Predictors of persistent pain after total knee arthroplasty: a systematic review and meta-analysis

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Editor’s key points

- Chronic, persistent pain after surgery is common but poorly understood.
- This study identifies some risk factors that might lessen consideration of knee arthroplasty.
- Some preoperative features may be amenable to treatment but it is unknown whether this can reduce persistent pain.

Background. Several studies have identified clinical, psychosocial, patient characteristic, and perioperative variables that are associated with persistent postsurgical pain; however, the relative effect of these variables has yet to be quantified. The aim of the study was to provide a systematic review and meta-analysis of predictor variables associated with persistent pain after total knee arthroplasty (TKA).

Methods. Included studies were required to measure predictor variables prior to or at the time of surgery, include a pain outcome measure at least 3 months post-TKA, and include a statistical analysis of the effect of the predictor variable(s) on the outcome measure. Counts were undertaken of the number of times each predictor was analysed and the number of times it was found to have a significant relationship with persistent pain. Separate meta-analyses were performed to determine the effect size of each predictor on persistent pain. Outcomes from studies implementing uni- and multivariable statistical models were analysed separately.

Results. Thirty-two studies involving almost 30 000 patients were included in the review. Preoperative pain was the predictor that most commonly demonstrated a significant relationship with persistent pain across uni- and multivariable analyses. In the meta-analyses of data from univariate models, the largest effect sizes were found for: other pain sites, catastrophizing, and depression. For data from multivariate models, significant effects were evident for: catastrophizing, preoperative pain, mental health, and comorbidities.

Conclusions. Catastrophizing, mental health, preoperative knee pain, and pain at other sites are the strongest independent predictors of persistent pain after TKA.

Keywords: arthroplasty; chronic pain; knee joint; meta-analysis

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Total knee arthroplasty (TKA), or knee joint replacement, is one of the most common orthopaedic surgeries performed. TKA is usually undertaken in patients with end-stage osteoarthritis (OA) of the knee when non-surgical management is no longer effective. One of the primary reasons that TKA is performed is to reduce pain associated with the joint.¹ However, a significant number of patients report ongoing pain in the affected joint after surgery. Several studies have reported the prevalence of chronic pain at 3–24 months after surgery to be 20% or more.²-⁶ Given the expected exponential increase in the number of primary TKA that will be performed in the future,⁷ along with potential corrective revision surgical procedures, this outcome should be a significant concern to patients, healthcare providers, and policy-makers.⁸⁹

A number of observational studies have investigated the risk factors associated with the presence of chronic pain after TKA (for systematic reviews see references¹⁰-¹³). Such studies are critically important for recognizing patients at risk of persistent pain and identifying potentially modifiable risk factors. Variables that were commonly associated with a greater risk of chronic postoperative pain included female gender, lower age, greater preoperative pain, and psychological factors indicating negative affect. Although not all are modifiable, these factors may indicate the population at greatest risk of persistent pain. Although these variables have been highlighted multiple times, the primary studies have incorporated a range of predictor variables, study designs, outcome measures, and statistical analyses, making comparisons across studies
difficult. More importantly, it has not been possible to quantify the relative influence of the identified risk factors from the range of studies analysed. While particular variables may be consistently associated with poor pain outcomes, gauging the extent of their influence is important to determine the priority for intervention. Therefore, the aim of this review was to identify and objectively quantify pre- and perioperative variables associated with ongoing pain at 3 months or more post-TKA. To facilitate comparison among predictor variables, meta-analyses were performed to evaluate the relative predictive capacity of the variables identified.

Methods

Search strategy

A systematic search in the databases Medline, EBSCO, Scopus, CINahl, SPORTDiscus, and AMED was performed. Article titles, keywords, and abstracts were searched for the following keywords: knee AND (arthroplast*, replacement, TKA, OR TKJR) AND (postoperative, ongoing, chronic, persistent, OR long term) AND (predict* OR risk factor) AND (prospective, cohort, case–control, OR cross-sectional) AND pain. The full text was scanned of any study abstract that potentially met the inclusion criteria. To be included in the review, the studies had to involve a population who had undergone TKA, provide a measure of pain ≥3 months post-TKA, identify at least one pre- or perioperative risk factor, and identify the relationship between the risk factor(s) and ongoing pain at ≥3 months post-TKA. Prospective, retrospective, and cross-sectional study designs were included. Studies that had a combination of TKA and total hip arthroplasty (THA) populations were included if separate results were available for the TKA participants. Studies were required to be in English, be published between 1980 and December 2012, and have full text available. The reference lists of included studies were also examined for additional potentially eligible studies.

