RHEUMATOLOGY

Original article

Medical and psychological comorbidity predicts poor pain outcomes after total knee arthroplasty

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Abstract

Objective. To study comorbidity correlates of moderate to severe pain after total knee arthroplasty (TKA).

Methods. We analysed prospectively collected Total Joint Registry data to examine whether medical (heart disease, peripheral vascular disease, renal disease, chronic obstructive pulmonary disease, diabetes and CTD) and psychological (anxiety and depression) comorbidity is associated with moderate to severe pain after primary or revision TKA. Multivariable-adjusted logistic regression simultaneously adjusted for all comorbidities, age, sex, BMI, underlying diagnosis, American Society of Anesthesiologist (ASA) class, distance from medical centre and implant fixation (only for primary TKA) was used to analyse primary and revision TKA separately.

Results. The primary TKA cohort consisted of 7139 and 4234 TKAs (response rates 65% and 57%) and the revision TKA cohort consisted of 1533 and 881 TKAs at 2 and 5 years (response rates 57% and 48%), respectively. In the primary TKA cohort, anxiety was associated with 1.4 higher odds (95% CI 1.0, 2.0) of moderate to severe index knee pain at 2 years; at 5 years, heart disease (OR 1.7; 95% CI 1.1, 2.6), depression (OR 1.7; 95% CI 1.1, 2.5) and anxiety (OR 1.9; 95% CI 1.2, 3.1) were significantly associated with moderate to severe pain. For revision TKA, CTD (OR 0.5; 95% CI 0.2, 0.9) and depression (OR 1.8; 95% CI 1.1, 3.1) were significantly associated with moderate to severe pain.

Conclusion. This study identified medical and psychological comorbidity risk factors for moderate to severe pain after primary and revision TKA. This information can be used to provide realistic outcome expectations for patients before undergoing primary or revision TKA.

Key words: pain, function, functional limitation, total knee replacement, primary, arthroplasty, joint replacement, outcomes, patient-reported outcomes.

Introduction

Total knee arthroplasty (TKA) is the most common joint arthroplasty surgery performed in the United States. According to the 2009 report by the Healthcare Cost and Utilization Project (HCUP), 22 TKAs and 14 total hip arthroplasties (THAs) were performed per 10 000 US inhabitants, leading to an estimated 672 000 TKAs and 427 700 THAs in 2009, for a population estimate of 305 million in 2009 [1]. The annual volume of primary TKA has increased in the past few decades [2] and is projected to grow six times between 2005 and 2030 [3]. The indications for primary and revision TKA are expanding to younger patients who are more active as well as older patients with more comorbidities [4-6]. In a recent study, Lubbeke et al. [7] reported that medical comorbidities and age partially explained the difference in pain and function outcomes between primary and revision THA. Medical comorbidity is also associated with perioperative complications and longer hospital stay after TKA [8-10]. Previous studies reported that the overall medical comorbidity score was associated with poor pain [11] and composite pain and function [12] outcomes after primary TKA. However, it is unknown which specific medical conditions are associated with pain outcomes after TKA, which were reported by 13% of patients at 1 year and 8% at 2 years after primary TKA [11, 13, 14], making it a notable clinical concern.

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In a study using prospectively collected data from the Mayo Clinic Total Joint Registry, we examined whether medical comorbidities at the time of undergoing TKA surgery were associated with poor pain outcomes at 2 and 5 years after primary or revision TKA.

Methods

Data source and study population

We used prospectively collected data from the Mayo Clinic Total Joint Registry. A validated standardized institutional questionnaire [15] that assesses knee pain and function is administered by mail, phone call or during an in-person clinic visit at the 2- and 5-year time points after arthroplasty to all patients who undergo TKA. A very high correlation (correlation coefficient 0.74) between mailed and in-person physician-administered Mayo knee questionnaires has been demonstrated [15]. Several studies using data from these validated questionnaires have been published [11, 13, 16-18]. This guestionnaire is similar to the Knee Society Scale [19]. Patient questionnaire data were used if the questionnaire was received within 6 months of their 2- or 5-year follow-up, subsequent to TKA (responders). Patients were included in this study if they had undergone a primary or revision TKA between 1993 and 2005 and responded to follow-up assessments at 2 or 5 years. The period 1993-2005 was chosen, since questionnaire data have been captured electronically starting in 1993 and to allow 5-year follow-up for patients in the cohort. This study was approved by the Mayo Clinic Institutional Review Board and all investigations were conducted in conformity with ethical principles of research.

