# **RESEARCH PAPER**

# The impact of frailty on patient-reported outcomes following hip and knee arthroplasty

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# 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 post-operative 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 ( $\geq$ 8 points) and OKS ( $\geq$ 7 points) and the proportion who reported a successful outcome (hip/knee problems either 'much better' or 'a little better' following surgery). **Results:** About 42,512 people who had a hip arthroplasty and 49,208 who had a knee arthroplasty contributed data. In a Tobit model adjusted for pre-operative OHS/OKS, age, sex and quintile of index of multiple deprivation, increasing frailty was associated with decreasing post-operative OHS and OKS, respectively,  $\beta$ -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.

Keywords: hip arthroplasty, knee arthroplasty, frailty, patient-reported outcomes, epidemiology, older people

## **Key Points**

- Increasing frailty is associated with lower Oxford hip/knee scores following hip/knee arthroplasty.
- Frailty is associated with a reduced likelihood of achieving a minimally important change in Oxford hip/knee scores, following hip/knee arthroplasty.
- Following hip/knee arthroplasty, however, the large majority of those with frailty achieve the minimally important change and report a successful outcome.

## 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 [1–4]. Limited previous data have also suggested an association between increasing frailty and poorer functional outcomes following hip and knee replacement [5, 6].

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) [7]. 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 [8–10].

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 [11]. 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.

# Methods

#### Data

We used data from the Clinical Practice Research Datalink (CPRD), a large primary care electronic health record database [12,13]. We included both CPRD Gold (comprising primary care practices using the Vision<sup>®</sup> patient management system) and CPRD Aurum (comprising practices using the EMIS Health<sup>®</sup> system). The CPRD database was linked to the Hospital Episode Statistics database [14], which includes data about 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.

#### 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 [15]

(Supplementary Table 1). To apply the eFI in practices using the EMIS Health<sup>®</sup> software system, we mapped the original eFI Read code lists to SNOMED codes using mapping tables from the National Health Service Data Migration Programme [16].

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  $\leq$  0.12), mild frailty (0.12 < eFI  $\leq$  0.24), moderate frailty (0.24 < eFI  $\leq$  0.36) and severe frailty (eFI > 0.36) [15]. The eFI was calculated at the date the pre-operative questionnaire was completed.

The eFI has been validated in multiple databases and populations and is currently used in primary care practice in the UK [15,17,18].

#### 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 [19]. Data are collected from patients undergoing elective, unilateral primary and revision surgery. Data are collected from patients pre-operatively (after being passed as fit for surgery and before the surgery takes place) and post-operatively (around 6 months after surgery) via a paper questionnaire [19].

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 [20]. We did not place any restrictions on the age of patients included.

#### The Oxford hip and knee scores

The pre- and post-operative 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 [21,22]. 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) [8,23], we also looked at the association between frailty and achieving the MIC in the OHS (improvement of  $\geq$ 8 points) and OKS (improvement  $\geq$ 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 [24,25]. The OHS and OKS pain subscales, respectively, are calculated based on 6 and 7 questions relating to pain from the OHS

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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).

#### **Patient-reported success**

In the post-operative 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.

#### Covariates

We included age (at date the pre-operative questionnaire was completed), sex and deprivation as covariates in our analyses, since these variables have previously been associated with outcomes following THA and TKA [26].

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 [27]. IMD was categorised based on quintiles.

#### 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.

#### Association between frailty and Oxford hip and knee score

We calculated the median and IQR pre-operative, postoperative and absolute change in OHS and OKS overall and by frailty category. The distributions of the post-operative 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 post-operative 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 [28]. We looked at a model adjusted for (i) age, sex, and quintile of IMD and (ii) a model adjusted additionally for pre-operative 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, was 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.

# Association between frailty and MIC 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.

#### 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 patientreported 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 post-operative questionnaire.

