJA. Related to socioeconomic deprivation, differences in health insurance status in the USA between non-White and White ethnic groups may also contribute to ethnic disparities.

A study using data from the National Joint Registry (NJR) looked at rates of hip and knee replacement among different ethnic groups in England (102). The study used indirect age-

and sex-standardisation to compare the expected and observed number of hip and knee replacements among people of White, Black, and Asian ethnicity. The standardised ratio (observed/expected) (95% CI) for hip replacement surgery among people of White, Black, and Asian ethnicity, respectively was 1.05 (1.05, 1.06), 0.33 (0.31, 0.35), and 0.20 (0.19, 0.21). The corresponding results for knee replacement surgery were 1.01 (1.01, 1.02), 0.64 (0.61, 0.67), and 0.86 (0.84, 0.88) (102).

1.4.3.5. Body mass index

Higher BMI has been linked with an increased likelihood of THA and TKA among individuals with hip and knee OA (103, 104). One study of 48,311 individuals with knee OA, using data from Catalonia, Spain, found that BMI increasing from 25 to 35 was associated with a lifetime risk of knee replacement increasing from 24% (95% CI, 20%, 28%) to 32% (95% CI, 26%, 37%) (103).

1.4.3.6. Comorbidity

Data form the USA suggest that higher levels of pre-existing morbidity increases the risk of general medical or surgical complications following THA (105). There may be a reluctance (among patients and also healthcare professionals) for patients with pre-existing multimorbidity to undergo THA and THA due to concerns about the risk of complications. One study of 28,025 individuals with hip OA from the UK found that increasing morbidity was associated with reduced likelihood of THA (106). The crude incidence of THA per 100 person-years decreased from 12.2 (95% CI 11.9, 12.4) among those with a Charlson comorbidity index of zero, to 9.2 (8.6, 9.9) among those with a Charlson comorbidity index of ≥3. In a model adjusted for age, sex, region, and year of OA diagnosis, compared to those with a Charlson comorbidity index of zero, the HR (95% CI) for THA among those with a Charlson comorbidity index of 2, 3, and ≥3, respectively, was 0.84 (0.79, 0.89), 0.81 (0.76, 0.87), and 0.65 (0.60, 0.70) (106).

1.4.3.7. Frailty

One study of 28,025 individuals with hip OA from the UK determined the association between frailty, assessed using the eFI, and the likelihood of receiving THA (106). The crude incidence of THA per 100 person-years decreased from 12.0 (95% CI 11.8, 12.3) among those with an eFI score (defined as a count of deficits) of 0-4, to 5.8 (3.4, 8.1)

among those with an eFI score of ≥13. In a model adjusted for age, sex, region, and year of OA diagnosis, compared to those with an eFI score of 0-4, the HR (95% CI) for THA among those with an eFI score of 5-8, 9-12, and ≥13, respectively, was 0.77 (0.74, 0.81), 0.52 (0.47, 0.59), and 0.34 (0.22, 0.51) (106).

1.4.4. Outcomes following total hip and knee arthroplasty

In this section outcome measures and outcomes following hip and knee joint replacement surgery are considered. The section on outcome measures focuses on those measures which are routinely collected in clinical practice.

1.4.4.1. Patient-reported outcome measures

The Oxford Hip Score and the Oxford Knee Score

The OHS (107) and OKS (108) were developed in order to assess patients' perceptions of the outcomes of hip and knee arthroplasty. The OHS and OKS were developed by interviewing patients to identify how they experience and report problems with their hips and knees. Following these interviews and initial analysis, a set of 12 questions, including questions about pain, and ability to carry out basic activities, such as walking, using transport, dressing, climbing stairs, and rising from a chair, each with five categories of response were produced. The OKS also includes some questions specific to knee problems, such as ability to kneel. An overall score is obtained by summing the responses to each of the 12 questions, resulting in a range from zero to 48, with higher scores indicating better outcomes. Validation studies have shown that the instruments perform well (107, 108).

Most patients respond well to THA/TKA as assessed by the Oxford hip/knee score. A prospective analysis of data from the South West London Elective Orthopaedic Centre database, including 1,523 patients who had a THA and 1,784 patients who had a TKA between 2004 and 2009 showed that the mean (standard deviation (SD)) pre- and 6-month postoperative OHS was 19.7 (8.8) and 38.8 (8.7), respectively, and the mean (SD) pre- and 6-month postoperative OKS was 19.9 (8.0) and 34.5 (9.1), respectively (109).

Minimal important change (MIC) in OHS and OKS has previously been estimated using both distribution and anchor-based methods. Anchor-based methods used to estimate MIC within individuals over time are based on receiver operating characteristic curve

analysis to distinguish patients who achieve the smallest meaningful clinical improvement (reporting that their hip/knee problems are “a little better” versus those who report their problems are “about the same” following surgery compared to before surgery). Previous analysis has reported that the MIC in OHS corresponds to an improvement of about ≥8 points and the MIC in OKS corresponds to an improvement of about ≥7 points (110, 111).

Patient-reported satisfaction and success

Patient satisfaction with THA and TKA has been assessed in a number of different ways using questionnaires, numerical, or Likert scales, however there is currently no general consensus on how best to measure patient satisfaction (112). One review of patient satisfaction reported that at least 7% of patients are dissatisfied following THA (112). Another review reported that patient satisfaction after TKA ranges from 75% to 92% (113).

In the NHS in England, PROMs data collected 6 months following THA and TKA includes data relating to the following question about patient-reported success: “overall, how are the problems now in the <hip/knee> on which you had the surgery, compared to before your operation?”. Possible responses are “much better”, “a little better”, “about the same”, “a little worse”, and “much worse”. A study of 277,430 primary THAs and 308,007 TKAs carried out in England between 2009 and 2020 looked at patient-reported success (111). A successful outcome was defined as a patient reporting that their hip/knee problems were “much better” or “a little better”. Patients who reported that their hip/knee problems were “about the same”, “a little worse”, and “much worse” were classified as not having a successful outcome. The study reported that, following THA, 95% of patients had a successful outcome and following TKA, 89% of patients had a successful outcome (111).

The postoperative NHS England PROMs data also contains data relating to the following question about patient-reported satisfaction: “how would you describe the results of your operation?”. Possible responses are “excellent”, “very good”, “good”, “fair”, and “poor”. A study of 277,430 primary THAs and 308,007 TKAs carried out in England between 2009 and 2020 looked at patient-reported success (111). Patients who reported the results of their operation to be “excellent”, “very good”, or “good” were classified as being satisfied with their surgery and those who reported the results of their operation to be “fair”, and “poor” were classified as not being satisfied. The study reported that, following THA, 92%

of patients were satisfied with their surgery and following TKA, 86% of patients were satisfied (111).

Other patient-reported outcome measures

There are a number of other OA outcome measures which have been used in joint replacement surgery, including the Western Ontario and McMaster Universities Osteoarthritis (WOMAC) index (114) and the Knee Injury and Osteoarthritis Outcome Score (115). Both are OA disease-specific instruments. Neither are currently routinely collected in clinical practice in the UK.

The EuroQol- 5 Dimension (EQ-5D) is a generic health related quality of life instrument which aims to assess health status across different disease areas (116), and has been used to assess outcomes following THA and TKA. The EQ-5D comprises 5 questions about mobility, self-care, usual activities, pain/discomfort, and anxiety and depression, with responses on a 3-point scale (EQ-5D-3L). The EQ-5D has been shown to be a valid and reliable instrument among people with OA, and to correlate with the WOMAC osteoarthritis index (117).

In a study from Sweden of 2,444 people who had hip or knee arthroplasty between 2001 and 2005 there was an improvement in EQ-5D 12 months after surgery compared to preoperative score (118). Overall, the mean (SD) preoperative EQ-5D score was 0.49 (0.34) among those undergoing hip arthroplasty and 0.51 (0.33) among those undergoing knee arthroplasty. At 12 months after arthroplasty, the overall EQ-5D score had increased, suggesting improved health status, to 0.80 (0.25) among those who had a hip arthroplasty and 0.73 (0.27) among those who had a knee arthroplasty (118).

1.4.4.2. Mortality

Serious complications following THA and TKA are not common; the adjusted 45-day mortality rate in people who have total knee replacement surgery is 0.20% and the 90-day mortality in people who have total hip replacement is 0.29% (119). However, due to the large number of THAs and TKAs carried out each year, the absolute number of deaths is not insignificant. From April 2003 to December 2011, 1,183 patients died within 45 days of TKA (120) and 1,743 patients died within 90 days of THA in the UK (119).

Results from the Danish Hip Arthroplasty Register suggested that all-cause 30-day mortality was increased in people who had a total hip replacement compared to the general population matched on age and gender (hazard ratio (95%CI) 1.4 (1.2, 1.7)) (121). All-cause 90-day and longer term (up to a maximum follow up of 12.7 years) mortality was, however, reduced in people who had a total hip replacement compared to matched controls (matched by age and sex) from the general population (hazard ratio (95%CI) 0.6 (0.5, 0.8) and 0.7 (0.7, 0.7), respectively). Participants who had a total hip replacement were less likely to have a moderate or high Charlson comorbidity index compared to their matched controls, which was more pronounced among individuals aged >60 years (121). This illustrates that people selected for THA may be, on average, fitter than people from the general population of the same age.

1.4.4.3. The impact of total hip and knee arthroplasty on the progression of frailty

It is not clear whether THA and TKA impact on the progression of frailty; no previous studies have compared the progression of frailty before and after THA and TKA. One study from the USA of 5,341 patients who had either a THA or TKA (analysed as one combined group) looked at changes in levels of frailty following THA/TKA (122). Frailty was assessed at the time of THA/TKA and 6-18 months post THA/TKA using a 32-item FI and was categorised as non-frail (FI<0.11), vulnerable (FI≥0.11≤0.20) and frail (FI>0.20). Timing of the postoperative assessment of frailty varied depending on clinical visits. At the time of THA/TKA, 2,009 individuals (37.6%) were non-frail, 2,102 (39.4%) were vulnerable, and 1,230 (23.0%) were frail. Of those classified as non-frail at the time of THA/TKA, 14% subsequently deteriorated to vulnerable or frail. Of those classified as vulnerable at the time of THA/TKA, 60% remained vulnerable 6-18 months following THA/TKA, 29% improved to non-frail, and 11% deteriorated to frail. Of those classified as frail at the time of THA/TKA, 60% remained frail 6-18 months following THA/TKA, 34% improved to vulnerable and 6% improved to non-frail 6-18 months following THA/TKA (122).

While data on transitions in frailty levels following THA and TKA are useful, change in frailty in the lead up to THA/TKA was not reported, therefore it is not possible to determine what impact THA/TKA may have had on trajectories of frailty. Previous population-based cohort studies have shown that improvement in frailty status is possible among individuals who do not have arthroplasty. Further work is needed to assess whether the occurrence of THA and TKA might modify frailty trajectories.

Although no previous data have assessed the impact of THA/TKA on change in frailty, previous studies have indicated that TKA may have a beneficial impact on the risk of falls (123), and increasing frailty is associated with increasing risk of falls (124).

1.4.5. Factors affecting outcomes following hip and knee arthroplasty

A number of factors have been shown to predict outcomes following THA and TKA; these are reviewed below with a focus on mortality and also PROMs as outcomes. The impact of frailty on outcomes will be considered in section 1.5.

1.4.5.1. Age

The effect of age on outcomes following THA and TKA has been summarised in a recent systematic review (125). Thirteen studies looked at the impact of age on mortality following THA or TKA. Among octogenarians, the rate of in-hospital mortality following THA was 1.54%, and 1.09% following TKA, which was around 3.4 times higher than people aged less than 80 (125). Among nonagenarians, peri-operative mortality following total joint arthroplasty was between 2.6% and 2.9%, which was around 11.5 times higher than younger patients (125). Another systematic review reported that mortality following TKA was increased among older patients (defined as >80 years in most studies), compared to younger patients (OR (95% CI), 3.90 (2.68, 5.67)) (126). Furthermore, older age was also associated with other adverse outcomes following TKA, including myocardial infarction (MI) (OR (95% CI), 2.71 (1.04, 7.08)), deep vein thrombosis (DVT) (1.20 (1.08, 1.34)), and increased length of hospital stay (126).

In a systematic review, patients aged over 80 years were more likely to experience a range of complications following total joint arthroplasty, compared to younger patients, including myocardial infarction (2.7 times more likely), confusion or delirium (3.6 times more likely), and urogenital issues (2.2 times more likely) (125).

A systematic review suggested that improvement in pain following THA is similar among older individuals compared to younger individuals, (125). Studies looking at the impact of age on function following THA have shown mixed results. One study looked at function following THA, assessed using the WOMAC index, among older participants compared to younger participants (125). The study showed that improvements in joint function and stiffness compared to the preoperative level were similar in older participants compared

to younger individuals (125). However, other studies, assessing function using the OHS, Harris hip score (HHS), and WOMAC, demonstrated a lack of functional improvement among older participants following THA (125).

The review also identified 3 studies which considered patient satisfaction following total joint arthroplasty; all indicated that older patients were equally satisfied as younger individuals following surgery (125).

Most studies have shown that improvements in health-related quality of life, measured using the EQ-5D and short-form-36 (SF-36), were similar among individuals aged over 80 years compared to those younger (125).

1.4.5.2. Sex

A number of studies have reported higher mortality among men, compared to women, following THA and TKA (127-129). One large study including over 200,000 men and women found that male sex predicted 30- and 90-day mortality, respectively following TKA in multivariable analysis controlling for age and comorbidities (OR, 1.9 ,and 1.7, $p<0.001$) (128). Similar results were reported in a study of 17,994 primary TKAs, median age 69 years, showing higher 1-year mortality among men compared to women (OR (95% CI) 1.48 (1.13, 1.94)) (129). In this study, no significant differences between men and women in 30-day overall complications, myocardial infarction, or venous thromboembolism were found (129). However, 30-day surgical wound infection rates were higher in men compared to women, OR (95% CI), 1.31 (1.08, 1.60) (129).

Studies looking at differences in functional outcomes following total joint replacement between men and women have shown mixed results. One systematic review looking at functional outcomes following THA found that four out of seven studies found better outcomes among men, while three out of seven studies reported better outcomes among women (130).

A review looking at patient satisfaction following THA noted that pain and satisfaction measures are often poorer among women compared to men (112). One study found slightly greater satisfaction among men following THA, despite less improvement in pain (112). One study including 100 men and women, mean (SD) age 65.7 (8.8) years looked at sex differences in postoperative pain following TKA (131). Women reported higher acute

postoperative pain scores two weeks following TKA compared to men ($p<0.01$). However, by postoperative week six, there were no significant differences in pain between men and women (131).

1.4.5.3. Body mass index

In a study of 3,627 men and women who had a THA between 2010 and 2013, compared to those who were normal weight ($18.5 \leq BMI < 23$ kg/m^2), those who were underweight ($BMI < 18.5$ kg/m^2) and obese ($25 \leq BMI < 30$ kg/m^2), respectively had an increased 30-day mortality (HR (95% CI), 2.37 (1.13, 4.96) and 2.02 (1.01, 4.06)) (132).

A recent meta-analysis comprising 14 studies reported the association between obesity and short-term (up to 24 months) and long-term (>24 months) outcomes following elective hip or knee surgery. Overall, compared to those who were not obese, those who were obese had greater short-term and long-term pain, respectively, following surgery (standardised mean difference (95%CI), -0.44 (-0.68, -0.20)) and -0.36 (-0.47, -0.25)) (133). Non-obese participants were also less likely to experience a range of complications following surgery, including short-term infection (OR (95% CI), 0.33 (0.19, 0.59)), short-term (0.49 (0.26, 0.91) and long-term (0.58 (0.36, 0.94) DVT and long-term dislocation (0.50 (0.31, 0.80)) (133). No significant association was found between being non-obese (compared to obese) and long-term revision surgery (OR (95% CI), 0.66 (0.34, 1.28)) (133).

A further review reported on the association between BMI and physical function following THA and concluded that there was strong evidence of an association between increasing BMI and worse physical function following THA (130). BMI has also been associated with lower functional outcome scores following TKA. In an analysis of 1,991 men and women from the UK, each 5-unit increase in BMI was associated with a 0.92 (95% CI, 0.82, 1.04) point lower OKS function score 6 months following TKA, in a multivariable model, adjusting for preoperative OKS function score (134).

1.4.5.4. Comorbidity

A systematic review looked at the impact of comorbid conditions on outcomes following THA and TKA, compared to those without individual comorbidities (135). Short-term mortality (within 90 days) following THA or TKA was significantly increased among those with comorbidity in the majority of studies, with the greatest risk among people with

heart disease (pooled OR (95% CI), 2.96 (1.95, 4.48)) (135). Most studies included in the review found that long-term mortality following THA or TKA was also higher among people with comorbidity, compared to people without comorbidity. The pooled OR (95% CI) ranged from 1.38 (1.05, 1.80) for lung disease to 3.40 (1.17, 9.86) for liver disease (135).

The review also found that any surgical complication, including venous thromboembolism and surgical site infection, was more common among patients with cancer (pooled OR (95% CI), 1.33 (1.09, 1.62)), diabetes (1.12 (1.01, 1.25)), kidney disease (1.97 (1.84, 2.10)), and stroke (1.40 (1.03, 1.90)) (135).

Ten studies reported the association between comorbid conditions and pain following THA or TKA. All studies included in the review found no statistically significant difference in postoperative pain among individuals with comorbidity, compared to those without comorbidity (135).

The impact of comorbidity on postoperative function, assessed using various measures including the WOMAC score and the OKS, was variable, with no significant association between postoperative function and certain comorbidities, including high blood pressure, kidney disease, liver disease, lung disease, and poor circulation (135). Overall, individuals with depression (pooled OR (95% CI), 1.69 (1.26, 2.28)), heart disease (1.24 (1.01, 1.52)), and stroke (1.32 (1.02, 1.71)), had, however, worse function after surgery (135).

Preoperative depression or anxiety have been associated also with postoperative complications and patient-reported outcomes (136). One study from Sweden showed that individuals with anxiety or depression were 6 times more likely to report that they were not satisfied with the result of their TKA 4 years following surgery (137). Another study demonstrated that preoperative depression was associated with postoperative medical complications including anaemia (OR (95% CI), 1.14 (1.09, 1.17)) and infection (1.33 (1.21, 1.41)) (138).

1.4.5.5. Ethnicity

Disparity in outcomes among different ethnic groups following total joint arthroplasty have been reported (139). A study of 17,385 men and women looked at the impact of ethnicity on outcomes after TKA (140). While there were no significant differences in 30-

day or in-hospital complication rates, or 30-day or 1-year mortality rates in unadjusted analyses, African American participants (compared to Whites) had an increased risk of revision surgery over a 5 year follow up in an adjusted model (140).

One study of 10,325 women from the US found that Black women had lower physical function scores (assessed using the RAND 36-Item Health Survey (RAND-36) physical function scale) compared to White women prior to TKA (mean difference (95% CI), -5.8 (-8.0, -3.6)), which persisted 1 year after TKA (-7.8 (-10.8, -4.9)) (141).

Another study of 989 men and women who had a TKA found that African American participants were 3.0 (95% CI, 1.5, 6.0) times more likely to report being not satisfied with their TKA at a median (SD) 3.5 (1.5) years following surgery, compared to Caucasian participants (142).

1.4.5.6. Socioeconomic status

One longitudinal study from Australia of 1,016 patients who had a TKA and 835 who had a THA looked at the association between socioeconomic status and postoperative pain and function (143). Socioeconomic status was assessed based on decile of "Index of Relative Advantage and Disadvantage", which includes variables such as income, education, occupation, housing and employment and is compiled using national census data by the Australian Bureau of Statistics. Outcome measures were the HHS and the short-form health survey (SF-12). The authors found that socioeconomic status was not an independent predictor of outcomes following THA and TKA at 12 months, after adjustment for preoperative scores, in a multivariable model.

However, a study from the UK, using data from 191 patients who received a primary TKA in south-west London from 2005 to 2008, found that greater deprivation, assessed using the 2004 IMD, was associated with poorer OKS and lower levels of patient acceptable symptom state following TKA (134).

Another study from the UK using data from the NJR also reported a small statistically significant association between deprivation and change in OKS following TKA (144). In total, 66,796 patients who had a TKA contributed data. The mean (SD) age of participants was 69.7 (9.0) years and 56.5% were women. Deprivation was assessed using the 2007 English index of multiple deprivation (IMD). Crude difference in change in OKS

(preoperative minus 6 month postoperative score) decreased from a mean (SD) of 15.44 (9.58) among those in the first (least deprived quintile) to 14.22 (10.42) among those in the fifth (most deprived) quintile, indicating worse outcomes in the most deprived compared to least deprived quintile (144). The association between quintile of IMD and smaller change in OKS persisted in a multivariable linear regression model adjusted for a range of putative cofounders, beta coefficient (95% CI) -0.71 (-0.76, -0.66) per quintile increase in IMD (144).

1.4.6. Summary

Total hip and knee arthroplasty is an effective intervention for patients with hip and knee OA that are not adequately managed by conservative therapies. Total hip and knee arthroplasty are among the most common surgical procedures undertaken on older people with around 200,000 procedures caried out in the UK each year. The majority of patients report a successful outcome following surgery, though around 4% of patients who have a THA and around 10% of patients who have a TKA report that their surgery was not successful. There are no data looking at change in frailty status following THA and TKA compared to before surgery, therefore whether THA and TKA impact on the progression of frailty is not known. A number of factors have been linked with outcomes following THA and TKA, including age, sex, BMI, comorbidity and ethnicity. The literature relating to the impact of frailty on outcomes following THA and TKA, is reviewed in section 1.5.

1.5. The impact of frailty on outcomes of total hip and knee arthroplasty

This section reviews the literature relating to the impact of frailty on outcomes following THA and TKA. The focus is on outcomes relevant to the objectives of this thesis: short-term mortality and patient-reported outcomes. Gaps in the literature are also highlighted.

1.5.1. Search strategy and inclusion and exclusion criteria

The purpose of the literature search was to identify studies that have looked at the impact of frailty on short-term mortality (up to 90 days) and patient-reported outcomes including pain and functional impairment following primary total hip or knee arthroplasty.

Ovid Medline was searched to identify relevant studies. The search was last updated in April 2022. The search strategy is shown in Table 1.1. Medical subject heading (MeSH)

terms were used where possible, and for non-MeSH search terms, titles, abstracts and whole texts were searched.

The following inclusion and exclusion criteria were applied.

Inclusion criteria:

1. Primary total hip or knee arthroplasty
2. Assessment of frailty using a validated frailty instrument
3. Data on outcomes following joint surgery including short-term mortality (up to 90 days) or patient-reported functional outcomes including pain following joint surgery

Exclusion criteria:

1. Conference abstracts
2. Case studies
3. Studies including a range of orthopaedic or other surgical procedures as one group, with results specific to total hip/knee arthroplasty not reported separately
4. Period during which postoperative mortality was determined not specified
5. Timing of collection of postoperative patient-reported outcomes relative to date of joint surgery not specified
6. Studies not published in English

Table 1.1. Literature search strategy

	Search	Number of results
1	exp Frail Elderly/	13,795
2	exp Frailty/	6,452
3	frail*.mp.	34,731
4	Geriatric Assessment/	31,044
5	Geriatrics/	31,013
6	Cumulative deficit*.mp	143
7	Phenotype model*.mp	233
8	1 or 2 or 3 or 4 or 5 or 6 or 7	89,311
9	Arthroplasty/	9,620
10	Hip Prosthesis/	24,749
11	Arthroplasty, Replacement, Hip/	31,952
12	(hip adj2 (replace* or arthroplast* or surgery*)).mp.	53,532
13	Knee Prosthesis/	12,960
14	Arthroplasty, Replacement, Knee/	28,920
15	(knee adj2 (replace* or arthroplast* or surgery*)).mp.	45,010
16	Orthopedic Procedures/	28,065
17	9 or 10 or 11 or 12 or 13 or 14 or 15 or 16	132,662
18	8 and 17	652

1.5.2. Overview of studies identified by the literature search

The search strategy returned 652 studies and the title and abstracts of these studies were reviewed. Following review of titles and abstracts, 37 studies were identified that potentially met the inclusion criteria and the full text of these studies was reviewed. After full text review, 13 studies were identified which met the inclusion criteria. Ten studies looked at the association between frailty and postoperative mortality up to 90 days following hip or knee arthroplasty (Table 1.2) and 3 studies looked at the association between frailty and patient-reported functional outcomes (Table 1.3).

1.5.3. Identification of frailty

The studies identified in the literature review assessed frailty using a FI (two studies), the modified frailty index (mFI) (one study), the 5-component modified frailty index (mFI-5) (five studies), the eFI (two studies), the hospital frailty risk score (20) (one study), and the Groningen frailty indicator (one study). One study used both the mFI and mFI-5 (Table 1.2 and Table 1.3). The frailty instruments used in these papers are briefly described below.

1.5.3.1. Frailty index

One study used a frailty index comprising 32 health deficits based on review of clinical notes and self-reported functional ability (145). The FI was categorised as non-frail (FI<0.11), vulnerable (0.11≤FI<0.20) and frail (FI≥0.21). The development of the frailty index used in this study had been described previously and had been shown to predict mortality among people with heart failure (146).

1.5.3.2. The modified frailty index

Two studies identified in the literature review used the mFI. The mFI was developed in the American College of Surgeons National Surgical Quality Improvement Program (NSQIP) (147). The mFI was developed by mapping the original 70 variables included in the Canadian Study of Health and Aging (CSHA) frailty index, to data available in the NSQIP database. Of the original 70 variables included in the CSHA frailty index, 16 were available in the NSQIP database, grouped into 11 factors (functional status, history of diabetes mellitus, respiratory problems, congestive heart failure, history of MI, cardiac problems, arterial hypertension, delirium, history related to cognitive impairment, cerebrovascular problems, history of stroke) (147).

The mFI has since been widely used to predict a range of adverse surgical outcomes, including complications, mortality, reoperation, discharge to skilled care, and readmission. A systematic review and meta-analysis identified 34 studies that have looked at the association between the mFI and surgical outcomes (148). The systematic review and meta-analysis highlighted substantial variation in the application of the mFI between studies, with different thresholds used to identify frailty. For this reason, in the meta-analysis, the authors reduced the mFI to a binary variable, with a score of zero indicating a non-frail individual and a score of greater than zero indicating a frail individual.

Identifying frailty on the basis of one or more health deficits does, however, remove the ability to consider different levels of frailty. It is also difficult to reconcile the dysregulation across multiple organ systems as a characteristic of advanced frailty (27, 149) with the identification of frailty on the basis of a single health deficit.

1.5.3.3. The 5-component modified frailty index

Four studies identified in the literature review used a 5-factor modified frailty index (mFI-5). The mFI-5 was developed following changes to the NSQIP databases which meant that all 16 variables which make up the mFI were no longer available from 2012 (150). From 2015, only 5 of the original 16 variables included in the mFI were available.

A previous study had looked at the correlation between the original mFI and mFI-5 and their ability to predict mortality, postoperative complications, and unplanned 30-day readmission following general, cardiovascular, and orthopaedic surgery (150). The authors found high correlation between the mFI and mFI-5 (Spearman's correlation ≥0.9 for all surgical specialities except cardiac and vascular). The authors found similar c-statistic values for the mFI and mFI-5 in relation to prediction of mortality, postoperative complications, and unplanned 30-day readmission based on a logistic regression model. The authors reported similar c-statistics for the mFI and mFI-5 for all outcomes. For example, based on a univariate logistic model with the mFI and mFI-5, respectively predicting mortality following orthopaedic surgery, the c-statistics (95% CI) were 0.73 (0.70, 0.75) and 0.74 (0.72, 0.76) (150).

The mFI-5 has been widely used and previous studies have demonstrated the ability of the mFI-5 to predict adverse surgical outcomes, including following orthopaedic surgery (151). However, further studies assessing the construct validity of the mFI-5 may be warranted given the small number of variables that make up the mFI-5. Previous data suggest that a minimum of 30 variables indicating deficits across multiple physiologic systems is needed to produce a frailty index with good ability to predict adverse outcomes (16).

1.5.3.4. The electronic frailty index

One study identified in the literature review assessed frailty using the eFI. The eFI was developed using primary care electronic medical records in the UK (152) and is described in section 3.7.2.

1.5.3.5. The hospital frailty risk score

The hospital frailty risk score identifies frailty based on ICD-10 codes recorded in secondary care records, using data form the HES (20). In the study that developed the hospital frailty risk score, the authors specified a priory a list of ICD-10 codes that were candidate markers of frailty (including, for example, codes relating to dementia, mobility problems, cognitive impairment, falls, and care-provider dependency). Using cluster analysis, a group of individuals were identified that had a higher incidence of the pre-specified candidate frailty marker ICD-10 codes (20).

Within this group, a broad set of 109 ICD-codes were identified that were over represented in this cluster (at least twice as prevalent compared to the rest of the cohort). The hospital frailty risk score was constructed by weighting the broad set of ICD codes identified based on how strongly they predicted membership of the cluster. The hospital frailty risk score was categorised as low risk, intermediate risk and high risk, with cut-points chosen that best discriminated people with adverse outcomes following hospital admission. The adverse outcomes considered were 30-day mortality, hospital stay >10 days and emergency readmission within 30 days of discharge. The hospital frailty risk score discriminated individuals with these adverse outcomes poorly: the c statistic was 0.60 for 30-day mortality, 0.68 for hospital stay >10 days, and 0.56 for 30-day readmission (20).

The hospital frailty risk score was also compared to the frailty phenotype and a frailty index in a linked cohort of 569 patients. Patients had hospital frailty risk scores ranging from 0 to 99 and were categorised as low risk (score <5), intermediate risk (score 5-15) and high risk (score>15). A dichotomised hospital frailty risk score (>5 compared to ≤5) was compared to a dichotomised Fried frailty phenotype (≥3 items of the Fried frailty phenotype present) and a dichotomised frailty index (score ≥0.25). When comparing the dichotomised hospital frailty risk score and the dichotomised Fried frailty phenotype, the

kappa score was 0.22 (95% CI 0.15, 0.30) and the equivalent score for the dichotomised frailty index was 0.30 (0.22, 0.38) (20).

1.5.3.6. Groningen Frailty Indicator

One study identified in the literature review assessed frailty using the Groningen Frailty Indicator (GFI), a 15-item frailty screening instrument (153). The GFI is based on answers to a questionnaire including 15 questions relating to daily activities, health problems and psychosocial functioning. The GFI score ranges from zero to 15, with higher scores indicating a higher level of frailty.

1.5.4. The association between frailty and short-term mortality following hip and knee arthroplasty

Ten studies, published between 2016 and 2021, looked at the association between frailty and mortality following hip and knee arthroplasty, including in-hospital mortality, 30-, 45- and 90-day mortality. Eight studies were from the USA and 2 studies were from the UK (Table 1.2). Of the 8 studies from the USA, 6 used data from the NSQIP and 2 used data from a single centre database (Mayo Clinic College of Medicine). One study from the UK used data from the CPRD Gold database and one study used data from the National Joint Registry. Despite using a range of different frailty instruments, all studies consistently demonstrated increasing mortality in the period up to 90-days following hip and knee arthroplasty with increasing frailty.

1.5.4.1. In-hospital mortality

One single-centre study of 8,640 people who had a primary or revision THA looked at the association between frailty, assessed using a 32-deficit FI, and in-hospital mortality (154). The FI was categorised as non-frail (FI<0.11), vulnerable (0.11≤FI<0.20) and frail (FI≥0.21). However, the number of in-hospital deaths was insufficient to allow detailed analysis. There were only two in-hospital deaths among those who wo were non-frail (0.1%), five deaths among those who were vulnerable (0.2%), and 4 deaths among those who were frail (0.2%) (154).

1.5.4.2. 30-day mortality

Six studies, all from the USA, looked at the association between frailty and 30-day mortality following hip and knee arthroplasty (155-160). All studies used data from the NSQIP database. Two studies assessed frailty using the mFI and 4 studies used the mFI-5 (Table 1.2). All studies found that frailty predicted 30-day mortality following hip and knee arthroplasty.

There was variation in the application of the mFI-5; one study looked at the association between the mFI-5 and 30-day mortality per 1 point increase in mFI-5 (157), two studies which looked at the impact of frailty and also malnutrition on 30-day mortality identified frailty based on the presence of 2 or more components of the mFI-5 (otherwise classified as "healthy" if <2 mFI components present) (158, 159), and one study did not specify whether the mFI was analysed as a continuous or categorical variable, or how it was categorised (160).

Despite differences between studies, all studies reported increased 30-day mortality following hip and knee arthroplasty among individuals with frailty compared to individuals who were not frail. One study of 140,158 individuals who had a THA and 226,398 who had a TKA looked at the association between the mFI-5 and 30-day mortality following surgery (157). The authors found that 30-day mortality increased with increasing mFI score following THA; from 0.1% among those with an mFI score of zero, to around 7% among those with an mFI score of 4 (the results were plotted on a graph, though numerical percentages were not reported). Following TKA, 30-day mortality increased from 0.1% among those with an mFI score of zero, to around 2% among those with an mFI score of 4 (no individuals with an mFI score of 5 died within 30 days following THA or TKA (157).