Predictors of interest

The main predictors of interest were medical comorbidities (constituting the Deyo-Charlson index) and psychological comorbidities (anxiety and depression), based on the presence of diagnostic codes for each at the time of TKA. Diagnostic codes are captured in the Mayo Clinic's electronic databases using the Mayo Clinic's Hospital Adaptation of International Code for Diseases (H-ICDA) codes [20]. The Deyo-Charlson index is a validated measure of comorbidity [21] and is the most commonly used comorbidity measure in medical research. It includes 19 comorbidities (including cardiac, pulmonary, renal, hepatic disease, diabetes, cancer, hemiplegia, HIV, etc.) [22, 23]. We grouped the Deyo-Charlson comorbidities into six disease groups of interest that we hypothesized might potentially be associated with moderate to severe pain-heart disease [myocardial infarction (MI) and congestive heart failure (CHF)], peripheral vascular disease, renal disease, chronic obstructive pulmonary disease, diabetes (with or without organ damage) and CTD.

Covariates and confounders

We adjusted the multivariable models for additional covariates and potential confounders. The following variables were abstracted from the registry: (i) demographic characteristics: age, categorized as ≤60, >60-70, >70-80, >80; gender and BMI categorized as follows: normal, <25; overweight, 25-29.9; obese, 30-34.9; very obese, 35–39.9 or extremely obese, \geq 40, as previously [24] and per WHO classification [25]; (ii) American Society of Anesthesiology (ASA) Physical Status score, categorized as class I-II vs III-IV [26], a validated measure of perioperative mortality and immediate postoperative morbidity [8, 26], retrieved from a database managed by the Department of Anesthesiology; (iii) distance from medical centre (0-100 miles, >100-500 miles, >500 miles), calculated using zip codes and country codes from the patients' registration records at the time of surgery (if available) or at present; (iv) operative diagnosis: OA, RA/ inflammatory arthritis or other (avascular necrosis, fracture, etc.) for primary TKA; loosening/wear/osteolysis, dislocation/bone or prosthesis fracture/instability/non-union or failed prior arthroplasty with components removed/infection for revision TKA and (v) implant fixation: cemented or uncemented/hybrid for primary TKA only. The confounders/covariates chosen have been shown to impact post-TKA outcomes, including demographics [11, 13], underlying condition [27], implant fixation [28] and ASA score [29, 30]. Distance from the medical centre was included as a covariate, since the Mayo Clinic is a tertiary referral centre providing care to local patients as well as those travelling from a distance and these patients may differ in complexity and risk of poorer outcome.

Outcome of interest

Patients answered the following pain question at 2 and 5 years post-TKA: Do you have pain in the knee in which the joint was replaced? The responses were no pain, mild (occasional), stairs only, walking and stairs (all combined into reference category), moderate (occasional), moderate (continuous) and severe categories—combined into the outcome variable moderate to severe pain, based on *a priori* decision. Moderate to severe pain was assessed at 2 and 5 years post-primary and post-revision TKA.

Statistical analyses

All analyses were performed using logistic regression using a generalized estimating equation (GEE) approach to adjust the s.E. for the correlation between observations on the same subject due to both knees having been replaced and/or multiple operations on the same knee.

Univariate and multivariable models were used to assess the association of medical comorbidities from the Deyo-Charlson index, anxiety and depression with the odds of moderate to severe pain at both 2 and 5 years post-primary and post-revision TKA. In addition to six comorbidities, depression and anxiety, the multivariable model included gender, age, BMI, ASA score, distance from medical centre, operative diagnosis and implant fixation (for primary only). Odds ratios (ORs), 95% CIs and *P*-values are reported. The alpha level was set at 0.05 for statistical significance.