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

#### Results

#### **Patient characteristics**

After excluding individuals with missing data for the preor post-operative scores, the number of individuals who contributed to the analysis of the OHS and OKS, respectively, was 42,512 and 49,208 (Supplementary Figure 1). The proportion of patients who had complete pre- and post-operative OHS and OKS data, respectively, decreased with increasing frailty from 80.9 to 78.5% among those who were fit, to 58.7 and 57.9% among those with severe frailty (Supplementary Table 2). Women were slightly less likely than men to have complete pre- and post-operative OHS/OKS data and also increasing quintile of IMD was associated with decreasing likelihood of complete data (Supplementary Table 2).

In the hip and knee cohorts, respectively, the median (IQR) 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 1).

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#### Table 1. Participant characteristics

Hip replacement ( $n = 42,512$ )	Knee replacement ( $n = 49,208$ )	
Median (IQR)		
71.4 (66.2, 77.2)	70.9 (66.0, 76.6)	
18.0 (12.0, 24.0)	19.0 (14.0, 25.0)	
42.0 (35.0, 46.0)	38.0 (30.0, 43.0)	
21.0 (14.0, 28.0)	16.0 (10.0, 23.0)	
n (%)		
25,425 (59.8)	27,310 (55.5)	
15,801 (37.2)	14,882 (30.2)	
17,854 (42.0)	22,418 (45.6)	
7,096 (16.7)	9,612 (19.5)	
1,761 (4.1)	2,296 (4.7)	
12,359 (29.1)	13,462 (27.4)	
11,009 (25.9)	12,042 (24.5)	
9,078 (21.4)	10,589 (21.5)	
6,278 (14.8)	7,770 (15.8)	
3,788 (8.9)	5,345 (10.9)	
36,033 (84.8)	36,034 (73.2)	
3,631 (8.5)	7,786 (15.8)	
1,110 (2.6)	2,326 (4.7)	
607 (1.4)	1,738 (3.5)	
415 (1.0)	1,101 (2.2)	
716 (1.7)	223 (0.5)	
	Hip replacement $(n = 42,512)$ Median (IQR) 71.4 (66.2, 77.2) 18.0 (12.0, 24.0) 42.0 (35.0, 46.0) 21.0 (14.0, 28.0) n (%) 25,425 (59.8) 15,801 (37.2) 17,854 (42.0) 7,096 (16.7) 1,761 (4.1) 12,359 (29.1) 11,009 (25.9) 9,078 (21.4) 6,278 (14.8) 3,788 (8.9) 36,033 (84.8) 3,631 (8.5) 1,110 (2.6) 607 (1.4) 415 (1.0) 716 (1.7)	

<sup>a</sup>Age and frailty category are at the date the pre-operative questionnaire was completed

#### Association between frailty, pre-operative, post-operative and change in Oxford hip and knee score

Crude pre-operative and post-operative OHS and OKS decreased with increasing frailty (Table 2). Crude absolute change in OHS and OKS also decreased with increasing frailty, though the decrease was less marked (Table 2). In a multivariable Tobit regression model adjusted for age, sex, quintile of IMD and pre-operative score, increasing frailty category was associated with lower post-operative OHS and OKS (Table 3). Compared with those who were fit, post-operative OHS and OKS, respectively, among those with severe frailty were lower,  $\beta$ -coefficient (95% confidence interval (CI)), -6.97 (-7.44, -6.49), P < 0.001 and -5.88 (-6.28, -5.47), P < 0.001 (Table 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 3).

Similarly, we also found a trend between increasing frailty and lower crude pre-operative, post-operative and absolute change in the OHS and OKS pain subscales (Supplementary Table 4), which persisted in a multivariable model (Supplementary Table 5).

# Association between frailty, MIC 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 (ORs) for achieving a MIC in the OHS and OKS (Table 4). Following THA, compared with those who were fit, the OR (95% CI) of achieving the MIC in OHS ( $\geq$ 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 4). However, even among those with severe frailty, 83.9% achieved the MIC in OHS (Table 4). Broadly, similar results were found in the knee cohort (Table 4).

In the hip and knee cohorts, respectively, 41,796 and 48,985 individuals contributed to the analysis of patient-reported success (Supplementary Figure 1). In a multivariable model adjusted for age, sex and quintile of IMD, increasing frailty was associated with reducing ORs for reporting a successful outcome (problems either 'much better' or 'a little better' following THA and TKA) (Table 4). Following THA, compared with 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 4). However, even among those with severe frailty, 90.0% reported a successful outcome following THA (Table 4). Broadly, similar results were found in the knee cohort (Table 4).