There is consistent evidence that 30-day mortality following THA and TKA increases with increasing frailty. However, this is perhaps not surprising, since mortality also increases with increasing frailty in the general population (161). No studies identified in the literature review have accounted for the increased risk of mortality in the general population when looking at the association between frailty and 30-day mortality following THA and TKA. It is therefore not known whether, and to what extent, THA and TKA impact on 30-day mortality risk among those with frailty, compared to the underlying increased risk of mortality among those with frailty in the general population.

1.5.4.3. 90-day mortality

Four studies identified in the literature review looked at the impact of frailty on 90-day mortality; two from the USA (one looking at THA only (154) and one looking at TKA only (145)) and two from the UK (one looking at THA only (152) and one looking at both THA and TKA (162)).

Two studies from the USA looked at the association between frailty, assessed using a 32-item FI, and 90-day mortality following TKA and THA, respectively (145, 154). The studies used data from a single centre and included both primary and revision arthroplasty. In the study looking at 90-day mortality following TKA, 9,818 individuals were included in the analysis. The mean age of study participants was 69 years and 57% were women. The number (%) of deaths within 90 days were 3 (0.1%) among those not frail (FI<0.11), 7 (0.2%) among those who were "vulnerable" (0.11≤FI<0.20) and 16 (0.8%) among those who were "frail" (FI≥0.20) (145). In the study looking at 90-day mortality following THA, 8,640 individuals were included. The median age was 68 years and 51% were women. The number (%) of deaths within 90 days were 6 (0.2%) among those not frail, 12 (0.4%) among those who were "vulnerable" and 21 (1.1%) among those who were "frail". The categorisation of frailty was the same as in the TKA study (145).

A study from the UK using data from the NJR included 276,594 primary THAs and 338,287 primary TKAs (162). Frailty was assessed using the hospital frailty risk score, a frailty instrument based on a range of international classification of diseases version 10 (ICD-10) codes (20). The median age at surgery among individuals who had a THA was 70 years and 60% were women. Among individuals who had TKA, the median age at surgery was 69 years and 57% were women. In total there were 954 deaths within 90 days of THA (0.3% of the cohort) and 870 deaths within 90 days of TKA (0.3% of the cohort). The authors reported that the hospital frailty risk score (as a continuous variable) predicted 90-day mortality following THA and TKA, respectively, with an area under receiver operating characteristic (ROC) curve (95% CI) of 0.77 (0.75, 0.78) and 0.78 (0.76, 0.79) (162).

A second study from the UK used data from CPRD Gold and assessed frailty using the eFI, which was categorised, based on the number of deficits present (maximum 36), as 0-4, 5-8, 9-12, and >13 (152). In total 6,682 individuals who had a THA were included. The mean age at surgery was 76 years and 61% were women. The number (%) of deaths within 90 days of THA among individuals with an eFI score of 0-4, 5-8, and 9-12, respectively, was

27 (0.65), 20 (0.97), and 10 (2.54) (152). There were no deaths within 90 days among individuals with an eFI score >13. Compared to individuals with an eFI score 0-4, those with an eFI score of 5-8 and 9-12, respectively were more likely to die within 90 days of THA after adjustment for age, sex, region, and calendar year of surgery (OR (95% CI), 1.33 (0.72, 2.44) and 2.78 (1.24, 6.23) (152).

This study was limited by the small number of deaths within 90 days in each of the frailty groups (no deaths among individuals with an eFI score >13). Also, the study did not account for the background rate of mortality in the general population among individuals in the different categories of frailty. Therefore, it is not possible to determine from this study whether THA impacts on mortality risk among individuals with frailty over and above the increased risk of mortality seen among those with frailty compared to those who are not frail in the general population.

Table 1.2. Studies examining the association between frailty and mortality up to 90 days following hip or knee arthroplasty

Author, year, (ref)	Country	Hip or knee arthroplasty	Age of participants	Data / setting	Frailty measure	Number of patients	Outcomes	Summary of key findings
Shin, 2016, (156)	USA	Hip and knee	≥18 years	American College of Surgeons National Surgical Quality Improvement Program (NSQIP)	mFI	Hip: 14,583; knee: 25,223	30-day mortality	Thirty-day mortality increased from 0.3% among those with mFI=0 following THA and 0.07% following TKA, to 4.17% among those with mFI≥0.45 following THA and 1.95% among those with 0.45<mFI≥0.36 following TKA (no deaths following TKA among those with mFI≥0.45
Runner, 2017, (155)	USA	Knee	≥60 years	NSQIP	mFI	90,260	30-day mortality	Thirty-day mortality increased with increasing mFI; from 0.007% among those with mFI=0.0, to 1.6% among those with mFI≥0.36
Johnson, 2019, (154)	USA	Hip	≥50 years	Single centre	FI	8,640	In-hospital and 90-day mortality	In-hospital and 90-day mortality increased with increasing frailty. 90-day mortality was 0.2% among "nonfrail", 0.4% among "vulnerable" and 1.1% among "frail"
Traven, 2019, (157)	USA	Hip and knee	Mean age, hip: 64.8yrs; knee: 66.6yrs	NSQIP	5-component mFI (mFI-5)	Hip: 140,158; knee: 226,398	30-day mortality	Increasing mFI was associated with increasing 30-day mortality, odds ratio (95% CI) 1.5 (1.3, 1.7) per 1-point increase in mFI following THA and 1.6

								(1.3, 1.8) per 1-point increase in mFI following TKA
Schwartz, 2020, (159)	USA	Knee	Mean age 66.4 years	NSQIP	5-component mFI (mFI-5)	179,702	30-day mortality	Thirty-day mortality following THA among those who were "healthy" (<2 mFI deficits present) and not hypoalbuminemic (albumin<3.5 g/dL) was 0.1% and among those who were "frail" (≥2 mFI components present) and not hypoalbuminemic was 0.2%
Wilson, 2020, (158)	USA	Hip	≥18 years, mean age 64.9 years	NSQIP	5-component mFI (mFI-5)	105,997	30-day mortality	Thirty-day mortality following THA among those who were "healthy" (<2 mFI deficits present) and not hypoalbuminemic (albumin<3.5 g/dL) was 0.1% and among those who were "frail" (≥2 mFI components present) and not hypoalbuminemic was 0.3%
Ferguson, 2021, (152)	UK	Hip	≥65 years. Mean age 76 years	CPRD Gold	Electronic frailty index (eFI)	6,682	90-day mortality	Increasing eFI associated with increasing 90-day mortality: 112 deaths among those with eFI 0-4 (2.7%), 75 deaths among those with eFI 5-8 (3.6%), 26 deaths among those with eFI 9-12 (6.6%), <5 deaths among those with eFI >13 (% not reported)

Johnson, 2019, (145)	USA	Knee	≥50 years, median age 69 years	Single centre	FI	9,818	In-hospital and 90-day mortality	In-hospital and 90-day mortality increased with increasing frailty. 90-day mortality was 0.1% among "nonfrail", 0.2% among "vulnerable" and 0.8% among "frail"
McConaghy, 2021, (160)	USA	Hip and knee	18-89 years	NSQIP	5-component mFI (mFI-5)	THA:202,488, TKA:230,823	30-day mortality	30-day mortality increased with increasing mFI
Penfold, 2021, (162)	UK	Hip and knee	THA: median 70 years, TKA: median 69 years	National Joint Registry (UK)	Hospital frailty risk score	THA: 276,594, TKA: 338,287	90-day mortality	Hospital frailty risk score predicted 90-day mortality (area under ROC curve, 0.76)

mFI: modified frailty index; FI: frailty index; THA: total hip arthroplasty; TKA: total knee arthroplasty; ROC: receiver operating characteristic curve

1.5.5. The association between frailty and patient-reported outcomes following hip and knee arthroplasty

Three studies, published between 2019 and 2021, looked at the association between frailty and patient-reported outcomes following THA and TKA: one from the Netherlands (which looked at THA and TKA) (163), one from Poland (which looked at THA only) (164), and one from the UK (which looked at THA only) (152) (Table 1.3).

A study from the Netherlands of 873 individuals who had a THA and 697 individuals who had a TKA in one of 7 hospitals looked at the association between frailty, assessed using the GFI and patient-reported functional outcomes assessed using the Hip disability Osteoarthritis Outcome Score/Knee injury Osteoarthritis Outcome Score (HOOS/KOOS) (163).

The authors found that individuals with frailty (defined as GFI≥4) had significantly lower HOOS/KOOS subscale scores (lower scores indicate worse problems) at baseline and 12-months postoperatively compared to those who were not frail, except for the KOOS symptom subscale, which was not statistically significantly different between the two groups (163). The authors reported that the crude mean change in both the HOOS and KOOS sports subscale scores at 12 months following THA and TKA were significantly lower among individuals with frailty compared to those who were not frail (mean change in HOOS sports subscale following THA among frail was 42.6 and among non-frail 49.4 (difference, p=0.002), and mean change in KOOS sports subscale following TKA among those who were frail was 27.9 and among those who were non-frail 36.4 (difference, p<0.001)). Also, the crude mean change in the KOOS quality of life subscale at 12 months following TKA was significantly lower among individuals with frailty (mean change 16.1) compared to those who were not frail (mean change 19.1, difference p=0.02), though there was no statistically significant difference in the crude mean change in the HOOS quality of life subscale following THA between the two groups. Crude mean change in the other HOOS/KOOS subscales (pain, symptoms, and activities of daily living) were not statistically significant between those with frailty and those who were not frail.

However, using a dichotomous frailty indicator does not allow for an association between degree of frailty and change in outcome measures to be assessed. Also, the authors did not account for differences in patient factors between the participants with frailty and

those who were not frail, such as age and sex, therefore it is not possible to assess differences in change in HOOS/KOOS subscales independent of other patient factors such as age and sex.

A single centre study of 365 individuals from Poland looked at the correlation between frailty, assessed using the mFI and mFI-5, and postoperative functional outcomes following THA (164). The authors reported correlation coefficients (Spearman's r) between the mFI and mFI-5 and the postoperative HHS, the WOMAC, the Hip and Knee Arthroplasty Satisfaction Scale (HKASS), and a pain Visual Analogue Scale (VAS). Only the age-adjusted correlation between the mFI and postoperative WOMAC score was significant at the 95% confidence level after age adjustment (Spearman's correlation coefficient 0.17), though no further specific detail was reported (164). The correlation between both the mFI and mFI-5 and the HHS, HKASS, or pain VAS were not statistically significant at the 95% confidence level.

However, the number of participants included in this study was relatively small and the number of participants with higher mFI and mFI-5 scores was limited. For example, there were no participants with an mFI-5 score of 5, and only 5 participants with an mFI-5 score of 4. In addition, preoperative pain and functional scores were not available, therefore the study did not look at the association between frailty and change in pain and functional scores. Also, the study did not look at outcomes following TKA.

A study from the UK using data from the CPRD Gold database looked at the association between frailty and preoperative, postoperative (6 months) and change in patient-reported outcomes following THA (152). Frailty was assessed using the eFI and categorised, based on the number of deficits present (maximum 36) as 0-4, 5-8, 9-12, and >13. Patient-reported outcomes were the joint specific OHS and also the general outcome measure, EuroQoL (EQ-5D). The authors reported that the absolute change in OHS and EQ-5D (postoperative score minus preoperative score) did not vary importantly between different levels of frailty. The crude mean (SD) absolute change in OHS among individuals with an eFI score of 0-4, 5-8, 9-12 and >13, respectively was 21.8 (9.4), 20.5 (10.2), 21.4 (8.8), and 24.4 (8.7) (152). Compared to individuals with an eFI score of 0-4, the age, sex, region, and calendar year adjusted change in OHS was lower among individuals with an eFI score of 5-8 and 9-12, respectively, mean change (95% CI), −2.0 (−2.9 to –1.2) and −2.9 (−4.7 to –1.1), though there was no significant difference among those with an eFI score

>13. However, the number of individuals who had postoperative OHS available and who had advanced frailty (eFI score >13) was small (7 individuals).

While the crude absolute change in OHS was similar among the different eFI categories, the crude mean (SD) preoperative score decreased with increasing eFI category; from 18.8 (7.9) among those with a preoperative eFI score of 0-4, to 14.7 (8.2) among those with a preoperative eFI score of >13. The authors found similar results when looking at the EQ-5D; the crude mean (SD) change in EQ-5D among those with an eFI score of 0-4, 5-8, 9-12 and >13, respectively was 0.45 (0.33), 0.45 (0.36), 0.47 (0.34), and 0.59 (0.32) (152).

The study did not, however, look at the association between frailty and patient-reported success following THA, nor did the study look at outcomes following TKA.

While there is some variation in findings between studies and between different outcome measures and subscales, a number of studies have established a link between frailty and poorer postoperative patient-reported functional outcome measures following THA and TKA, including WOMAC, HOOS, KOOS, OHS, OKS, and EQ-5D. However, the literature review did not identify any data looking at the association between frailty and patient-reported success. Since individuals with frailty may have more limited capacity to improve in functional ability following arthroplasty compared to individuals without frailty, regardless of the technical success of the surgery, it is relevant to consider the impact of frailty on patient-reported-success following arthroplasty, alongside functional outcome scores. The literature review also did not identify any previous studies looking at the association between frailty and achieving the MIC in outcome measures.

Table 1.3. Studies examining the association between frailty and patient-reported outcomes

Author, year, (ref)	Country	Total hip or knee arthroplasty	Age of participants	Data / setting	Frailty measure	Number of patients	Outcomes	Summary of key findings
Meessen, 2019 (163)	Netherlands	Hip and knee	≥18 years, mean age 65.1 years	Longitudinal Leiden Orthopaedics Outcomes of Osteo-Arthritis Study (LOAS)	Groningen Frailty Indicator	THA: 873, TKA: 697	Hip disability Osteoarthritis Outcome Score/Knee injury Osteoarthritis Outcome Score (HOOS/KOOS)	Individuals with frailty had significantly lower baseline HOOS and KOOS, though crude absolute change in scores were similar for those with and without frailty, except for the "sports" and "quality of life" subscales, which were significantly lower among those with frailty
Pulik, 2020 (164)	Poland	Hip	≥18 years, mean age 65.1 years	Clinical database at the Department of Orthopedics and Traumatology, Infant Jesus Teaching Hospital, Medical University of Warsaw	mFI-5 and mFI-11	365	Western Ontario and McMaster Universities Index of Osteoarthritis (WOMAC), Harris hip score (HHS)	Patients with frailty had poorer postoperative WOMAC scores. Only the correlation between the mFI and postoperative WOMAC score was statistically significant at the 95% confidence level after adjustment for age
Ferguson, 2021 (152)	UK	Hip	≥65 years. Mean age 76 years	Clinical practice research datalink (CPRD) (gold)	Electronic frailty index (eFI)	6,682	Oxford Hip Score (OHS), EQ-5D	Crude mean preoperative OHS and EQ-5D score decreased with increasing frailty. However, crude absolute change in OHS and EQ-5D did not vary

									importantly between different levels of frailty

THA: Total hip arthroplasty; TKA: total knee arthroplasty; HOOS: hip disability osteoarthritis outcome score; KOOS: knee disability osteoarthritis outcome score; mFI: modified frailty index; EQ-5D: EuroQol- 5 Dimension

1.5.6. The impact of frailty on other outcomes following hip and knee arthroplasty

A systematic review of studies looking at the impact of frailty on outcomes following THA and TKA was published by Schmucker and colleagues in 2019 (165). Some studies included in the systematic review by Schmucker, et al. were outside of the scope of the literature review included in this thesis, including studies looking at the impact of frailty on the risk of complications (including pulmonary embolism, myocardial infarction, and reoperation within 30 days (165)).

Since the systematic review by Schmucker, et al. a number of other studies have been published looking at the impact of frailty on outcomes following THA and TKA, though again were outside of the scope of the literature review for this thesis (166-173). These include studies that have reported a link between frailty and increased length of hospital stay and increased risk of 30-day readmission (167, 170, 173), increased risk of medical and surgical complications (152, 154, 158-160, 169-173), postoperative neurocognitive disorders (168), and periprosthetic fracture (145).

Another systematic review was published by Lemos and colleagues in 2021, though the focus of this review was to assess definitions of frailty used in studies looking at the impact of frailty on outcomes following a range of orthopaedic procedures (151). This review highlighted that the mFI was the most commonly used frailty instrument (38% of the studies identified used either the mFI-11 or mFI-5), though 24 different frailty instruments were used in total across the studies identified (151). Among studies that looked at the association between frailty and outcomes following total joint replacement surgery, the review highlighted that the most commonly reported outcomes were complications (72% of identified studies), and mortality (56% of identified studies) (151).

1.5.7. Summary

THA and TKA are indicated in people with hip and knee OA not adequately managed by conservative therapy. Previous studies have linked increasing frailty with increasing short-term mortality following THA and TKA and poorer postoperative patient-reported outcomes.

There was variation between studies which made direct comparison and synthesis of evidence difficult. For example, there was variation in the way different studies had assessed and categorised frailty. Some studies were also limited by small numbers of deaths within 90 days of THA/TKA. Since short-term deaths following THA and TKA are rare events, and also the proportion of individuals who have a THA and TKA and have advanced frailty is also relatively small, large samples are needed to robustly determine the association between frailty and short-term mortality.

None of the studies identified accounted for the fact that a higher level of frailty is linked with increased mortality in the general population. Therefore, it is not clear to what extent the surgery itself may be attributable to increased mortality among patients with frailty following THA and TKA.

Three previous studies have also linked frailty with poorer postoperative patient-reported outcomes following THA and TKA, although there are data suggesting that crude, absolute changes in functional outcome scores are similar between different levels of frailty. The literature review did not, however, identify any data looking at the association between frailty and patients' assessment of success of arthroplasty. Since frailty may limit capacity to improve in functional ability, data looking at the association between frailty and patient-reported success is an important complementary outcome. In addition, no previous studies have looked at the association between frailty and achieving the MIC in OHS and OKS outcomes following THA and TKA.

Chapter 2. Aims and objectives

2.1. Aim

The broad aim of this thesis was to determine the impact of frailty on outcomes following hip and knee arthroplasty.

2.2. Specific objectives

The specific objectives of this thesis were to determine:

1. (i) The impact of frailty on the likelihood of 30-, 60-, and 90-day mortality following total hip arthroplasty (THA) and total knee arthroplasty (TKA)

   (ii) To estimate the probability of 30-day mortality following THA and TKA, stratified by age, sex, and frailty status

   (iii) The likelihood of 30-, 60-, and 90-day mortality among people who had a THA or TKA, compared to controls with OA, but no previous arthroplasty, stratified by frailty status

2. The impact of frailty on patient-reported outcomes following THA and TKA. Specifically, to determine the impact of frailty on the following outcomes:
   (i) The Oxford hip and knee score,
   (ii) Achieving the minimal important change in Oxford hip and knee scores
   (iii) Patient-reported success

3. Whether THA and TKA impact on the rate of change in frailty over time

Chapter 3. Methods

3.1. Overview

This chapter summarises the methods used to address the study aim and objectives. It includes a summary of the data sources used in the analyses including the clinical practice research datalink (CPRD), hospital episode statistics (HES) and linked patient-reported outcomes (PROMs) for patients who had had either a total hip arthroplasty (THA) or total knee arthroplasty (TKA). Details about how the data were accessed, ethics, and data management are also included. Details about the development and assessment of frailty using the electronic frailty index (eFI) are outlined and the outcome variables (mortality and PROMs) and also covariates used in the different analyses are described. The chapter ends with an overview about the statistical methods used to address the study objectives and data management processes.

3.2. Study participants and setting

Men and women aged 60 years and older living in England who were registered with a primary care general practice that submits data to the CPRD contributed data to the analysis. In order to address the study objectives only those practices which had consented to participate in data linkage (to secondary care, Office for National Statistics (ONS) mortality and IMD datasets) were included.

3.3. Data sources

3.3.1. Overview

This section describes the content and structure of the datasets used in the analyses, as well as a description of clinical coding systems used in the datasets.

3.3.2. The Clinical Practice Research Datalink

The primary data source for this thesis was the CPRD. The CPRD is a UK government, not-for-profit research service that supplies anonymised primary care data, as well as linked

secondary care, deprivation, and death data, for the purpose of health research (174, 175).

The CPRD was originally developed from the Value Added Medical Products database, which was established in London in 1987, and grew to become the General Practice Research Database in 1993. This was developed further to become the CPRD in 2012 (174). Originally, the CPRD comprised data from general practices using the Vision® patient management system. In 2017, general practices using the Egton Medical Information Systems (EMIS) Web® patient management system were added to the CPRD.

The CPRD database is made up of two databases: Aurum (175), which comprises data from practices using the EMIS Web® patient management system and Gold (174), which comprises data from practices using the Vision® patient management system. Both the CPRD Aurum and CPRD Gold databases were used in this thesis. CPRD Gold includes practices in England, Wales, Scotland, and Northern Ireland, whilst CPRD Aurum includes practices in England, and Northern Ireland from 2019 (174, 175). However, data linkage to secondary care and other datasets are only available for consenting practices in England and therefore only data from practices in England were included in the analyses described in this thesis.

The CPRD is a dynamic database, with data from contributing practices collected daily. Snapshots of the data are created periodically for use in research. In this thesis, data set 18 was used, which was downloaded between July-August 2020. Due to the dynamic nature of CPRD, the number of patients included in the databases varies over time. The CPRD data profiles reported that, as at July 2013, about 6.9% of the UK population were included in the CPRD Gold database (174) and, as at September 2018, about 13% of the English population were included in the CPRD Aurum database (175).

The CPRD database is structured as a set of data files relating to different aspects of administrative and clinical data. For example, one file contains data about patients, including sex, year and month of birth, and date of registration with the practice; another file contains coded clinical diagnostic data; and another file contains coded prescription data. Each of the data files includes unique identifiers, including practice and patient pseudo-identifiers, which can be used to link information in the different data files. There are some differences in the structure of the Aurum and Gold databases, which are described in more detail elsewhere (174, 175).

The CPRD database includes data recorded during routine clinical interactions, including demographics, diagnoses, symptoms, signs, prescriptions, referrals, immunisations, behavioural factors, and tests. Clinical coding in the CPRD is discussed in section 3.3.4.

The CPRD database has been linked to secondary care data (hospital episode statistics (HES)), deprivation (index of multiple deprivation), and the Office of National Statistics (ONS) mortality database. These data bases and the method of linkage are outlined further below.

3.3.3. Linked datasets

Data linkage between the CPRD databases and linked datasets is done by a third party, NHS Digital, following a robust process, which has been previously described in detail (176). Briefly, for general practices that have consented to participate in record linkage, person identifiers (NHS number, sex, date of birth, and postcode), are supplied by the general practice software suppliers to NHS Digital. External data custodians also submit person identifiers to NHS Digital, which then matches identifiers from the general practices and external datasets. A de-identified file of linked datasets, with pseudonymised identifiers, is then passed to the CPRD (176).

For general practices in England that contribute to the CPRD and have consented to participate in data linkage, linked secondary care data (Hospital Episode Statistics (HES), admitted patient care), patient-reported outcome measures (PROMs), and ONS mortality data are available. In the CPRD databases used in this thesis, linked secondary care data were available for the period January 1998 to March 2019.

In this thesis, the following linked datasets were used: HES, admitted patient care; patient-reported outcome measures; ONS mortality; and index of multiple deprivation. These are described below.

3.3.3.1. Hospital Episode Statistics, Admitted Patient Care

The HES, admitted patient care database includes data on all admissions to NHS funded hospitals in England and is curated by NHS Digital (177).

The HES, admitted patient care database includes routinely recorded data for each hospital episode, including admission and discharge dates, coded diagnostic data, and

coded procedures undertaken. Diagnostic data are coded using the International Classification of Diseases version 10 (ICD10), and procedures undertaken are coded using the UK Office of Population, Census and Surveys classification (OPCS) 4.6.

For the CPRD dataset used in this thesis, linked HES admitted patient care data were available from April 1997 to June 2019.

3.3.3.2. Patient-reported outcome measures

PROMs following hip and knee arthroplasty have been collected nationally since April 2009 under the Standard NHS Contract for Acute Services and are held by NHS digital (177, 178).

NHS providers ask patients undergoing hip or knee arthroplasty to complete a paper PROMs questionnaire prior to their surgery. Six months following surgery, a follow up questionnaire is posted to patients. Questionnaires are securely collated and electronically scanned by a contractor (178).

The pre- and postoperative questionnaires include the Oxford hip and knee score. The postoperative questionnaire also includes a question about success of the surgery. Further details about the patient-reported outcome measures are described in section 3.7.

For the CPRD dataset used in this thesis, linked PROMs data were available from April 2009 to June 2019.

3.3.3.3. Office for National Statistics mortality data

The ONS mortality database contains the date and coded cause of death based on information recorded on the death certificate for the population of England and Wales and is considered the gold standard record of mortality (179).

For the CPRD dataset used in this thesis, linked ONS mortality data were available from January 1998 to May 2019.

3.3.3.4. Index of multiple deprivation

Linked data for the 2019 English IMD was available. The IMD is briefly discussed in section 3.7.7.

3.3.4. Clinical coding in the clinical practice research datalink

In CPRD Gold (Vision® patient management system), clinical coding is done using Clinical Terms Version 3 (CTV3) Read codes (174). In CPRD Aurum (EMIS Web® patient management system), clinical coding is done using a combination of the systematized nomenclature of medicine clinical terms (SNOMED CT) and CTV3 Read codes, as well as local EMIS Web® codes (175).

Clinical coding in the UK is changing as a result of the Department of Health ten-year strategy framework aimed at transforming information for health and social care, which was published in 2012 (180). Part of the framework aimed to improve the integration of information across the entire health and social care sector. To enable this, the framework recommended a convergence of clinical coding terminology across all relevant systems to the SNOMED CT system. Consequently, NHS Digital set out to produce a set of mappings from Read version 2 and Read version 3 (CTV3) to the SNOMED CT system.

3.3.5. Mapping between coding systems

The eFI was originally developed using CTV3 Read codes to identify health deficits based on diagnostic codes (18). In order to apply the eFI to both the CPRD Gold and Aurum databases, mapping tables published by NHS digital (181) were used to produce SNOMED CT codes for each of the eFI deficits, based on the original CTV3 Read code lists, which were obtained from the group that developed the eFI (18).

3.4. Data access and ethics

Data used in this thesis were accessed from the CPRD. At the time data for this thesis were accessed, the CPRD required researchers to submit a detailed study protocol to the Independent Scientific Advisory Committee (ISAC). The ISAC was responsible for reviewing the public health benefits and scientific merit of proposed projects seeking to use CPRD data, (182). The ISAC application relating to the work carried out in this thesis (reference 20_119) was approved in May 2020. A summary of the protocol is available on

the CPRD website (183). The CPRD data used in this thesis were downloaded between July-August 2020.

After obtaining the data and carrying out initial data preparation work, minor changes to original ISAC protocol were necessary. A revised protocol was submitted to the ISAC and was approved February 2022.

CPRD has ethical approval from the Health Research Authority to support research approved by the ISAC (IRAS number 242149).

3.5. Data management

Anonymised personal data from the CPRD and linked dataset used in this thesis were stored on secure research data storage servers at the University of Manchester.

The authorised CPRD user (MC) was responsible for data management tasks including the appropriate storage, restricted access and use of the CPRD dataset. The principal investigator, (TON), had overall responsibility for the quality of the data acquired, and its storage. All personal data was anonymised by third parties. Only anonymised data was used in this research. Individual-level patient data was not shared outside of the University of Manchester, in accordance with the CPRD license agreement.

All electronic data were stored and backed up daily on secure servers. The project made use of the University of Manchester Research Data Storage (RDS). The RDS allows researchers to store, manage and curate their data, as well as preserve data after project completion. This service ensures the data is securely stored and backed up at regular intervals. Access to the data servers was restricted and managed. No data were saved or stored on local or mobile drives.

All raw data as well as intermediate data analysis files, as outlined in the CPRD data sharing agreement, will be destroyed within 12 months of study end. Should analysis or publication be delayed, an extension request to retain the data will be made to CPRD.

3.6. Summary

The core dataset used in this thesis was the CPRD (Aurum and Gold), which is a database of coded primary care electronic medical records. To ascertain exposure and outcome

variables and covariates used in statistical models, the CPRD was linked to the HES database, including PROMs, the ONS mortality database, and data on the 2019 IMD.

In order to facilitate applying code lists in both CPRD Aurum and Gold (which use different clinical coding systems), clinical coding mapping tables published by NHS digital were used.

3.7. Exposures and outcomes

3.7.1. Overview

This section describes how the exposure and outcome variables and covariates used in this thesis were ascertained.

3.7.2. Assessment of frailty – the electronic frailty index

Frailty was assessed using the eFI, which was previously developed by Clegg and colleagues using data from routinely collected electronic medical records (EMRs) and published in 2016 (18). This section describes the development, validation, and application of the eFI.

3.7.2.1. Development of the electronic frailty index

The eFI was developed using routinely collected EMRs from the ResearchOne and The Health Improvement Network (THIN) databases. ResearchOne includes data from general practices using The Phoenix Partnership (TPP) SystemOne clinical patient management software and THIN includes data from general practices using the Vision clinical patient management software. The ResearchOne database was used as a development and internal validation dataset and THIN was used as an external validation dataset.

The eFI was developed in the ResearchOne database by reviewing CTV3 Read codes in order to identify candidate health deficits in the eFI, based on deficits included in the Canadian Study of Health and Aging (CSHA) frailty index (23). Codes were selected for inclusion as deficits in the eFI based on previously published guidelines for the creation of a frailty index based on the cumulative deficit model of frailty (13). Briefly, codes were selected in order to identify health deficits that increase in prevalence with age, are not ubiquitous before age 65 years, are associated with health outcomes, and cover a range of physiological systems (13).

The eFI was developed in a cohort of 207,814 randomly selected individuals aged 65-95 years from the ResearchOne database. In total, 36 health deficits, comprising 2,171 clinical codes met the inclusion criteria and were selected for inclusion in the eFI. A list of the 36 deficits included in the eFI is shown in Table 3.1. The eFI is calculated as a simple, unweighted sum of the number of eFI health deficits present in an individual, divided by the total number of deficits considered (36). For example an individual with 9 of the eFI deficits present has an eFI score of 9/36, or 0.25. Polypharmacy was included as one of the eFI deficits, defined as using five or more medications simultaneously. The eFI was categorised as fit, mild frailty, moderate frailty and severe frailty based on quartiles of the eFI, using the 99th centile as the upper limit (18).

In the development cohort, the mean age of participants was 75 years and 55% were women. The proportion of individuals who were classified as fit, mild frailty, moderate frailty, and severe frailty, respectively was 50%, 35%, 12%, and 3%.

3.7.2.2. Validation of the electronic frailty index

A random cohort of 207,720 individuals from the ResearchOne database, separate from the development cohort, was used as an internal validation cohort. External validation was also carried out in a cohort of 516,007 individuals from the THIN database.

In the internal validation cohort, the ability of the eFI to predict key outcomes: (i) all-cause mortality, (ii) unplanned hospitalisation, and (iii) nursing home admission was assessed. The association between the eFI and 1-, 3-, and 5-year mortality, hospitalisation, and nursing home admission was assessed using Cox regression. ROC curves and c-statistics were calculated for the outcomes of interest. In the external validation cohort, all-cause mortality and unplanned hospitalisation were considered as outcomes, though data on nursing home admission were not available in the external validation cohort.

In the internal validation cohort, the eFI was shown to have good discrimination for mortality and nursing home admission within 12 months (c-statistic 0.72 and 0.74, respectively) and moderate discrimination for hospitalisation within 12 months (c-statistic 0.66) (18). Similar results were seen in the external validation cohort for 12-month mortality and hospitalisation, respectively (c-statistic 0.76 and 0.71).

More recently, the eFI has been externally validated in a Welsh cohort of 469,000 men and women aged 65-95 years, where the eFI was shown to predict mortality, unplanned hospitalisation, and care home admission, with similar results to those obtained in the original development and validation cohorts (184).

3.7.2.3. Application of the electronic frailty index

The feasibility and acceptability of using the eFI has been assessed in primary care (185). In a pilot study involving one primary care practice in the south of England, practice staff reported that the eFI was a feasible and acceptable tool for the identification of patients with frailty. The mean eFI score was higher for patients aged ≥75 years attending the comprehensive geriatric assessment (CGA) clinic (18 individuals, mean (SD) eFI score 0.33 (0.09)), compared to the mean eFI score for all patients registered at the practice aged ≥75 years (589 patients, mean (SD) eFI score 0.23 (0.12)).

The eFI is available in primary care electronic patient management systems in the UK (186) and its use is recommended by NICE as a suitable frailty tool to comply with the general medical services contractual agreement to identify individuals living with moderate and severe frailty (187, 188).

Table 3.1. Deficits included in the eFI

Deficit
Activity limitation
Anaemia & haematinic deficiency
Arthritis
Atrial fibrillation
Cerebrovascular disease
Chronic kidney disease
Diabetes
Dizziness
Dyspnoea
Falls
Foot problems
Fragility fracture
Hearing impairment
Heart failure
Heart valve disease
Housebound
Hypertension
Hypotension / syncope
Ischaemic heart disease
Memory & cognitive problems
Mobility and transfer problems
Osteoporosis
Parkinsonism & tremor
Peptic ulcer
Peripheral vascular disease
Polypharmacy
Requirement for care
Respiratory disease
Skin ulcer
Sleep disturbance
Social vulnerability
Thyroid disease
Urinary incontinence
Urinary system disease
Visual impairment
Weight loss & anorexia

3.7.3. Identification of hip and knee arthroplasty

The HES, admitted patient care database was used to identify patients who had a THA or TKA, using OPCS codes published by the NJR (189). THAs and TKAs with a primary indication for surgery relating to fractures, osteonecrosis, rheumatoid arthritis, and malignant neoplasm of bone were excluded.

