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Review Article

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Predictors of Persistent Post-Surgical Pain Following Total Knee Arthroplasty: A Systematic Review and Meta-Analysis of Observational Studies

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Abstract

Objective. Approximately one in four total knee replacement patients develop persistent pain. Identification of those at higher risk could help inform optimal management. **Methods**. We searched MEDLINE, EMBASE, CINAHL, AMED, SPORTDiscus, and PsycINFO for observational studies that explored the association between risk factors and persistent pain ($\geq$3 months) after total knee replacement. We pooled estimates of association for all independent variables reported by $>$1 study. **Results**. Thirty studies (26,517 patients) reported the association of 151 independent variables with persistent pain after knee replacement. High certainty evidence demonstrated an increased risk of persistent

pain with pain catastrophizing (absolute risk increase [ARI] 23%, 95% confidence interval [CI] 12 to 35), younger age (ARI for every 10-year decrement from age 80, 4%, 95% CI 2 to 6), and moderate-to-severe acute post-operative pain (ARI 30%, 95% CI 20 to 39). Moderate certainty evidence suggested an association with female sex (ARI 7%, 95% CI 3 to 11) and higher pre-operative pain (ARI 35%, 95% CI 7 to 58). Studies did not adjust for both peri-operative pain severity and pain catastrophizing, which are unlikely to be independent. High to moderate certainty evidence demonstrated no association with pre-operative range of motion, body mass index, bilateral or unilateral knee replacement, and American Society of Anesthesiologists score. **Conclusions.** Rigorously conducted observational studies are required to establish the relative importance of higher levels of peri-operative pain and pain catastrophizing with persistent pain after knee replacement surgery.

Key Words: Chronic Pain; Meta-Analysis; Prognosis; Risk Factors; Systematic Review; Total Knee Replacement

Introduction

Total knee arthroplasty (TKA) is commonly performed for patients with advanced osteoarthritis who find insufficient relief with non-operative treatment [1]. The UK National Joint Registry recorded 312,167 knee replacement surgeries between 2017 and 2019 [2]; however, the prevalence of osteoarthritis is rising due to high rates of obesity and increasing life expectancy in western societies [3]. A modelling study using data from the UK National Joint Registry estimated that 186,302 patients would require primary knee replacement in 2030 [4].

The US Nationwide Inpatient Sample estimates that 1.3M Americans will undergo knee replacement in 2025, and that this figure will increase to 1.9M by 2030 [5].

Pain and consequent functional limitations are the primary indication for knee replacement, and patients anticipate that surgery will provide relief [6]; however, approximately 25% of patients report persistent post-surgical pain after TKA with higher rates after revision surgery [7, 8]. In 2017, the International Association for the study of Pain highlighted the importance of identifying surgical patients at high risk for the development of persistent pain to optimize care [9]. The 2021 Canadian Pain Task Force report has similarly called for guidance in this area [10]. We conducted a systematic review and meta-analysis of observational studies to identify predictors of persistent pain following TKA.

Methods

We followed the Meta-Analysis of Observational Studies in Epidemiology (MOOSE) statement [11], registered our review (PROSPERO Identifier: CRD42018065943), and published our protocol [12].

Data Sources and Searches

An academic librarian developed our search strategies (Supplementary Data eTable 1) that we implemented in MEDLINE, EMBASE, CINAHL, AMED, SPORTDiscus, and PsycINFO, from inception to April 30, 2021. We reviewed reference lists of eligible studies and related reviews for additional potentially eligible articles.

Eligibility Criteria and Study Selection

We included cohort and case-control studies in any language that: (1) enrolled adults ($\geq$18 years) who received knee replacement surgery and (2) investigated, in an adjusted analysis, risk factors for persistent post-surgical pain after total knee replacement. Specifically, we required that eligible primary studies report an adjusted logistic regression model exploring predictors of persistent pain following TKA. We excluded randomized trials as strict eligibility criteria may systematically exclude patients with potentially important prognostic factors. We compared the definition of persistent post-surgical pain used in eligible studies with the definition introduced by the World Health Organization in 2015: (1) pain that began after surgery or a tissue trauma is experienced, (2) pain is in an area of preceding surgery, (3) pain has persisted for $\geq$3 months after surgery, and (4) the pain is not better explained by an infection, a malignancy, a pre-existing condition or other alternative cause [13]. We excluded conference abstracts.

Studies were ineligible if their predictive model(s) included significant associations with variables collected at the same time the outcome was measured. In such instances, the status of the predictor may be a result, rather than a cause, of persistent pain. If study populations overlapped by >50% among eligible articles, we included only the study with the largest sample size, longest follow-up, or larger number of independent factors explored in their regression model. Pairs of reviewers screened titles, abstracts, and full-text articles of potentially eligible studies, independently and in duplicate. We used online systematic review software (DistillerSR, Evidence Partners, Ottawa, Canada; http://systematic-review.net) to facilitate literature screening.