Results

Clinical and demographic characteristics

The mean age of the primary TKA cohort was 68 years, 55% were female, 87% were overweight or obese and 42% had ASA class III or IV (Table 1). The underlying diagnosis was OA in 94%, RA in 4% and others in 2%. Twenty-three per cent of primary TKAs at 2 years and 23% at 5 years were bilateral. Medical comorbidities were common in these patients, ranging from 5% for peripheral vascular disease to 11% for chronic obstructive pulmonary disease (Table 1). Anxiety and depression were prevalent at 6% and 11%, respectively, for the 2-year follow-up cohort.

In the revision TKA cohort, the mean age was 69 years, 50% were female, 87% were overweight or obese and 50% had ASA class III or IV (Table 1). The underlying diagnosis was loosening, wear or osteolysis in 62%, dislocation, bone or prosthesis fracture, instability or non-union in 25% and failed previous arthroplasty with components removed or infection in 12%. Medical comorbidities were common, with 9% with chronic obstructive pulmonary disease and 10% with diabetes. Anxiety was seen in 5% and depression in 8%.

The response rates for primary and revision TKA cohorts at 2 years were 65% and 57% and at 5 years were 57% and 48%, respectively. Responders at 2- and 5-year follow-up in the primary TKA group were more likely to be men, older, have OA as underlying diagnosis, lower ASA class of I or II and live less than 500 miles from the medical centre. Similar patterns were noted for revision TKA patients.

Correlates of index knee pain after primary TKA

Unadjusted analyses showed significant association of chronic obstructive pulmonary disease, diabetes, depression and anxiety with a higher risk of moderate to severe pain 2 years after primary TKA and heart disease, depression and anxiety with moderate to severe pain 5 years after primary TKA (Table 2).

A multivariable-adjusted model showed that anxiety was associated with a 1.4 times greater risk of moderate to severe pain 2 years after primary TKA, while medial comorbidities (chronic obstructive pulmonary disease and diabetes) and depression were no longer significantly associated with risk of moderate to severe pain. In the multivariable-adjusted model for outcomes at 5 years after primary TKA, we found that heart disease, depression and anxiety were associated with an OR of 1.7, 1.7 and 1.9, respectively, for moderate to severe pain (Table 3).

Correlates of index knee pain after revision TKA

In unadjusted analyses, we found that CTD, depression and anxiety were each associated with moderate to

TABLE 1 Demographic and clinical features of primary and revision TKA cohorts

	Primar	y TKA	Revision TKA		
	2-year (<i>n</i> = 7139)	5-year (<i>n</i> = 4234)	2-year (<i>n</i> = 1533)	5-year (<i>n</i> = 881)	
Mean age (s.p.), years	68 (10)	68 (10)	69 (10)	69 (10)	
Men/women (%)	44/56	45/55	49/51	51/49	
Age groups (%), years					
≤60	18	18	20	20	
>60-70	35	37	29	31	
>70-80	38	38	42	41	
>80	8	7	9	8	
BMI (%), kg/m ²					
<25	13	13	13	14	
25-29.9	35	36	36	39	
30-34.9	29	43	29	27	
35-39.9	14	7	14	14	
≥40	9	7	7	5	
ASA score (%)					
Class I-II	58	58	50	53	
Class III-IV	42	41	50	47	
Deyo-Charlson comorbidities (%)					
Heart disease	8	7	7	5	
Peripheral vascular disease	5	4	4	2	
Renal disease	6	4	4	2	
Chronic obstructive pulmonary disease	11	10	9	9	
Diabetes (with or without organ damage)	9	8	10	7	
CTD	7	8	8	8	
Psychological comorbidity (%)					
Anxiety	6	5	5	3	
Depression	11	8	8	6	

TABLE 2 Univariate association of comorbidity with moderate to severe pain at 2 and 5 years after primary TKA