3.7.4. Identification of hip and knee osteoarthritis

For objective 1. (iii) (likelihood of 30-, 60-, and 90-day mortality among people who had a THA or TKA, compared to controls with OA, but no previous arthroplasty, stratified by frailty status), hip and knee osteoarthritis was identified for controls based on codes relating to hip and knee OA recorded in primary care records. Read code lists used to identify hip and knee OA in the primary care records are shown in Table 3.2. The code lists were compiled by reviewing code lists produced by Keele University, which are available online (190). Code browsers provided by the CPRD were also reviewed based on searches using the key words “osteoarthritis”, “coxarthrosis”, and “gonarthrosis”. The code lists were reviewed and agreed by clinical supervisors of the PhD project.

Table 3.2. Read codes used to identify (A) hip osteoarthritis and (B) knee osteoarthritis

(A) Hip osteoarthritis

Read code	Read term
N051500	Localised, primary osteoarthritis of the pelvic region/thigh
N051900	Primary coxarthrosis, bilateral
N053500	Localised osteoarthritis, unspecified, pelvic region/thigh
N053512	Hip osteoarthritis NOS
N05z500	Osteoarthritis NOS, pelvic region/thigh
N05z511	Hip osteoarthritis NOS
N05zJ00	Osteoarthritis NOS, of hip
N06z500	Arthropathy NOS, of the pelvic region and thigh
Nyu2100	[X]Other primary coxarthrosis

(B) Knee osteoarthritis

Read code	Read term
N051B00	Primary gonarthrosis, bilateral
N053611	Patellofemoral osteoarthritis
N05z611	Knee osteoarthritis NOS
N05zL00	Osteoarthritis NOS, of knee
N06z611	Knee osteoarthritis NOS

3.7.5. Patient-reported outcome measures

Patient-reported outcome measures have been collected by all providers of NHS funded care since April 2009 in order to measure health gains in patients undergoing a THA or TKA. PROMs are collected via questionnaires completed by patients before and about 6 months after surgery. The questionnaire includes the general health EuroQol 5-dimension (EQ-5D)), as well as the joint-specific OHS and OKS, and also a question about patient-perception of the success of surgery. These patient-reported outcome measures are described in more detail below.

3.7.5.1. The Oxford hip score and Oxford knee score

The OHS and OKS were developed to assess patients' perceptions of the outcomes of hip and knee arthroplasty. The OHS and OKS are each based on a questionnaire comprising 12 questions about pain and ability to carry out basic daily activities. An overall score is

calculated which ranges from zero to 48. Further details about the OHS and OKS are presented in section 1.4.4.1.

Data on these outcomes measured was obtained via linked Hospital Episode Statistics in-patient data.

3.7.5.2. Patient-reported success

The questionnaire completed by patients postoperatively includes a question about success of the surgery. Patients are asked “overall, how are the problems now in the <hip/knee> on which you had the surgery, compared to before your operation?”. Possible responses are “much better”, “a little better”, “about the same”, “a little worse”, and “much worse”.

3.7.6. Identification of mortality

Mortality was determined using linked data from the ONS. Cause-specific mortality was also ascertained based on the ICD code recorded as the primary cause of death and categorised based on ICD chapter headings.

3.7.7. Identification of neighbourhood deprivation – the index of multiple deprivation

The 2019 English IMD provides a measure of area deprivation at lower-layer super output area level. In this thesis, IMD was calculated for each individual based on their latest home postcode and was categorised based on quintiles. The IMD is calculated based on seven distinct domains of deprivation: income deprivation, employment deprivation, education, skills, and training deprivation, health deprivation and disability, crime, barriers to housing and services, and living environment deprivation (191). Further details about the construction of the IMD are available in a technical report (192).

3.7.8. Identification of covariates

3.7.8.1. Ethnicity

Ethnicity was identified from either the primary or secondary care (HES) records.

In order to identify ethnicity in the primary care record, a modified version of a script produced by our group which has been used in a previous publication (193). Briefly, the clinical code descriptions in the coding dictionary provided by CPRD were searched using key word searches based on the ethnic groups used in the 2021 census of England and Wales to identify clinical codes relating to ethnic groups. Codes identifying ethnic groups were categorised as “Asian”, “Black”, “Mixed”, “White”, “other” and “unknown”.

In the HES dataset, a pre-populated field indicated ethnicity and was coded as “Bangladeshi”, “Black African”, “Black Caribbean”, “Black other”, “Chinese”, “Indian”, “Mixed”, “Pakistani”, “White”, “other Asian”, “other” and “unknown”. In order to combine the ethnicity groups in the primary care record with the ethnicity groups in the HES data, ethnicity groups in the HES data were combined as follows: “Bangladeshi”, “Chinese”, “Indian”, “other Asian”, “Pakistani” were combined as “Asian”; “Black African”, “Black Caribbean”, and “Black other” were combined as “Black”

Where there was disagreement between the primary and secondary care records in the ethnicity of an individual, ethnicity was set to missing.

3.7.8.2. Body mass index

Body mass index (BMI) was determined based on data recorded in the primary care record. Where a value of BMI was recorded, this value was used. If BMI was not recorded directly but height and weight was recorded, then BMI was calculated as height (measured in metres) divided by weight (measured in kg) squared.

When assessing BMI at a particular date, the BMI measurement closest to the date of interest, prior to the date of interest, and within 12 months prior to the date of interest was used. If no BMI or height and weight measurements were recorded within 12 months prior to the date of interest, then BMI was set to missing.

3.7.8.3. Age and sex

Age and sex were determined based on data recorded in the primary care record. Since only year of birth was available to us (day and month of birth were not available), age at a given date was approximated by assuming the day and month of birth was 30 June for all individuals.

3.8. Statistical analysis

This section provides a broad overview of the statistical methods used in addressing the objectives of this thesis. Detail about specific analyses are presented in the methods sections of each of the results chapters.

Summary statistics were used to describe the distribution of data. For continuous variables that were approximately normally distributed, mean and SD was reported. For continuous variables that were not normally distributed, median and inter-quartile range (IQR) was reported. For categorical variables, summary statistics included frequency and percentage. To compare the distribution of continuous variables between two groups, the Mann - Whitney rank sum test was used. To compare the distribution of categorical variables between two groups, the chi-square test was used. In all analyses, statistical significance was determined at the 95% confidence level.

Regression methods were used to explore the relationship between exposures and outcomes. Linear regression was used to model continuous outcomes while binary outcomes were modelled using logistic regression. A brief review of specific statistical methods used to address each of the objectives is included below.

3.8.1. Statistical analysis – objective 1

In the analysis addressing objective 1, which is presented in Chapter 4, the association between eFI category and all-cause 30-, 60-, and 90-day mortality following THA and TKA was assessed using survival analysis. Survival methods are used to analyse data where the outcome of interest is time until an event occurs. In survival analysis, often information about whether the event of interest occurs is only known up to a particular point in time. For example, it may not be possible to determine whether or not an event of interest has occurred for a given individual after the individual has been lost to follow up. In survival analysis, observations are said to be *censored* at the point beyond which we do not have any information about survival and observations no longer contribute to the analysis beyond this time.

A simple way to present survival data is to use Kaplan-Meier survival curves. While this approach can be useful, often a model incorporating the effect of multiple variables on survival is needed. The most commonly used multivariable method is the Cox regression

model. This approach determines, for an individual that has survived to time *t*, the instantaneous probability of the outcome of interest, which is known as the *hazard*. It is assumed that any predictor that affects the hazard does so by the same proportion at all time points, which is known as the *proportional hazards assumption*. The *baseline hazard function*, $h_0(t)$ is the hazard function for individuals with all predictor variables x_1, x_2, …, x_p, equal to zero. The hazard function $h(t,x)$ is assumed to take the form $h_0(t)*f(x)$, where $f(x)$ for a given individual is the *hazard ratio* for that individual and is time-invariant. For statistical convenience, the natural logarithm of the hazard ratio, $f(x)$, is estimated as a linear sum of the predictor variables (194).

The association between eFI category and all-cause 30-, 60-, and 90-day mortality following THA and TKA was first assessed using Kaplan-Meir estimates. Next, a multivariable Cox model was used to determine the association between eFI category ('fit' was the reference category) and 30-, 60-, and 90-day all-cause mortality, in separate models. Sex, 5-year age band, quintile of IMD, and year of surgery were included as covariates in the model and results were presented as HRs and 95% CI. Participants contributed person-time from the date of THA/TKA until the date of death, the date the participant's primary care practice stopped contributing to CPRD, or the end of the study period (30-, 60-, or 90 days).

In addition, the association between eFI-category and cause-specific mortality was also assessed. Cause-specific mortality was determined based on the primary cause of death recorded in the ONS mortality database and was grouped based on ICD chapter headings.

When considering time to cause-specific mortality as the outcome of interest, mortality due to a particular cause (such as 'diseases of the circulatory system') prevent mortality due to other causes (such as 'diseases of the respiratory system') from being observed. Events that preclude a particular event of interest from being observed are referred to as *competing risks*. One approach to modelling outcomes in the presence of competing risks is to model each outcome of interest separately and censor at the time of a competing risk (194). However, for this approach to provide reliable estimates, the primary outcome of interest and the competing risks must be independent and censoring due to competing risks must be *noninformative*. This means that, at a given point in time, study participants who remain under follow up have the same future risk of the outcome of interest as those who were censored, had they remained under follow up (195). Even when competing

events are independent, censoring individuals at the time of a competing event may lead to incorrect conclusions, since the event probability being estimated is interpreted as occurring in a setting where competing events and censoring do not occur (195). For example when considering mortality due to a specific cause, such as cardiovascular disease, and censoring at the time of other causes of death, the results are interpreted as occurring in a setting where death due to causes other than cardiovascular disease is not possible.

A method of modelling time to event outcomes in the presence of competing risks was developed by Fine and Gray and this method was used when considering the impact of frailty on cause-specific mortality following THA and TKA, using the function 'stcrreg' in Stata (195). The method developed by Fine and Gray involves estimating the *subdistribution hazard function*, which is the instantaneous risk of the k^{th} event of interest among individuals who have not yet experienced the k^{th} event of interest. The risk set used to calculate the subdistribution hazard function includes individuals who have experienced none of the events of interest, as well as individuals who have previously experienced a competing event. This differs from the risk set for the cause-specific hazard function, which includes only those who are currently event free (195).

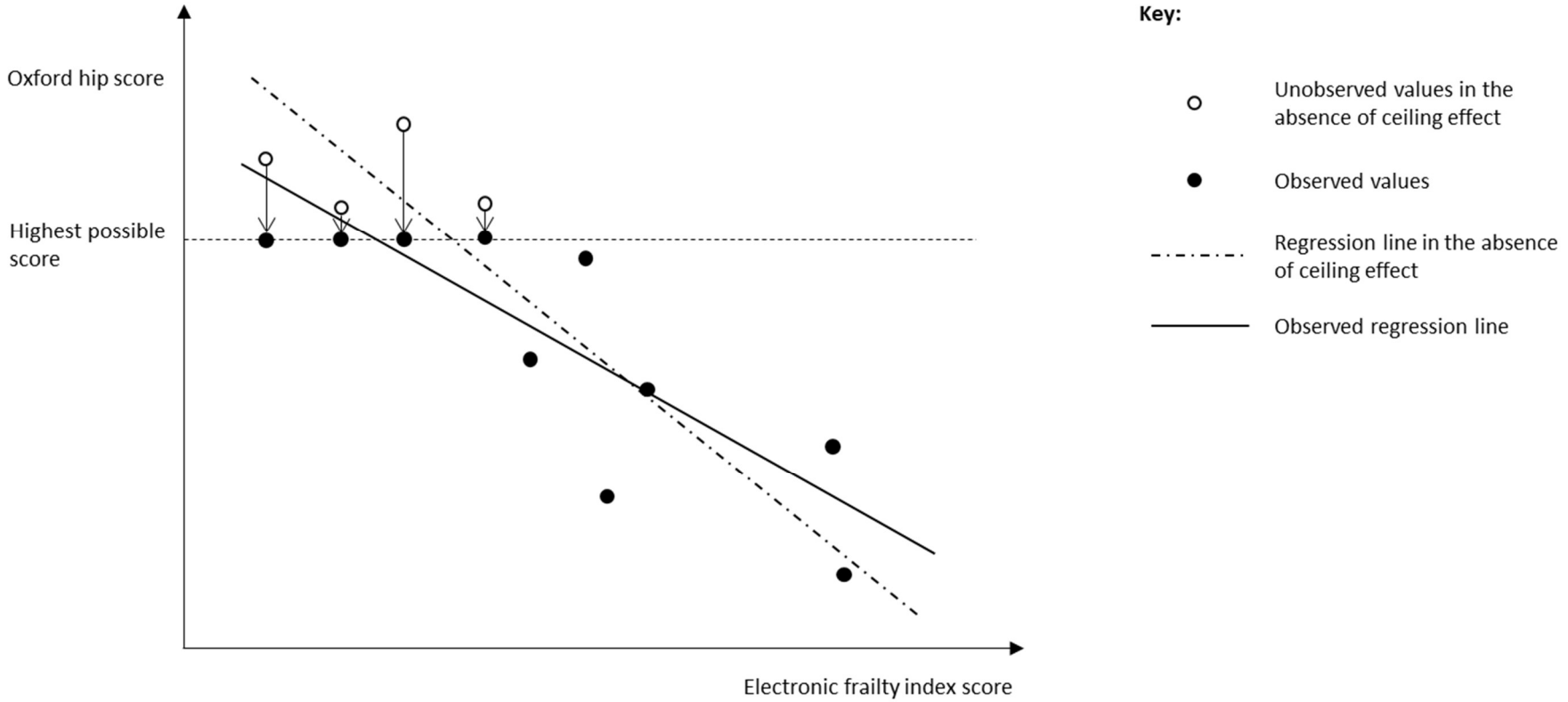
The predicted probability of all-cause 30-day mortality following THA and TKA was also calculated. This was done using a logistic regression model with 30-day mortality as the outcome and eFI category as the predictor. Year of surgery, sex, 5-year age band, and quintile of IMD were included as covariates. Predicted probabilities were presented as percentage (95% CI) for each sex and 5-year age band stratum, with year of surgery and quintile of IMD set to their median values. Predicted probabilities were calculated using the post estimation command 'margins' in Stata.

The association between eFI category 30-, 60-, and 90-day mortality among cases who had THA/TKA, compared to controls who had hip/knee OA but no previous arthroplasty was also estimated using Cox regression. In this analysis, cases were matched to controls at the date of surgery of the case. Matching was done on year of birth, sex, and quintile of IMD. The HRs and 95% CIs for 30-, 60-, and 90-day mortality among cases, compared to controls (reference group) were presented, stratified by frailty category. Further detail of the analysis carried out for objective 1 is provided in section 4.3.5.

3.8.2. Statistical analysis – objective 2

The association between frailty (independent variable) and postoperative OHS and OKS (dependent variables) was assessed in Chapter 5. Possible values of the postoperative OHS and OKS are constrained to lie within the range zero to 48. A significant proportion of individuals achieve the maximum possible OHS/OKS following THA/TKA, thus the OHS and OKS exhibit a *ceiling effect.* If the ceiling effect was not present, some individuals may have achieved a higher score, though the true score beyond the ceiling cannot be observed. Traditional techniques for modelling continuous outcomes, such as ordinary least squares linear regression, can give biased estimates when outcomes exhibit ceiling effects (196). This bias occurs because unobserved values beyond the maximum possible score are constrained at the ceiling, which affects the fitted regression line, compared to the regression line that would be fitted if the true values beyond the ceiling were observed (Figure 3.1).

Figure 3.1. Illustration of the impact of a ceiling effect on regression modelling



Modified from (196).

The Tobit model provides unbiased estimates in the presence of ceiling effects using a two-part maximum likelihood estimation. The standard maximum likelihood estimation involves assuming a normal distribution around each point on the regression line and each observed value is assigned a likelihood based on how far from the mean of the normal distribution the point is. The likelihood of the regression line is calculated as the product of the likelihood of each of the observed values. Regression coefficients are chosen to maximise the likelihood of the regression line. In Tobit regression, the likelihood function is calculated in two parts. The first part applies to all observations. For each observation, the likelihood that observation is censored given the predictor variables is estimated. Regression coefficients are chosen that most accurately predict whether or not observations are censored. The second part of the likelihood function applies only to uncensored observations and is the standard maximum likelihood process as described above. In the Tobit model, a set of regression coefficients are chosen that simultaneously maximise both parts of the likelihood function (196).

In Chapter 5, the association between eFI category (independent variable) and postoperative OHS and OKS (dependent variables) was modelled using Tobit regression. The models were adjusted for age, sex, and quintile of IMD. Results were presented as regression coefficients and 95% CIs. Further detail of the analysis carried out for objective 1 is provided in section 5.3.7.

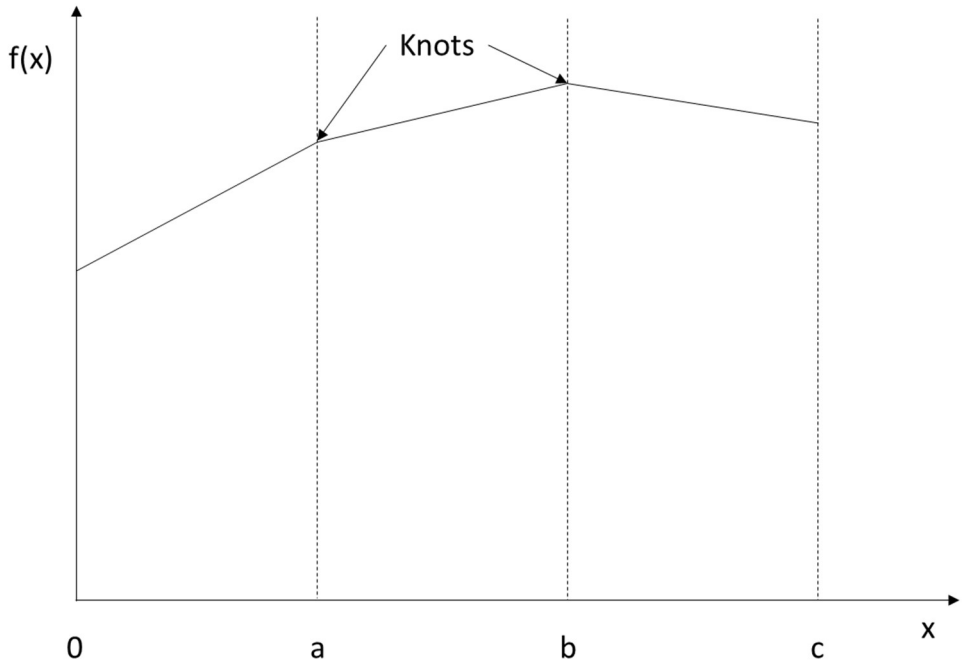
3.8.3. Statistical analysis – objective 3

In Chapter 6, the impact of THA and TKA on the trajectory of frailty was estimated. This was done by comparing the rate of change in the eFI score before and after THA/TKA within individuals. Repeated measures of eFI within individuals were used to model change over time. Each time a new deficit included in the eFI was coded in an individual's primary care record, the eFI was updated. Correlation between repeated measures in eFI within individuals was modelled using random effects models, using the function 'xtreg' in Stata.

Differences in the rate of change in eFI before and after THA/TKA was assessed using both linear and restricted cubic splines. Linear splines are piecewise linear functions that model continuous outcomes over a number of intervals with fixed start and end points. The piecewise linear models are constrained to be continuous, i.e. the linear model in a given

interval starts at the point where the linear model of the previous interval ends (Figure 3.2). The points at which the piecewise linear models meet are called 'knots'. The number and position of the knots can be chosen depending on the data being modelled.

Figure 3.2. Linear spline with knots at *a* and *b*



Modified from (197)

In some circumstances, assuming a linear relationship between an exposure and outcome may not fit the data well. Higher order polynomials can be used to model nonlinear relationship between an exposure an outcome within each interval. Cubic polynomials are generally used and can often fit nonlinear data well (197). Cubic splines are also constrained to be continuous (i.e. the cubic splines meet at 'knots'). There can be statistical advantages in constraining the tails (before the first knot and after the last knot) to be linear (197). This modelling approach is referred to as *restricted cubic splines*.

The impact of THA and TKA on trajectories of frailty was assessed by comparing the rate of change in eFI before and after THA and TKA. This was done using linear splines with a knot placed at the date of THA or TKA and a random effects model was used to assess the rate of change in eFI before and after THA and TKA. The analysis period was restricted to up to two years before THA/TKA until up to two years after THA/TKA. To assess whether the change in eFI before and after THA and TKA was nonlinear in time, restricted cubic

spline models were also considered. Multivariable models were used with year of surgery, age at surgery, sex, and quintile of IMD included as covariates. Further detail about the statistical modelling for objective 4 is presented in section 6.3.6.

Chapter 4. The impact of frailty on short-term mortality following primary total hip and knee arthroplasty due to osteoarthritis

Age and Ageing 2022; **51:** 1–8
https://doi.org/10.1093/ageing/afac118

Michael J. Cook[1], Mark Lunt[1], Timothy Board[2], Terence W. O'Neill[1,3]
[1]Centre for Epidemiology Versus Arthritis, Division of Musculoskeletal and Dermatological Sciences, Faculty of Biology Medicine and Health, University of Manchester, Manchester, UK
[2]Department of Trauma and Orthopaedic Surgery, Wrightington Hospital, Wigan, UK
[3]NIHR Manchester Biomedical Research Centre, Manchester University NHS Foundation Trust, Manchester Academic Health Science Centre, Manchester, UK

4.1. Abstract

Background We determined the association between frailty and short-term mortality following total hip and knee arthroplasty (THA/TKA) for osteoarthritis and also the impact of THA/TKA on short-term mortality compared to a control population.

Methods Frailty was assessed using a frailty index (categorised: fit, mild, moderate, severe frailty). The association between frailty and short-term mortality following THA/TKA was assessed using Cox regression. Mortality following THA/TKA was also compared to a control population with osteoarthritis but no previous THA/TKA, matched on year of birth, sex, and quintile of index of multiple deprivation (IMD).

Results 103,563 cases who had a THA, 125,367 who had a TKA, and matched controls contributed. Among those who had surgery, mortality increased with increasing frailty; adjusted hazard ratio (HR) (95% CI) at 30 days in severely frail vs fit: following THA, 2.85 (1.84, 4.39); following TKA, 2.14 (1.29, 3.53). The predicted probability of 30-day mortality following THA/TKA varied by age, sex, and frailty: following THA from 0.05% among fit women aged 60-64 years to 6.55% among men with severe frailty aged ≥90 years. All-

cause 30-day mortality was increased in fit cases following THA and TKA, respectively versus fit controls (adjusted HR (95% CI), 1.60 (1.15, 2.21) and 2.98 (1.81, 4.89)), though not among cases with mild, moderate or severe frailty versus controls in the same frailty category.

Conclusion Short-term mortality increased with increasing frailty following THA/TKA. Comparison of mortality among cases and controls may be affected by a 'healthy surgery' effect.

4.2. Background

Among patients with osteoarthritis (OA), joint replacement surgery, including total hip arthroplasty (THA) and total knee arthroplasty (TKA) may be indicated in those who remain symptomatic despite conservative therapy. Both THA and TKA are associated with a short-term peak in mortality, which subsides in the 90 day period following surgery (119, 120). A number of factors have been linked with increased mortality post THA and TKA, including age and also frailty (119, 120, 154-159, 198).

Previous studies have indicated that mortality up to 90 days following THA and TKA increases with increasing frailty, independent of age (154-159, 198). However, frailty is associated also with increased mortality in the general population (27). Therefore, it is not clear whether the impact of frailty on short-term mortality following hip and knee arthroplasty is different from the impact of frailty on mortality among individuals who do not have surgery. No previous studies have looked at the association between frailty and short-term mortality following THA and TKA among people with OA, which has been associated with an increased risk of mortality (199), compared to an age-, sex-, and deprivation-matched control population who had OA but had not had joint surgery. Such data are important and may potentially help to inform shared decision making between patients and healthcare professionals about whether to proceed with THA or TKA.

The aims of this study were, using large linked primary and secondary care clinical databases from the UK, to determine the impact of frailty on the risk of 30-, 60-, and 90-day mortality following THA and TKA, including predicted probability of short-term mortality by age, gender and frailty. Second, we determined the risk of short-term mortality among people who had a THA/TKA, compared to controls who had OA but no

previous THA/TKA. We also looked at cause-specific mortality following THA/TKA and also among controls.

4.3. Methods

4.3.1. Data sources

We used a primary care clinical database from the UK; the Clinical Practice Research Datalink (CPRD) to carry out a retrospective cohort study (174, 175). The CPRD was linked to secondary care medical records, the Hospital Episode Statistics (HES) (177), and also the Office for National Statistics (ONS) mortality database, using robust methods of data linkage (176). The protocol for this work was approved by the Independent Scientific Advisory Committee for CPRD research (protocol number 20_119). CPRD has ethics approval from the Health Research Authority to support research using anonymised patient data.

4.3.2. Assessment of frailty

Frailty was assessed using the electronic Frailty Index (eFI) (18). The eFI comprises 36 age-related deficits identified by coded data in primary care electronic medical records and was developed using a standard procedure (13) (Table 3.1). In order to apply the eFI in practices using the SNOMED coding system, we mapped the original eFI Read code lists to SNOMED codes using mapping tables from the National Health Service Data Migration Programme (181).

The eFI is calculated as the total number of the eFI deficits present in an individual, divided by 36. Based on previously published thresholds, we categorised the eFI as fit (eFI≤0.12), mild frailty (0.12<eFI≤0.24), moderate frailty (0.24<eFI≤0.36), and severe frailty (eFI>0.36) (18). The eFI has been validated in multiple databases and criterion validity has been demonstrated by comparing the eFI to other frailty instruments, including the phenotype model of frailty and the Clinical Frailty Scale (18, 184, 200).

4.3.3. Identification of THA and TKA

We identified individuals who had a primary THA or TKA from 2 January 1998 to 31 March 2019 based on OPCS codes recorded in secondary care (HES) records, using code lists from the National Joint Registry (189). We included people who were 60 years or older at the

time of their THA or TKA, since the prevalence of frailty is relatively low at younger ages. We excluded people who had a THA or TKA with a primary indication for surgery relating to fractures, osteonecrosis, rheumatoid arthritis, and malignant neoplasm of bone. In addition, we excluded cases where the coded primary indication for THA/TKA was used in <0.05% of cases.

4.3.4. Identification of hip and knee OA

We identified individuals with hip or knee OA based on diagnostic codes recorded in primary care electronic medical records (Table 3.2).

4.3.5. Statistical analysis

We matched individuals who had a THA or TKA (cases), respectively to individuals who had a diagnostic code for hip or knee OA in their primary care record at the time of the arthroplasty of the case, but had not had a THA or TKA recorded in the HES data prior to the date of THA or TKA of the matched case (controls). Matching was done on year of birth, sex, and quintile of index of multiple deprivation (IMD). Each control was matched to one and only one case. We determined the eFI at the date of THA/TKA for cases and the date of THA/TKA of the matched case for controls.

We used Kaplan-Meir estimates to calculate 30-, 60- and 90-day mortality among cases. We plotted the hazard function for mortality among cases for the first 90 days following surgery, applying smoothing using changes in the Nelson-Aalen cumulative hazard estimate with band half-width 7 days.

We determined the association between eFI category (referent category: 'fit') and 30-, 60- and 90-day mortality following THA/TKA using Cox regression, adjusted for sex, 5-year age bands, quintile of IMD, and year of surgery. Results were presented as hazard ratios (HR) and 95% CI. The index date was the date of the THA/TKA. Participants contributed person-time from the index date to the date of death, the date the individual's primary care practice stopped contributing data to the CPRD, or after 90 days, whichever came first.

We estimated the predicted probability of 30-day mortality following hip and knee arthroplasty for men and women by 5-year age band and frailty category. We did this

using a multivariable logistic regression model with year of surgery, frailty category, age band, sex, and quintile of IMD included as covariates and calculated predicted probabilities using the “margins” command in Stata. Covariates were set to their median values. We assessed the performance of the logistic model in predicting 30-day mortality by calculating the area under the receiver operating characteristic (ROC) curve.

We looked then at the association between case/control status and 30-, 60- and 90-day mortality, using Cox regression models, adjusted for age category, sex, quintile of IMD, and eFI category. The index date for controls was the date of the THA/TKA of the matched case. Controls were censored if they had a THA or TKA during the follow up period. To determine the influence of frailty status on mortality, we looked at the interaction between case/control status and frailty category. In the Cox regression models, clustering of matched pairs was taken into account and robust variance estimation was used to calculate the 95% CIs.

We performed sensitivity analyses when looking at the association between case/control status and mortality in order to mitigate possible residual imbalance in frailty between cases and controls within the same frailty strata. First, we adjusted for the eFI score, as a continuous variable. Second, we adjusted for each of the individual 36 deficits of the eFI.

We looked at the primary cause of death (by ICD code) in cases and controls. Because of the substantially fewer deaths due to neoplasms among the cases than controls, we looked also at the association between case/control status and 30-, 60- and 90-day mortality due to causes of death other than neoplasms, with deaths due to neoplasms modelled as competing risks.

All primary care practices included in our analyses consented to data linkage to secondary care, ONS mortality, and IMD databases. Determination of the eFI, mortality, occurrence of THA and TKA, and all covariates was possible for all study participants, with no missing data.

Analyses were carried out using Stata/MP v13.1.

4.4. Results

4.4.1. Participants

In total, 133,439 THAs and 139,211 TKAs were identified. After exclusions, 108,941 eligible THAs and 125,439 eligible TKAs remained. Suitable controls were found for 103,563 (95%) eligible THA cases and 125,367 (>99.9%) eligible TKA cases and these cases and controls were included in the analysis.

In the hip and knee cohort, respectively, the mean (standard deviation) age was 72.6 (7.5) and 72.3 (7.2) years and 61.2% and 56.8% were female (Table 4.1). The prevalence of frailty was lower among cases compared to controls. For example, in the hip cohort the prevalence of severe frailty was 3.6% among cases and 7.0% among controls, with similar results in the knee cohort (Table 4.1).

Table 4.1. Patient characteristics

	Hip cohort		Knee cohort	
	Cases (THA), n=103,563	Controls (hip OA), n=103,563	Cases (TKA), n=125,367	Controls (knee OA), N=125,367
	Mean (SD)			
Age	72.6 (7.5)	72.6 (7.5)	72.3 (7.2)	72.3 (7.2)
	n (%)			
Female	63,405 (61.2)	63,405 (61.2)	71,169 (56.8)	71,169 (56.8)
Fifths of index of multiple deprivation				
1 (least deprived)	27,436 (26.5)	27,436 (26.5)	30,568 (24.4)	30,568 (24.4)
2	25,162 (24.3)	25,162 (24.3)	29,450 (23.5)	29,450 (23.5)
3	22,317 (21.6)	22,317 (21.6)	27,042 (21.6)	27,042 (21.6)
4	16,834 (16.3)	16,834 (16.3)	21,467 (17.1)	21,467 (17.1)
5 (most deprived)	11,759 (11.4)	11,759 (11.4)	16,747 (13.4)	16,747 (13.4)
Frailty category				
Fit	42,427 (41.0)	34,103 (32.9)	42,339 (33.8)	39,251 (31.3)
Mild frailty	42,181 (40.7)	42,055 (40.6)	55,845 (44.6)	52,822 (42.1)
Moderate frailty	15,269 (14.7)	20,158 (19.5)	22,056 (17.6)	24,875 (19.8)
Severe frailty	3,686 (3.6)	7,247 (7.0)	5,127 (4.1)	8,419 (6.7)

THA: total hip arthroplasty; TKA: total knee arthroplasty; OA: osteoarthritis; SD: standard deviation

4.4.2. Crude 30-, 60- and 90-day mortality following THA and TKA

Among those who had a THA, the number of people who died: within 30 days was 319 (0.31%); within 60 days was 464 (0.45%); and within 90 days was 588 (0.57%). The corresponding deaths among TKA cases were: 30 days, 291 (0.23%); 60 days, 405 (0.32%) and 90 days, 506 (0.40%). Cause-specific 30-day mortality following THA and TKA is shown in Supplementary Table 4.1. Among cases, diseases of the circulatory system, including heart disease and stroke, were the most common causes of death. There were substantial differences between cases and controls in the proportion of deaths due to neoplasms: among controls, about one third of deaths were due to neoplasms, while among cases only 2% were due to neoplasms. The hazard function (deaths per day) among cases who had a THA and TKA peaked in the early postoperative period, then declined during the remainder of the 90-day period following surgery (Supplementary Figure 4.1).

Among those who had joint surgery, mortality at 30, 60, and 90 days was higher in men than women and increased with increasing frailty and also with increasing age following both THA and TKA (Table 4.2).