Data Extraction

Pairs of reviewers extracted, independently and in duplicate, the following information from all eligible studies: (1) study characteristics; (2) study population features; (3) surgical details; and (4) adjusted measures of association with persistent post-surgical pain for all reported risk factors. Reviewers resolved disagreements by discussion or by consultation with an adjudicator when

required. When a study reported more than one regression model, we used the model with the largest number of risk factors. We contacted authors for clarification of eligibility, to request missing data, or verify information.

Risk of Bias Assessment

We used the following criteria to assess risk of bias among eligible studies: (1) representativeness of the study population; (2) validity of outcome assessment; (3) proportion of missing data (≥20% was considered high risk of bias); and (4) whether predictive models included, at minimum, age, sex, and a measure of disease severity. (Supplementary Data eTable 2) [14].

Data Synthesis

We converted all pain scales used to measure intensity of persistent post-surgical pain to a 10 cm visual analogue scale (VAS) [15, 16]. When age or body mass index (BMI) were reported as categorical variables in regression models, we assumed linearity and that the association across categories were independent of each other. We then calculated the odds ratio (OR) and 95% confidence interval (CI) for each category using Bucher's approach and combined ORs using the inverse variance method to produce a single value [17, 18].

We pooled all independent factors that were reported by more than 1 study as an OR and associated 95% CI. We complemented relative measures of association (OR) with the absolute risk increase for each predictor amenable to meta-analysis. We used a baseline risk for persistent post-surgical pain of 25%, which we acquired from the low risk group in the study with the largest sample size among studies eligible for our review at low risk of bias [19]. We used the following formula to calculate absolute effects of all pooled predictors: Absolute effect = $((OR_{predictor} * \text{Baseline risk})/((1\text{-Baseline risk}) + (OR_{predictor} * \text{Baseline risk}))) - \text{Baseline risk}$. See Supplementary file for a practical example (eEquation 1).

We used DerSimonian–Laird random-effects models for all meta-analyses [20]. It was decided a priori in the research protocol that random effects models would be used for all analyses to be conservative. Thus, random effects analyses was presented even for predictors for which the results were quite homogeneous and I^2 was low. We performed all analyses using Stata statistical software version 15.1 (StataCorp). All comparisons were two-tailed with a threshold P of .05.

When individual studies did not provide data that allowed their inclusion in pooled estimates, we explored the consistency of association between pooled results and those. When studies explored predictors in which no pooling was possible, we labelled them as promising for future study if they met the following criteria: (1) a statistically significant association with persistent pain of $P \leq .01$, (2) a large magnitude of association (OR ≥ 2.0 or ≤0.5), and (3) a sample size of ≥500 patients. We were unable to pool predictors reported by a single study, or when two studies reported the same predictor but one as a binary variable and the other as a continuous variable.

Subgroup Analyses, Meta-Regression, and Sensitivity Analyses

We evaluated heterogeneity for all pooled estimates through visual inspection of forest plots and I^2 statistic was also provided for all figures, for use by readers. We explored three a priori hypotheses to explain variability between studies assuming larger associations with persistent pain and: (1) shorter duration of follow up, (2) lower pain threshold (i.e., pain vs no pain) rather than a higher threshold (e.g., no pain/mild pain vs moderate to severe pain), and (3) greater risk of bias on a criterion-by-criterion basis. We conducted subgroup analyses if there were two or more studies in a given subgroup and assessed credibility of significant subgroup effects using modified ICEMAN criteria [21].

We performed sensitivity analyses to explore the impact of imputing data for non-significant predictors and converting categorical to continuous data. Specifically, in studies that excluded predictors from their final adjusted analysis due to non-significant association in univariate analysis, or the magnitude of association was not reported due to non-significant association in the final adjusted model, we used an OR of 1 and imputed the associated variance using the hot deck approach [18, 22]. However, imputation requires assumptions that may or may not be met, and we therefore imputed data only when the proportion of trials not reporting measures of association was <25% of the total number of studies contributing to a meta-analysis.

Certainty of Evidence

We used the GRADE (Grading of Recommendations, Assessment, Development and Evaluations) approach to assess the certainty of evidence for all pooled measures of association as high, moderate, low, or very low [23]. With GRADE, evidence from prognostic studies begins as high certainty but can be rated down for risk of bias, indirectness, imprecision, or publication bias [24]. If, in subgroup analysis for risk of bias, we did not find a significant association, we included all studies and did not rate down for risk of bias. If we found a credible subgroup effect for risk of bias, we pooled only low risk studies. When we could not conduct subgroup analysis due to small number of studies, we followed GRADE guidance for assessing certainty of evidence [25].

Given the high baseline risk of 25% for persistent pain after TKA, our clinical experts (A.A., M.R.) estimated that a 5% increase in absolute risk would be sufficient for clinicians to address modifiable risk factors, which can be directly targeted in an effort to prevent persistent pain. The same experts estimated that an absolute

difference in risk of 10% between groups at low and high risk for persistent pain would be sufficient for clinicians to selectively target nonmodifiable risk factors to identify high-risk candidates for additional intervention. Therefore, we rated down for imprecision if the 95% CI associated with the risk difference included 5% for modifiable risk factors, or 10% for nonmodifiable risk factors. When at least 10 studies were included in a meta-analysis, we assessed publication bias by visual assessment of funnel plots and Egger's test [23, 26]. When we were able to pool the same predictor as both a continuous and binary variable, we reported the result supported by higher certainty of evidence.