## Discussion

We found, using a large national database of routinely collected PROMs data, that increasing frailty was associated

	Median (IQR) <sup>a</sup>	Median (IQR) <sup>a</sup>				
	Pre-operative	Post-operative	Absolute change			
	Oxford hip score	Oxford hip score				
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	Oxford knee score				
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)			

Table 2. Pre-operative, post-operative and absolute change in Oxford hip score and Oxford knee score by frailty category

Table 3. Association between frailty category and post-operative Oxford hip and knee scores

Frailty category	$\beta$ -coefficient (95% CI) <sup>a</sup>				
	Oxford hip score		Oxford knee score		
	Model 1 <sup>b</sup>	Model 2 <sup>c</sup>	Model 1 <sup>b</sup>	Model 2 <sup>c</sup>	
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 post-operative Oxford hip/knee score as the outcome variable and frailty category as the predictor variable  ${}^{a}P < 0.001$  for all regression coefficients  ${}^{b}Model$  1 is adjusted for age, sex and quintile of IMD  ${}^{c}Model$  2 is adjusted for age, sex and quintile of IMD, and pre-operative Oxford hip/knee score

**Table 4.** Proportion and OR of achieving MIC in Oxford hip/knee score and reporting a successful outcome, by frailty category

Frailty category	Achieved MIC in Oxfo	Achieved MIC in Oxford hip/knee score <sup>a</sup>		Achieved a patient-reported successful outcome <sup>b</sup>	
	n (%)	OR (95% CI) <sup>c</sup>	n (%)	OR (95% CI) <sup>d</sup>	
	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)	

<sup>a</sup>MIC was defined as  $\geq$ 8 point in OHS and  $\geq$ 7 points in OKS. MIC could be calculated for 42,512 individuals who had complete pre- and post-operative Oxford hip score and 49,208 individuals who had complete pre- and post-operative Oxford knee score <sup>b</sup>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'). In the hip cohort, 41,796 patients answered the question about success and 43,820 patients in the knee cohort <sup>c</sup>Logistic regression model with achieving MIC as the binary outcome variable and frailty category as the predictor variable. OR adjusted for age, sex and quintile of IMD. *P* < 0.001 for all reported ORs <sup>d</sup>Logistic regression model with patient-reported successful outcome as the binary outcome variable and frailty category as the predictor variable. OR adjusted for age, sex and quintile of IMD. *P* < 0.001 for all reported ORs

with poorer post-operative 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 pre-operative score of 13 to a post-operative 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 [5,6,11]. One single-centre study from Poland of 365 patients found that frailty, assessed using a 5-item and 11item frailty index, was associated with poorer functional outcome, assessed using the Western Ontario and McMaster Universities Index of Osteoarthritis, 3 years after primary THA, compared with those without frailty, though this was not statistically significant at the 95% confidence level after age adjustment [5].

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 [6]. Patients classified as having frailty had significantly lower pre-operative 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 with those without frailty [6].

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) [11]. Consistent though with data in our study, the mean improvement in OHS was lower in the mild and moderate frail compared with the fit group. There were no data presented looking at patient-reported success, MIC, nor outcomes following TKA.

As shown by others, we found that increasing frailty was associated with a lower pre-operative 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 wellvalidated frailty index which is currently used in clinical practice in the UK, and a range of PROMs routinely collected in the UK NHS, 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 post-operative questionnaire. Compared with those who had complete pre- and post-operative 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 with 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 with 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 post-operative 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.

**Supplementary Data:** Supplementary data mentioned in the text are available to subscribers in *Age and Ageing* online.

**Data Availability Statement:** Data were obtained under license from the Clinical Practice Research Datalink (CPRD). Data are available from the CPRD.

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Episode Data © 2022 are reused with the permission of NHS Digital. All rights reserved. The protocol for this work was approved by the Independent Scientific Advisory Committee for CPRD research (protocol number 20\_119). The authors acknowledge the assistance given by IT Services and the use of the Computational Shared Facility at The University of Manchester.

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