Table 4.2. Crude mortality at 30, 60, and 90 days following total hip arthroplasty and total knee arthroplasty

	30 days				60 days				90 days			
	Total hip arthroplasty		Total knee arthroplasty		Total hip arthroplasty		Total knee arthroplasty		Total hip arthroplasty		Total knee arthroplasty	
	Number of deaths	Mortality, % (95% CI)	Number of deaths	Mortality, % (95% CI)	Number of deaths	Mortality, % (95% CI)	Number of deaths	Mortality, % (95% CI)	Number of deaths	Mortality, % (95% CI)	Number of deaths	Mortality, % (95% CI)
Frailty category												
Fit	109	0.25 (0.21, 0.30)	71	0.16 (0.13, 0.21)	137	0.32 (0.27, 0.38)	99	0.23 (0.19, 0.28)	166	0.39 (0.34, 0.46)	133	0.31 (0.27, 0.37)
Mild frailty	101	0.23 (0.19, 0.28)	125	0.22 (0.18, 0.26)	166	0.39 (0.34, 0.45)	168	0.30 (0.26, 0.35)	219	0.52 (0.46, 0.59)	197	0.35 (0.31, 0.41)
Moderate frailty	77	0.49 (0.39, 0.61)	72	0.32 (0.25, 0.40)	116	0.76 (0.63, 0.91)	107	0.48 (0.40, 0.58)	153	1.01 (0.86, 1.18)	136	0.62 (0.52, 0.73)
Severe frailty	32	0.85 (0.60, 1.20)	23	0.44 (0.29, 0.66)	45	1.22 (0.91, 1.64)	31	0.60 (0.42, 0.86)	50	1.37 (1.04, 1.81)	40	0.79 (0.58, 1.07)
Sex												
Women	147	0.23 (0.19, 0.26)	148	0.20 (0.17, 0.24)	232	0.36 (0.32, 0.41)	194	0.27 (0.24, 0.31)	290	0.46 (0.41, 0.51)	235	0.33 (0.29, 0.38)
Men	172	0.42 (0.36, 0.48)	143	0.26 (0.22, 0.30)	232	0.57 (0.50, 0.65)	211	0.39 (0.34, 0.44)	298	0.75 (0.67, 0.83)	271	0.50 (0.45, 0.57)
Age group (years)												
60-64	20	0.10 (0.06, 0.15)	13	0.05 (0.03, 0.09)	28	0.14 (0.10, 0.20)	23	0.10 (0.06, 0.15)	35	0.18 (0.13, 0.25)	29	0.12 (0.09, 0.18)
65-69	25	0.11 (0.07, 0.16)	34	0.12 (0.08, 0.16)	36	0.16 (0.12, 0.22)	46	0.16 (0.12, 0.22)	41	0.18 (0.14, 0.25)	56	0.20 (0.15, 0.26)
70-74	29	0.12 (0.09, 0.18)	37	0.13 (0.09, 0.17)	45	0.20 (0.15, 0.26)	52	0.18 (0.14, 0.24)	78	0.34 (0.27, 0.43)	70	0.24 (0.19, 0.31)
75-79	82	0.40 (0.32, 0.50)	63	0.25 (0.19, 0.32)	121	0.60 (0.50, 0.72)	94	0.38 (0.31, 0.46)	150	0.76 (0.64, 0.89)	120	0.49 (0.41, 0.58)
80-84	77	0.59 (0.47, 0.73)	78	0.53 (0.43, 0.67)	118	0.92 (0.77, 1.10)	107	0.75 (0.62, 0.90)	146	1.15 (0.98, 1.35)	126	0.89 (0.75, 1.06)
85-89	66	1.25 (0.98, 1.59)	47	0.89 (0.67, 1.19)	92	1.79 (1.46, 2.19)	61	1.19 (0.92, 1.52)	111	2.18 (1.81, 2.63)	82	1.61 (1.30, 2.00)
≥90	20	2.05 (1.32, 3.17)	19	3.00 (1.92, 4.10)	24	2.51 (1.68, 3.75)	22	3.58 (2.35, 5.43)	27	2.86 (1.96, 4.17)	23	3.79 (2.52, 5.70)
Fifths of IMD												
1 (least deprived)	74	0.26 (0.21, 0.33)	71	0.23 (0.18, 0.29)	102	0.37 (0.30, 0.45)	92	0.30 (0.24, 0.37)	132	0.48 (0.41, 0.57)	112	0.37 (0.31, 0.44)
2	71	0.27 (0.22, 0.35)	61	0.20 (0.16, 0.26)	110	0.43 (0.36, 0.52)	89	0.30 (0.24, 0.37)	140	0.56 (0.47, 0.66)	113	0.38 (0.32, 0.46)
3	79	0.34 (0.28, 0.43)	60	0.22 (0.17, 0.28)	115	0.51 (0.43, 0.61)	82	0.30 (0.24, 0.37)	143	0.64 (0.55, 0.76)	103	0.38 (0.31, 0.46)
4	51	0.29 (0.22, 0.39)	43	0.19 (0.14, 0.26)	72	0.42 (0.34, 0.53)	66	0.31 (0.24, 0.39)	88	0.52 (0.42, 0.65)	85	0.40 (0.32, 0.49)
5 (most deprived)	44	0.36 (0.27, 0.49)	56	0.33 (0.25, 0.42)	65	0.55 (0.43, 0.70)	76	0.45 (0.36, 0.56)	85	0.73 (0.59, 0.90)	93	0.56 (0.45, 0.68)

CI: confidence interval; IMD: index of multiple deprivation

4.4.3. Influence of frailty on short-term mortality following THA and TKA

Among those who had joint surgery, in a model adjusted for sex, age group, quintile of IMD, and year of surgery, the HR for 30, 60 and 90 day mortality increased with increasing frailty in both the knee and hip cohorts. Compared to fit individuals, the adjusted HR (95% CI) for 30-day mortality following THA for mild, moderate, and severely frail individuals, respectively was 0.87 (0.66, 1.15), 1.73 (1.26, 2.38), and 2.85 (1.84, 4.39) (Table 4.3). The corresponding results following TKA were 1.31 (0.97, 1.77), 1.73 (1.22, 2.46), and 2.14 (1.29, 3.53). Similar results were observed at 60 days and 90 days.

A multivariable logistic model predicting 30-day mortality following THA and TKA (with frailty category, 5-year age band, sex, year of surgery and quintile of IMD included as covariates) showed good discriminative ability (area under ROC curve: 0.81 for THA and 0.78 for TKA). There was variation in the predicted probability of 30-day mortality following THA and TKA in men and women by age band and frailty category (Table 4.4). The predicted probability (95% CI) of 30-day mortality following THA among fit men aged 60-64 years was 0.13% (0.06, 0.20), while the corresponding value for severely frail men aged ≥90 years was 6.55% (2.99, 10.11).

Table 4.3. Hazard ratio for 30-, 60-, and 90-day mortality by frailty category among people who had a total hip arthroplasty or total knee arthroplasty

	Hazard ratio for mortality (95% CI)					
	30 days		60 days		90 days	
	Model 1[1]	Model 2[2]	Model 1[1]	Model 2[2]	Model 1[1]	Model 2[2]
			Total hip arthroplasty			
Fit			1 (reference)			
Mild frailty	1.19 (0.90, 1.56)	0.87 (0.66, 1.15)	1.57 (1.25, 1.97)	1.16 (0.92, 1.47)	1.66 (1.36, 2.04)	1.25 (1.02, 1.54)
Moderate frailty	3.13 (2.31, 4.25)	1.73 (1.26, 2.38)	3.82 (2.95, 4.94)	2.16 (1.65, 2.83)	3.95 (3.15, 4.97)	2.30 (1.81, 2.92)
Severe frailty	6.43 (4.26, 9.72)	2.85 (1.84, 4.39)	7.37 (5.18, 10.49)	3.37 (2.33, 4.88)	6.30 (4.53, 8.75)	2.99 (2.12, 4.21)
			Total knee arthroplasty			
Fit			1 (reference)			
Mild frailty	1.70 (1.26, 2.28)	1.31 (0.97, 1.77)	1.61 (1.25, 2.07)	1.28 (0.99, 1.65)	1.40 (1.12, 1.75)	1.12 (0.89, 1.40)
Moderate frailty	2.93 (2.09, 4.11)	1.73 (1.22, 2.46)	3.04 (2.29, 4.04)	1.90 (1.41, 2.55)	2.86 (2.23, 3.66)	1.81 (1.40, 2.34)
Severe frailty	4.56 (2.81, 7.38)	2.14 (1.29, 3.53)	4.25 (2.80, 6.43)	2.16 (1.40, 3.32)	4.04 (2.81, 5.81)	2.10 (1.44, 3.07)

[1]Model 1 is adjusted for year of surgery only
[2]Model 2 is adjusted for year of birth, sex, quintile of index of multiple deprivation, and year of surgery

CI: confidence interval

Table 4.4. Predicted probability of 30-day mortality following hip and knee arthroplasty in men and women, by age and frailty

Age group (years)	Fit		Mild frailty		Moderate frailty		Severe frailty	
	Predicted probability of 30-day mortality, % (95% CI)[1]							
	Total hip arthroplasty							
	Women	*Men*	*Women*	*Men*	*Women*	*Men*	*Women*	Men
60-64	0.05 (0.03, 0.08)	0.13 (0.06, 0.20)	0.05 (0.02, 0.07)	0.11 (0.05, 0.17)	0.09 (0.04, 0.14)	0.23 (0.10, 0.35)	0.15 (0.06, 0.24)	0.37 (0.14, 0.60)
65-69	0.06 (0.03, 0.09)	0.14 (0.08, 0.21)	0.05 (0.03, 0.08)	0.13 (0.07, 0.19)	0.10 (0.05, 0.15)	0.25 (0.12, 0.38)	0.16 (0.07, 0.26)	0.41 (0.17, 0.64)
70-74	0.06 (0.03, 0.10)	0.16 (0.09, 0.23)	0.06 (0.03, 0.08)	0.14 (0.08, 0.20)	0.11 (0.06, 0.17)	0.28 (0.15, 0.41)	0.18 (0.08, 0.29)	0.45 (0.20, 0.71)
75-79	0.20 (0.12, 0.28)	0.50 (0.32, 0.68)	0.18 (0.11, 0.24)	0.44 (0.28, 0.59)	0.35 (0.22, 0.48)	0.86 (0.55, 1.18)	0.57 (0.30, 0.84)	1.4 (0.75, 2.05)
80-84	0.29 (0.18, 0.41)	0.73 (0.45, 1.01)	0.26 (0.16, 0.35)	0.64 (0.41, 0.87)	0.51 (0.32, 0.7)	1.26 (0.80, 1.72)	0.83 (0.45, 1.21)	2.04 (1.11, 2.96)
85-89	0.60 (0.35, 0.84)	1.47 (0.88, 2.06)	0.53 (0.32, 0.73)	1.29 (0.80, 1.78)	1.04 (0.65, 1.42)	2.53 (1.59, 3.46)	1.68 (0.93, 2.43)	4.06 (2.27, 5.86)
≥90	0.99 (0.44, 1.53)	2.41 (1.1, 3.71)	0.87 (0.41, 1.33)	2.12 (1.01, 3.24)	1.70 (0.82, 2.59)	4.11 (2.01, 6.22)	2.75 (1.22, 4.29)	6.55 (2.99, 10.11)
	Total knee arthroplasty							
	Women	*Men*	*Women*	*Men*	*Women*	*Men*	*Women*	Men
60-64	0.03 (0.01, 0.05)	0.05 (0.02, 0.08)	0.04 (0.02, 0.07)	0.06 (0.02, 0.10)	0.05 (0.02, 0.09)	0.08 (0.03, 0.14)	0.06 (0.02, 0.11)	0.10 (0.03, 0.17)
65-69	0.06 (0.03, 0.10)	0.10 (0.05, 0.15)	0.09 (0.05, 0.12)	0.13 (0.07, 0.19)	0.11 (0.06, 0.17)	0.17 (0.09, 0.26)	0.13 (0.05, 0.21)	0.21 (0.08, 0.33)
70-74	0.06 (0.03, 0.09)	0.10 (0.05, 0.15)	0.09 (0.05, 0.12)	0.13 (0.07, 0.19)	0.11 (0.06, 0.16)	0.17 (0.09, 0.25)	0.13 (0.05, 0.21)	0.21 (0.08, 0.33)
75-79	0.12 (0.07, 0.17)	0.18 (0.10, 0.26)	0.16 (0.10, 0.22)	0.24 (0.15, 0.33)	0.2 (0.12, 0.29)	0.32 (0.19, 0.45)	0.24 (0.11, 0.37)	0.37 (0.17, 0.58)
80-84	0.25 (0.14, 0.36)	0.39 (0.22, 0.55)	0.33 (0.21, 0.46)	0.51 (0.32, 0.70)	0.44 (0.27, 0.60)	0.67 (0.41, 0.94)	0.52 (0.25, 0.78)	0.80 (0.38, 1.21)
85-89	0.42 (0.22, 0.61)	0.64 (0.34, 0.94)	0.55 (0.32, 0.78)	0.85 (0.49, 1.21)	0.72 (0.42, 1.03)	1.11 (0.64, 1.59)	0.86 (0.40, 1.31)	1.32 (0.60, 2.03)
≥90	1.47 (0.60, 2.35)	2.26 (0.93, 3.59)	1.95 (0.89, 3.02)	2.99 (1.37, 4.61)	2.55 (1.17, 3.92)	3.88 (1.79, 5.98)	3.00 (1.18, 4.82)	4.56 (1.79, 7.33)

[1] Predicted probabilities of 30-day mortality were calculated at the median values of quintile of IMD (which was 3) and year of surgery (which was 2010)

CI: confidence interval

4.4.4. Influence of total hip and knee arthroplasty on short-term mortality

In a multivariable model adjusted for frailty category, age category, sex, quintile of IMD, and year of surgery, the overall HR (95% CI) for mortality at 30, 60, and 90 days, respectively among those who had THA compared to controls, was 1.05 (0.91, 1.23), 0.82 (0.73, 0.92), and 0.68 (0.62, 0.76). The corresponding results among cases who had TKA, compared to controls, was: 30 days, 1.14 (0.97, 1.34); 60 days, 0.83 (0.74, 0.95); and 90 days, 0.70 (0.63, 0.78). Mortality, however varied by frailty status. In an adjusted model, mortality was increased at 30 days among fit cases compared to fit controls in both the hip and knee cohorts, respectively, 1.60 (1.15, 2.21) and 2.98 (1.81, 4.89) (Table 4.5). There was no statistically significant difference in 30-day mortality among mild, moderate, and severe frail cases compared to controls in the same frailty category in both the hip and knee cohorts (Table 5.5). At 90 days following THA and TKA, mortality was reduced among cases with mild, moderate, and severe frailty compared to controls in the same frailty category (Table 4.5). The effect was more marked among the severely frail group.

Table 4.5. Hazard ratio for 30-, 60-, and 90-day mortality among cases compared to controls, by frailty category

Frailty category	Hazard ratio for mortality among cases versus controls (95% CI) [1]					
	30 days		60 days		90 days	
	Hip cohort	Knee cohort	Hip cohort	Knee cohort	Hip cohort	Knee cohort
Fit	1.60 (1.15, 2.21)	2.98 (1.81, 4.89)	1.07 (0.83, 1.39)	1.71 (1.22, 2.41)	0.83 (0.67, 1.03)	1.38 (1.05, 1.81)
Mild frailty	0.90 (0.69, 1.17)	1.27 (0.97, 1.66)	0.79 (0.65, 0.97)	0.94 (0.76, 1.16)	0.64 (0.54, 0.76)	0.71 (0.59, 0.85)
Moderate frailty	0.99 (0.74, 1.33)	0.82 (0.61, 1.10)	0.77 (0.62, 0.97)	0.67 (0.53, 0.85)	0.71 (0.59, 0.87)	0.59 (0.48, 0.73)
Severe frailty	0.88 (0.58, 1.34)	0.68 (0.42, 1.10)	0.65 (0.46, 0.91)	0.44 (0.29, 0.65)	0.52 (0.38, 0.71)	0.40 (0.28, 0.56)

[1]Results calculated by considering a statistical interaction term between case/control status and frailty category to estimate HR for mortality in cases compared to controls in the same strata of frailty. Adjusted for year of birth, sex, and IMD and year of surgery of case

CI: confidence interval

There were small differences in the mean eFI between cases and controls in the same frailty category (Supplementary Table 5.2). However, a sensitivity analysis adjusting additionally for the eFI score as a continuous measure did not materially impact on the results (Supplementary Table 5.3). Among cases and controls in the same frailty category, there were differences in the prevalence of some of the individual deficits that make up the eFI, however, adjusting for each of the individual deficits of the eFI in a sensitivity analysis did not materially impact on the results (Supplementary Table 4.4).

Modelling deaths due to causes other than neoplasms among cases and controls, with deaths due to neoplasms modelled as competing risks, was associated with a small increase in mortality among cases compared to controls in each frailty strata compared to analysis looking at all-cause mortality, though the gradient of risk across the frailty strata was similar (Supplementary Table 4.5).

Comparison of short-term mortality following THA relative to a non-surgical control population may be impacted by a residual 'healthy selection' effect, with those selected for surgery relatively fitter than non-surgical controls (see section 4.5).

4.5. Discussion

In this study, the hazard ratio for 30-, 60-, and 90-day mortality increased with increasing frailty following THA and TKA. The probability of 30-day mortality following THA varied by age, gender and frailty; from 0.05% among non-frail women aged 60-64 years to 6.55% among severely frail men aged ≥90. The hazard ratio for mortality among cases compared to controls varied by frailty. Mortality was increased in fit cases compared to fit controls at 30 days in both the hip and knee cohorts, though by 90 days there was no statistically significant difference. Among cases with mild, moderate, or severe frailty compared to controls in the same frailty stratum, there was no statistically significant difference in all-cause mortality at 30 days in both the hip and knee cohorts, and reduced mortality at 60 and 90 days.

Previous studies, all from the United States, have consistently demonstrated increased mortality up to 90 days following THA and TKA with increasing frailty (154-159, 198). Direct comparison with our study is difficult due to differences in the assessment of frailty. In one study of 8,640 individuals who had a primary or revision THA (median age (inter

quartile range) 68 (60, 76) years), frailty was assessed using a 32-component frailty index and categorised as non-frail (FI<0.11), vulnerable (0.11≤FI<0.20), and frail (FI≤0.21) (154). In an adjusted model, the HR (95% CI) for 90 day mortality among those who were vulnerable and frail, respectively was 2.31 (0.89, 6.18) and 5.61 (2.24, 14.03), compared to those who were non-frail (154). These results are similar to our findings, though the relationship between frailty and 90-day mortality following THA was less strong in our study. These differences may potentially be explained by differences in the cohort (we did not include revision surgery in our study), and differences in the thresholds for frailty categories.

The explanation for reduced all-cause mortality at 90-days among people with mild, moderate and severe frailty who have a THA or TKA compared to controls in the same frailty category is not clear. It is likely that there may have been a residual healthy surgery effect, with those listed for surgery relatively fitter than those who were not listed for surgery (120), despite accounting for frailty category in our analyses. The greater reduction in mortality among the severely frail group who had surgery compared to severely frail controls would be consistent with this; also the relatively fewer number of deaths due to neoplasia among those who had surgery compared to controls. After accounting for the differential mortality due to neoplasia, there was a small increase in the risk of mortality (among cases compared to controls) though the gradient of risk across the frailty strata was similar. It is possible though also that interventions in preparation for surgery, related for example to prehabilitation, preoperative assessment, and also increased monitoring and care following surgery, may have had a beneficial impact on reducing mortality among those with higher frailty scores who had joint surgery compared to those who had not had surgery.

Our study has a number of strengths, including a large sample size, linkage to secondary care and national mortality data, and the use of a well validated frailty index. There are also limitations to our analysis. A key limitation is in the analysis of short-term mortality following THA/TKA relative to a non-surgical control population, with a likely residual 'healthy selection effect', resulting in relatively fitter cases compared to non-surgical controls, despite accounting for frailty in our analysis. We attempted to account for residual imbalance in frailty status between cases and controls in the same frailty category by adjusting for the eFI as a continuous measure and also adjusting for each of the 36 deficits of the eFI. However, it is likely that residual imbalance persisted, which is difficult

to address completely using routinely collected coded clinical data. Other factors which impact on who is selected for surgery which are not well captured in routine clinical records, such as OA disease severity, severity of comorbidities, and patient willingness to undergo surgery, may result in residual confounding if these factors also influence the outcome. In particular, robust measures of the severity of the individual deficits which make up the eFI were not available to us, so individuals with the same eFI score and the same underlying deficits may differ in the severity of their comorbidities.

In summary in this study using data from the UK, short-term mortality increased with increasing frailty following THA and TKA. The predicted probability of 30-day mortality following surgery varied by age, gender and frailty status, in the case of THA from 0.05% to 6.5%. Among those with frailty, the reduction in mortality at 60 and 90 days following THA/TKA compared to controls who did not have surgery may be due to a healthy surgery effect which could in part be explained by a reduction in deaths due to neoplasia.

4.6. Supplementary data

Supplementary Table 4.1. Cause-specific 30-day mortality among cases and controls

Cause of death (30-day mortality)	Hip cohort		Knee cohort	
	Cases (THA)	Controls	Cases (TKA)	Controls
	n (%)			
Diseases of the circulatory system	134 (42.0)	124 (35.5)	137 (47.1)	99 (35.5)
Diseases of the musculoskeletal system and connective tissue	90 (28.2)	5 (1.4)	93 (32.0)	4 (1.4)
Diseases of the digestive system	41 (12.9)	21 (6.0)	25 (8.6)	12 (4.3)
Diseases of the respiratory system	22 (6.9)	38 (10.9)	12 (4.1)	36 (12.9)
External causes of morbidity and mortality (accident/injury)	11 (3.5)	6 (1.7)	6 (2.1)	6 (2.2)
Diseases of the genitourinary system	8 (2.5)	10 (2.9)	7 (2.4)	8 (2.9)
Neoplasms	5 (1.6)	117 (33.5)	4 (1.4)	93 (33.3)
Diseases of the nervous system	2 (0.6)	8 (2.3)	0 (0.0)	5 (1.8)
Endocrine and metabolic diseases	2 (0.6)	6 (1.7)	2 (0.7)	3 (1.1)
Infections	2 (0.6)	3 (0.9)	1 (0.3)	2 (0.7)
Injury, poisoning and certain other consequences of external causes	2 (0.6)	0 (0.0)	2 (0.7)	0 (0.0)
Symptoms and signs not elsewhere classified	0 (0.0)	0 (0.0)	2 (0.7)	0 (0.0)
Mental disorders	0 (0.0)	6 (1.7)	0 (0.0)	9 (3.2)
Diseases of the skin and subcutaneous tissue	0 (0.0)	3 (0.9)	0 (0.0)	0 (0.0)
Diseases of the blood	0 (0.0)	2 (0.6)	0 (0.0)	2 (0.7)

Cause of death (30-day mortality) was determined from the primary cause of death recorded in the Office for National Statistics mortality database. Cause of death was recorded using the ICD-9 and ICD-10 classification systems. Cause of death was grouped by ICD-9 and ICD-10 chapter headings. Cause of death (30-day mortality) are presented for cases (individuals who had a THA or TKA) and also matched controls

THA: total hip arthroplasty; TKA: total knee arthroplasty

Supplementary Table 4.2. Mean eFI by frailty strata among cases and controls

	Hip cohort		Knee cohort	
	Cases	Controls	Cases	Controls
	Mean eFI score (SD)		Mean eFI score (SD)	
Fit	0.080 (0.029)	0.080 (0.028)	0.077 (0.029)	0.079 (0.029)
Mild frailty	0.176 (0.030)	0.177 (0.031)	0.175 (0.030)	0.177 (0.031)
Moderate frailty	0.280 (0.029)	0.283 (0.030)	0.280 (0.029)	0.283 (0.030)
Severe frailty	0.400 (0.047)	0.412 (0.057)	0.401 (0.048)	0.414 (0.058)

eFI: electronic frailty index; SD: standard deviation

Supplementary Table 4.3. Hazard ratio for 30-, 60-, and 90-day mortality among cases compared to controls, by frailty category, adjusted for eFI as a continuous variable

	HR for mortality among cases versus controls (95% CI) [1]					
Frailty category	30 days		60 days		90 days	
	Hip cohort	Knee cohort	Hip cohort	Knee cohort	Hip cohort	Knee cohort
Fit	1.61 (1.16, 2.23)	2.99 (1.82, 4.91)	1.09 (0.84, 1.40)	1.72 (1.22, 2.42)	0.84 (0.68, 1.05)	1.38 (1.05, 1.82)
Mild frailty	0.90 (0.69, 1.18)	1.28 (0.98, 1.67)	0.80 (0.65, 0.98)	0.95 (0.77, 1.17)	0.65 (0.55, 0.77)	0.72 (0.60, 0.86)
Moderate frailty	1.00 (0.75, 1.34)	0.83 (0.61, 1.12)	0.79 (0.63, 0.99)	0.68 (0.54, 0.86)	0.73 (0.60, 0.88)	0.60 (0.49, 0.74)
Severe frailty	0.92 (0.61, 1.38)	0.73 (0.45, 1.18)	0.68 (0.49, 0.95)	0.48 (0.32, 0.71)	0.55 (0.40, 0.75)	0.43 (0.31, 0.61)

[1]Results calculated by considering a statistical interaction term between case/control status and frailty category to estimate HR for mortality in cases compared to controls in the same strata of frailty. Adjusted for year of birth, sex, and IMD, year of surgery of case, and eFI (as a continuous variable)

Supplementary Table 4.4. Hazard ratio for 30-, 60-, and 90-day mortality among cases compared to controls, by frailty category, adjusting for each of the individual eFI deficits

Frailty category	Hazard ratio for mortality among cases versus controls (95% CI) [1]					
	30 days		60 days		90 days	
	Hip cohort	Knee cohort	Hip cohort	Knee cohort	Hip cohort	Knee cohort
Fit	1.57 (1.13, 2.18)	2.93 (1.78, 4.84)	1.06 (0.82, 1.37)	1.69 (1.20, 2.39)	0.82 (0.66, 1.02)	1.35 (1.02, 1.78)
Mild frailty	0.89 (0.68, 1.16)	1.29 (0.99, 1.69)	0.79 (0.65, 0.97)	0.95 (0.77, 1.17)	0.64 (0.54, 0.76)	0.72 (0.60, 0.87)
Moderate frailty	1.05 (0.78, 1.41)	0.89 (0.66, 1.21)	0.83 (0.66, 1.04)	0.72 (0.57, 0.91)	0.76 (0.63, 0.93)	0.64 (0.52, 0.79)
Severe frailty	1.01 (0.67, 1.52)	0.90 (0.55, 1.47)	0.76 (0.54, 1.07)	0.57 (0.38, 0.86)	0.62 (0.45, 0.84)	0.52 (0.37, 0.73)

[1]Results calculated by considering a statistical interaction term between case/control status and frailty category to estimate hazard ratio for mortality in cases compared to controls in the same strata of frailty. Adjusted for year of birth, sex, and quintile of index of multiple deprivation, year of surgery of case, and each of the individual eFI deficits
CI: confidence interval

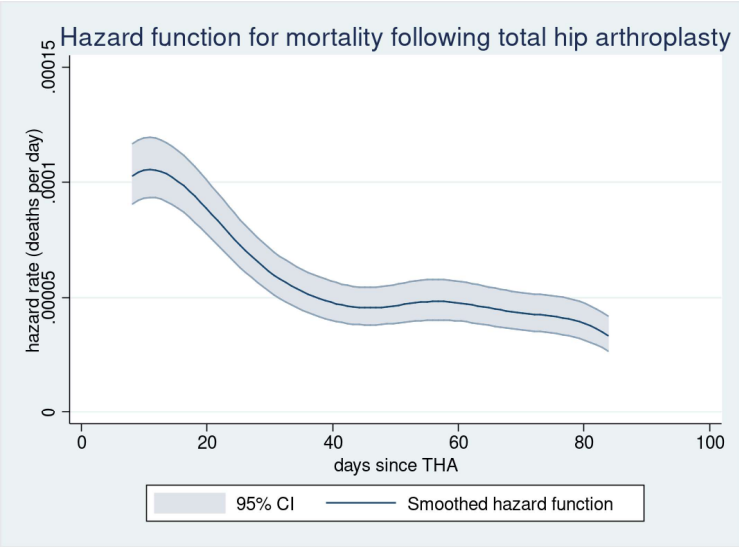
Supplementary Table 4.5. Subhazard ratio for 30-, 60-, and 90-day mortality (deaths not due to neoplasms) among cases compared to controls, by frailty category

Frailty category	Subhazard ratio for mortality among cases versus controls (95% CI) [1]					
	30 days		60 days		90 days	
	Hip cohort	Knee cohort	Hip cohort	Knee cohort	Hip cohort	Knee cohort
Fit	2.18 (1.51, 3.16)	3.86 (2.21, 6.74)	1.46 (1.09, 1.96)	2.23 (1.52, 3.27)	1.22 (0.95, 1.57)	1.79 (1.31, 2.44)
Mild frailty	1.53 (1.12, 2.09)	2.17 (1.58, 3.00)	1.25 (0.99, 1.59)	1.52 (1.18, 1.94)	0.95 (0.78, 1.15)	1.13 (0.91, 1.40)
Moderate frailty	1.50 (1.08, 2.07)	1.15 (0.83, 1.59)	1.19 (0.93, 1.54)	0.94 (0.73, 1.22)	1.04 (0.83, 1.29)	0.86 (0.68, 1.07)
Severe frailty	1.08 (0.69, 1.67)	0.97 (0.58, 1.61)	0.77 (0.54, 1.10)	0.57 (0.38, 0.86)	0.64 (0.46, 0.88)	0.52 (0.36, 0.74)

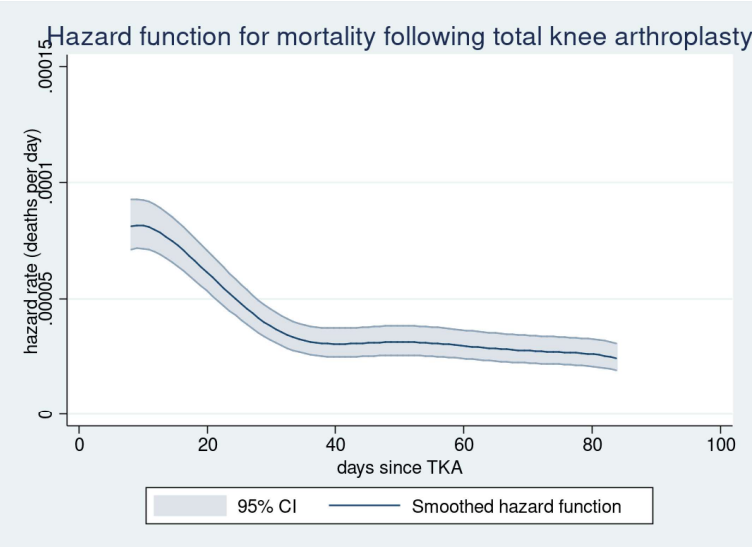
[1]Results calculated from a competing risk survival analysis with mortality due to causes other than neoplasms as the outcome and deaths due to neoplasm as competing risks. We considered a statistical interaction term between case/control status and frailty category to estimate subhazard ratio for mortality in cases compared to controls in the same strata of frailty. Adjusted for year of birth, sex, and IMD and year of surgery of case
CI: confidence interval

Supplementary Figure 4.1. Hazard function in the 90-day period following hip arthroplasty (A) and knee arthroplasty (B)

A. Hip arthroplasty



B. Knee arthroplasty



Smoothing based on changes in the Nelson-Aalen cumulative hazard estimate with band half-width 7 day

Supplementary Text 4.1. Calculation of predicted probability of 30-day mortality

The predicted probabilities of 30-day mortality were calculated using logistic regression. The linear prediction (LP) is given by:

$$\text{LP} = \text{constant} + \beta_{frailty} + \beta_{age} + \beta_{sex} + \beta_{IMD} + \beta_{year} \times \text{year of surgery}$$

The outcome, Y is 30-day mortality, $Y \sim binomial(\hat{\pi})$, where $\hat{\pi}$ is the predicted probability of 30-day mortality.

The values for each of the β terms in the hip and knee cohorts are given in the tables below.

Hip cohort

Term	Value	Category
constant	210.26	
$\beta_{frailty}$	0	Fit
	-0.13	Mild frailty
	0.55	Moderate frailty
	1.05	Severe frailty
β_{age}	0	60≤age<65
	0.10	65≤age<70
	0.21	70≤age<75
	1.35	75≤age<80
	1.73	85≤age<85
	2.44	85≤age<90
	2.94	age≥90
β_{sex}	0	Male
	-0.91	Female
β_{IMD}	0	IMD quintile 1
	0.02	IMD quintile 2
	0.22	IMD quintile 3
	0.07	IMD quintile 4
	0.30	IMD quintile 5
β_{year}	-0.11	Year of surgery

Knee cohort

Term	Value	Category
constant	190.57	
$\beta_{frailty}$	0	Fit
	0.29	Mild frailty
	0.56	Moderate frailty
	0.73	Severe frailty
β_{age}	0	60≤age<65
	0.74	65≤age<70
	0.74	70≤age<75
	1.34	75≤age<80
	2.10	85≤age<85
	2.61	85≤age<90
	3.88	age≥90
β_{sex}	0	Male
	-0.44	Female
β_{IMD}	0	IMD quintile 1
	-0.14	IMD quintile 2
	-0.07	IMD quintile 3
	-0.19	IMD quintile 4
	0.35	IMD quintile 5
β_{year}	-0.10	Year of surgery

The predicted probability of 30-day mortality, $\hat{\pi}$, is given by:

$$\hat{\pi} = \frac{\exp(LP)}{1 + \exp(LP)}$$

In Table 4.4, we the predicted probabilities of 30-day mortality was calculated at the median values of quintile of IMD (which was 3) and year of surgery (which was 2010).