Variable	2 years			5 years		
	n/N (%)	Odds ratio (95% Cl)	<i>P</i> -value	n/N (%)	Odds ratio (95% Cl)	<i>P</i> -value
Heart disease (MI, CHF)						
No	465/6343 (7.3)	Reference		292/3806 (7.7)	Reference	
Yes	40/535 (7.5)	1.0 (0.7, 1.5)	0.91	39/288 (13.5)	1.9 (1.3, 2.8)	<0.01
Peripheral vascular disease						
No	476/6521 (7.3)	Reference		313/3914 (8)	Reference	
Yes	29/357 (8.1)	1.1 (0.8, 1.7)	0.56	18/180 (10)	1.3 (0.7, 2.2)	0.38
Renal disease						
No	473/6495 (7.3)	Reference		320/3925 (8.2)	Reference	
Yes	32/383 (8.4)	1.2 (0.8, 1.7)	0.47	11/169 (6.5)	0.8 (0.4, 1.6)	0.51
Chronic obstructive pulmonary disease	()					
No	434/6140 (7.1)	Reference		294/3698 (8)	Reference	
Yes	71/738 (9.6)	1.4 (1.1, 1.8)*	0.02	37/396 (9.3)	1.2 (0.8, 1.7)	0.36
Diabetes (with or without organ damage)						
No	444/6225 (7.1)	Reference		293/3750 (7.8)	Reference	
Yes	61/653 (9.3)	1.3 (1.0, 1.8)*	0.05	38/344 (11)	1.5 (1.0, 2.2)	0.06
CTD	. ,			. ,		
No	468/6387 (7.3)	Reference		301/3752 (8)	Reference	
Yes	37/491 (7.5)	1.0 (0.7, 1.5)	0.88	30/342 (8.8)	1.1 (0.7, 1.7)	0.65
Depression	. ,	/		. /	/	
No	430/6154 (7)	Reference		286/3773 (7.6)	Reference	
Yes	75/727 (10.3)	1.5 (1.2, 2.0)*	<0.01	45/321 (14)	2.0 (1.4, 2.9)*	<0.01
Anxiety	. ,			. ,		
No	456/6436 (7.1)	Reference		295/3881 (7.6)	Reference	
Yes	49/445 (11)	1.6 (1.2, 2.3)*	<0.01	36/213 (16.9)	2.5 (1.6, 3.8)*	<0.01

*Significant values.

TABLE 3 Multivariable-adjusted^a odds of moderate to severe pain at 2 and 5 years after primary TKA

Variable	Moderate to severe pain at 2 years, odds ratio (95% CI)	<i>P</i> -value	Moderate to severe pain at 5 years, odds ratio (95% CI)	<i>P</i> -value
Heart disease (MI, CHF)	1.0 (0.7, 1.5)	0.97	1.7 (1.1, 2.6)*	0.01*
Peripheral vascular disease	1.1 (0.7, 1.6)	0.70	1.1 (0.6, 2.1)	0.67
Renal disease	1.2 (0.8, 1.8)	0.45	0.7 (0.3, 1.4)	0.27
Chronic obstructive pulmonary disease	1.3 (1.0, 1.8)	0.06	0.9 (0.6, 1.4)	0.66
Diabetes (with or without organ damage)	1.3 (0.9, 1.8)	0.12	1.2 (0.8, 1.9)	0.33
CTD	0.9 (0.5, 1.5)	0.70	0.9 (0.5, 1.6)	0.65
Depression	1.3 (1.0, 1.8)	0.08	1.7 (1.1, 2.5)*	0.01*
Anxiety	1.4 (1.0, 2.0)*	0.05*	1.9 (1.2, 3.1)*	<0.01*

^aMultivariable model simultaneously adjusted for age, gender, BMI, ASA class, distance from medical centre, operative diagnosis, implant fixation (cement status), six Deyo-Charlson comorbidity categories, anxiety and depression. *Significant values.

severe pain 2 years after revision TKA. Medical comorbidities, depression and anxiety were not associated with moderate to severe pain 5 years after revision TKA (Table 4).

Is, we found that the

In multivariable-adjusted models, we found that the presence of CTD was associated with significantly lower risk and depression with significantly higher risk of moderate to severe pain 2 years after revision TKA (Table 5). Similar to the univariate analyses, multivariable-adjusted analyses failed to show any association between medical

In this study we found that anxiety was associated with higher risk of moderate to severe pain 2 years after primary TKA, while heart disease, anxiety and depression were risk factors for moderate to severe pain 5 years after primary TKA. The presence of CTD was associated

comorbidities, anxiety or depression and moderate to severe index knee pain at 5 years post-revision TKA.