Results

We identified 9,652 unique records, of which 30 English reports met our eligibility criteria. (Supplementary Data eFigure 1, Supplementary Data eTable 3) We attempted contact with four authors to verify data; one responded [27], providing additional details on their regression model and dependent variable. Ten studies enrolled patients from North American [28–37], 12 from Europe [38–49], and the remainder from Australia [50, 51], New Zealand [52], and Asia [53–57]. (Supplementary Data eFigure 2). Definitions of persistent pain varied across studies (Supplementary Data eTable 4). All studies reported persistent pain at least 3 months after knee arthroplasty; however, no study explicitly reported if the three remaining World Health Organization's criteria for persistent post-surgical pain were met. The median sample size among eligible studies was 350 (interquartile range [IQR]: 245 to 617), and the median duration of follow-up was 13 months (IQR: 6 to 24 months). The median proportion of female patients among eligible studies was 67% (IQR: 59 to 70) and median age was 68 years (IQR: 67 to 69) (Supplementary Data eTable 4).

Risk of Bias

Among eligible studies, 73% (22 of 30) were at high risk of bias for at least one criterion. Two studies did not enroll a representative study population, four did not use a valid tool to assess persistent pain, 18 reported high loss to follow up, and the regression models reported in eight studies did not adjust for one of age, sex, or disease severity (Supplementary Data eTable 5). We detected no evidence of publication bias for sex (Supplementary Data eFigures 3), and Egger's test was non-significant ($P = .43$).

Prevalence and Intensity of Persistent Pain after TKA

The median prevalence of persistent pain after TKA among the 29 studies (n = 13,863) reporting this information was 25% (IQR: 14% to 33%); there was no credible subgroup effect based on the threshold used for defining persistent pain (Supplementary Data eTable 11). The overall pooled pain intensity among TKA patients reporting persistent pain, among 6 studies (n = 2,388) that reported pain severity, was 6.1 cm on a 10 cm VAS (95% CI 5.4 to 6.8) (Supplementary Data eFigure 4).

Predictors of Persistent Pain after TKA

Thirty studies involving 26,517 patients reported the association of 151 independent variables with persistent pain following TKA. Twenty (67%) included only variables significant in univariate analysis in their final regression model, and 13 studies (43%) failed to present data for non-significant predictors in their adjusted analysis.

High certainty evidence demonstrated a significant association between three factors and persistent post-surgical pain after TKA: (1) younger age (4% absolute risk increase [ARI] for every 10-year decrement from age 80, 95% CI 1.7% to 6.4%, $P = .015$; six studies), (2) moderate-to-severe acute post-operative pain (29.5% ARI, 95% CI 20.2% to 38.5%, $P < .001$; three studies), and (3) pain catastrophizing (23% ARI, 95% CI 11.7% to 34.5%, $P < .001$; three studies). (Figures 1–3) Moderate-to-severe acute post-operative pain was defined as ≥4/10 on a 10-point scale. All 3 studies contributing to the pooled measure of association for pain catastrophizing used the Pain Catastrophizing Scale (PCS), which generates scores from 0 (no catastrophizing) to 52 (severe catastrophizing). A single cutoff on the PCS has not been agreed upon [58, 59], and studies used either 16, 20, or 21 as their threshold for designating meaningful pain catastrophizing.

Moderate certainty evidence suggested an association with pre-operative pain (35% ARI, 95% CI 7.3% to 57.7%, $P = .010$; 5 studies), female sex (6.7% ARI, 95% CI 2.5% to 11.2%, $P = 0.001$; 10 studies), non-white race (9.5% ARI, 95% CI 0.4% to 20%, $P = .039$; two studies) and comorbid diabetes mellitus (11% ARI, 95% CI 1.1% to 22.3%, $P = 0.026$; 2 studies). (Figure 4, Supplementary Data eFigures 5–7, Table 1) Four studies [40, 50, 55, 60] reporting the association with pre-operative pain compared lower vs higher pain severity on a 10-point scale, and one study [42] explored no pain (0/10) vs any pain (≥1/10) at rest; only 22 patients did not report pain at rest before surgery in this study which resulted in very little variability to detect an association with persistent pain. The association between pre-operative pain and persistent pain was rated down to moderate certainty evidence based on inconsistency, due to the one study that used a low threshold for pain severity.