Chapter 5. The impact of frailty on patient-reported outcomes following hip and knee arthroplasty

Accepted for publication in the journal Age and Ageing

5.1. Abstract

Aim: To determine the impact of frailty on patient-reported outcomes following hip and knee arthroplasty.

Methods: We used linked primary and secondary care electronic health records. Frailty was assessed using the electronic frailty index (categorised: fit, mild, moderate, severe frailty). We determined the association between frailty category and postoperative Oxford hip/knee score (OHS/OKS) using Tobit regression. We calculated the proportion of patients in each frailty category who achieved the minimally important change (MIC) in OHS (≥8 points) and OKS (≥7 points) and the proportion who reported a successful outcome (hip/knee problems either "much better" or "a little better" following surgery).

Results: 42,512 people who had a hip arthroplasty and 49,208 who had a knee arthroplasty contributed data. In a Tobit model adjusted for preoperative OHS/OKS, age, sex, and quintile of index of multiple deprivation, increasing frailty was associated with decreasing postoperative OHS and OKS, respectively, β-coefficient (95% CI) in severely frail versus fit, -6.97 (-7.44, -6.49) and -5.88 (-6.28, -5.47). The proportion of people who achieved the MIC in OHS and OKS, respectively decreased from 92% and 86% among fit individuals to 84% and 78% among those with severe frailty. Patient-reported success following hip and knee arthroplasty, respectively decreased from 97% and 93% among fit individuals to 90% and 83% among those with severe frailty.

Conclusion: Frailty adversely impacts on patient-reported outcomes following hip and knee arthroplasty. However, even among those with severe frailty, the large majority achieved the MIC in OHS/OKS and reported a successful outcome.

5.2. Background

Frailty has been linked with an increased risk of adverse outcomes following total hip and knee arthroplasty (THA,TKA), including surgical and medical complications, readmission

to hospital, and mortality (154, 165, 171, 201). Limited previous data have also suggested an association between increasing frailty and poorer functional outcomes following hip and knee replacement (163, 164).

Since 2009, patient-reported outcome measures (PROMs) before and after THA and TKA have been routinely collected by the United Kingdom (UK) National Health Service (NHS) (202). Previous analysis of UK NHS PROMs data indicates significant improvements in the Oxford hip and knee scores (OHS/OKS) at 6 months following hip and knee replacement surgery (mean change in OHS about 23 points and mean change in OKS about 17 points), and about 94% and 86% of patients, respectively report being satisfied with their hip or knee replacement surgery (109, 111, 203).

Assessment of the impact of frailty on the benefits of THA and TKA, including PROMs, is important so that a balanced assessment of the risk and benefits of surgery among people with frailty can be made. One recent study reported that improvement in OHS following THA was similar among people with different levels of frailty (152). However, this previous study was limited by a small number of individuals with a high level of frailty. In addition, this previous study did not look at patient-reported success following THA, nor did it look at outcomes following TKA.

The aim of this study was to determine the impact of frailty on patient-reported outcomes following THA and TKA including the OHS and OKS, patient-reported success, and also minimal important change.

5.3. Methods

5.3.1. Data

We used data from the Clinical Practice Research Datalink (CPRD), a large primary care electronic health record database (174, 175). We included both CPRD Gold (comprising primary care practices using the Vision® patient management system) and CPRD Aurum (comprising practices using the EMIS Health® system). The CPRD database was linked to the Hospital Episode Statistics (HES) database (177), which includes data about patient-reported outcome measures (PROMs).

The protocol for this work was approved by the Independent Scientific Advisory Committee for CPRD research (protocol number 20_119). CPRD has ethics approval from the Health Research Authority to support research using anonymised patient data.

5.3.2. Assessment of frailty

Frailty was assessed using the electronic frailty index (eFI), which comprises 36 age-related health deficits identified by coded data in primary care records (18) (Table 3.1). In order to apply the eFI in practices using the EMIS Health® software system, we mapped the original eFI Read code lists to SNOMED codes using mapping tables from the National Health Service Data Migration Programme (181).

The eFI is calculated as the total number of the eFI deficits present in an individual, divided by 36. Based on previously published thresholds, we categorised the eFI as fit (eFI≤0.12), mild frailty (0.12<eFI≤0.24), moderate frailty (0.24<eFI≤0.36), and severe frailty (eFI>0.36) (18). The eFI was calculated at the date the preoperative questionnaire was completed.

The eFI has been validated in multiple databases and populations and is currently used in primary care practice in the UK (18, 184, 200).

5.3.3. Assessment of patient-reported outcomes

Since April 2009, NHS funded providers of hip and knee replacement surgery have been contractually required to collect PROMs data (178). Data are collected from patients undergoing elective, unilateral primary and revision surgery. Data are collected from patients preoperatively (after being passed as fit for surgery and before the surgery takes place) and postoperatively (around six months after surgery) via a paper questionnaire (178).

In our study cohort, data on PROMs were available for patients who had a THA or TKA between April 2009 and June 2019, and who were registered at a general practice in England that had consented to data linkage. We did not place any restrictions on the indication for surgery, though the large majority of elective THAs and TKAs are due to osteoarthritis (204). We did not place any restrictions on the age of patients included.

5.3.4. The Oxford hip and knee scores

The pre- and postoperative OHS and OKS are calculated based on patients' responses to a 12-item questionnaire, comprising questions about pain and functional ability in relation to patients' hip and knee problems (107, 108). Responses to each question are on a 5-point Likert scale (from 0: worst possible, to 4: best possible). An overall score is calculated as the simple sum of responses to each of the 12 questions, which ranges from 0 (worst possible) to 48 (best possible). The OHS and OKS were analysed as continuous variables.

Based on previously published data relating to the minimally important change (MIC) (110, 111), we also looked at the association between frailty and achieving the MIC in the OHS (improvement of ≥8 points) and OKS (improvement ≥7 points).

Since frailty may impact on an individual's capacity to improve in functional ability, as a secondary outcome, we looked at the OHS and OKS pain subscales (205, 206). The OHS and OKS pain subscales, respectively are calculated based on 6 and 7 questions relating to pain from the OHS and OKS questionnaires. The pain subscales range from 0 (worst possible score) to 24 for the OHS pain subscale and 28 for the OKS pain subscale (best possible scores).

5.3.5. Patient-reported success

In the postoperative questionnaire, patients were asked "overall, how are the problems now in the <hip/knee> on which you had the surgery, compared to before your operation?". Possible responses were "much better", "a little better", "about the same", "a little worse", and "much worse". We defined a patient-reported successful outcomes as reporting being either "much better" or "a little better" and an unsuccessful outcome as being "about the same", "a little worse" or "much worse" following THA and TKA.

5.3.6. Covariates

We included age (at date the preoperative questionnaire was completed), sex, and deprivation as covariates in our analyses, since these variables have previously been associated with outcomes following THA and TKA (207).

Age and sex were identified from the primary care medical records. Deprivation was assessed using the Index of Multiple Deprivation (IMD), a multi-dimensional measure of

neighbourhood-level deprivation based on an individual patient's postcode (208). IMD was categorised based on quintiles.

5.3.7. Statistical analysis

Summary statistics of patient characteristics were calculated with median and inter-quartile range (IQR) reported for continuous variables and number (%) reported for categorical variables.

5.3.7.1. Association between frailty and Oxford hip and knee score

We calculated the median and inter-quartile range (IQR) preoperative, postoperative, and absolute change in OHS and OKS overall and by frailty category. The distributions of the postoperative OHS and OKS in OHS and OKS exhibited right-censoring (ceiling effect), particularly the OHS. We therefore used Tobit regression to determine the association between frailty category (predictor variable) and postoperative OHS and OKS (outcome variables). Tobit regression models account for right- and/or left-censoring, by modelling the probability that observations are censored given the covariates, which is used in the maximum likelihood estimation (196). We looked at a model adjusted for (i) age, sex, and quintile of IMD and (ii) a model adjusted additionally for preoperative OHS/OKS. Since frailty may impact on an individual's capacity to improve in functional ability, as a secondary outcome, we repeated this analysis looking at the OHS and OKS pain subscales.

The absolute change in OHS and OKS, as well as baseline scores, were approximately normally distributed (data not shown). In a secondary analysis, we looked at the association between frailty category (predictor variable) and absolute change in OHS/OKS (outcome variable) using linear regression. We adjusted the model for age, sex, and quintile of IMD.

5.3.7.2. Association between frailty and minimally important change in Oxford hip and knee score

We used logistic regression to determine the association between achieving a MIC in OHS/OKS (binary outcome variable) and frailty category, adjusted for age, sex, and quintile of IMD.

5.3.7.3. Association between frailty and patient-reported success

We defined a successful outcome as reporting being either “much better” or “a little better” and an unsuccessful outcome as reporting being either “about the same”, “a little worse” or “much worse”. We calculated the proportion of patients in each frailty category who reported a successful outcome. We used logistic regression to determine the association between achieving a patient-reported successful outcome and frailty category, adjusted for age, sex, and quintile of IMD. In the analysis looking at patient-reported success, we included only individuals who answered the questions about success in the postoperative questionnaire.

In all analyses, we included only individuals who answered all of the questions needed to calculate the pre- and postoperative Oxford hip/knee score. There were no missing data for the eFI, age, sex, or IMD.

5.4. Results

5.4.1. Patient characteristics

After excluding individuals with missing data for the pre- or postoperative scores, the number of individuals who contributed to the analysis of the OHS and OKS, respectively was 42,512 and 49,208 (Supplementary Figure 5.1). The proportion of patients who had complete pre- and postoperative OHS and OKS data, respectively, decreased with increasing frailty from 80.9% and 78.5% among those who were fit, to 58.7% and 57.9% among those with severe frailty (Supplementary Table 5.1). Women were slightly less likely than men to have complete pre- and postoperative OHS/OKS data and also increasing quintile of IMD was associated with decreasing likelihood of complete data (Supplementary Table 5.1).

In the hip and knee cohorts, respectively, the median (inter-quartile range) age was 71.4 (66.2, 77.2) and 70.9 (66.0, 76.6) years and 59.8% and 55.5% were women. In the hip and knee cohorts, respectively, the proportion who were: fit was 37.2% and 30.2%; mildly frail was 42.0% and 45.6%; moderately frail was 16.7% and 19.5%; and severely frail was 4.1% and 4.7% (Table 5.1).

Table 5.1. Participant characteristics

	Hip replacement (n=42,512)	Knee replacement (n=49,208)
	Median (25th percentile, 75th percentile))	
Age (years)[1]	71.4 (66.2, 77.2)	70.9 (66.0, 76.6)
Preoperative Oxford hip/knee score	18.0 (12.0, 24.0)	19.0 (14.0, 25.0)
Postoperative Oxford hip/knee score	42.0 (35.0, 46.0)	38.0 (30.0, 43.0)
Absolute change in Oxford hip/knee score	21.0 (14.0, 28.0)	16.0 (10.0, 23.0)
	n (%)	
Women	25,425 (59.8)	27,310 (55.5)
Frailty category[1]		
*Fit (*eFI≤0.12)	15,801 (37.2)	14,882 (30.2)
*Mild frailty (*0.12<eFI≤0.24)	17,854 (42.0)	22,418 (45.6)
*Moderate frailty (*0.24<eFI≤0.36)	7,096 (16.7)	9,612 (19.5)
Severe frailty ((eFI>0.36))	1,761 (4.1)	2,296 (4.7)
Fifth of Index of Multiple Deprivation		
1 (least deprived)	12,359 (29.1)	13,462 (27.4)
2	11,009 (25.9)	12,042 (24.5)
3	9,078 (21.4)	10,589 (21.5)
4	6,278 (14.8)	7,770 (15.8)
5 (most deprived)	3,788 (8.9)	5,345 (10.9)
Self-reported success category following THA/TKA[2]		
Much better	36,033 (84.8)	36,034 (73.2)
A little better	3,631 (8.5)	7,786 (15.8)
About the same	1,110 (2.6)	2,326 (4.7)
A little worse	607 (1.4)	1,738 (3.5)
Much worse	415 (1.0)	1,101 (2.2)
Missing	716 (1.7)	223 (0.5)

[1]Age and frailty category at the date the preoperative questionnaire was completed

5.4.2. Association between frailty, preoperative, postoperative and change in Oxford hip and knee scores

Crude preoperative and postoperative OHS and OKS decreased with increasing frailty (Table 5.2). Crude absolute change in OHS and OKS also decreased with increasing frailty, though the decrease was less marked (Table 5.2). In a multivariable Tobit regression model adjusted for age, sex, quintile of IMD, and preoperative score, increasing frailty category was associated with lower postoperative OHS and OKS (Table 5.3). Compared to

those who were fit, postoperative OHS and OKS, respectively among those with severe frailty were lower, β-coefficient (95 % CI), -6.97 (-7.44, -6.49), p<0.001 and -5.88 (-6.28, -5.47), p<0.001 (Table 6.3). In a secondary analysis, we saw a similar association between frailty category and absolute change in OHS and OKS, assessed using linear regression (Supplementary Table 5.2).

Similarly, we also found a trend between increasing frailty and lower crude preoperative, postoperative, and absolute change in the OHS and OKS pain subscales (Supplementary Table 5.3), which persisted in a multivariable model (Supplementary Table 5.4).

Table 5.2. Preoperative, postoperative and absolute change in Oxford hip and knee scores by frailty category

	Median (Inter-quartile range)		
	Preoperative	Postoperative	Absolute change
		Oxford hip score[1]	
Fit	20.0 (14.0, 26.0)	44.0 (39.0, 47.0)	22.0 (16.0, 29.0)
Mild frailty	18.0 (12.0, 24.0)	41.0 (34.0, 46.0)	21.0 (14.0, 28.0)
Moderate frailty	15.0 (10.0, 22.0)	38.0 (30.0, 44.0)	20.0 (12.0, 28.0)
Severe frailty	13.0 (8.0, 19.0)	34.0 (26.0, 41.0)	19.0 (12.0, 27.0)
		Oxford knee score[1]	
Fit	21.0 (16.0, 27.0)	40.0 (34.0, 44.0)	17.0 (11.0, 23.0)
Mild frailty	20.0 (14.0, 25.0)	38.0 (30.0, 43.0)	16.0 (9.0, 23.0)
Moderate frailty	17.0 (12.0, 23.0)	35.0 (26.0, 41.0)	16.0 (8.0, 22.0)
Severe frailty	15.0 (10.0, 20.0)	30.0 (22.0, 38.0)	14.0 (8.0, 22.0)

[1]The Oxford hip and knee scores range from zero to 48, with higher scores indicating better outcomes

Table 5.3. Association between frailty category and postoperative Oxford hip and knee scores

Frailty category	β-coefficient (95% CI)[1]			
	Oxford hip score		Oxford knee score	
	Model 1[2]	Model 2[3]	Model 1[2]	Model 2[3]
Fit	Reference			
Mild frailty	-2.96 (-3.18, -2.75)	-2.51 (-2.72, -2.31)	-2.51 (-2.70, -2.31)	-1.91 (-2.10, -1.72)
Moderate frailty	-5.84 (-6.13, -5.56)	-4.87 (-5.14, -4.59)	-5.11 (-5.36, -4.85)	-3.75 (-4.00, -3.51)
Severe frailty	-8.54 (-9.02, -8.05)	-6.97 (-7.44, -6.49)	-8.10 (-8.52, -7.67)	-5.88 (-6.28, -5.47)

Tobit regression model with postoperative Oxford hip/knee score as the outcome variable and frailty category as the predictor variable
[1]$p<0.001$ for all regression coefficients
[2]Model 1 is adjusted for age, sex, and quintile of index of multiple deprivation
[3]Model 2 is adjusted for age, sex, and quintile of index of multiple deprivation, and preoperative Oxford hip/knee score
CI: confidence interval

Similarly, crude pre- and postoperative OHS and OKS pain subscale scores also decreased with increasing frailty (Supplementary Table 5.3). We also saw that increasing frailty was associated with lower postoperative OHS and OKS pain subscale scores in a Tobit model adjusted for age, sex, and quintile of IMD, which persisted after additional adjustment for preoperative OHS/OKS pain subscale score (Supplementary Table 5.4). Association between frailty, minimally important change in Oxford hip and knee score, and patient-reported success

In a multivariable model adjusted for age, sex, and quintile of IMD, increasing frailty category was associated with reducing odds ratios (OR) for achieving a MIC in the OHS and OKS (Table 5.4). Following THA, compared to those who were fit the OR (95% CI) of achieving the MIC in OHS (≥8 points) among those with mild, moderate, and severe frailty was 0.71 (0.66, 0.77), 0.51 (0.46, 0.56), and 0.44 (0.38, 0.51) (Table 5.4). However, even among those with severe frailty, 83.9% achieved the MIC in OHS (Table 5.4). Broadly similar results were found in the knee cohort (Table 5.4).

In the hip and knee cohorts, respectively 41,796 and 48,985 individuals contributed to the analysis of patient-reported success (Supplementary Figure 5.1). In a multivariable model adjusted for age, sex, and quintile of IMD, increasing frailty was associated with reducing odds ratios for reporting a successful outcome (problems either “much better” or “a little better” following THA and TKA) (Table 5.4). Following THA, compared to those who were fit, the OR (95% CI) of reporting a successful outcome among those with mild, moderate, and severe frailty was 0.54 (0.48, 0.61), 0.33 (0.29, 0.38), and 0.27 (0.22, 0.32) (Table 5.4). However, even among those with severe frailty, 90.0% reported a successful outcome following THA (Supplementary Table .4). Broadly similar results were found in the knee cohort.

Table 5.4. Proportion and odds ratio of achieving minimally important change in Oxford hip and knee scores and reporting a successful outcome, by frailty category

Frailty category	Achieved minimally important change in Oxford hip/knee score[1]		Achieved a patient-reported successful outcome[3]	
	n (%)	Odds ratio (95% CI)[2]	n (%)	Odds ratio (95% CI)[4]
		Hip cohort		
Fit	14,594 (92.4)	Reference	15,114 (97.0)	Reference
Mild frailty	15,971 (89.5)	0.71 (0.66, 0.77)	16,630 (94.7)	0.54 (0.48, 0.61)
Moderate frailty	6,083 (85.7)	0.51 (0.46, 0.56)	6,370 (91.8)	0.33 (0.29, 0.38)
Severe frailty	1,477 (83.9)	0.44 (0.38, 0.51)	1,550 (90.0)	0.27 (0.22, 0.32)
		Knee cohort		
Fit	12,848 (86.3)	Reference	13,730 (92.6)	Reference
Mild frailty	18,542 (82.7)	0.72 (0.68, 0.77)	19,937 (89.3)	0.63 (0.58, 0.68)
Moderate frailty	7,741 (80.5)	0.60 (0.56, 0.65)	8,259 (86.5)	0.45 (0.41, 0.49)
Severe frailty	1,797 (78.3)	0.50 (0.45, 0.57)	1,894 (83.0)	0.32 (0.28, 0.37)

[1]Minimally important change was defined as ≥8 point in OHS and ≥7 points in OKS. Minimally important change could be calculated for 42,512 individuals who had complete pre- and postoperative Oxford hip score and 49,208 individuals who had complete pre- and postoperative Oxford knee score

[2]Logistic regression model with achieving minimally important change as the binary outcome variable and frailty category as the predictor variable. Odds ratio adjusted for age, sex, and quintile of index of multiple deprivation. $p<0.001$ for all reported odds ratios

[3]Successful outcome was defined as the patient reporting that their problems were either "much better" or "a little better" following surgery (other possible responses were "about the same", "a little worse" or "much worse". 41,796 patients in the hip cohort answered the question about success and 43,820 patients in the knee cohort

[4]Logistic regression model with patient-reported successful outcome as the binary outcome variable and frailty category as the predictor variable. Odds ratio adjusted for age, sex, and quintile of index of multiple deprivation. $p<0.001$ for all reported odds ratio

CI: confidence interval

5.5. Discussion

We found, using a large national database of routinely collected PROMs data, that increasing frailty was associated with poorer postoperative OHS and OKS, reduced likelihood of achieving the MIC in OHS and OKS, and reduced likelihood of a patient-reported successful outcome following hip and knee replacement surgery. However, even among those with severe frailty, the large majority experienced substantial improvements in OHS/OKS, improving from a median preoperative score of 13 to a postoperative score of 34 in the hip cohort and improving from 15 to 30 in the knee cohort. Among those with severe frailty, the proportion who experienced a MIC in OHS and OKS, respectively was 84% and 78% and the proportion of those with severe frailty who reported a successful outcome following THA and TKA, respectively, was 90% and 83%.

There are limited previous studies looking at the impact of frailty on functional outcomes following THA and TKA (152, 163, 164). One single-centre study from Poland of 365 patients found that frailty, assessed using a 5-item and 11-item frailty index, was associated with poorer functional outcome, assessed using the Western Ontario and McMaster Universities Index of Osteoarthritis (WOMAC), 3 years after primary total hip arthroplasty, compared to those without frailty, though this was not statistically significant at the 95% confidence level after age adjustment (164).

Another study of 805 patients who had hip arthroplasty and 640 who had knee arthroplasty in one of seven centres in the Netherlands assessed the association between frailty, assessed using the Groningen frailty indicator and change in the Hip Osteoarthritis Outcome Score/Knee Osteoarthritis Outcome Score (HOOS/KOOS) at 1 year following surgery (163). Patients classified as having frailty had significantly lower preoperative HOOS/KOOS, though had similar change in HOOS/KOOS, except for the “function in sports and recreation” and “quality of life” subscales, which showed significantly lower change among those with frailty compared to those without frailty (163).

In a UK study of 6,682 patients who had a THA, the mean improvement in OHS following THA was reported to not vary importantly between different levels of frailty (assessed using the eFI), however, the number of patients in the severely frail category was small (n=7) (152). Consistent though with data in our study, the mean improvement in OHS was lower in the mild and moderate frail compared to the fit group. There were no data

presented looking at patient-reported success, minimally important change, nor outcomes following TKA.

As shown by others, we found that increasing frailty was associated with a lower preoperative OHS and OKS score. This may in part be due to a combination of pre-existing functional impairment among individuals with a higher level of frailty as well as any functional impairment relating to the underlying joint disease. Increasing frailty was associated also with a gradual decrease in OHS and OKS pain sub-scores suggesting more severe pain in those with frailty. We did not have any information though about structural joint damage to determine whether the underlying severity of disease was greater among those with more severe frailty.

Our study has a number of strengths, including the use of large, national databases of electronic health records, a well-validated frailty index which is currently used in clinical practice in the UK, and a range of PROMs routinely collected in the UK National Health Service, including the OHS and OKS pain subscales and also patient-reported success. However, our study also has limitations. Not all patients returned a complete pre- and postoperative questionnaire. Compared to those who had complete pre- and postoperative OHS/OKS, those without were more likely to be frail, more likely to be in a higher quintile of IMD, slightly more likely to be female, and were slightly older. The effect of a higher proportion of missing data among those with higher levels of frailty would tend to result in an underestimate of the degree of frailty in the analytical sample compared to the whole cohort, however, it seems unlikely that it would influence the observed association between frailty and outcomes which was based on an internal comparison of responders (those who contributed data to the analysis). Finally, there are limitations in using routinely collected primary care electronic medical records to assess frailty. The occurrence of comorbidity and degree of frailty may be underestimated in the electronic medical records compared to a more detailed assessment such as a comprehensive geriatric assessment which may reveal health deficits that had not previously come to clinical attention. The effect of this would be to underestimate the degree of frailty.

Patients with frailty who are selected for THA/TKA may be different from patients with frailty who do not have surgery and it is difficult, using routinely collected data, to account for all factors which may influence clinical decision making about suitability for THA/TKA and also factors which may influence patients' decision making about surgery. Caution

therefore is needed in extrapolation of our findings to those with hip/knee OA who have not had surgery.

Further work is needed to assess the broader impact of hip and knee arthroplasty on quality of life among patients with frailty and also to better understand how patients assess the success of surgery. There are limitations of routinely collected patient-reported outcome data in assessing the impact of frailty on outcomes following hip and knee arthroplasty and additional data, including qualitative data, may provide additional novel insights.

In conclusion, we found that increasing frailty was associated with lower postoperative OHS and OKS following THA and TKA, reduced likelihood of achieving MIC in OHS and OKS, and reduced likelihood of a patient-reported successful outcome. However, even among those with severe frailty, the majority achieved the MIC in OHS/OKS and reported a successful outcome. By providing more personalised information about outcomes, our data may help inform shared decision making among patients who are considered potentially suitable for joint surgery.

5.6. Supplementary data

Supplementary Table 5.1. Patient characteristics of those included in the analysis of the Oxford hip and knee scores and those excluded due to missing data

	Patients with complete pre- and postoperative OHS/OKS	Patients with missing pre- and/or postoperative OHS/OKS	Difference, p-value[1]
	Hip replacement surgery		
	Median (25th percentile, 75th percentile)		
Age at arthroplasty (years)	71.4 (66.2, 77.2)	72.3 (66.3, 78.7)	<0.0001
	n (row %)		
Sex			
Men	17,087 (76.0)	5,407 (24.0)	<0.0001
Women	25,425 (74.5)	8,727 (25.6)	
Frailty category			
Fit	15,801 (80.9)	3,730 (19.1)	<0.001
Mild frailty	17,854 (75.4)	5,819 (24.6)	
Moderate frailty	7,096 (68.0)	3,344 (32.0)	
Severe frailty	1,761 (58.7)	1,241 (41.3)	
Fifth of index of multiple deprivation			
1 least deprived)	12,359 (78.3)	3,432 (21.7)	<0.001
2	11,009 (76.5)	3,380 (23.5)	
3	9,078 (75.6)	2,933 (24.4)	
4	6,278 (72.2)	2,422 (27.8)	
5 (most deprived)	3,788 (66.4)	1,917 (33.6)	
	Knee replacement surgery		
	Median (25th percentile, 75th percentile)		
Age at arthroplasty (years)	70.9 (66.0, 76.6)	71.2 (65.6, 77.4)	0.002
	n (row %)		
Sex			
Men	21,898 (73.7)	7,810 (26.3)	<0.001
Women	27,310 (72.5)	10,353 (27.5)	
Frailty category			
Fit	14,882 (78.5)	4,070 (21.5)	<0.001
Mild frailty	22,418 (74.4)	7,704 (25.6)	
Moderate frailty	9,612 (67.1)	4,719 (32.9)	
Severe frailty	2,296 (57.9)	1,670 (27.0)	
Fifth of index of multiple deprivation			
1 least deprived)	13,462 (76.0)	4,263 (24.1)	<0.001
2	12,042 (74.9)	4,039 (25.1)	
3	10,589 (73.3)	3,857 (26.7)	
4	7,770 (71.1)	3,153 (28.9)	
5 (most deprived)	5,345 (65.7)	2,795 (34.3)	

OHS: Oxford hip score; OKS, Oxford knee score

[1]Differences in the distribution of patient characteristics among those complete pre- and postoperative OHS/OKS and those with missing pre- and/or postoperative OHS/OKS was tested using chi-square tests for categorical variables and the Mann –Whitney rank sum test for continuous variables

Supplementary Table 5.2. Association between frailty category and absolute change in Oxford hip and knee scores

Frailty category	β-coefficient (95% CI)[1]	
	Model 1[2]	Model 2[3]
	Oxford hip score	
Fit	Reference	
Mild frailty	-1.03 (-1.25, -0.81)	-2.12 (-2.29, -1.94)
Moderate frailty	-1.90 (-2.20, -1.60)	-4.28 (-4.52, -4.03)
Severe frailty	-2.53 (-3.05, -2.01)	-6.37 (-6.79, -5.95)
	Oxford knee score	
Fit	Reference	
Mild frailty	-0.95 (-1.15, -0.74)	-1.81 (-1.99, -1.62)
Moderate frailty	-1.68 (-1.94, -1.42)	-3.61 (-3.85, -3.80)
Severe frailty	-2.57 (-3.01, -2.13)	-5.74 (-6.14, -5.34)

Linear regression model, with absolute change in OHS/OKS as the dependent variables and frailty category as the independent variable.
[1]p<0.001 for all regression coefficients
[2]Model 1 is adjusted for age, sex, and quintile of index of multiple deprivation
[3]Model 2 is adjusted for age, sex, and quintile of index of multiple deprivation, and preoperative Oxford hip/knee score
CI: confidence interval

Supplementary Table 5.3. Preoperative, postoperative, and absolute change in Oxford hip and knee pain subscore by frailty category

	Median (Inter-quartile range)		
	Preoperative	Postoperative	Absolute change
	Oxford hip pain subscore[1]		
Fit	7.0 (4.0, 10.0)	22.0 (19.0, 23.0)	13.0 (10.0, 17.0)
Mild frailty	6.0 (4.0, 10.0)	20.0 (16.0, 23.0)	13.0 (8.0, 16.0)
Moderate frailty	6.0 (3.0, 9.0)	19.0 (14.0, 22.0)	12.0 (7.0, 16.0)
Severe frailty	5.0 (2.0, 8.0)	18.0 (13.0, 21.0)	12.0 (7.0, 16.0)
	Oxford knee pain subscore[2]		
Fit	11.0 (7.0, 14.0)	24.0 (20.0, 27.0)	12.0 (8.0, 16.0)
Mild frailty	10.0 (7.0, 13.0)	23.0 (18.0, 26.0)	12.0 (7.0, 16.0)
Moderate frailty	9.0 (6.0, 12.0)	21.0 (16.0, 25.0)	11.0 (7.0, 16.0)
Severe frailty	8.0 (5.0, 11.0)	19.0 (14.0, 24.0)	11.0 (6.0, 15.0)

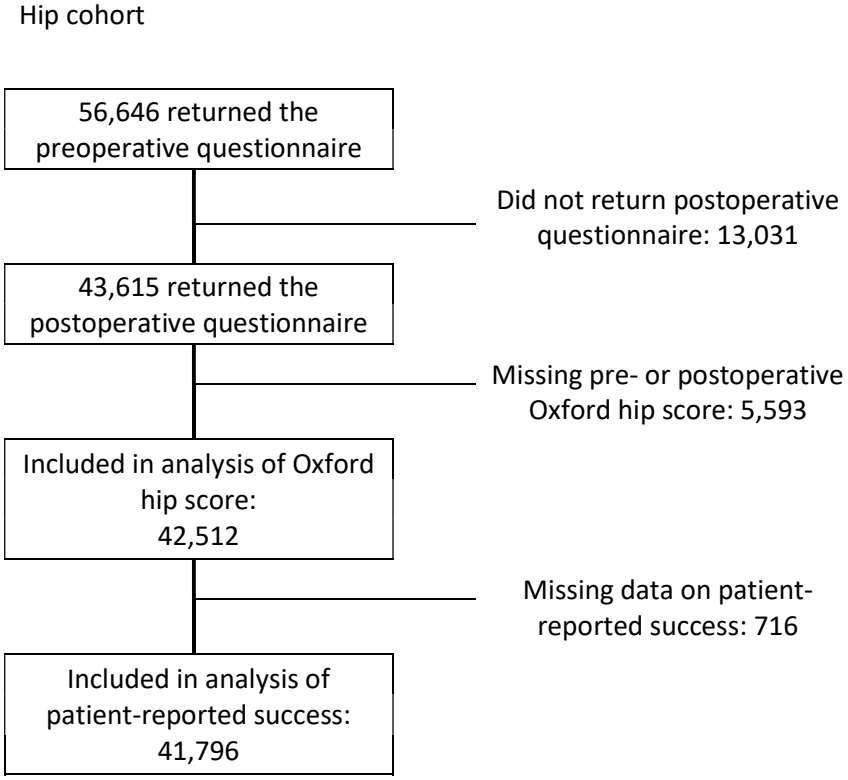
[1]The Oxford hip pain subscore ranges from 0 (worst possible score) to 24 (best possible score)
[2]The Oxford knee pain subscore ranges from 0 (worst possible score) to 28 (best possible score)

Supplementary Table 5.4. Association between frailty category and postoperative Oxford hip and knee pain subscores

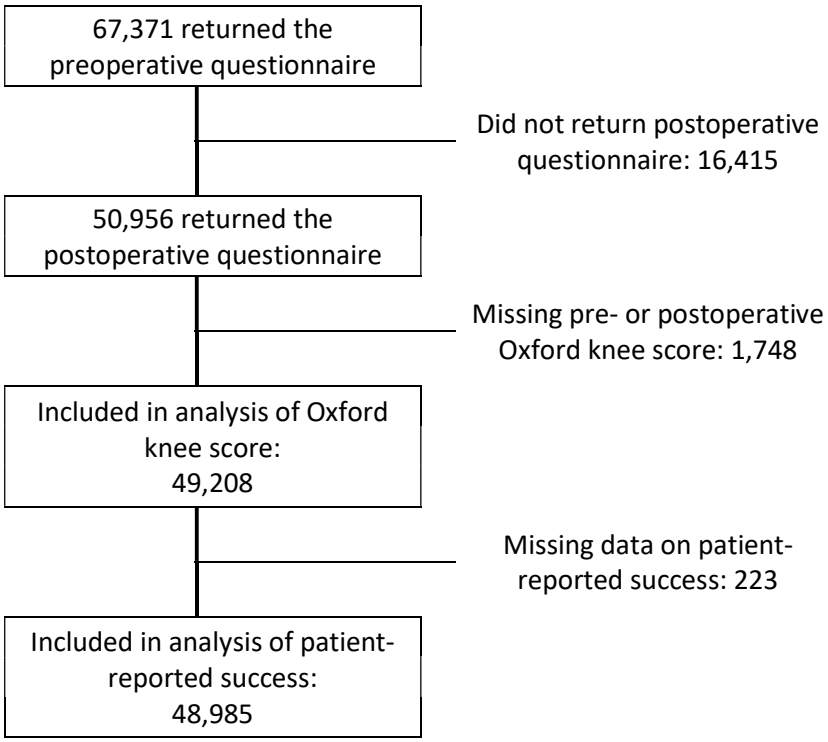
Frailty category	β-coefficient (95% CI)[1]			
	Oxford hip pain subscore		Oxford knee pain subscore	
	Model 1[2]	Model 2[3]	Model 1[2]	Model 2[3]
Fit	Reference			
Mild frailty	-1.28 (-1.38, -1.80)	-1.16 (-1.26, -1.06)	-1.30 (-1.41, -1.18)	-1.11 (-1.22, -0.99)
Moderate frailty	-2.51 (-2.64, -2.37)	-2.25 (-2.39, -2.11)	-2.58 (-2.73, -2.43)	-2.14 (-2.28, -2.00)
Severe frailty	-3.53 (-3.77, -3.30)	-3.13 (-3.37, -2.90)	-4.04 (-4.29, -3.79)	-3.31 (-3.55, -3.06)

Tobit regression model with postoperative Oxford hip/knee pain sub-score as the outcome variable and frailty category as the predictor variable
[1]$p<0.001$ for all regression coefficients
[2]Model 1 is adjusted for age, sex, and quintile of index of multiple deprivation
[3]Model 2 is adjusted for age, sex, and quintile of index of multiple deprivation, and preoperative Oxford hip/knee pain sub-score
CI: confidence interval

Supplementary Figure 5.1. Patient flow diagram



Knee cohort


67,371 returned the preoperative questionnaire
Did not return postoperative questionnaire: 16,415
50,956 returned the postoperative questionnaire
Missing pre- or postoperative Oxford knee score: 1,748
Included in analysis of Oxford knee score: 49,208
Missing data on patient-reported success: 223
Included in analysis of patient-reported success: 48,985

Chapter 6. The impact of total hip and knee arthroplasty on the trajectory of frailty

6.1. Abstract

Aim: To determine the influences of total hip and knee arthroplasty (THA/TKA) on within individual rates of change in frailty assessed by the electronic Frailty Index.