TABLE 4 Univariate association of comorbidity with moderate to severe pain after revision TKA

Variable	2 years (<i>n</i> = 332/1494)			5 years (<i>n</i> = 207/843)		
	n/N (%)	Odds ratio (95% Cl)	<i>P</i> -value	n/N (%)	Odds ratio (95% Cl)	P-value
Heart disease (MI, CHF)						
No	314/1386 (22.7)	Reference		196/798 (24.6)	Reference	
Yes	18/106 (17)	0.7 (0.4, 1.2)	0.18	11/45 (24.4)	1.0 (0.5, 2.0)	0.99
Peripheral vascular disease						
No	323/1442 (22.4)	Reference		202/824 (24.5)	Reference	
Yes	9/50 (18)	0.8 (0.4, 1.6)	0.47	5/19 (26.3)	1.1 (0.4, 3.3)	0.86
Renal disease	. ,			. ,		
No	321/1428 (22.5)	Reference		202/824 (24.5)	Reference	
Yes	11/64 (17.2)	0.7 (0.4, 1.4)	0.31	5/19 (26.3)	1.1 (0.3, 3.5)	0.87
Chronic obstructive pulmonary disease	. ,			. ,		
No	294/1353 (21.7)	Reference		195/771 (25.3)	Reference	
Yes	38/139 (27.3)	1.4 (0.9, 2.0)	0.14	12/72 (16.7)	0.6 (0.3, 1.1)	0.10
Diabetes (with or without organ damage)						
No	298/1338 (22.3)	Reference		188/780 (24.1)	Reference	
Yes	34/154 (22.1)	1.0 (0.7, 1.5)	0.96	19/63 (30.2)	1.4 (0.8, 2.4)	0.29
CTD						
No	317/1378 (23)	Reference		197/777 (25.4)	Reference	
Yes	15/114 (13.2)	0.5 (0.3, 0.9)*	0.02	10/66 (15.2)	0.5 (0.2, 1.1)	0.09
Depression						
No	294/1377 (21.4)	Reference		193/797 (24.2)	Reference	
Yes	38/117 (32.5)	1.8 (1.1, 2.7)*	<0.01	14/47 (29.8)	1.3 (0.7, 2.6)	0.40
Anxiety		,		. ,		
No	308/1423 (21.6)	Reference		199/817 (24.4)	Reference	
Yes	24/71 (33.8)	1.8 (1.1, 3.1)*	0.02	8/27 (29.6)	1.3 (0.5, 3.4)	0.58

*Significant values.

Variable	Moderate to severe pain at 2 years, odds ratio (95% CI)	<i>P</i> -value	Moderate to severe pain at 5 years, odds ratio (95% CI)	<i>P</i> -value
Heart disease (MI, CHF)	0.9 (0.5, 1.6)	0.73	1.5 (0.6, 3.5)	0.38
Peripheral vascular disease	0.9 (0.4, 2.0)	0.74	1.8 (0.5, 6.6)	0.41
Renal disease	0.9 (0.4, 1.7)	0.65	1.4 (0.5, 4.5)	0.54
Chronic obstructive pulmonary disease	1.5 (0.9, 2.3)	0.09	0.6 (0.3, 1.3)	0.20
Diabetes (with or without organ damage)	1.1 (0.7, 1.7)	0.76	1.3 (0.7, 2.5)	0.42
CTD	0.5 (0.2, 0.9)*	0.02*	0.6 (0.2, 1.4)	0.24
Depression	1.8 (1.1, 3.1)*	0.02*	1.1 (0.5, 2.6)	0.80
Anxiety	1.5 (0.8, 2.8)	0.26	1.3 (0.4, 3.6)	0.66

^aMultivariable model simultaneously adjusted for age, gender, BMI, ASA class, distance from medical centre, operative diagnosis, implant fixation (cement status), six Deyo-Charlson comorbidity categories, anxiety and depression. *Significant values.

with a lower risk and depression with a higher risk of moderate to severe pain after revision TKA. Another important observation was that univariate associations noted with several comorbidities and moderate to severe pain were no longer significant in the multivariable-adjusted model, signifying that after adjustment for important covariates and confounders, there were no independent associations of these comorbidities with moderate to severe pain. Although we controlled for several important known risk factors (age, gender, BMI, ASA class, distance from medical centre, operative diagnosis and implant fixation), other factors not controlled for in this analysis, such as complications after TKA, adherence to rehabilitation programme, patient expectation and patient satisfaction, can influence the pain outcome. Lower response rates at 5 years reduces our confidence in estimates at the 5-year follow-up. Several findings in this study merit further discussion.