Information extracted

Information was extracted on the participant characteristics, prognostic risk factor(s), pain outcome measure(s), follow-up duration, statistical analysis, and study design. Comparable predictor variables (e.g. weight, BMI) were clustered and then categorized as patient characteristic, psychosocial, clinical, perioperative, or biomechanical. See Supplementary material S1A for a full list of predictor variable categories.

Risk of bias assessment

The risk of bias was assessed by two independent researchers using a custom checklist (see Supplementary material). It included six sections that assessed the study population, participant attrition, prognostic factor measurement, outcome measurement, confounding measurement, and statistical analysis. Each section had from 3 to 6 questions that were evaluated in a yes/no format. Based on these responses, each section was evaluated as ‘conditions met’, ‘conditions partly met’, ‘conditions not met’. Where appropriate, separate questions were used to evaluate prospective, retrospective, and cross-sectional studies.

Data analysis

Two levels of analyses were undertaken. A descriptive analysis of the results of all studies was completed first. Consistency of reporting was undertaken at an individual predictor level to determine variables that showed a significant association with postoperative pain. The number of times a predictor variable was reported as having a statistically significant association with a pain outcome measure was counted, along with the total number of times that the predictor was analysed. If an individual study reported outcomes at multiple follow-up periods, each follow-up period was counted individually if they were more than 6 months apart; otherwise, only the first follow-up period was counted. Separate summaries were undertaken for statistical analyses using univariable models.

At the second level of analysis, a meta-analysis was completed for predictor variables that were analysed in at least four studies. Information was provided from a range of statistical analyses to inform the meta-analyses, including correlation, odds ratio, t-tests, analysis of variance, \( \chi^2 \), linear regression, and logistic regression. Outcomes from these analyses were converted to an effect size (Fisher’s Z) using standard formulae. Where raw values or exact \( P \)-values were not provided, a \( P \)-value equivalent to \( \alpha \) was entered if the association between the predictor and outcome measure was described as statistically significant, while an effect size of 0 was entered where a non-significant association was reported. When multiple categories of a predictor were analysed, the category with the largest difference from the reference category was entered. When multiple follow-up periods were studied or multiple pain-related outcome measures were used, a single, mean effect size was entered. Separate meta-analyses were undertaken for each predictor variable and for data obtained from univariable and multivariable analyses. Random effects models were used because of the heterogeneity of predictor variables and pain outcome measures.

The potential moderating effect of the follow-up period was investigated using meta-regression. To enable sufficient data for these analyses, all follow-up periods from each study and data from both univariable and multivariable analyses were entered. When the same study had undertaken both univariable and multivariable analyses, only data from the multivariable analysis were included. For each predictor variable, the effect size data were regressed with the follow-up time period using method of moments. The moderating effects of primary diagnosis, surgery type, and study design were investigated by performing additional meta-analyses restricting study inclusion to those involving people with OA only, those involving primary surgery only, and those involving prospective study designs only, respectively. For all of these, data from both univariable and multivariable analyses were entered. When the same study had undertaken both univariable and multivariable analyses, only data from the multivariable analysis were included.
All statistical analyses were performed using Comprehensive Meta-Analysis (version 2.2). Heterogeneity was assessed by measuring the degree of inconsistency in the study results ($I^2$). An $\alpha$ level of 0.05 was adopted with no adjustment for multiple models made.

**Results**

Thirty-two studies were selected for the final review (see Fig. 1 and Table 1). After full text screening, the most common reasons for exclusion of studies were lack of a clear pain outcome measure, separate data for TKA patients unavailable, and an insufficient follow-up time. Of the 32 studies reviewed, data from 28 were included in the meta-analyses.

**Description of included studies**

In total, 29,993 participants who had undergone a TKA were included in the review. Sample size ranged from 38 to 8672, with a median of 140 participants. The mean average age reported was 69 yr (range, 56–77 yr) and there were slightly more female participants in total (58%). The mean BMI (reported in 17 studies) ranged from 24.1 to 31.6 kg $m^{-2}$. The majority of the study designs were prospective (23 studies). Most studies restricted inclusion to people with a diagnosis of OA (21 studies), although a number (8 studies) included patients with other conditions, such as rheumatoid arthritis (RA) or non-specific anterior knee pain. Five studies included both primary and revision surgery, 11 included unilateral TKA only, 13 included unilateral or bilateral TKA, and 8 did not describe the type of surgery performed. Four studies included people undergoing total hip joint arthroplasty in addition to TKA but reported separate outcomes for TKA patients. The follow-up intervals ranged from 3 months to 7 yr (mode: 12 months; median: 21 months).