High certainty evidence showed no significant association between persistent pain and preoperative range of motion. (Supplementary Data eFigure 8, Table1) Moderate certainty evidence suggested no association with pre-surgical BMI, bilateral vs unilateral TKA,

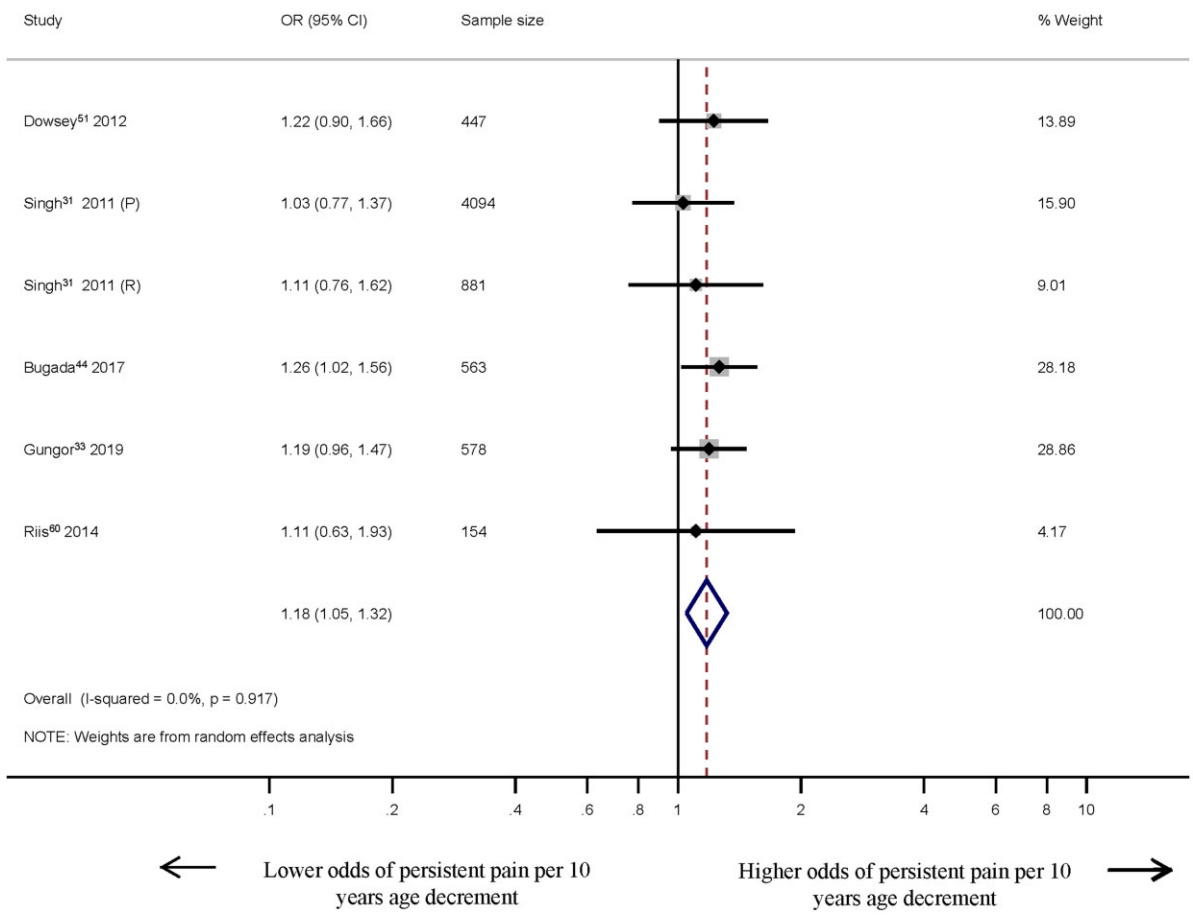

Figure 1. Meta-analysis of the association between every 10 years decrease from age 80 years old and persistent pain.