The association of depression with moderate to severe pain after primary TKA confirms a similar finding noted in one previous randomized study in patients with primary TKA [31]. Another small prospective study found no association of depression with pain at 5 years after primary TKA [32]. Our study controlled for not only important demographic factors (age, sex), but also clinical factors (underlying diagnosis), implant fixation and several comorbidities. Thus our findings are unlikely to be confounded. This is an important finding, in light of the fact that very few previous studies have addressed this important aspect of TKA outcomes. While studies have found that overall, comorbidity predicts poor outcomes after TKA [11, 33], which conditions are associated with poor pain outcome is not known. We also found that heart disease was associated with worse pain outcome at 5 years after primary TKA. A potential mechanism for this finding is the pain associated with peripheral oedema in patients with CHF, which can contribute to lower extremity pain. These findings build on recent findings that the preoperative medical comorbidity score is associated with poorer pain outcomes [11, 12]. Similar findings have been noted in hip arthroplasty cohorts [9, 10]. Our study specifies which medical and psychological comorbidities are independently associated with worse

Anxiety was associated with a higher risk of moderate to severe pain 2 and 5 years after primary TKA. To our knowledge, this is a new finding. In a previous study in a cohort of 83 patients, anxiety was associated with 1-year pain and function outcomes, but not at longer follow-up up to 5 years [32]. However, the sample size in the previous study was small and very few patients had moderate to severe pain at 5-year follow-up, making the study underpowered to detect this association. Thus this finding of an association between anxiety and moderate to severe pain is intuitive. Since anxiety is treatable, it remains to be seen whether optimal treatment of anxiety before and after TKA can decrease the risk of moderate to severe index TKA pain. Other correlates of poor pain outcomes after primary TKA are younger age, female gender and greater preoperative pain [13], while obesity is predictive of poorer function after TKA [34].

pain outcomes after TKA.

A new finding from our study was the association of depression with moderate to severe pain after revision TKA. To our knowledge, there are no published data that have investigated the role of specific medical comorbidities in moderate to severe pain after revision TKA except one study that reported that younger age and higher preoperative pain are predictive of poor pain outcomes after revision TKA [13], which are unmodifiable factors. What remains to be seen is whether screening for depression and treatment of depression before revision TKA can improve its outcomes.

Study cohort characteristics are similar to those previously reported in the literature for both primary and revision TKA. Due to the small numbers, our finding of association of CTD with lower risk of moderate to severe pain needs further confirmation in a larger cohort. Findings are similar to a low risk of failure with RA versus OA after TKA [35] and shorter hospital stay in RA patients compared with those with other diagnoses undergoing shoulder arthroplasty [36].

An important observation is that several other comorbidities were only significant in univariate analyses, but after adjustment for important covariates, these comorbidities were no longer significantly associated with moderate to severe pain. This shows the importance of controlling for important covariates and confounders rather than presenting univariate analyses. Twenty-three per cent of patients had undergone bilateral primary TKA; however, our outcome was index TKA pain, which is less likely to be biased due to surgery on the other knee.

Our study has several strengths and limitations. With a large sample size, we saw enough outcome events (the percentage with moderate to severe pain at 2 and 5 years), making our study adequately powered. The availability of information on important covariates and confounders makes this a robust study. Our study has several limitations. Despite controlling for several factors, residual confounding is possible due to the study design being cohort rather than randomized. Response rates were lower for 5-year cohorts, making our confidence slightly lower in these estimates. These results should be interpreted with caution. Non-response probably biased our findings and limits their generalizability. Since we relied on the presence of diagnostic codes for anxiety and depression, we likely underestimated their prevalence. This made our findings liable to misclassification bias. The direction of this bias is unclear. A non-differential misclassification biases findings towards null. However, if the misclassification bias is differential and systematic, it can bias findings towards or away from the null. For example, if young men more likely got misclassified with depression (who are at higher risk of worse pain outcome due to age, but at lower risk due to gender) compared with elderly women, the direction of bias would be unclear. A chart review to validate diagnosis of anxiety and depression, although desirable, was not feasible due to the limited resources available to us. We considered incorporating comorbidity data at the two follow-up time points, but decided against it for several reasons: (i) this would lead to creation of four variables for each of the eight comorbidities, leading to multiple variables, which are difficult to report and interpret; (ii) the post-operative follow-up variables would be assessed at the same time as the outcome assessment, therefore considering them causal would be a challenge; (iii) since most patients travelling from a distance come only for follow-up orthopaedic surgery assessments, not primary care follow-up, misclassification of depression/anxiety may be higher.