Methods: We included in the analysis individuals who had a THA or TKA between April 1997 and June 2019. Participants were drawn from the Clinical Practice Research Datalink, a database of primary care electronic medical records. We assessed frailty using the electronic frailty index (eFI) and used linked secondary care data to identify THA and TKA. Change in eFI scores over time within individuals was assessed using multivariable random effects regression models, with age at date of THA/TKA, year of THA/TKA and quintile of index of multiple deprivation (IMD) included as covariates. We looked at the rate of change of the eFI in the period up to two years before and up to two years after THA and TKA using random effects models and linear splines.

Results: In total 80,956 individuals who had a THA and 95,540 individuals who had a TKA contributed data. In a multivariable model, the rate of increase in the eFI (95% CI) in the two-year period before THA was 0.025 (0.024, 0.025) units per year (increasing eFI indicates increasing frailty severity) and the rate of increase in the two-year period after THA was lower by -0.0036 (-0.0041, -0.0032) units per year compared to the preoperative rate of increase. Similarly, the rate of increase in the eFI in the two years before TKA was 0.025 (0.025, 0.025) units per year and was lower by -0.0030 (-0.0034, -0.0026) units per year in the two-year period following TKA.

Conclusions: The rate of increase in eFI is statistically significantly lower in the period up to two years following THA and TKA compared to the period up to two years before surgery, though on absolute terms the difference is small. Our results are consistent with THA and TKA having a modest beneficial impact on the progression of frailty at least in

the short term. Further work is needed to determine the longer-term impact of THA and TKA on frailty progression.

6.2. Background

Osteoarthritis (OA) is the most frequent form of arthritis and a leading cause of pain and disability worldwide (59, 209). OA can affect any synovial joint, although the hip and knee are commonly affected. Common symptoms of OA in the hip and knee include pain and impaired physical function. There is increasing evidence that people with OA, including knee OA, are at increased risk of frailty (210). For people with hip and knee OA who are not adequately managed by more conservative therapies, total hip and knee arthroplasty (THA and TKA) may be indicated. Each year in the UK, around 100,000 THAs and around 100,000 TKAs are carried out (204). While THA and TKA are associated with significant improvements in physical function, pain, and also quality of life (211), the impact of THA and TKA on the progression of frailty is not known.

One previous study based on data from an institutional joint register looked at change in frailty *following* THA and TKA (THA and TKA analysed as one combined group) (122). Frailty was assessed using a FI (comprising 32 deficits of which 17 were comorbidities and 14 activities of daily living (ADL)). The authors reported that a proportion of patients improved in their frailty state (assessed using the frailty index) 1 year following surgery: among those who had frailty preoperatively, 6% improved to 'non-frail', 34% improved to 'vulnerable', and 60% remained frail (122). There was though no information about change of frailty leading up to joint surgery and thus the impact of joint surgery on rate of change in frailty is not clear. Improvement in frailty status is also observed among the general population who do not have arthroplasty (33).

People with OA are at increased risk of frailty and experience a higher rate of progression of frailty over time compared to people without OA. It is important therefore to identify interventions that may reduce the progression of frailty in people with OA. It is not clear whether THA and TKA impact on the progression of frailty among people with hip and knee OA. The aim of our study was to determine whether THA and TKA impacts on the rate of change in the primary care based electronic frailty index over time among people with hip and knee OA. We hypothesised that THA and TKA would be linked with a reduction in the rate of change of frailty.

6.3. Methods

6.3.1. Data sources

We used a UK database of primary care electronic medical records from the Clinical Practice Research Datalink (CPRD) with linkage to the Hospital Episode Statistics (HES) admitted patient care database, and office for national statistics (ONS) mortality data. CPRD comprises two databases; Gold, which includes data from general practices using the Vision® patient management system and Aurum, which includes general practices using the EMIS Web® patient management system. We used both CPRD Gold and Aurum databases in our study.

The protocol for this work was approved by the Independent Scientific Advisory Committee for CPRD research (protocol number 20_119). CPRD has ethics approval from the Health Research Authority to support research using anonymised patient data.

6.3.2. Assessment of frailty

As described previously (201), we assessed frailty using the electronic frailty index (eFI), a well validated frailty index based on 36 age-related health deficits identified from coded data in primary care electronic medical records (18, 184, 200) (Table 3.1). The eFI is calculated as the number of deficits present in an individual, divided by 36 (eFI range 0-1). Based on previously published thresholds, we categorised the eFI as fit (eFI≤0.12), mild frailty (0.12<eFI≤0.24), moderate frailty (0.24<eFI≤0.36), and severe frailty (eFI>0.36) (18). The eFI is a cumulative frailty index and increases monotonically over time (212).

One of the 36 eFI deficits is 'arthritis', the primary indication for THA and TKA. So that the 'arthritis' deficit did not affect the rate of increase in eFI in the period before arthroplasty, we restricted the analysis to those who had an 'arthritis' eFI deficit prior to the date of THA or TKA, and patients did not contribute to the analysis before they developed the 'arthritis' eFI deficit. For each individual, we calculated the eFI at the date of entry to the study. We updated the eFI score on each occasion that it changed, based on new diagnostic codes recorded in the primary care record indicating an incident eFI deficit.

6.3.3. Identification of THA and TKA

We identified THA and TKA based on intervention and procedure codes (OPCS-4) recorded in the HES admitted patient care database, using code lists from the National Joint Registry (189).

6.3.4. Covariates

We included year of surgery, age at date of surgery, sex, quintile of index of multiple deprivation (IMD), and a time-varying binary variable which was coded as zero before arthroplasty and one after arthroplasty as covariates in a multivariable model. Age and sex were identified from the primary care record. Year of surgery was determined from the HES data. IMD is a multi-dimensional measure of neighbourhood-level deprivation at lower layer super output area level (208). IMD was determined based on patients' home postcode and was provided to us by CPRD categorised into quintiles.

6.3.5. Study cohort and follow up period

Individuals who had a THA or TKA from April 1997 to June 2019 were identified, since this was the date range for which linked HES data was available. We excluded individuals who had a primary indication for arthroplasty relating to fractures, osteonecrosis, rheumatoid arthritis and malignant neoplasm of bone. In addition, we excluded cases where the coded primary indication for THA/TKA was used in <0.05% of cases. For individuals who had more than one THA or TKA during the study period, only the first was included. We excluded individuals who did not have eFI 'arthritis' deficit coded in their primary care record before the date of THA or TKA.

We restricted our analysis to the period from up to two years before THA or TKA until up to two years after THA or TKA. Individuals entered the study 2 years before their THA/TKA, the date at which they developed the 'arthritis' deficit, or the date at which they were registered at a general practice contributing to the CPRD (whichever came latest). Individuals exited the study 2 years after THA/TKA, the date of death, or the date on which the individual was no longer registered at a GP practice contributing to the CPRD (whichever came earliest) (see Supplementary Figure 6.1).

6.3.6. Statistical analysis

Summary statistics of patient characteristics were calculated with median and inter-quartile range (IQR) reported for continuous variables and number (%) reported for categorical variables.

To account for correlation between repeated measures of eFI within individuals, we assessed trajectories of eFI over time using random effects regression models. Separate models were used for the THA and the TKA cohorts.

First, we assessed trajectories of eFI before and after arthroplasty using linear spines (piecewise straight lines that meet at 'knots'). A knot was placed at the date of THA/TKA in order to assess the rate of change in eFI in the two years before THA/TKA and in the two years after THA/TKA. Initially we assessed the rate of change of eFI before and after THA/TKA using a base model with repeated measures of eFI as the outcome and time (years, centred at the date of THA/TKA) as the predictor.

To allow for nonlinear trajectories of eFI over time, we then repeated the analysis using restricted cubic splines (smooth curves that join at 'knots'). Knots were placed at two years before THA/TKA, the date of THA/TKA, and two years after THA/TKA, so that nonlinear trajectories of frailty before and after THA/TKA could be assessed. We visually compared plots of expected values of eFI over time in the two years before THA/TKA and two years after THA/TKA from the linear and cubic spline models.

We then ran final multivariable models including the covariates described above. Year of surgery and age at surgery were analysed as continuous variables and sex and quintile of IMD were analysed as categorical variables.

To assess whether the rate of change of frailty differed between men and women, we considered multiplicative interaction terms between time and sex before and after THA/TKA. Similarly, we considered multiplicative interaction terms between quintile of IMD and time before and after THA/TKA.

6.4. Results

6.4.1. Participants

In total, 133,442 THAs and 139,211 TKAs during the study period were identified. After excluding arthroplasties relating to fractures, osteonecrosis, rheumatoid arthritis, neoplasms, second arthroplasties, and after excluding individuals who did not have the 'arthritis' eFI deficit recorded prior to THA or THA, the number of people who contributed to the hip and knee cohorts, respectively was 80,956 and 95,540 (Supplementary Figure 6.2). In the THA and TKA cohorts, respectively, the median (inter-quartile range) age at study entry was 68.8 (63.0, 75.1) and 68.2 (62.3, 74.4) years and 61.4% and 57.5% were women (Table 6.1). IMD was missing for 67 individuals in the THA cohort and 96 individuals in the TKA cohort. Individuals with missing IMD were excluded from the multivariable models. There were no missing data for other covariates or the eFI.

Table 6.1. Participant characteristics at study entry

	Hip arthroplasty (n=80,956)	Knee arthroplasty (n=95,540)
	Median (25th percentile, 75th percentile)	
Age	68.8 (63.0, 75.1)	68.2 (62.3, 74.4)
eFI	0.14 (0.08, 0.19)	0.14 (0.08, 0.19)
	n (%)	
Female	49,683 (61.4)	54,932 (57.5)
Fifth of index of multiple deprivation[1]		
1 (least deprived)	21,116 (26.1)	22,981 (24.1)
2	19,461 (24.1)	22,257 (23.3)
3	17,510 (21.7)	20,588 (21.6)
4	13,189 (16.3)	16,475 (17.3)
5 (most deprived)	9,613 (11.9)	13,143 (13.8)

[1]Index of multiple deprivation was missing for 67 individuals in the hip arthroplasty cohort and 96 individuals in the knee arthroplasty cohort
eFI: electronic frailty index

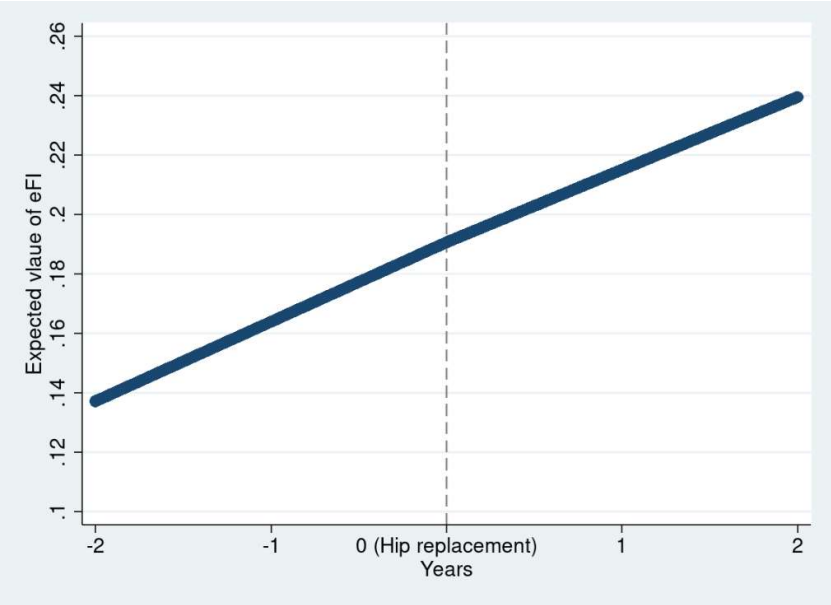
6.4.2. Change in electronic frailty index before and after hip and knee arthroplasty

The expected values of eFI over time before and after THA and TKA based on linear spline models are shown in Figure 6.1. Expected values over time based on cubic spline models are shown in Supplementary Figure 6.3. Since trajectories of the eFI based on cubic spline

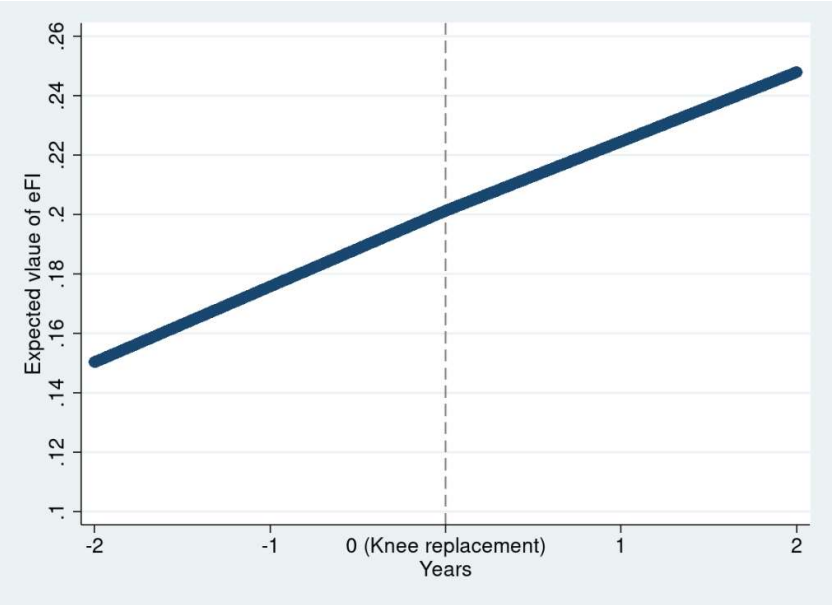
models did not deviate substantially from linearity, we report the results based on the linear spline models.

Figure 6.1. Linear spline trajectories of the electronic frailty index before and after (A) total hip arthroplasty and (B) total knee arthroplasty

(A) Total hip arthroplasty



(B) Total knee arthroplasty



Based on the linear spline model, for THA the eFI increased in the period up to two years before surgery at a rate of 0.025 (95% CI 0.024, 0.025) units per year and increased in the two years after THA at a rate of 0.021 (95% CI, 0.021, 0.021) units per year (Table 6.2). The difference in rate of increase after THA compared to before THA was statistically significantly lower by -0.0036 (-0.0041, -0.0032) units per year. Similarly, the eFI increased in the period up to two years before TKA at a rate of 0.025 (95% CI 0.025, 0.025) units per year and increased in the period up to two years after THA at a rate of 0.022 (95% CI, 0.021, 0.022) units per year (Table 6.2). The difference in rate of increase after TKA compared to before TKA was statistically significantly lower by -0.0030 (-0.0034, -0.0026) units per year (Table 6.2).

Table 6.2. Rate of change in eFI before and after total hip and knee arthroplasty from linear spline model

	Coefficient (95% CI)	
	Hip arthroplasty	Knee arthroplasty
Change in eFI (per year)[1]		
Before arthroplasty	0.025 (0.024, 0.025)	0.025 (0.025, 0.025)
After arthroplasty	0.021 (0.021, 0.021)	0.022 (0.021, 0.022)
Age at arthroplasty (years)	0.0041 (0.0040, 0.0041)	0.0035 (0.0034, 0.0036)
Sex		
Men	reference	reference
Women	0.012 (0.011, 0.013)	0.017 (0.016, 0.018)
Fifth of index of multiple deprivation		
1 (least deprived)	reference	reference
2	0.0019 (0.00042, 0.0035)	0.0021 (0.00063, 0.0035)
3	0.0062 (0.0046, 0.0077)	0.0069 (0.0054, 0.0084)
4	0.012 (0.010, 0.014)	0.011 (0.0097, 0.013)
5 (most deprived)	0.022 (0.021, 0.024)	0.022 (0.020, 0.023)

CI: confidence interval; eFI: electronic frailty index

[1]The difference in the rate of change per year in eFI after arthroplasty compared to before arthroplasty was -0.0036 (-0.0041, -0.0032) in the hip arthroplasty cohort and -0.0030 (-0.0034, -0.0026) in the knee arthroplasty cohort.

Women had higher eFI scores over time compared to men in both the THA and TKA cohorts. Increasing quintile of IMD (reflecting greater deprivation) was also associated with higher eFI scores over time in both cohorts. There was evidence of a statistically significant interaction between sex and time, indicating differences in the rate of change in eFI between men and women, though the differences were relatively small compared to the overall rate of change in eFI (Supplementary Table 6.1). There were also differences in the rate of change in eFI between quintiles of IMD. In the hip cohort, the preoperative rate of increase in eFI among those in the most deprived quintile of IMD was 0.0015 (0.00085, 0.0022) units per year higher than those in the least deprived quintile of IMD after accounting for age and sex, though there was no statistically significant difference in the preoperative rate of increase in eFI between IMD categories in the knee cohort. Post-operatively, the rate of increase in eFI was statistically significantly higher among those in the most deprived quintile of IMD compared to those in the least deprived quintile of IMD in both the hip and knee cohorts, respectively, by 0.0013 (0.00026, 0.0023) and 0.0015 (0.00065, 0.0024) units per year after accounting for age and sex (Supplementary Table 6.1).

6.5. Discussion

We found that the linear rate of increase in eFI in the two years after THA and TKA was statistically significantly lower than the rate of increase in eFI in the two years before arthroplasty. The difference in the rate of increase in eFI per year after arthroplasty compared to before arthroplasty was, however, modest, equivalent to a reduction of around 14% of the preoperative rate of increase in eFI in the THA cohort and a reduction of around 12% of the preoperative rate of increase in the TKA cohort.

No previous study has compared the rate of change in frailty following THA or TKA compared to the rate of change of frailty prior to surgery. One previous single-centre study of 5,341 individuals from the USA assessed frailty preoperatively and 1 year postoperatively among patients who had a primary THA or TKA (analysed as one combined group), using data recorded in electronic medical records and categorised individuals as “non-frail”, “vulnerable” or “frail” (122). The authors found that, among those who were frail preoperatively, 60% remained frail, 34% improved to vulnerable, and 6% improved to non-frail 1 year following arthroplasty. Among those who were vulnerable preoperatively, 60% remained vulnerable, 29% improved to non-frail and 11%

deteriorated to frail. Among those who were non-frail preoperatively, 14% deteriorated to vulnerable 1 year following arthroplasty (122). However, it is not possible to determine from this previous study the impact of arthroplasty on frailty transitions.

There are a number of plausible mechanisms through which THA and TKA may impact on the progression of frailty. First, chronic pain has been linked with the occurrence of frailty in cross-sectional studies, and also the progression of frailty in longitudinal studies (213), and THA and TKA are associated with a significant reduction in pain (211). Second, reduced physical activity and sedentary behaviour has been linked with an increased risk of frailty in the general population (214). A systematic review and meta-analysis concluded that, while physical activity levels do not increase at 6 months following THA/TKA, modest improvements in physical activity levels are seen at 12 months following arthroplasty (211). Therefore, it is plausible that long-term improvements in physical activity associated with THA/TKA may have a beneficial impact on the progression of frailty. Third, comorbidity, including cardiovascular comorbidity, has also been linked with an increased risk of frailty in people with OA (210). One previous observational study looked at the impact of THA/TKA on the occurrence of serious cardiovascular events and found a cardioprotective effect of THA/TKA (215).

Our study has a number of strengths, including a large national cohort, linked primary and secondary care data, and a validated frailty index that is currently used in primary care in the UK. There are though some limitations to consider when interpreting the results. The eFI is a cumulative frailty index and increases monotonically over time. Deficits in the eFI are coded as present from the first date they are recorded and improvement in the eFI score within an individual is not possible (212). It is possible that THA/TKA may improve deficits included in the eFI, such as “mobility and transfer problems”, however since clinical codes included in the eFI are not removed/ended in the primary care record once they have resolved, it is not possible to look at improvement in eFI deficits. Notwithstanding this limitation, the eFI does allow for the rate of accumulation of deficits over time to be studied. The eFI is based on health deficits recorded during routine primary care. The recording of health deficits may be influenced by factors such as patients’ likelihood to seek care and also variation in clinical practice and clinical coding. In addition, increased monitoring and increased contact with primary care services in the peri-operative period may impact on the likelihood of eFI deficits being recorded. In our analysis we looked at change in frailty up to two years before and two years after joint

surgery, given that the mean follow up in the CPRD is around 4 years (175). Further studies are needed to assess the longer-term impact of THA and TKA on the progression of frailty.

In summary, we found that the rate of increase in the eFI in the two-year period after THA and TKA was statistically significantly lower than the rate of increase in the eFI in the two-year period before arthroplasty, though the difference in the rate of increase before and after arthroplasty was modest. The mechanism is unknown though it is possible that reduction in pain and/or improved function following THA and TKA may play a role. Our data are consistent with THA and TKA having a beneficial impact on the progression of frailty. Further studies are needed to assess the longer-term impact of THA and TKA on frailty trajectories, and further studies using frailty instruments that allow improvement in frailty status to be assessed are also needed.

6.6. Supplementary data

Supplementary Table 6.1. Rate of change in eFI before and after total hip and knee arthroplasty from linear spline model, including interaction terms between sex and time and fifth of IMD and time

	Coefficient (95% CI)	
	Hip arthroplasty	Knee arthroplasty
Change in eFI (per year) (main effect)[1]		
Before arthroplasty	0.024 (0.023, 0.024)	0.025 (0.024, 0.025)
After arthroplasty	0.021 (0.020, 0.021)	0.021 (0.021, 0.022)
Age at arthroplasty (years)	0.0039 (0.0038, 0.0039)	0.0035 (0.0034, 0.0036)
Sex (main effect)		
Men	reference	reference
Women	0.013 (0.011, 0.014)	0.017 (0.016, 0.018)
Sex*time before arthroplasty		
*Men*time before arthroplasty*	reference	reference
*Women*time before arthroplasty*	0.00027 (-0.00014, 0.00068)	-0.00038 (-0.00073, -0.000024)
Sex*time after arthroplasty		
*Men*time after arthroplasty*	reference	reference
*Women*time after arthroplasty*	-0.00033 (-0.0096, -0.00029)	0.00023 (-0.00032, 0.00078)
Fifth of index of multiple deprivation (main effect)		
1 (least deprived)	reference	reference
2	0.0023 (0.00064, 0.0040)	0.0024 (0.00085, 0.0041)
3	0.0064 (0.0046, 0.0081)	0.0070 (0.0054, 0.0087)
4	0.013 (0.011, 0.015)	0.012 (0.010, 0.013)
5 (most deprived)	0.024 (0.022, 0.026)	0.022 (0.020, 0.024)
Fifth of index of multiple deprivation*time before arthroplasty		
*1 (least deprived)*time before arthroplasty*	reference	reference

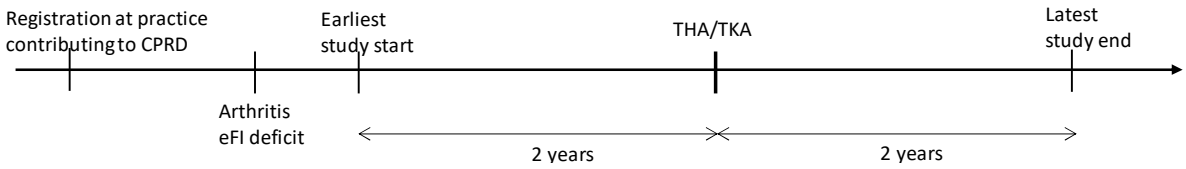
*2*time before arthroplasty*	0.00034 (-0.00023, 0.00091)	0.00019 (-0.00032, 0.00071)
*3*time before arthroplasty*	0.00038 (-0.00020, 0.00096)	0.00019 (-0.00033, 0.00071)
*4*time before arthroplasty*	0.0011 (0.00044, 0.0017)	0.00047 (-0.000085, 0.0010)
*5 (most deprived)*time before arthroplasty*	0.0015 (0.00085, 0.0022)	0.00043 (-0.00016, 0.0010)
Fifth of index of multiple deprivation*time after arthroplasty		
*1 (least deprived)*time after arthroplasty*	reference	reference
*2*time after arthroplasty*	-0.00013 (-0.0010, 0.0075)	-0.00074 (-0.0015, 0.000064)
*3*time after arthroplasty*	0.00092 (0.000041, 0.0018)	0.00043 (-0.00038, 0.0012)
*4*time after arthroplasty*	0.0011 (0.00021, 0.0021)	0.00013 (-0.00072, 0.00098)
*5 (most deprived)*time after arthroplasty*	0.0013 (0.00026, 0.0023)	0.0015 (0.00065, 0.0024)

CI: confidence interval; eFI: electronic frailty index

Random effects model with linear splines before and after arthroplasty. The model included year of surgery, age at date of surgery, sex, quintile of index of multiple deprivation (IMD), and a time-varying binary variable which was coded as zero before arthroplasty and one after arthroplasty, as well as multiplicative interaction terms between sex and time before and after arthroplasty and quintile of IMD and time before and after arthroplasty.

[1]The Change in eFI per year (main effect) relates to men in the least quintile of IMD in this model due to the inclusion of interaction terms between sex and time before and after surgery and interaction terms between quintile of IMD and time before and after surgery

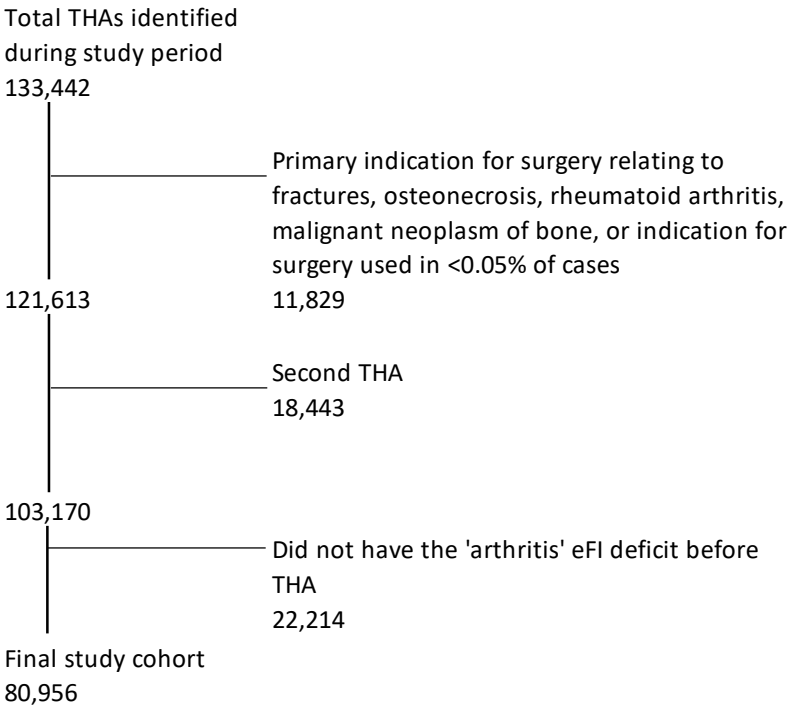
Supplementary Figure 6.1. Follow up period



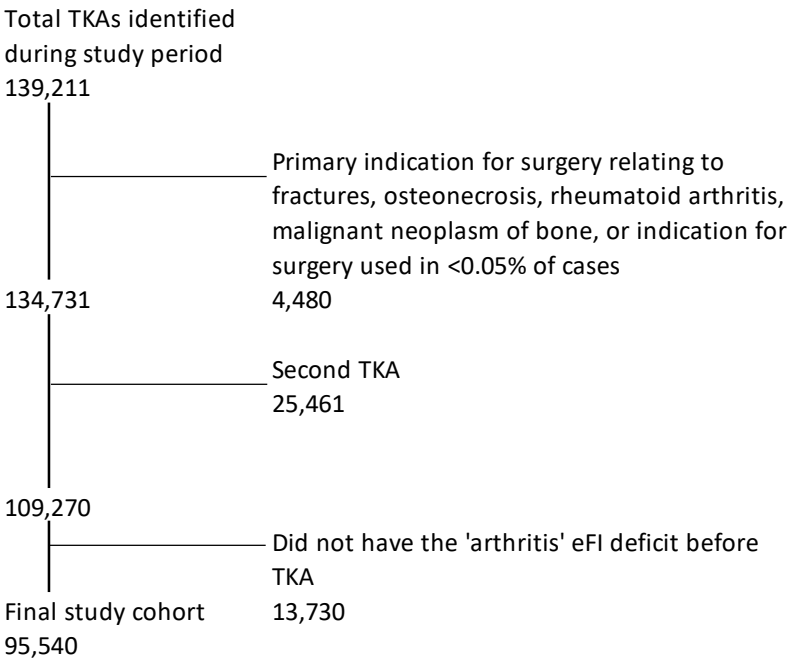
Individuals entered the study 2 years prior to THA/TKA, the date of registration with a primary care practice contributing to CPRD, or first date on which the 'arthritis' deficit of the eFI was recorded (whichever occurred latest). Individuals exited the study 2 years after THA/TKA, date of death, or date at which they were no longer registered at a primary care practice contributing to the CPRD (whichever occurred latest). Change in the electronic frailty index was assessed in the period up to two years before THA/TKA and up to two years after THA/TKA.