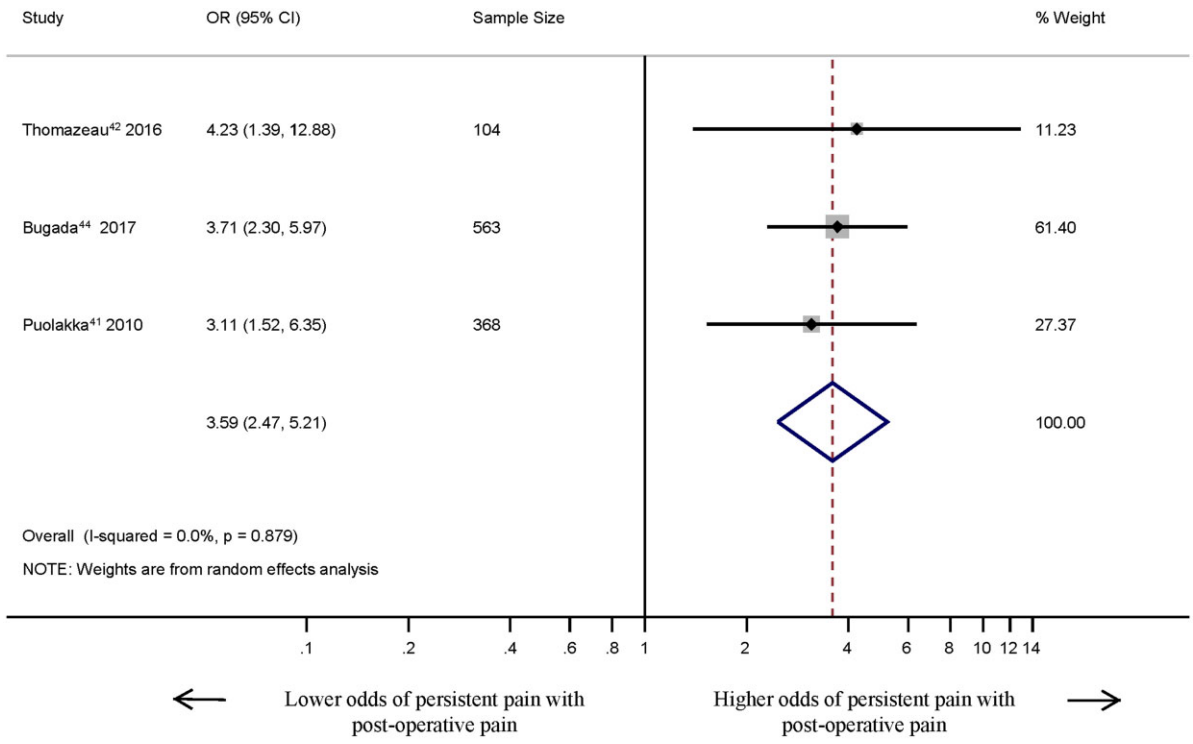

Figure 2. Meta-analysis of the association between acute post-operative pain and persistent post-surgical pain (binary predictor: acute moderate to severe post operative pain vs no to mild acute post operative pain).

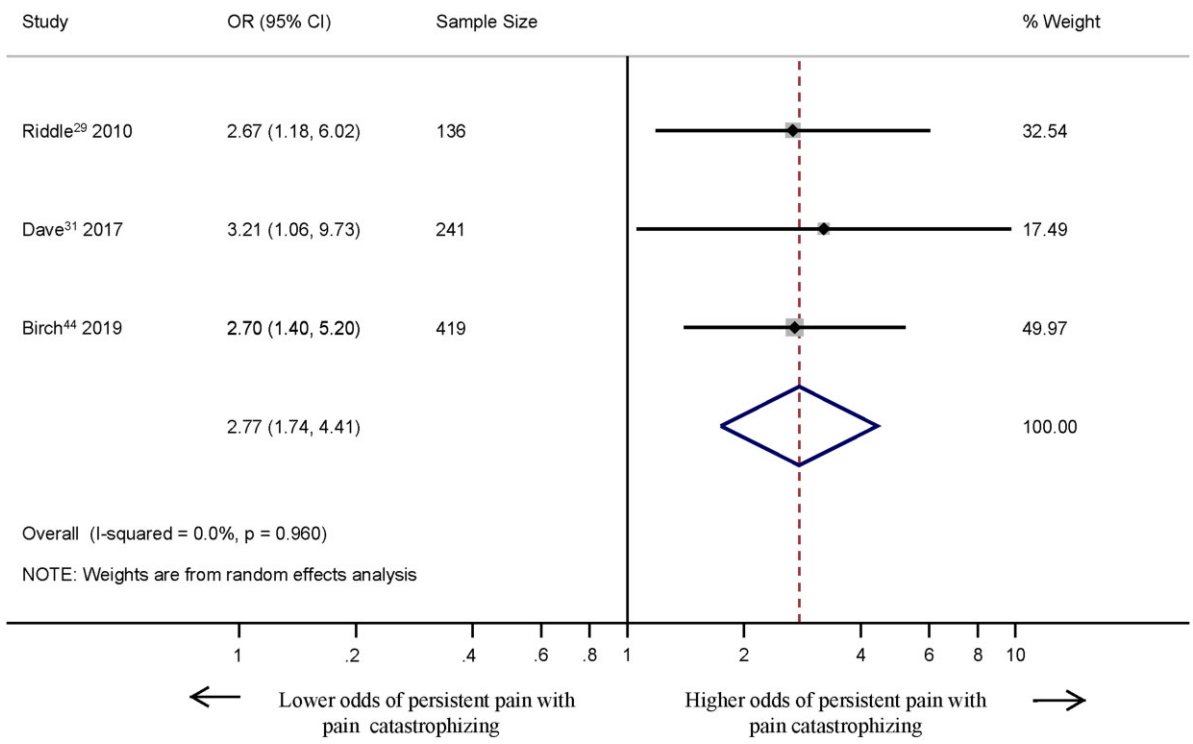

Figure 3. Meta-analysis of the association between pain catastrophizing and persistent post-surgical pain(binary predictor: pain catastrophizing vs no pain catastrophizing).