In summary, we found that specific medical and psychological comorbidities impact poor pain outcome at the intermediate follow-up after primary TKA and psychological comorbidities after revision TKA. These findings have important implications. By identifying specific comorbidities that impact pain outcomes after TKA, the data can be used to better inform patients with these conditions regarding a higher risk of poor pain outcomes. In addition, research studies should examine whether preoperative and possibly postoperative optimization of management of these comorbidities can potentially reduce the risk of poor pain outcomes after TKA. With an increasing volume of TKA in the United States, a better understanding of risk factors for poor outcomes is critical to allow patients and surgeons to have realistic and appropriate expectations of TKA.

Rheumatology key messages

- Anxiety was associated with higher risk of moderate to severe index knee pain at 2 years after primary TKA.
- Heart disease, depression and anxiety predicted moderate to severe index knee pain at 2 years after primary TKA.
- Depression was associated with the risk of moderate to severe pain index knee pain after revision TKA.

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References

- HCUP. HCUP facts and figures 2009. Section 3: inpatient hospital stays by procedure. Exhibit 3.1 Most frequent all-listed procedures. http://hcup-us.ahrq.gov/reports/ factsandfigures/2009/pdfs/FF_2009_section3.pdf (8 December 2012, date last accessed).
- 2 Singh JA, Vessely MB, Harmsen WS *et al*. A population-based study of trends in the use of total hip and total knee arthroplasty, 1969–2008. Mayo Clin Proc 2010;85:898–904.

- 3 Kurtz S, Ong K, Lau E *et al.* Projections of primary and revision hip and knee arthroplasty in the United States from 2005 to 2030. J Bone Joint Surg Am 2007;89:780-5.
- 4 Krishnan E, Fries JF, Kwoh CK. Primary knee and hip arthroplasty among nonagenarians and centenarians in the United States. Arthritis Rheum 2007;57:1038-42.
- 5 Tankersley WS, Hungerford DS. Total knee arthroplasty in the very aged. Clin Orthop Relat Res 1995;July (316):45-9.
- 6 Bisschop R, Brouwer RW, Van Raay JJ. Total knee arthroplasty in younger patients: a 13-year follow-up study. Orthopedics 2010;33:876.
- 7 Lubbeke A, Katz JN, Perneger TV *et al.* Primary and revision hip arthroplasty: 5-year outcomes and influence of age and comorbidity. J Rheumatol 2007;34: 394–400.
- 8 Weaver F, Hynes D, Hopkinson W et al. Preoperative risks and outcomes of hip and knee arthroplasty in the Veterans Health Administration. J Arthroplasty 2003;18: 693–708.
- 9 Koenig K, Huddleston JI III, Huddleston H *et al.* Advanced age and comorbidity increase the risk for adverse events after revision total hip arthroplasty. J Arthroplasty 2012;27: 1402–7.e1.
- 10 Huang CS, Cheu YD, Ying J *et al.* Association between provider volume and comorbidity on hospital utilization and outcomes of total hip arthroplasty among National Health Insurance enrollees. J Formos Med Assoc 2011; 110:401–9.
- 11 Singh JA, Gabriel SE, Lewallen DG. Higher body mass index is not associated with worse pain outcomes after primary or revision total knee arthroplasty. J Arthroplasty 2011;26:366-74.e1.
- 12 Wasielewski RC, Weed H, Prezioso C *et al.* Patient comorbidity: relationship to outcomes of total knee arthroplasty. Clin Orthop Relat Res 1998;85–92.
- 13 Singh JA, Gabriel S, Lewallen D. The impact of gender, age, and preoperative pain severity on pain after TKA. Clin Orthop Relat Res 2008;466:2717-23.
- 14 Brander VA, Stulberg SD, Adams AD *et al*. Predicting total knee replacement pain: a prospective, observational study. Clin Orthop Relat Res 2003;27–36.
- 15 McGrory BJ, Morrey BF, Rand JA *et al.* Correlation of patient questionnaire responses and physician history in grading clinical outcome following hip and knee arthroplasty. A prospective study of 201 joint arthroplasties. J Arthroplasty 1996;11:47–57.
- 16 Singh JA, O'Byrne MM, Harmsen WS et al. Predictors of moderate-severe functional limitation 2 and 5 years after revision total knee arthroplasty. J Arthroplasty 2010;25: 1091–5.e1–4.
- 17 Singh JA, O'Byrne MM, Colligan RC et al. Pessimistic explanatory style: a psychological risk factor for poor pain and functional outcomes two years after knee replacement. J Bone Joint Surg Br 2010;92:799-806.
- 18 Singh JA, O'Byrne M, Harmsen S *et al*. Predictors of moderate-severe functional limitation after primary total knee arthroplasty (TKA): 4701 TKAs at 2-years and 2935 TKAs at 5-years. Osteoarthritis Cartilage 2010;18:515–21.
- 19 Lingard EA, Katz JN, Wright RJ et al. Validity and responsiveness of the Knee Society Clinical Rating