Supplementary Figure 6.2. Participant flow diagram

(A) Total hip arthroplasty cohort



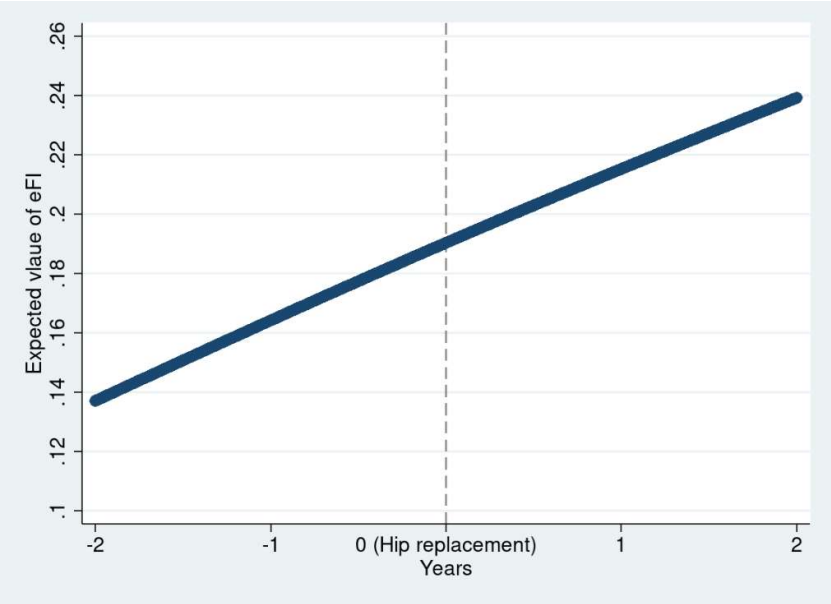
(B) Total knee arthroplasty cohort



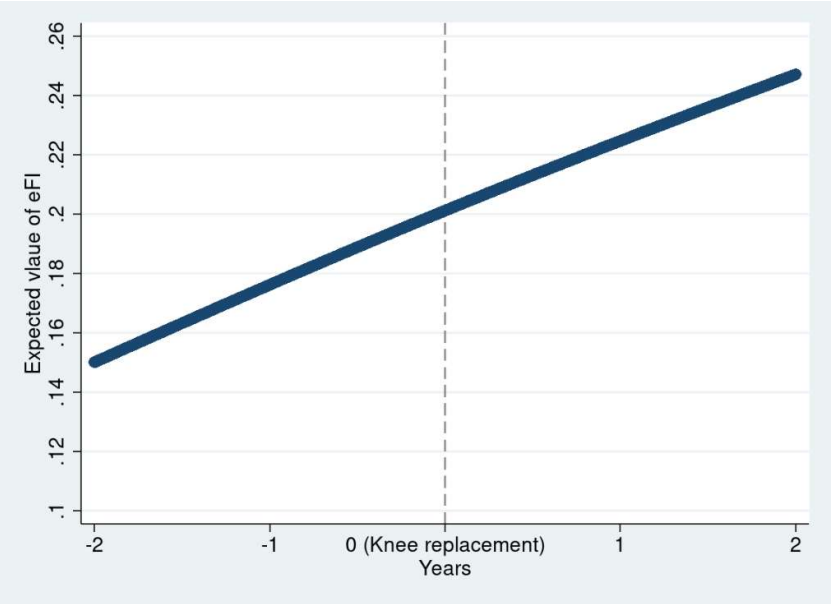
THA: total hip arthroplasty; TKA: total knee arthroplasty; OA: osteoarthritis

Supplementary Figure 6.3. Cubic spline trajectories of the electronic frailty index before and after (A) total hip arthroplasty and (B) total knee arthroplasty

(A) Total hip arthroplasty



(B) Total knee arthroplasty



Chapter 7. Discussion

7.1. Overview

This chapter summarises the main findings and considers also strengths and limitations of the research. The contribution to the literature is highlighted and the implication of the findings for clinical practice considered. Gaps in the literature are identified and areas for future work are discussed.

7.2. Summary of key findings

The aim of this thesis was to investigate the impact of frailty on outcomes following hip and knee arthroplasty. This section summarises the key findings relating to each of the three objectives of the thesis.

7.2.1. Short-term mortality

Following THA and TKA, 30-, 60-, and 90-day mortality increased with increasing frailty. In a multivariable model adjusted for year of birth, sex, quintile of IMD, and year of surgery, the HR (95% CI) for 30-day mortality following THA among those with severe frailty compared to those who were fit was 2.85 (1.84, 4.39) and following TKA was 2.14 (1.29, 3.53). Thirty-day mortality following THA and TKA was higher among men compared to women and increased with increasing age as well as increasing frailty. In a multivariable model, the predicted probability of 30-day mortality following THA and TKA, respectively was lowest among women who were fit and aged 60-64 years (0.05% and 0.03%) and was highest among men with severe frailty aged ≥90 years (6.6% and 4.6%).

The risk of short-term mortality following THA and TKA compared to controls with OA who had not had joint replacement surgery varied by level of frailty. Compared to controls matched on year of birth, sex, and quintile of IMD, all-cause 30-day mortality was increased among fit cases who had THA and TKA compared to fit controls, though by 90 days, there was no statistically significant difference in mortality between cases and controls. There was, however, no statistically significant difference in 30-day mortality between cases with mild, moderate or severe frailty compared to controls in the same frailty stratum in both the hip and knee cohorts. By 90 days, mortality was lower among

cases with mild, moderate and severe frailty compared to controls in the same frailty category in both the hip and knee cohorts.

7.2.2. Patient-reported outcomes

Increasing frailty was associated with decreasing postoperative OHS and OKS, indicating poorer outcome, following hip and knee joint replacement surgery. In a multivariable model adjusted for age, sex, and quintile of IMD, compared to those who were fit, postoperative OHS and OKS, respectively were lower among those with severe frailty, β-coefficient (95% CI) in severely frail group versus fit, -6.97 (-7.44, -6.49) and -5.88 (-6.28, -5.47).

The proportion of people who achieved the MIC in OHS and OKS, respectively decreased from 92% and 86% among fit individuals to 84% and 78% among those with severe frailty. Patient-reported success following hip and knee arthroplasty, respectively decreased from 97% and 93% among fit individuals to 90% and 83% among those with severe frailty. The association between increasing frailty and decreasing likelihood of achieving the MIC and decreasing likelihood of patient-reported success persisted in multivariable models adjusted for age, sex, and quintile of IMD. However, while frailty appears to adversely impact on patient-reported outcomes following hip and knee arthroplasty, even among those with severe frailty, the large majority of patients achieved the MIC in OHS/OKS and reported a successful outcome.

7.2.3. Frailty trajectory

In a multivariable model including year of surgery, age at surgery, sex, and quintile of IMD, the rate of increase in the eFI (95% CI) in the period up to two years *before* THA was 0.025 (0.024, 0.025) units per year while the rate of increase in the period up to two years *after* THA was lower by -0.0036 (-0.0041, -0.0032) units per year compared to the preoperative rate of increase. Similarly, the rate of increase in the eFI in the period up to two years *before* TKA was 0.025 (0.025, 0.025) units per year and was lower by -0.0030 (-0.0034, -0.0026) units per year in the period up to two years *after* TKA. These results are consistent with THA and TKA having a modest beneficial impact on the progression of frailty.

7.3. Strengths and limitations

The data used in this thesis have a number of strengths, including a large, national sample, the use of a well-validated frailty instrument that is currently used in clinical practice, linked primary care, secondary care, and national mortality databases, and the use of routinely collected national PROMs data.

There are though limitations to the data that should be considered when interpreting the findings. The results presented in this thesis are based on data relating to outcomes among individuals who had a THA and TKA and should not be extrapolated to individuals with OA who may be considering surgery though who have not been listed for surgery. A number of factors may impact on whether an individual with hip or knee OA undergoes THA or TKA, including the individual's willingness to have surgery, OA disease severity and impact on function, and clinical suitability and severity of comorbidities. These factors may also impact on outcomes of THA and TKA.

The data presented in Chapter 4 relating to short-term mortality following THA and TKA compared to mortality among individuals with OA who had not had arthroplasty is likely to have been influenced by confounding by indication, which may be impossible to address completely using data from routinely collected medical records. It is likely, for example that patients with OA who are listed for THA or TKA may have better general health with lower levels of comorbidity compared to patients with OA who are not listed for surgery. Since general health and comorbidity are also likely to impact on mortality risk, these factors may impact on the comparison of mortality among cases who had a THA or TKA compared to controls with OA but no previous THA or TKA. Furthermore, while the eFI accounts for a range of morbidities, there may be potential for confounding by morbidities not included in the eFI. This was highlighted when looking at cause-specific short-term mortality among cases who had THA and TKA compared to matched controls with OA and no previous THA or TKA. A significantly lower proportion of deaths due to neoplasia was observed among cases compared to controls, suggesting (and perhaps not surprisingly) that individuals with neoplastic disease are less likely to be selected for THA and TKA.

Attempts were made to mitigate confounding by indication when looking at short-term mortality among cases who had a THA or TKA compared to controls with OA who did not have surgery, including stratifying by frailty category, adjusting for eFI score as a

continuous measure, and adjusting for each of the 36 individual deficits making up the eFI. However, despite these measures it was not possible to exclude residual confounding by indication and so some caution is needed in interpreting the findings.

The results presented in Chapter 5 relating to the impact of frailty on PROMs was based on pre- and postoperative questionnaire data which are voluntarily provided by patients and collected as part of routine care. Not all individuals who have a THA or TKA return both the pre- and postoperative questionnaires. Analysis, which included looking at change in PROMs, was based on a subset of individuals with complete pre- and postoperative PROMs data. The prevalence of moderate and severe frailty was lower among individuals who had complete pre- and postoperative PROMs data compared to individuals who were excluded from the analysis due to missing pre- and/or postoperative PROMs data. However, it seems unlikely that the observed association between frailty and PROMs in the subset of individuals with complete data would be different from that which would have been seen in the full sample.

The association between frailty in PROMs would ideally be assessed in the total sample. Imputation techniques, such as multiple imputation by chained equations, could be used to impute missing PROMs data in order to avoid a restricted analytical sample, however it is not clear whether the missing at random assumption of multiple imputation by chained equations would be satisfied. Whether or not PROMs data were missing may depend on factors not available using routinely collected electronic medical records.

The OHS and OKS were used in this thesis, since these outcome measures are routinely collected in the NHS among patients who have a THA and TKA. However, it is not clear whether these outcome measures are optimal for assessing improvements following THA and TKA among older patients with frailty. While the OHS and OKS have been well validated, the original study that developed and validated the OHS and OKS, did not present data relating to the degree of frailty or comorbidity of the study participants. Therefore, it is not clear how these instruments perform among individuals with frailty. The OHS and OKS are based on a set of questions relating to function, ability to carry out activities of daily living, and pain. Underlying frailty may limit the potential of an individual to improve in functional ability, regardless of the technical success of surgery. Despite the limited ability of patients with frailty to improve in functional ability, this does not preclude a beneficial impact of THA and TKA on pain and quality of life.

It is possible also that frailty may impact on the MIC in OHS and OKS following THA and TKA. Previous studies have determined the MIC in OHS and OKS using anchor-based methods to best distinguish patients who report that their hip/knee problems are "a little better" versus those who report their problems are "about the same", as discussed in section 1.4.4.1. However, it is not clear whether an individual's level of frailty may impact on the relationship between change in the OHS and OKS and self-reported improvement in hip/knee problems and therefore impact on the MIC. Further work is needed to determine whether frailty impacts on the MIC in OHS and OKS. The eFI is a cumulative frailty index and increases monotonically over time. The advantage of using it is that it is widely available and can be calculated on routinely collected primary care data. One of the main limitations though is that it is relatively insensitive to improvements in health. The results presented in Chapter 6 relate to the rate of increase (rather than reduction) in eFI before and after THA and TKA.

In addition, the eFI is based on coded health deficits recorded during routine clinical care and factors such as patients' likelihood to seek care and variation in clinical practice and coding may impact on the assessment of frailty using the eFI, as discussed previously. Changes over time in clinical practice and coding and also in patients' propensity to seek care may impact on analysis of change in eFI over time. Also, the period of follow up available was limited and further work is needed to determine the longer-term impact of THA and TKA on frailty trajectories.

Increased interactions with primary care services may increase the likelihood of eFI deficits being recorded in electronic medical records. This may be problematic when assessing the impact of an intervention on the eFI over time, if the intervention is associated with increased monitoring and increased interactions with primary care services. For example, when looking at change in eFI before and after arthroplasty, increased interactions with primary care services in the peri-operative period may affect the likelihood of health deficits being recorded in the electronic medical record, and hence affect the eFI score, independently of any true change in frailty status. This affect may therefore bias the assessment of change in eFI score in the pre- and post-surgery periods.

7.4. Clinical implications

The findings presented in the thesis may be used to provide more personalised information, accounting for degree of frailty, to both patients listed for lower limb joint replacement surgery and health care professionals about expected short-term mortality risk, expected pain and functional improvement and likelihood of a self-reported successful outcome following hip and knee arthroplasty. An important caveat is that the data presented relates to patients who have had a THA or TKA and should not be used to inform patients' suitability or safety for surgery. Given the poorer outcomes linked with frailty it seems reasonable also to suggest that surgeons consider those individuals identified as frail for additional interventions both pre and postoperatively to reduce their short-term mortality risk and optimise function.

7.5. Future work

This thesis has addressed gaps in the research literature relating to the impact of frailty on outcomes following THA and TKA. However, there remains areas where further work is needed, which are discussed below.

As noted previously, there are limitations in using the eFI to assess outcomes following THA and TKA (216). One notable limitation is that eFI scores can only increase over time and it is therefore not possible to assess *improvement* in frailty status using the eFI. Further work is therefore needed to assess the impact of THA and TKA on frailty status using alternative frailty instruments that allow improvement in frailty state to be assessed. Such alternative frailty instruments could include the Fried frailty phenotype, or a frailty index including deficits that are amenable to change, such as ability to carry out activities of daily living. Such data would need to be collected prospectively and patients would need to be asked about their ability to carry out activities of daily living before and after arthroplasty in order for change, including improvement, to be assessed.

One of the key findings of this thesis was that increasing frailty was associated with reduced likelihood of a patient-reported successful outcome following THA and TKA. Further work is needed to identify why this is the case and to consider strategies to improve the likelihood of a patient-reported successful outcome among those with frailty. Prehabilitation for example may potentially improve outcomes of older people with frailty

following THA and TKA, though there are limited and low-certainty data on this topic (217).

Higher rates of early postoperative complications (such as for example infection / venous thromoboembolism) among people with frailty who have a THA or TKA may be relevant in explaining the lower likelihood of patient-reported success among those with frailty. Further work is needed to identify the impact of frailty on the risk of such complications following THA and TKA and to identify strategies to reduce risk among people with frailty. The impact of frailty also on longer term joint related complications including infection, periprosthetic fracture and loosening, all of which may require further surgery, has been poorly studied and further research is needed. One particular concern is the risk of periprosthetic fracture given the known increased risk of falls (124) and also poorer bone health among people with frailty (218). One previous study has linked increasing frailty with increasing risk of periprosthetic fracture (145). Further work to better identify individuals at increased risk of periprosthetic fracture would potentially help inform targeting of preventative therapies.

Further work is needed also looking at whether the outcome measures currently used in the NHS, including the OHS and OKS are optimal for assessing outcomes of THA and TKA among people with frailty. People with pre-existing frailty may be limited in their potential to improve in functional ability, regardless of the technical success of arthroplasty. The OHS and OKS include questions relating to practical tasks which older people with frailty may always experience some difficulty in achieving, such as putting on a pair of socks or stockings. Therefore, it may be unrealistic to expect that THA and TKA will have a significant impact on the ability of older people with frailty to complete such tasks without difficulty.

Previous research has determined the MIC in OHS and OKS using both distribution and anchor-based methods (110, 203). The MIC for individual patients has previously been determined using ROC curves to discriminate individuals who achieve the smallest meaningful clinical improvement, for example to discriminate patients who reported being ‘a little better’ versus those who reported being ‘about the same’ on a Likert scale following surgery. However, it is not clear whether the improvement in OHS and OKS that best discriminates patients achieving the smallest meaningful clinical improvement from those who do not may vary by frailty status, and further research on this topic is needed.

Data presented in this thesis show that the rate of increase in frailty is lower in the two years following THA and TKA compared to the two years prior to THA and TKA. Further research is needed looking at the longer-term impact of THA and TKA on the progression of frailty, and also using frailty measures which are more sensitive to change, including improvement. Further work is needed also to look at the impact of THA and TKA on the risk of adverse outcomes related to frailty, such as healthcare utilisation, polypharmacy, need for social care, admission to residential care, and unplanned hospital admission. In addition, while there is some evidence that TKA may reduce the risk of falls (123), further work is needed to determine the impact of THA on the occurrence of falls.

7.6. Conclusions

Frailty is associated with a greater risk of adverse outcomes following THA and TKA, including an increase in short-term mortality and also poorer patient-reported outcomes. The majority of individuals with frailty, however, experience significant improvement in pain and function following THA and TKA and report a successful outcome. Furthermore, THA and TKA may reduce the progression of frailty at least in the short-term. Further work is needed to assess the impact of THA and TKA on the longer-term progression of frailty, as well as the impact of THA and TKA on adverse outcomes associated with frailty.

References

1. Rockwood K. What would make a definition of frailty successful? Age and ageing. 2005;34(5):432-4.

2. Morley JE, Vellas B, van Kan GA, Anker SD, Bauer JM, Bernabei R, et al. Frailty consensus: a call to action. Journal of the American Medical Directors Association. 2013;14(6):392-7.

3. Fried LP, Ferrucci L, Darer J, Williamson JD, Anderson G. Untangling the concepts of disability, frailty, and comorbidity: implications for improved targeting and care. The journals of gerontology Series A, Biological sciences and medical sciences. 2004;59(3):255-63.

4. Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J, et al. Frailty in older adults: evidence for a phenotype. The journals of gerontology Series A, Biological sciences and medical sciences. 2001;56(3):M146-56.

5. Bandeen-Roche K, Xue QL, Ferrucci L, Walston J, Guralnik JM, Chaves P, et al. Phenotype of frailty: characterization in the women's health and aging studies. The journals of gerontology Series A, Biological sciences and medical sciences. 2006;61(3):262-6.

6. Fried LP. Interventions for Human Frailty: Physical Activity as a Model. Cold Spring Harbor perspectives in medicine. 2016;6(6).

7. Xue QL, Bandeen-Roche K, Mielenz TJ, Seplaki CL, Szanton SL, Thorpe RJ, et al. Patterns of 12-year change in physical activity levels in community-dwelling older women: can modest levels of physical activity help older women live longer? American journal of epidemiology. 2012;176(6):534-43.

8. Buta BJ, Walston JD, Godino JG, Park M, Kalyani RR, Xue QL, et al. Frailty assessment instruments: Systematic characterization of the uses and contexts of highly-cited instruments. Ageing Res Rev. 2016;26:53-61.

9. Theou O, Cann L, Blodgett J, Wallace LM, Brothers TD, Rockwood K. Modifications to the frailty phenotype criteria: Systematic review of the current literature and investigation of 262 frailty phenotypes in the Survey of Health, Ageing, and Retirement in Europe. Ageing research reviews. 2015;21:78-94.

10. Rockwood K, Mitnitski A. Frailty in relation to the accumulation of deficits. The journals of gerontology Series A, Biological sciences and medical sciences. 2007;62(7):722-7.

11. Rockwood K, Mitnitski AB, MacKnight C. Some mathematical models of frailty and their clinical implications. Reviews in Clinical Gerontology. 2002;12(2):109-17.

12. Mitnitski AB, Mogilner AJ, MacKnight C, Rockwood K. The mortality rate as a function of accumulated deficits in a frailty index. Mechanisms of ageing and development. 2002;123(11):1457-60.

13. Searle SD, Mitnitski A, Gahbauer EA, Gill TM, Rockwood K. A standard procedure for creating a frailty index. BMC geriatrics. 2008;8.

14. Rockwood K, Mitnitski A. Frailty defined by deficit accumulation and geriatric medicine defined by frailty. Clinics in geriatric medicine. 2011;27.

15. Theou O, Rockwood MR, Mitnitski A, Rockwood K. Disability and co-morbidity in relation to frailty: how much do they overlap? Archives of gerontology and geriatrics. 2012;55(2):e1-8.

16. Mitnitski A, Song X, Skoog I, Broe GA, Cox JL, Grunfeld E, et al. Relative fitness and frailty of elderly men and women in developed countries and their relationship with mortality. Journal of the American Geriatrics Society. 2005;53(12):2184-9.

17. Theou O, Walston J, Rockwood K. Operationalizing frailty using the frailty phenotype and deficit accumulation approaches. Frailty in Aging. 41: Karger Publishers; 2015. p. 66-73.

18. Clegg A, Bates C, Young J, Ryan R, Nichols L, Ann Teale E, et al. Development and validation of an electronic frailty index using routine primary care electronic health record data. Age and ageing. 2016;45(3):353-60.

19. Drubbel I, de Wit NJ, Bleijenberg N, Eijkemans RJ, Schuurmans MJ, Numans ME. Prediction of adverse health outcomes in older people using a frailty index based on routine primary care data. The journals of gerontology Series A, Biological sciences and medical sciences. 2013;68(3):301-8.

20. Gilbert T, Neuburger J, Kraindler J, Keeble E, Smith P, Ariti C, et al. Development and validation of a Hospital Frailty Risk Score focusing on older people in acute care settings using electronic hospital records: an observational study. Lancet. 2018;391(10132):1775-82.

21. Morley JE, Malmstrom TK, Miller DK. A simple frailty questionnaire (FRAIL) predicts outcomes in middle aged African Americans. The journal of nutrition, health & aging. 2012;16(7):601-8.

22. Subra J, Gillette-Guyonnet S, Cesari M, Oustric S, Vellas B, Platform T. The integration of frailty into clinical practice: preliminary results from the Gerontopole. The journal of nutrition, health & aging. 2012;16(8):714-20.

23. Rockwood K, Song X, MacKnight C, Bergman H, Hogan DB, McDowell I, et al. A global clinical measure of fitness and frailty in elderly people. CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne. 2005;173(5):489-95.

24. Collard RM, Boter H, Schoevers RA, Oude Voshaar RC. Prevalence of frailty in community-dwelling older persons: a systematic review. Journal of the American Geriatrics Society. 2012;60(8):1487-92.

25. Syddall H, Roberts HC, Evandrou M, Cooper C, Bergman H, Aihie Sayer A. Prevalence and correlates of frailty among community-dwelling older men and women: findings from the Hertfordshire Cohort Study. Age and ageing. 2010;39(2):197-203.

26. Gale CR, Cooper C, Sayer AA. Prevalence of frailty and disability: findings from the English Longitudinal Study of Ageing. Age and ageing. 2015;44(1):162-5.

27. Hoogendijk EO, Afilalo J, Ensrud KE, Kowal P, Onder G, Fried LP. Frailty: implications for clinical practice and public health. Lancet. 2019;394(10206):1365-75.

28. Feng Z, Lugtenberg M, Franse C, Fang X, Hu S, Jin C, et al. Risk factors and protective factors associated with incident or increase of frailty among community-dwelling older adults: A systematic review of longitudinal studies. PloS one. 2017;12(6):e0178383.

29. Gordon EH, Peel NM, Samanta M, Theou O, Howlett SE, Hubbard RE. Sex differences in frailty: A systematic review and meta-analysis. Experimental gerontology. 2017;89:30-40.

30. Gill TM, Gahbauer EA, Allore HG, Han L. Transitions Between Frailty States Among Community-Living Older Persons. Archives of Internal Medicine. 2006;166(4):418-23.

31. Pollack LR, Litwack-Harrison S, Cawthon PM, Ensrud K, Lane NE, Barrett-Connor E, et al. Patterns and Predictors of Frailty Transitions in Older Men: The Osteoporotic Fractures in Men Study. Journal of the American Geriatrics Society. 2017;65(11):2473-9.

32. Trevisan C, Veronese N, Maggi S, Baggio G, Toffanello ED, Zambon S, et al. Factors Influencing Transitions Between Frailty States in Elderly Adults: The Progetto Veneto Anziani Longitudinal Study. Journal of the American Geriatrics Society. 2017;65(1):179-84.

33. Kojima G, Taniguchi Y, Iliffe S, Jivraj S, Walters K. Transitions between frailty states among community-dwelling older people: A systematic review and meta-analysis. Ageing Research Reviews. 2019;50:81-8.

34. Ofori-Asenso R, Chin KL, Mazidi M, Zomer E, Ilomaki J, Zullo AR, et al. Global Incidence of Frailty and Prefrailty Among Community-Dwelling Older Adults A Systematic Review and Meta-analysis. Jama Network Open. 2019;2(8).

35. Hoogendijk EO, Rockwood K, Theou O, Armstrong JJ, Onwuteaka-Philipsen BD, Deeg DJH, et al. Tracking changes in frailty throughout later life: results from a 17-year longitudinal study in the Netherlands. Age and ageing. 2018;47(5):727-33.

36. Marshall A, Nazroo J, Tampubolon G, Vanhoutte B. Cohort differences in the levels and trajectories of frailty among older people in England. Journal of epidemiology and community health. 2015;69(4):316-21.

37. Mousa A, Savva GM, Mitnitski A, Rockwood K, Jagger C, Brayne C, et al. Is frailty a stable predictor of mortality across time? Evidence from the Cognitive Function and Ageing Studies. Age and ageing. 2018;47(5):721-7.

38. Yu R, Wong M, Chong KC, Chang B, Lum CM, Auyeung TW, et al. Trajectories of frailty among Chinese older people in Hong Kong between 2001 and 2012: an age-period-cohort analysis. Age and ageing. 2018;47(2):254-61.

39. Backman K, Joas E, Falk H, Mitnitski A, Rockwood K, Skoog I. Changes in the Lethality of Frailty Over 30 Years: Evidence From Two Cohorts of 70-Year-Olds in Gothenburg Sweden. The journals of gerontology Series A, Biological sciences and medical sciences. 2017;72(7):945-50.

40. Woods NF, LaCroix AZ, Gray SL, Aragaki A, Cochrane BB, Brunner RL, et al. Frailty: emergence and consequences in women aged 65 and older in the Women's Health Initiative Observational Study. Journal of the American Geriatrics Society. 2005;53(8):1321-30.

41. Bessa B, Ribeiro O, Coelho T. Assessing the social dimension of frailty in old age: A systematic review. Archives of gerontology and geriatrics. 2018;78:101-13.

42. Gale CR, Westbury L, Cooper C. Social isolation and loneliness as risk factors for the progression of frailty: the English Longitudinal Study of Ageing. Age and ageing. 2018;47(3):392-7.

43. Gruenewald TL, Seeman TE, Karlamangla AS, Sarkisian CA. Allostatic load and frailty in older adults. Journal of the American Geriatrics Society. 2009;57(9):1525-31.

44. Vetrano DL, Palmer K, Marengoni A, Marzetti E, Lattanzio F, Roller-Wirnsberger R, et al. Frailty and Multimorbidity: A Systematic Review and Meta-analysis. The journals of gerontology Series A, Biological sciences and medical sciences. 2019;74(5):659-66.

45. Soysal P, Veronese N, Thompson T, Kahl KG, Fernandes BS, Prina AM, et al. Relationship between depression and frailty in older adults: A systematic review and meta-analysis. Ageing Research Reviews. 2017;36:78-87.

46. Hanlon P, Nicholl BI, Jani BD, Lee D, McQueenie R, Mair FS. Frailty and pre-frailty in middle-aged and older adults and its association with multimorbidity and mortality: a prospective analysis of 493 737 UK Biobank participants. The Lancet Public health. 2018;3(7):e323-e32.

47. Gutierrez-Valencia M, Izquierdo M, Cesari M, Casas-Herrero A, Inzitari M, Martinez-Velilla N. The relationship between frailty and polypharmacy in older people: A systematic review. British journal of clinical pharmacology. 2018;84(7):1432-44.

48. Cruz-Jentoft AJ, Kiesswetter E, Drey M, Sieber CC. Nutrition, frailty, and sarcopenia. Aging clinical and experimental research. 2017;29(1):43-8.

49. Lorenzo-Lopez L, Maseda A, de Labra C, Regueiro-Folgueira L, Rodriguez-Villamil JL, Millan-Calenti JC. Nutritional determinants of frailty in older adults: A systematic review. BMC geriatrics. 2017;17(1):108.

50. Semba RD, Bartali B, Zhou J, Blaum C, Ko CW, Fried LP. Low serum micronutrient concentrations predict frailty among older women living in the community. The Journals of Gerontology: Series A. 2006;61(6):594-9.

51. Hoogendijk EO, van Hout HP, Heymans MW, van der Horst HE, Frijters DH, van Groenou MIB, et al. Explaining the association between educational level and frailty in older adults: results from a 13-year longitudinal study in the Netherlands. Annals of epidemiology. 2014;24(7):538-44. e2.

52. Gerli R, Monti D, Bistoni O, Mazzone AM, Peri G, Cossarizza A, et al. Chemokines, sTNF-Rs and sCD30 serum levels in healthy aged people and centenarians. Mechanisms of ageing and development. 2000;121(1-3):37-46.

53. Ferrucci L, Fabbri E. Inflammageing: chronic inflammation in ageing, cardiovascular disease, and frailty. Nature reviews Cardiology. 2018;15(9):505-22.

54. Soysal P, Stubbs B, Lucato P, Luchini C, Solmi M, Peluso R, et al. Inflammation and frailty in the elderly: A systematic review and meta-analysis. Ageing Research Reviews. 2016;31:1-8.

55. Afilalo J. Androgen Deficiency as a Biological Determinant of Frailty: Hope or Hype? Journal of the American Geriatrics Society. 2014;62(6):1174-8.

56. Hyde Z, Flicker L, Almeida OP, Hankey GJ, McCaul KA, Chubb SA, et al. Low free testosterone predicts frailty in older men: the health in men study. The Journal of clinical endocrinology and metabolism. 2010;95(7):3165-72.

57. Swiecicka A, Lunt M, Ahern T, O'Neill TW, Bartfai G, Casanueva FF, et al. Nonandrogenic Anabolic Hormones Predict Risk of Frailty: European Male Ageing Study Prospective Data. The Journal of clinical endocrinology and metabolism. 2017;102(8):2798-806.

58. Kraus VB, Blanco FJ, Englund M, Karsdal MA, Lohmander LS. Call for standardized definitions of osteoarthritis and risk stratification for clinical trials and clinical use. Osteoarthritis and cartilage. 2015;23(8):1233-41.

59. Hunter DJ, Bierma-Zeinstra S. Osteoarthritis. Lancet. 2019;393(10182):1745-59.

60. Kohn MD, Sassoon AA, Fernando ND. Classifications in Brief: Kellgren-Lawrence Classification of Osteoarthritis. Clinical orthopaedics and related research. 2016;474(8):1886-93.

61. Prieto-Alhambra D, Judge A, Javaid MK, Cooper C, Diez-Perez A, Arden NK. Incidence and risk factors for clinically diagnosed knee, hip and hand osteoarthritis: influences of age, gender and osteoarthritis affecting other joints. Annals of the rheumatic diseases. 2014;73(9):1659-64.

62. Swain S, Sarmanova A, Mallen C, Kuo CF, Coupland C, Doherty M, et al. Trends in incidence and prevalence of osteoarthritis in the United Kingdom: findings from the Clinical Practice Research Datalink (CPRD). Osteoarthritis and cartilage. 2020;28(6):792-801.

63. Felson DT, Naimark A, Anderson J, Kazis L, Castelli W, Meenan RF. The prevalence of knee osteoarthritis in the elderly. the framingham osteoarthritis study. Arthritis & Rheumatism. 1987;30(8):914-8.

64. Oliveria SA, Felson DT, Reed JI, Cirillo PA, Walker AM. Incidence of symptomatic hand, hip, and knee osteoarthritis among patients in a health maintenance organization. Arthritis & Rheumatism. 1995;38(8):1134-41.

65. Srikanth VK, Fryer JL, Zhai G, Winzenberg TM, Hosmer D, Jones G. A meta-analysis of sex differences prevalence, incidence and severity of osteoarthritis. Osteoarthritis and cartilage. 2005;13(9):769-81.

66. Jin Z, Wang D, Zhang H, Liang J, Feng X, Zhao J, et al. Incidence trend of five common musculoskeletal disorders from 1990 to 2017 at the global, regional and national level: results from the global burden of disease study 2017. Annals of the rheumatic diseases. 2020.

67. Turkiewicz A, Petersson IF, Bjork J, Hawker G, Dahlberg LE, Lohmander LS, et al. Current and future impact of osteoarthritis on health care: a population-based study with projections to year 2032. Osteoarthritis and cartilage. 2014;22(11):1826-32.

68. Yu D, Jordan KP, Bedson J, Englund M, Blyth F, Turkiewicz A, et al. Population trends in the incidence and initial management of osteoarthritis: age-period-cohort analysis of the Clinical Practice Research Datalink, 1992-2013. Rheumatology. 2017;56(11):1902-17.

69. O'Neill TW, McCabe PS, McBeth J. Update on the epidemiology, risk factors and disease outcomes of osteoarthritis. Best practice & research Clinical rheumatology. 2018;32(2):312-26.

70. Hunter DJ, Eckstein F. Exercise and osteoarthritis. Journal of anatomy. 2009;214(2):197-207.

71. Silverwood V, Blagojevic-Bucknall M, Jinks C, Jordan JL, Protheroe J, Jordan KP. Current evidence on risk factors for knee osteoarthritis in older adults: a systematic review and meta-analysis. Osteoarthritis and cartilage. 2015;23(4):507-15.

72. Oiestad BE, Juhl CB, Eitzen I, Thorlund JB. Knee extensor muscle weakness is a risk factor for development of knee osteoarthritis. A systematic review and meta-analysis. Osteoarthritis and cartilage. 2015;23(2):171-7.

73. Jiang LY, Rong JS, Wang YC, Hu FL, Bao CD, Li X, et al. The relationship between body mass index and hip osteoarthritis: A systematic review and meta-analysis. Joint, bone, spine. 2011;78(2):150-5.

74. Jiang L, Tian W, Wang Y, Rong J, Bao C, Liu Y, et al. Body mass index and susceptibility to knee osteoarthritis: A systematic review and meta-analysis. Joint, bone, spine. 2012;79(3):291-7.

75. Neogi T. The epidemiology and impact of pain in osteoarthritis. Osteoarthritis and cartilage. 2013;21(9):1145-53.

76. Guccione AA, Felson DT, Anderson JJ, Anthony JM, Zhang Y, Wilson PW, et al. The effects of specific medical conditions on the functional limitations of elders in the Framingham Study. American Journal of Public Health. 1994;84(3):351-8.

77. Schellevis FG, van der Velden J, van de Lisdonk E, van Eijk JT, van Weel C. Comorbidity of chronic diseases in general practice. Journal of clinical epidemiology. 1993;46(5):469-73.