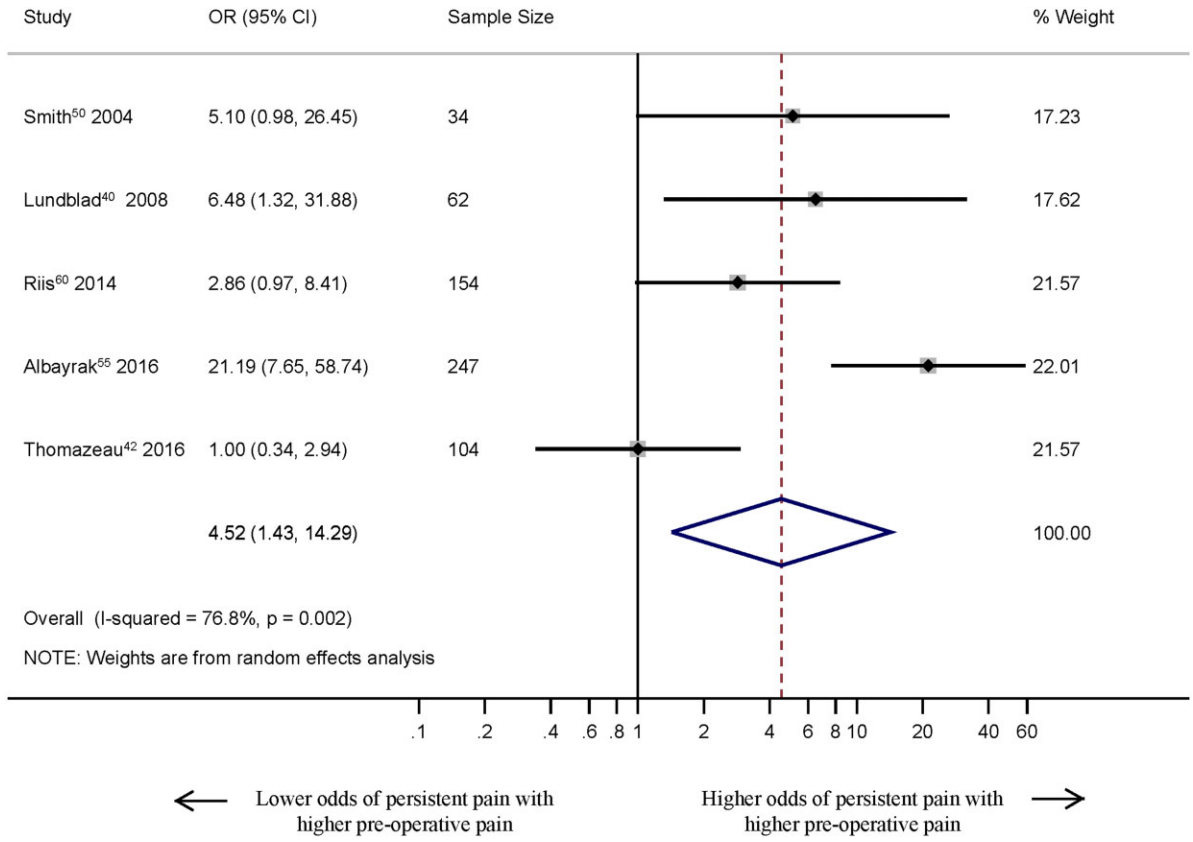

Figure 4. Meta-analysis of the association between pre-operative pain and persistent pain (binary predictor: pre-operative pain vs no pre-operative pain).

Table 1. GRADE evidence profile predictors of persistent pain after total knee arthroplasty

GRADE Evidence Profile: Predictors of Persistent Pain after Total Knee Arthroplasty

	Quality Assessment						Relative Effect OR (95% CI)	Anticipated Absolute Effect	
Predictor	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Overall		Baseline Risk	Risk Difference (95% CI)*
Age: Every 10 yr. decrease									
6,717 patients, (6 studies) Median follow-up 18 mo	No serious risk of bias[a]	No serious inconsistency	No serious Indirectness	No serious Imprecision	Undetected; only 6 studies	High	1.22 (1.09– 1.37)	25%	3.9% more (95% CI: 1.7% more to 6.4% more) patients experience persistent pain per 10 years decrease from age 80
Sex: Female vs Male									
7,632 patients, (10 studies) Median follow-up 14 mo	No Serious risk of bias[a]	No serious inconsistency	No serious Indirectness	Serious Imprecision[b]	Symmetric funnel plot; Egger test $P = .430$	Moderate	1.39 (1.14–1.7)	25%	Females experience 6.7% more (2.5% more to 11.2% more) persistent pain
BMI: Every 5-score Increase									
5,385 patients, (3 studies) Median follow-up 24 mo	No serious risk of bias[a]	No serious inconsistency	No serious Indirectness	Serious Imprecision[d]	Undetected; only 3 studies	Moderate	1.16 (1–1.35)	25%	2.9% more (95% CI: 0% to 6 % more) patients experience persistent pain for every 5-point increase in BMI
Pre-operative Pain in Knee (Threshold used was no vs some pain in 1 study, and lower vs higher pain in 4 studies[c])									
601 patients, (5 studies) median follow-up 14 mo	No serious risk of bias[a]	Serious inconsistency	No serious Indirectness	No Serious Imprecision	Undetected; only 5 studies	Moderate	4.52 (1.43–14.29)	25%	35.1% more (7.3% more to 57.7% more) patients experience persistent pain