System in comparison with the SF-36 and WOMAC. J Bone Joint Surg Am 2001;83-A:1856-64.

- 20 Commission on Professional and Hospital Activities. Hospital adaptation of ICDA. Vol. 1, 2nd edn. Ann Arbor, MI: Commission on Professional and Hospital Activities, 1973.
- 21 Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. J Clin Epidemiol 1992;45:613-9.
- 22 Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987;40:373–83.
- 23 Charlson ME, Sax FL, MacKenzie CR *et al.* Morbidity during hospitalization: can we predict it? J Chronic Dis 1987;40:705–12.
- 24 Singh JA, Lewallen DG. Predictors of activity limitation and dependence on walking aids after primary total hip arthroplasty. J Am Geriatr Soc 2010;58:2387–93.
- 25 WHO. Obesity: preventing and managing the global epidemic. Geneva: World Health Organization, 2000.
- 26 Dripps RD, Lamont A, Eckenhoff JE. The role of anesthesia in surgical mortality. JAMA 1961;178:261-6.
- 27 Rand JA, Trousdale RT, Ilstrup DM *et al.* Factors affecting the durability of primary total knee prostheses. J Bone Joint Surg Am 2003;85-A:259-65.
- 28 Jones CA, Voaklander DC, Suarez-Alma ME. Determinants of function after total knee arthroplasty. Phys Ther 2003;83:696-706.

- 29 Schneider M, Kawahara I, Ballantyne G *et al.* Predictive factors influencing fast track rehabilitation following primary total hip and knee arthroplasty. Arch Orthop Trauma Surg 2009;129:1585–91.
- 30 Gordon SM, Culver DH, Simmons BP et al. Risk factors for wound infections after total knee arthroplasty. Am J Epidemiol 1990;131:905–16.
- 31 Lingard EA, Riddle DL. Impact of psychological distress on pain and function following knee arthroplasty. J Bone Joint Surg Am 2007;89:1161–9.
- 32 Brander V, Gondek S, Martin E *et al*. Pain and depression influence outcome 5 years after knee replacement surgery. Clin Orthop Relat Res 2007;464:21–6.
- 33 Jones CA, Voaklander DC, Johnston DW et al. The effect of age on pain, function, and quality of life after total hip and knee arthroplasty. Arch Intern Med 2001;161:454–60.
- 34 Santaguida PL, Hawker GA, Hudak PL *et al.* Patient characteristics affecting the prognosis of total hip and knee joint arthroplasty: a systematic review. Can J Surg 2008;51:428–36.
- 35 Rand JA, Ilstrup DM. Survivorship analysis of total knee arthroplasty. Cumulative rates of survival of 9200 total knee arthroplasties. J Bone Joint Surg Am 1991;73: 397–409.
- 36 Hambright D, Henderson RA, Cook C et al. A comparison of perioperative outcomes in patients with and without rheumatoid arthritis after receiving a total shoulder replacement arthroplasty. J Shoulder Elbow Surg 2011;20: 77–85.