78. Muckelt PE, Roos EM, Stokes M, McDonough S, Gronne DT, Ewings S, et al. Comorbidities and their link with individual health status: A cross-sectional analysis of 23,892 people with knee and hip osteoarthritis from primary care. Journal of comorbidity. 2020;10:2235042X20920456.

79. Nuesch E, Dieppe P, Reichenbach S, Williams S, Iff S, Juni P. All cause and disease specific mortality in patients with knee or hip osteoarthritis: population based cohort study. Bmj. 2011;342:d1165.

80. Veronese N, Cereda E, Maggi S, Luchini C, Solmi M, Smith T, et al. Osteoarthritis and mortality: A prospective cohort study and systematic review with meta-analysis. Seminars in arthritis and rheumatism. 2016;46(2):160-7.

81. Puig-Junoy J, Ruiz Zamora A. Socio-economic costs of osteoarthritis: a systematic review of cost-of-illness studies. Seminars in arthritis and rheumatism. 2015;44(5):531-41.

82. Chen A, Gupte C, Akhtar K, Smith P, Cobb J. The Global Economic Cost of Osteoarthritis: How the UK Compares. Arthritis. 2012;2012:698709.

83. Leopoldino AO, Machado GC, Ferreira PH, Pinheiro MB, Day R, McLachlan AJ, et al. Paracetamol versus placebo for knee and hip osteoarthritis. The Cochrane database of systematic reviews. 2019;2:CD013273.

84. Geenen R, Overman CL, Christensen R, Asenlof P, Capela S, Huisinga KL, et al. EULAR recommendations for the health professional's approach to pain management in inflammatory arthritis and osteoarthritis. Annals of the rheumatic diseases. 2018;77(6):797-807.

85. National Institute for Health and Care Excellence. Joint replacement (primary): hip, knee and shoulder 2022. Accessed 05/08/2022. Available from: https://www.nice.org.uk/guidance/qs206/resources/joint-replacement-primary-hip-knee-and-shoulder-pdf-75547417785541.

86. Elixhauser A, Andrews RM. Profile of inpatient operating room procedures in US hospitals in 2007. Archives of surgery. 2010;145(12):1201-8.

87. Board TNE. National Joint Registry 14th Annual Report2017.

88. Culliford DJ, Maskell J, Beard DJ, Murray DW, Price AJ, Arden NK. Temporal trends in hip and knee replacement in the United Kingdom: 1991 to 2006. The Journal of bone and joint surgery British volume. 2010;92(1):130-5.

89. Culliford D, Maskell J, Judge A, Cooper C, Prieto-Alhambra D, Arden NK, et al. Future projections of total hip and knee arthroplasty in the UK: results from the UK Clinical Practice Research Datalink. Osteoarthritis and cartilage. 2015;23(4):594-600.

90. Ackerman IN, Bohensky MA, Zomer E, Tacey M, Gorelik A, Brand CA, et al. The projected burden of primary total knee and hip replacement for osteoarthritis in Australia to the year 2030. BMC musculoskeletal disorders. 2019;20(1):90.

91. Inacio MCS, Paxton EW, Graves SE, Namba RS, Nemes S. Projected increase in total knee arthroplasty in the United States; an alternative projection model. Osteoarthritis and cartilage. 2017;25(11):1797-803.

92. Hawker GA, Wright JG, Coyte PC, Williams JI, Harvey B, Glazier R, et al. Differences between Men and Women in the Rate of Use of Hip and Knee Arthroplasty. New England Journal of Medicine. 2000;342(14):1016-22.

93. Jüni P, Low N, Reichenbach S, Villiger PM, Williams S, Dieppe PA. Gender inequity in the provision of care for hip disease: population-based cross-sectional study. Osteoarthritis and cartilage. 2010;18(5):640-5.

94. Borkhoff CM, Hawker GA, Kreder HJ, Glazier RH, Mahomed NN, Wright JG. The effect of patients' sex on physicians' recommendations for total knee arthroplasty. Canadian Medical Association Journal. 2008;178(6):681-7.

95. Allen KD, Golightly YM, Callahan LF, Helmick CG, Ibrahim SA, Kwoh CK, et al. Race and Sex Differences in Willingness to Undergo Total Joint Replacement: The Johnston County Osteoarthritis Project. Arthritis care & research. 2014;66(8):1193-202.

96. Yong PFK, Milner PC, Payne JN, Lewis PA, Jennison C. Inequalities in access to knee joint replacements for people in need. Annals of the rheumatic diseases. 2004;63(11):1483-9.

97. Dixon T, Shaw M, Ebrahim S, Dieppe P. Trends in hip and knee joint replacement: socioeconomic inequalities and projections of need. Annals of the rheumatic diseases. 2004;63(7):825-30.

98. Judge A, Welton NJ, Sandhu J, Ben-Shlomo Y. Equity in access to total joint replacement of the hip and knee in England: cross sectional study. Bmj. 2010;341:c4092.

99. Wetterholm M, Turkiewicz A, Stigmar K, Hubertsson J, Englund M. The rate of joint replacement in osteoarthritis depends on the patient's socioeconomic status. Acta orthopaedica. 2016;87(3):245-51.

100. Michel M, Bryere J, Maravic M, Marcelli C. Knee replacement incidence and social deprivation: results from a French ecological study. Joint, bone, spine. 2019;86(5):637-41.

101. Chun DS, Leonard AK, Enchill Z, Suleiman LI. Racial Disparities in Total Joint Arthroplasty. Current Reviews in Musculoskeletal Medicine. 2021.

102. Smith MC, Ben-Shlomo Y, Dieppe P, Beswick AD, Adebajo AO, Wilkinson JM, et al. Rates of hip and knee joint replacement amongst different ethnic groups in England: an analysis of National Joint Registry data. Osteoarthritis and cartilage. 2017;25(4):448-54.

103. Burn E, Murray DW, Hawker GA, Pinedo-Villanueva R, Prieto-Alhambra D. Lifetime risk of knee and hip replacement following a GP diagnosis of osteoarthritis: a real-world cohort study. Osteoarthritis and cartilage. 2019;27(11):1627-35.

104. Franklin J, Ingvarsson T, Englund M, Lohmander LS. Sex differences in the association between body mass index and total hip or knee joint replacement resulting from osteoarthritis. Annals of the rheumatic diseases. 2009;68(4):536-40.

105. Mannion AF, Nauer S, Arsoy D, Impellizzeri FM, Leunig M. The Association Between Comorbidity and the Risks and Early Benefits of Total Hip Arthroplasty for Hip Osteoarthritis. The Journal of Arthroplasty. 2020;35(9):2480-7.

106. Ferguson R, Prieto-Alhambra D, Peat G, Delmestri A, Jordan KP, Strauss VY, et al. Influence of pre-existing multimorbidity on receiving a hip arthroplasty: cohort study of 28 025 elderly subjects from UK primary care. Bmj Open. 2021;11(9):e046713.

107. Dawson J, Fitzpatrick R, Carr A, Murray D. Questionnaire on the perceptions of patients about total hip replacement. Journal of Bone and Joint Surgery-British Volume. 1996;78B(2):185-90.

108. Dawson J, Fitzpatrick R, Murray D, Carr A. Questionnaire on the perceptions of patients about total knee replacement. Journal of Bone and Joint Surgery-British Volume. 1998;80B(1):63-9.

109. Judge A, Arden NK, Kiran A, Price A, Javaid MK, Beard D, et al. Interpretation of patient-reported outcomes for hip and knee replacement surgery: identification of thresholds associated with satisfaction with surgery. The Journal of bone and joint surgery British volume. 2012;94(3):412-8.

110. Sabah SA, Alvand A, Beard DJ, Price AJ. Minimal important changes and differences were estimated for Oxford hip and knee scores following primary and revision arthroplasty. Journal of clinical epidemiology. 2022;143:159-68.

111. Sabah SA, Knight R, Alvand A, Beard DJ, Price AJ. Early patient-reported outcomes from primary hip and knee arthroplasty have improved over the past seven years. The bone & joint journal. 2022;104-B(6):687-95.

112. Okafor L, Chen AF. Patient satisfaction and total hip arthroplasty: a review. Arthroplasty. 2019;1(1):6.

113. Choi YJ, Ra HJ. Patient Satisfaction after Total Knee Arthroplasty. Knee surgery & related research. 2016;28(1):1-15.

114. McConnell S, Kolopack P, Davis AM. The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC): a review of its utility and measurement properties. Arthritis and rheumatism. 2001;45(5):453-61.

115. Collins NJ, Prinsen CA, Christensen R, Bartels EM, Terwee CB, Roos EM. Knee Injury and Osteoarthritis Outcome Score (KOOS): systematic review and meta-analysis of measurement properties. Osteoarthritis and cartilage. 2016;24(8):1317-29.

116. Devlin NJ, Brooks R. EQ-5D and the EuroQol Group: Past, Present and Future. Applied health economics and health policy. 2017;15(2):127-37.

117. Fransen M, Edmonds J. Reliability and validity of the EuroQol in patients with osteoarthritis of the knee. Rheumatology. 1999;38(9):807-13.

118. Jansson KA, Granath F. Health-related quality of life (EQ-5D) before and after orthopedic surgery. Acta orthopaedica. 2011;82(1):82-9.

119. Hunt LP, Ben-Shlomo Y, Clark EM, Dieppe P, Judge A, MacGregor AJ, et al. 90-day mortality after 409,096 total hip replacements for osteoarthritis, from the National Joint Registry for England and Wales: a retrospective analysis. Lancet. 2013;382(9898):1097-104.

120. Hunt LP, Ben-Shlomo Y, Clark EM, Dieppe P, Judge A, MacGregor AJ, et al. 45-day mortality after 467,779 knee replacements for osteoarthritis from the National Joint Registry for England and Wales: an observational study. Lancet. 2014;384(9952):1429-36.

121. Pedersen AB, Baron JA, Overgaard S, Johnsen SP. Short- and long-term mortality following primary total hip replacement for osteoarthritis: a Danish nationwide epidemiological study. The Journal of bone and joint surgery British volume. 2011;93(2):172-7.

122. Johnson RL, Frank RD, Abdel MP, Habermann EB, Chamberlain AM, Mantilla CB. Frailty Transitions One Year After Total Joint Arthroplasty: A Cohort Study. The Journal of Arthroplasty. 2022;37(1):10-8.e2.

123. di Laura Frattura G, Filardo G, Giunchi D, Fusco A, Zaffagnini S, Candrian C. Risk of falls in patients with knee osteoarthritis undergoing total knee arthroplasty: A systematic review and best evidence synthesis. Journal of Orthopaedics. 2018;15(3):903-8.

124. Kojima G. Frailty as a predictor of fractures among community-dwelling older people: A systematic review and meta-analysis. Bone. 2016;90:116-22.

125. Murphy BPD, Dowsey MM, Choong PFM. The Impact of Advanced Age on the Outcomes of Primary Total Hip and Knee Arthroplasty for Osteoarthritis: A Systematic Review. JBJS reviews. 2018;6(2):e6.

126. Kuperman EF, Schweizer M, Joy P, Gu X, Fang MM. The effects of advanced age on primary total knee arthroplasty: a meta-analysis and systematic review. BMC geriatrics. 2016;16:41.

127. Berstock JR, Beswick AD, Lenguerrand E, Whitehouse MR, Blom AW. Mortality after total hip replacement surgery: A systematic review. Bone Joint Res. 2014;3(6):175-82.

128. Berstock JR, Beswick AD, Lopez-Lopez JA, Whitehouse MR, Blom AW. Mortality After Total Knee Arthroplasty: A Systematic Review of Incidence, Temporal Trends, and Risk Factors. The Journal of bone and joint surgery American volume. 2018;100(12):1064-70.

129. Singh JA, Kwoh CK, Richardson D, Chen W, Ibrahim SA. Sex and surgical outcomes and mortality after primary total knee arthroplasty: a risk-adjusted analysis. Arthritis care & research. 2013;65(7):1095-102.

130. Buirs LD, Van Beers LW, Scholtes VA, Pastoors T, Sprague S, Poolman RW. Predictors of physical functioning after total hip arthroplasty: a systematic review. BMJ Open. 2016;6(9):e010725.

131. Nandi M, Schreiber KL, Martel MO, Cornelius M, Campbell CM, Haythornthwaite JA, et al. Sex differences in negative affect and postoperative pain in patients undergoing total knee arthroplasty. Biology of sex differences. 2019;10(1):23.

132. Woo SH, Cha DH, Park EC, Kim SJ. The association of under-weight and obesity with mortality after hip arthroplasty. Age and ageing. 2019;48(1):94-100.

133. Pozzobon D, Ferreira PH, Blyth FM, Machado GC, Ferreira ML. Can obesity and physical activity predict outcomes of elective knee or hip surgery due to osteoarthritis? A meta-analysis of cohort studies. Bmj Open. 2018;8(2):e017689.

134. Judge A, Arden NK, Cooper C, Kassim Javaid M, Carr AJ, Field RE, et al. Predictors of outcomes of total knee replacement surgery. Rheumatology. 2012;51(10):1804-13.

135. Podmore B, Hutchings A, van der Meulen J, Aggarwal A, Konan S. Impact of comorbid conditions on outcomes of hip and knee replacement surgery: a systematic review and meta-analysis. Bmj Open. 2018;8(7):e021784.

136. Schwartz FH, Lange J. Factors That Affect Outcome Following Total Joint Arthroplasty: a Review of the Recent Literature. Current Reviews in Musculoskeletal Medicine. 2017;10(3):346-55.

137. Ali A, Lindstrand A, Sundberg M, Flivik G. Preoperative Anxiety and Depression Correlate With Dissatisfaction After Total Knee Arthroplasty: A Prospective Longitudinal Cohort Study of 186 Patients, With 4-Year Follow-Up. The jounral of arthroplasty. 2017;32(3):767-70.

138. Browne JA, Sandberg BF, D'Apuzzo MR, Novicoff WM. Depression Is Associated With Early Postoperative Outcomes Following Total Joint Arthroplasty: A Nationwide Database Study. The journal of arthroplasty. 2014;29(3):481-3.

139. Rudisill SS, Varady NH, Birir A, Goodman SM, Parks ML, Amen TB. Racial and Ethnic Disparities in Total Joint Arthroplasty Care: A Contemporary Systematic Review and Meta-Analysis. The journal of arthroplasty. 2022.

140. Blum MA, Singh JA, Lee G-C, Richardson D, Chen W, Ibrahim SA. Patient race and surgical outcomes after total knee arthroplasty: An analysis of a large regional database. Arthritis care & research. 2013;65(3):414-20.

141. Cavanaugh AM, Rauh MJ, Thompson CA, Alcaraz J, Mihalko WM, Bird CE, et al. Racial/Ethnic Disparities in Physical Function Before and After Total Knee Arthroplasty Among Women in the United States. Jama Network Open. 2020;3(5).

142. Jacobs CA, Christensen CP, Karthikeyan T. Patient and intraoperative factors influencing satisfaction two to five years after primary total knee arthroplasty. The journal of arthroplasty. 2014;29(8):1576-9.

143. Dowsey MM, Nikpour M, Choong PFM. Outcomes following large joint arthroplasty: does socio-economic status matter? BMC musculoskeletal disorders. 2014;15(1):148.

144. Edwards HB, Smith M, Herrett E, MacGregor A, Blom A, Ben-Shlomo Y. The Effect of Age, Sex, Area Deprivation, and Living Arrangements on Total Knee Replacement Outcomes: A Study Involving the United Kingdom National Joint Registry Dataset. JBJS Open Access. 2018;3(2):e0042.

145. Johnson RL, Abdel MP, Frank RD, Chamberlain AM, Habermann EB, Mantilla CB. Frailty Index Is Associated With Periprosthetic Fracture and Mortality After Total Knee Arthroplasty. Orthopedics (Online). 2019;42(6):335-43.

146. McNallan SM, Chamberlain AM, Gerber Y, Singh M, Kane RL, Weston SA, et al. Measuring frailty in heart failure: A community perspective. American Heart Journal. 2013;166(4):768-74.

147. Velanovich V, Antoine H, Swartz A, Peters D, Rubinfeld I. Accumulating deficits model of frailty and postoperative mortality and morbidity: its application to a national database. Journal of Surgical Research. 2013;183(1):104-10.

148. Panayi AC, Orkaby AR, Sakthivel D, Endo Y, Varon D, Roh D, et al. Impact of frailty on outcomes in surgical patients: A systematic review and meta-analysis. The American Journal of Surgery. 2019;218(2):393-400.

149. Dent E, Martin FC, Bergman H, Woo J, Romero-Ortuno R, Walston JD. Management of frailty: opportunities, challenges, and future directions. Lancet. 2019;394(10206):1376-86.

150. Subramaniam S, Aalberg JJ, Soriano RP, Divino CM. New 5-Factor Modified Frailty Index Using American College of Surgeons NSQIP Data. Journal of the American College of Surgeons. 2018;226(2):173-81.e8.

151. Lemos JL, Welch JM, Xiao M, Shapiro LM, Adeli E, Kamal RN. Is Frailty Associated with Adverse Outcomes After Orthopaedic Surgery?: A Systematic Review and Assessment of Definitions. JBJS Reviews. 2021;9(12):e21.00065.

152. Ferguson R, Prieto-Alhambra D, Peat G, Delmestri A, Jordan KP, Strauss VY, et al. Does pre-existing morbidity influences risks and benefits of total hip replacement for osteoarthritis: a prospective study of 6682 patients from linked national datasets in England. Bmj Open. 2021;11(9):e046712.

153. Steverink N. Measuring frailty: developing and testing the Groningen Frailty Indicator (GFI). The gerontologist. 2001;41:236-7.

154. Johnson RL, Abdel MP, Frank RD, Chamberlain AM, Habermann EB, Mantilla CB. Impact of Frailty on Outcomes After Primary and Revision Total Hip Arthroplasty. The journal of arthroplasty. 2019;34(1):56-64 e5.

155. Runner RP, Bellamy JL, Vu CCL, Erens GA, Schenker ML, Guild III GN. Modified frailty index is an effective risk assessment tool in primary total knee arthroplasty. The Journal of arthroplasty. 2017;32(9):S177-S82.

156. Shin JI, Keswani A, Lovy AJ, Moucha CS. Simplified Frailty Index as a Predictor of Adverse Outcomes in Total Hip and Knee Arthroplasty. The journal of arthroplasty. 2016;31(11):2389-94.

157. Traven SA, Reeves RA, Sekar MG, Slone HS, Walton ZJ. New 5-Factor Modified Frailty Index Predicts Morbidity and Mortality in Primary Hip and Knee Arthroplasty. The journal of arthroplasty. 2019;34(1):140-4.

158. Wilson JM, Schwartz AM, Farley KX, Bradbury TL, Guild GN. Combined malnutrition and frailty significantly increases complications and mortality in patients undergoing elective total hip arthroplasty. The Journal of Arthroplasty. 2020;35(9):2488-94.

159. Schwartz AM, Wilson JM, Farley KX, Bradbury TL, Jr., Guild GN, 3rd. Concomitant Malnutrition and Frailty Are Uncommon, but Significant Risk Factors for Mortality and Complication Following Primary Total Knee Arthroplasty. The journal of arthroplasty. 2020;35(10):2878-85.

160. McConaghy KM, Orr MN, Emara AK, Sinclair ST, Klika AK, Piuzzi NS. Can extant comorbidity indices identify patients who experience poor outcomes following total joint arthroplasty? Archives of orthopaedic and trauma surgery. 2021.

161. Kojima G, Iliffe S, Walters K. Frailty index as a predictor of mortality: a systematic review and meta-analysis. Age and ageing. 2018;47(2):193-200.

162. Penfold CM, Whitehouse MR, Blom AW, Judge A, Wilkinson JM, Sayers A. A comparison of comorbidity measures for predicting mortality after elective hip and knee replacement: A cohort study of data from the National Joint Registry in England and Wales. PloS one. 2021;16(8):e0255602.

163. Meessen JMTA, Fiocco M, Leichtenberg CS, Vliet Vlieland TPM, Slagboom PE, Nelissen RGHH. Frailty Questionnaire Is Not a Strong Prognostic Factor for Functional Outcomes in Hip or Knee Arthroplasty Patients. Geriatric orthopaedic surgery & rehabilitation. 2019;10:2151459318808164.

164. Pulik Ł, Jaśkiewicz K, Sarzyńska S, Małdyk P, Łęgosz P. Modified frailty index as a predictor of the long-term functional result in patients undergoing primary total hip arthroplasty. Reumatologia/Rheumatology. 2020;58(4):213-20.

165. Schmucker AM, Hupert N, Mandl LA. The Impact of Frailty on Short-Term Outcomes After Elective Hip and Knee Arthroplasty in Older Adults: A Systematic Review. Geriatric orthopaedic surgery & rehabilitation. 2019;10:2151459319835109.

166. Pepper AM, Novikov D, Cizmic Z, Barrett JT, Collins M, Iorio R, et al. Age and Frailty Influence Hip and Knee Arthroplasty Reimbursement in a Bundled Payment Care Improvement Initiative. The Journal of Arthroplasty. 2019;34(7, Supplement):S80-S3.

167. Dharmasukrit C, Chan SYS, Applegate RL, Tancredi DJ, Harvath TA, Joseph JG. Frailty, Race/Ethnicity, Functional Status, and Adverse Outcomes After Total Hip/Knee Arthroplasty: A Moderation Analysis. The Journal of Arthroplasty. 2021;36(6):1895-903.

168. Evered LA, Vitug S, Scott DA, Silbert B. Preoperative Frailty Predicts Postoperative Neurocognitive Disorders After Total Hip Joint Replacement Surgery. Anesthesia & Analgesia. 2020;131(5):1582-8.

169. Meyer M, Schwarz T, Renkawitz T, Maderbacher G, Grifka J, Weber M. Hospital Frailty Risk Score predicts adverse events in revision total hip and knee arthroplasty. International orthopaedics. 2021;45(11):2765-72.

170. Ong CB, Krueger CA, Star AM. The Hospital Frailty Risk Score is Not an Accurate Predictor of Treatment Costs for Total Joint Replacement Patients in a Medicare Bundled Payment Population. The Journal of Arthroplasty. 2021;36(8):2658-64.e2.

171. Meyer M, Parik L, Leiss F, Renkawitz T, Grifka J, Weber M. Hospital Frailty Risk Score Predicts Adverse Events in Primary Total Hip and Knee Arthroplasty. The journal of arthroplasty. 2020;35(12):3498-504 e3.

172. Seilern und Aspang J, Zamanzadeh RS, Schwartz AM, Premkumar A, Martin JR, Wilson JM. The Age-Adjusted Modified Frailty Index: An Improved Risk Stratification Tool for Patients Undergoing Primary Total Hip Arthroplasty. The Journal of Arthroplasty. 2022;37(6):1098-104.

173. Tram MK, O'Connor CM, Qian AS, Tram JT, Tetreault MW. Frailty Is Associated With Increased 30-Day Adverse Events and Hospitalization Costs After Primary Total Hip Arthroplasty. The Journal of Arthroplasty. 2022;37(8, Supplement):S925-S30.e4.

174. Herrett E, Gallagher AM, Bhaskaran K, Forbes H, Mathur R, van Staa T, et al. Data Resource Profile: Clinical Practice Research Datalink (CPRD). International journal of epidemiology. 2015;44(3):827-36.

175. Wolf A, Dedman D, Campbell J, Booth H, Lunn D, Chapman J, et al. Data resource profile: Clinical Practice Research Datalink (CPRD) Aurum. International journal of epidemiology. 2019;48(6):1740-g.

176. Padmanabhan S, Carty L, Cameron E, Ghosh RE, Williams R, Strongman H. Approach to record linkage of primary care data from Clinical Practice Research Datalink to other health-related patient data: overview and implications. European journal of epidemiology. 2019;34(1):91-9.

177. Herbert A, Wijlaars L, Zylbersztejn A, Cromwell D, Hardelid P. Data Resource Profile: Hospital Episode Statistics Admitted Patient Care (HES APC). International journal of epidemiology. 2017;46(4):1093-i.

178. Secondary Care Analysis (PROMs) NHS Digital. Patient Reported Outcome Measures (PROMs) in England 2017. Accessed 01/08/2022. Available from: https://webarchive.nationalarchives.gov.uk/ukgwa/20220105013505/https://digital.nhs.uk/binaries/content/assets/legacy/pdf/g/t/proms_guide_v12.pdf.

179. Gallagher AM, Dedman D, Padmanabhan S, Leufkens HGM, de Vries F. The accuracy of date of death recording in the Clinical Practice Research Datalink GOLD database in England compared with the Office for National Statistics death registrations. Pharmacoepidem Dr S. 2019;28(5):563-9.

180. Department of Health. The Power of Information: Putting all of us in control of the health and care information we need In: Department of Health, editor. Accessed 13/04/2022. Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/213689/dh_134205.pdf2012.

181. NHS Digital. Read Version 2 to SNOMED CT mapping tables 2020. Accessed 17/08/2021. Available from: https://isd.digital.nhs.uk/trud3/user/authenticated/group/0/pack/9.

182. Medicines & Healthcare products Regulatory Agency. Independent Scientific Committee (ISAC) annual report 2021. Accessed 13/09/2022. Available from: https://cprd.com/sites/default/files/2022-03/MHRA_ISAC%20Annual%20Report%202020-2021_0.pdf.

183. Medicines & Healthcare products Regulatory Agency. Clinical Practice Research Datalink 2020. Accessed 14/09/2022. Available from: https://cprd.com/investigating-impact-frailty-risks-and-benefits-hip-and-knee-replacement-surgery.

184. Hollinghurst J, Fry R, Akbari A, Clegg A, Lyons RA, Watkins A, et al. External validation of the electronic Frailty Index using the population of Wales within the Secure Anonymised Information Linkage Databank. Age and ageing. 2019;48(6):922-6.

185. Lansbury LN, Roberts HC, Clift E, Herklots A, Robinson N, Sayer AA. Use of the electronic Frailty Index to identify vulnerable patients: a pilot study in primary care. British Journal of General Practice. 2017;67(664):E751-E6.

186. NHS England. Electronic frailty index. Accessed 01/08/2022. Available from: https://www.england.nhs.uk/ourwork/clinical-policy/older-people/frailty/efi/#should-the-practice-i-work-in-use-the-efi-to-identify-people-who-may-be-living-with-frailty.

187. National Institute for Health and Care Excellence. Multimorbidity: clinical assessment and management2016. Accessed 01/08/2022. Available from: https://www.nice.org.uk/guidance/ng56.

188. Reeves D, Pye S, Ashcroft DM, Clegg A, Kontopantelis E, Blakeman T, et al. The challenge of ageing populations and patient frailty: can primary care adapt? Bmj. 2018;362:k3349.

189. National Joint Registry. OPCS Codes relevant to procedures recorded on the NJR 2018. Accessed 17/08/2022. Available from:

https://www.njrcentre.org.uk/njrcentre/Portals/0/Documents/England/Data%20collection%20forms/OPCS%20Procedure%20codes%20relevant%20to%20NJRv6%2020180413.pdf?ver=2019-03-24-221729-620.

190. Keele University. Musculoskeletal code lists 2022. Accessed 02/08/2022. Available from: https://www.keele.ac.uk/mrr/codelists/musculoskeletalcodelists/.

191. Ministry of Housing Communities and Local Government. English indices of deprivation 2019: research report 2019. Accessed 02/08/2022. Available from: https://www.gov.uk/government/publications/english-indices-of-deprivation-2019-research-report.

192. Ministry of Housing Communities and Local Government. The English Indices of Deprivation 2019 - Technical Report 2019. Accessed 08/08/2022. Available from: https://www.gov.uk/government/publications/english-indices-of-deprivation-2019-technical-report.

193. Jani M, Birlie Yimer B, Sheppard T, Lunt M, Dixon WG. Time trends and prescribing patterns of opioid drugs in UK primary care patients with non-cancer pain: A retrospective cohort study. PLOS Medicine. 2020;17(10):e1003270.

194. Kleinbaum DGKM. Survival Analysis : a Self-Learning Text, Third Edition. New York, NY: Springer Science+Business Media, LLC; 2012.

195. Austin PC, Lee DS, Fine JP. Introduction to the Analysis of Survival Data in the Presence of Competing Risks. Circulation. 2016;133(6):601-9.

196. McBee M. Modeling Outcomes With Floor or Ceiling Effects: An Introduction to the Tobit Model. Gifted Child Quarterly. 2010;54(4):314-20.

197. Harrell FE. Regression modeling strategies : with applications to linear models, logistic and ordinal regression, and survival analysis. Second edition. ed. Cham: Springer; 2015.

198. Bellamy JL, Runner RP, Vu CCL, Schenker ML, Bradbury TL, Roberson JR. Modified Frailty Index Is an Effective Risk Assessment Tool in Primary Total Hip Arthroplasty. The journal of arthroplasty. 2017;32(10):2963-8.

199. Constantino de Campos G, Mundi R, Whittington C, Toutounji MJ, Ngai W, Sheehan B. Osteoarthritis, mobility-related comorbidities and mortality: an overview of meta-analyses. Therapeutic Advances in Musculoskeletal Disease. 2020;12:1759720X20981219.

200. Brundle C, Heaven A, Brown L, Teale E, Young J, West R, et al. Convergent validity of the electronic frailty index. Age and ageing. 2019;48(1):152-6.

201. Cook MJ, Lunt M, Board T, O'Neill TW. The impact of frailty on short-term mortality following primary total hip and knee arthroplasty due to osteoarthritis. Age and ageing. 2022;51(6).

202. Kyte D, Cockwell P, Lencioni M, Skrybant M, Hildebrand MV, Price G, et al. Reflections on the national patient-reported outcome measures (PROMs) programme: Where do we go from here? Journal of the Royal Society of Medicine. 2016;109(12):441-5.

203. Beard DJ, Harris K, Dawson J, Doll H, Murray DW, Carr AJ, et al. Meaningful changes for the Oxford hip and knee scores after joint replacement surgery. Journal of clinical epidemiology. 2015;68(1):73-9.

204. NJR Editorial Board. National Joint Registry 18th Annual Report2021. Accessed 01/08/2022. Available from: https://reports.njrcentre.org.uk/Portals/0/PDFdownloads/NJR%2018th%20Annual%20Report%202021.pdf.

205. K. HK, J. PA, J. BD, R. F, C. J, J. D. Can pain and function be distinguished in the Oxford Hip Score in a meaningful way? Bone & Joint Research. 2014;3(11):305-9.

206. Harris K, Dawson J, Doll H, Field RE, Murray DW, Fitzpatrick R, et al. Can pain and function be distinguished in the Oxford Knee Score in a meaningful way? An exploratory and confirmatory factor analysis. Quality of Life Research. 2013;22(9):2561-8.

207. Arden N, Altman D, Beard D, Carr A, Clarke N, Collins G, et al. Lower limb arthroplasty: can we produce a tool to predict outcome and failure, and is it cost-effective? An epidemiological study. Southampton (UK). NIHR Journals Library; Programme Grants for Applied Research. 2017;5(12).

208. Payne RA, Abel GA. UK indices of multiple deprivation—a way to make comparisons across constituent countries easier. World Health Statistics Quarterly. 2012;53(22):2015-6.

209. Hunter DJ, March L, Chew M. Osteoarthritis in 2020 and beyond: a Lancet Commission. The Lancet. 2020;396(10264):1711-2.

210. Cook MJ, Verstappen SMM, Lunt M, O'Neill TW. Increased frailty in people with osteoarthritis and rheumatoid arthritis and the influence of co-morbidity: an analysis of the UK Biobank cohort. Arthritis care & research. 2021.

211. Hammett T, Simonian A, Austin M, Butler R, Allen KD, Ledbetter L, et al. Changes in Physical Activity After Total Hip or Knee Arthroplasty: A Systematic Review and Meta-Analysis of Six- and Twelve-Month Outcomes. Arthritis care & research. 2018;70(6):892-901.

212. Fogg C, Fraser SDS, Roderick P, de Lusignan S, Clegg A, Brailsford S, et al. The dynamics of frailty development and progression in older adults in primary care in England (2006–2017): a retrospective cohort profile. BMC geriatrics. 2022;22(1):30.

213. Otones Reyes P, García Perea E, Pedraz Marcos A. Chronic Pain and Frailty in Community-Dwelling Older Adults: A Systematic Review. Pain Management Nursing. 2019;20(4):309-15.

214. Kehler DS, Theou O. The impact of physical activity and sedentary behaviours on frailty levels. Mechanisms of ageing and development. 2019;180:29-41.

215. Ravi B, Croxford R, Austin PC, Lipscombe L, Bierman AS, Harvey PJ, et al. The relation between total joint arthroplasty and risk for serious cardiovascular events in patients with moderate-severe osteoarthritis: propensity score matched landmark analysis. Bmj. 2013;347:f6187.

216. Todd OM, Burton JK, Dodds RM, Hollinghurst J, Lyons RA, Quinn TJ, et al. New Horizons in the use of routine data for ageing research. Age and ageing. 2020;49(5):716-22.

217. McIsaac DI, Gill M, Boland L, Hutton B, Branje K, Shaw J, et al. Prehabilitation in adult patients undergoing surgery: an umbrella review of systematic reviews. British journal of anaesthesia. 2022;128(2):244-57.

218. Cook MJ, Oldroyd A, Pye SR, Ward KA, Gielen E, Ravindrarajah R, et al. Frailty and bone health in European men. Age and ageing. 2016.