(continued)

GRADE Evidence Profile: Predictors of Persistent Pain after Total Knee Arthroplasty

	Quality Assessment						Relative Effect OR (95% CI)	Anticipated Absolute Effect	
Predictor	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Overall		Baseline Risk	Risk Difference (95% CI)*
Acute Post-operative Pain (Binary: Moderate/Severe pain vs No/Mild pain)									
935 patients, (3 studies) median follow up 6 mo	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected; only 3 studies	High	3.59 (2.47–5.21)	25%	29.5% more (95% CI: 20.2% more to 38.5% more) patients experience persistent pain
Pain Catastrophizing (threshold varies between 16 and 21 on pain catastrophizing scale 0–52, 0 [no catastrophizing] to 52 [severe catastrophizing])									
796 patients, (3 studies) median follow-up 12 mo	No serious risk of bias[a]	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected; only 3 studies	High	2.77 (1.74–4.41)	25%	23% more (11.7% more to 34.5% more) patients experience persistent pain
Race (Non-White vs White)									
1,484 patients, (2 studies) median follow-up 9 mo	No serious risk of bias[a]	No serious inconsistency	No serious indirectness	Serious imprecision[b]	Undetected; only 4 studies	Moderate	1.58 (1.02–2.45)	25%	9.5% more (95% CI: 0.4% more to 20% more) patients experience persistent pain
Diabetes comorbidity									
824 patients, (2 studies) median follow-up 15 mo	No serious risk of bias[a]	No serious inconsistency	No serious indirectness	Serious imprecision[b]	Undetected; only 4 studies	Moderate	1.69 (1.06–2.69)	25%	11% more (95% CI: 1.11% more to 22.3% more) patients experience persistent pain
Bilateral vs Unilateral (Simultaneous or Staged Bilateral vs Unilateral)									
1,140 patients, (2 studies) median follow-up 8 mo	No serious risk of bias[a]	No serious inconsistency	No serious Indirectness	Serious imprecision	Undetected; only 2 studies	Moderate	0.74 (0.50–1.09)	25%	5.2% fewer (10.7% less to 1.7% more) patients experience persistent pain

(continued)

GRADE Evidence Profile: Predictors of Persistent Pain after Total Knee Arthroplasty

Predictor	Quality Assessment						Relative Effect OR (95% CI)	Anticipated Absolute Effect	
	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Overall		Baseline Risk	Risk Difference (95% CI)*
Preoperative Range of Motion (Change in 1 degree in range of motion, measured 2–4 week before surgery considered as non-modifiable factor)									
491 patients, (2 studies) range of follow-up 9 mo ASA III vs II	No serious risk of bias	No serious Inconsistency	No serious Indirectness	No serious imprecision[e]	Undetected; only 3 studies	High	1.04 (0.98–1.10)	25%	0.7% more (0.4% less to 1.8% more) patients experience persistent pain
823 patients, (2 studies) median follow-up 4.5 mo	No serious risk of bias[a]	No serious inconsistency	No serious indirectness	Serious imprecision	Undetected; only 2 studies	Moderate	0.60 (0.32–1.14)	25%	8.3% less (15.4% less to 2.5% more) patients experience persistent pain

[a]Certainty of evidence was not rated down on the basis of risk of bias, because the subgroup analyses and meta-regression did not show a significant difference between each risk-of-bias component and the estimates of association.

[b]Certainty of evidence was rated down on the basis of imprecision. Although the 95% CI for the pooled effect did not include a risk difference of 1 (no effect), clinical actions based on the estimate of the lower or upper boundary would change, according to the predefined threshold of $\geq$ 10% for non-modifiable factors.

[c]Four studies compared less vs more pre-operative pain (using thresholds from 2 to 6 on a 0–10 VAS, 10 = worst pain); one study compared no pre-operative pain vs any pain at rest.

[d]Three studies reported different thresholds for pain catastrophizing: 16, 20, and 21, on the 0- to 52-point pain catastrophizing scale.

[e]Certainty of evidence was not rated down on the basis of imprecision. Although the 95% CI for the pooled effect overlap a risk difference of 1 (no effect), clinical actions based on the estimate of the lower or upper boundary would not change, according to the predefined threshold of $\geq$ 10% for non-modifiable factors.

*We used the following formula to calculate absolute effects of all pooled predictors: Absolute effect = ((ORpredictor * Baseline risk)/((1-Baseline risk) + (ORpredictor * Baseline risk))) − Baseline risk. A practical example is provided in the Supplementary File (eEquation 1).

or American Society of Anesthesiology (ASA) score (Supplementary Data eFigures 9–11, and Table1).

The results from seven studies that reported 1 or more of the 11 predictors that we subjected to meta-analysis but whose data could not be pooled were reasonably consistent with our pooled analyses (Supplementary Data eTable 6). Of the 134 factors that were assessed for an association with persistent pain but not amenable to meta-analysis; none met our criteria as promising for future study (Supplementary Data eTables 7 and 8).

Subgroup Analysis, Meta-Regression and Sensitivity Analysis

Our sensitivity analysis imputing unreported non-significant associations rendered non-white race and comorbid diabetes as no longer significantly associated with persistent post operation pain. (Supplementary Data eTable 9) No additional subgroup analysis or meta-regression was credible (Supplementary Data eTables 10–12, Supplementary Data eFigure 12).

Discussion

We found high certainty evidence that pain catastrophizing, younger age and moderate to severe acute postoperative pain are associated with persistent pain after TKA, and moderate certainty evidence for an association with female sex and moderate to severe pre-operative pain. We also found moderate certainty evidence for an association with non-white race and comorbid diabetes; however, these associations became non-significant when imputing results for studies that found no association but reported no data. The strongest of these associations was for pain catastrophizing and greater peri-operative pain, with an absolute increase in the risk for persistent pain ranging from 23% to 35%. High to moderate certainty evidence suggests no association with BMI, preoperative range of motion, bilateral vs unilateral TKA, or ASA score. Investigators have tested 134 additional predictors that could not be statistically pooled, of which none clearly warrant additional study.

The most recent meta-analysis that explored risk factors for persistent pain after knee arthroplasty identified 32 studies, of which 16 were included in our review [61] (Supplementary Data eTable 13). Of the 16 not included in our review, seven reported only unadjusted associations with persistent pain [62–68], populations enrolled in seven overlapped with patients in other studies [7, 8, 69–73], and two studies were randomized trials [74, 75]. This prior review pooled measures of association as Fisher's Z and found that pain catastrophizing, preoperative pain, and presence of comorbidities were associated with persistent pain after TKA; better mental health before surgery had a protective effect [61]. They did not assess the certainty of evidence supporting these associations. We have confirmed and quantified the associations of pre-operative pain and pain catastrophizing with persistent pain, and established three additional risk factors: younger age, female sex, and acute postoperative pain. We also identified moderate to high certainty evidence that BMI, bilateral vs unilateral TKA, ASA score, preoperative range of motion are not important predictors.

We found three associations in which the absolute increase in risk would be sufficient to suggest intervening: pre-operative (ARI 35%) and acute postoperative pain (ARI 30%), and pain catastrophizing (ARI 23%). However, these factors are unlikely to be independent as pain catastrophizing is associated with reporting higher levels of pain [76]. None of the studies that contributed to our pooled estimates of association for pre-operative or acute post-operative pain were adjusted for pain catastrophizing. Clarifying this issue may be important to informing whether promising interventions to reduce the risk of persistent pain after TKA should focus on behavioural modification, further optimization of peri-operative pain relief, or both.

Strengths and Limitations

Strengths of our review include explicit eligibility criteria and a comprehensive search that identified 14 studies that were not included in the most recent published systematic review exploring factors associated with persistent pain after TKA [61, 77–80]. We pooled measures of association for predictive factors, conducted sensitivity analyses imputing data for missing nonsignificant predictors, used the GRADE approach to appraise the certainty of evidence and, presented associations as both relative and absolute measures to optimize interpretation.

Our study has limitations. We pooled measures of association reported at the longest follow-up time, which ranged from 3 months to 7 years; however, we found no credible subgroup effects based on length of follow-up. We assessed heterogeneity of pooled measures of association with I^2, and statistical tests of heterogeneity can be misleading when sample sizes are large and CIs are therefore narrow [81]; however, the number of patients enrolled in studies eligible or our review were typically modest with a median sample size of 350 (IQR: 245 to 617). We used the World Health Organization's criteria for the definition of persistent pain in this review; however, none of the included studies met all criteria and, as such, they may have overestimated the prevalence of persistent pain after TKA. Finally, the estimate of precision for the association with age and persistent pain from Singh et al.'s cohort of patients undergoing primary TKA is narrower than expected given their large sample size ($n = 4094$) [31]. This study reported a much lower event rate (8%) than other studies (e.g., 30% for Gungor et al.) [33], and reported ORs by age category which we then converted to a single estimate vs a reference of age ≥ 80. Our imputation approach assumed the correlation between age categories was zero, which is a conservative

assumption that can exaggerate the variances resulting in a wider CI. This is a limitation of estimating the variance when a correlation coefficient is not available; however, our sensitivity analyses showed consistent results for an association with younger age and persistent pain when excluding converted estimates (see Supplementary Data eTable 9).

Conclusion

Higher pre- and acute post- operative pain, and pain catastrophizing, were associated with large increases in the risk of persistent post-surgical pain after TKA; however, these factors are unlikely to be independent. Rigorously conducted observational studies are required to establish the relative importance of higher levels of peri-operative pain and pain catastrophizing in the development of persistent pain after knee replacement surgery. These factors may represent high-yield targets to prevent the development of persistent post-surgical pain.

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Supplementary Data

Supplementary Data may be found online at *Pain Medicine* online.

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