The most common outcome measures used to assess postoperative pain were the Western Ontario and McMaster Osteoarthritis Index (WOMAC) pain subsection (13 studies), a visual analogue scale (VAS) (7 studies), a custom-designed level of pain description (5 studies), and the Knee Society Score (4 studies). Three studies defined the presence of pain using a dichotomous yes/no response. Two studies used the

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**Fig 1** Flow diagram outlining the selection of studies for the review.
Body Pain section of the Short Form-36 (SF-36), while the McGill Pain Questionnaire and the Knee Injury and Osteoarthritis Outcome Score (KOOS) were each used once.

Across the 32 studies, 43 individual predictor variables were identified. Clinical (24 studies) and patient characteristic (22) variables were most commonly studied, followed by psychological (16 studies) and perioperative (11 studies). Six studies evaluated biomechanical variables. The predictor variables of age, gender, education, depression, social support, anxiety, mental health, preoperative pain, other pain sites, function, weight, co-morbidities, patella resurfacing, and the type of surgery were investigated by four or more studies. These variables were all included in the meta-analyses except for type of surgery, which was excluded because of the heterogeneous way that this was classified among the studies.

**Risk of bias assessment**

Scores on the risk of bias assessment ranged from 3 to 10 of 13 (median: 7). Overall, this indicates a moderate risk of bias in the included studies. Studies scored most poorly in the attrition, outcome measures, and analysis categories. The most
common sources of risk included lack of justification of sample size, insufficient controlling for known confounders, and providing inadequate information on participants lost to follow-up. In contrast, studies described the study population well and the majority used reliable and valid predictor variables and outcome measures. No studies using regression analysis completed a prospective validation of their prediction model.

Study outcomes: consistency of reporting

Table 2 shows the number of significant associations detected for each predictor variable and the number of times that the variable was analysed. A greater number of significant associations were reported from analyses using univariable models. Of the most frequently analysed variables, age, gender, preoperative pain, and preoperative function had the largest number of significant associations. A number of the psychosocial predictor variables (e.g. depression, catastrophizing, coping skills) showed consistent associations but there were a limited number of analyses undertaken for each variable.

There were fewer significant associations reported in the multivariable models. Of the predictor variables with three or more analyses, the most frequent significant associations were seen with catastrophizing, mental health, other pain sites, and preoperative pain. It is notable that the psychosocial and clinical variables were more frequently identified as significant predictors of postoperative pain than the patient characteristic, perioperative, and biomechanical variables.

Study outcomes: meta analyses

Fourteen separate predictor variables were analysed using data from 241 individual effect sizes. Analysis of data from univariable models identified 10 predictor variables with a significant effect size (Fig. 2). The largest effect sizes were evident for the variables: other pain sites, catastrophizing, and depression. In addition, preoperative pain, function, and anxiety all had an effect size > 0.1. A number of the remaining predictor variables that were identified as statistically significant had very small effect sizes (Fisher’s Z < 0.1), indicating a consistent but weak relationship with postoperative pain.

Fewer significant predictor variables were identified from analyses using multivariable models (Fig. 3). In these analyses,
only catastrophizing, preoperative pain, mental health, and co-morbidities had a significant effect size, and only three variables (catastrophizing, other pain sites, preoperative pain) had an effect size >0.1.

The results of the meta-regression with the follow-up period are shown in Figure 4. The predictor variables of preoperative pain and comorbidities were found to have a significant slope. In both cases, this was a negative relationship indicating that effect size reduced as the length of the follow-up time increased.

When the analyses were restricted to the inclusion of studies with participants with OA only (9663 patients), there were no marked changes in the predictor variables identified (Table 3). Catastrophizing, preoperative pain, and mental health all demonstrated significant effect sizes that were >0.1. Weight and the number of comorbidities also were significant but had small effect sizes (both Fisher’s Z = 0.08). When the analyses were restricted to the inclusion of studies involving primary TKA only (12 365 patients), there were again very similar predictor variables identified (Table 4). Catastrophizing, preoperative pain, and mental health all demonstrated significant effect sizes >0.1. Participant weight and the number of comorbidities also were significant but had small effect sizes (both Fisher’s Z <0.07).
Finally, when the analyses were restricted to the inclusion of studies with a prospective design only (6134 patients), similar results were evident (Table 5). Catastrophizing and preoperative pain again demonstrated significant effect sizes. Mental health, comorbidities, weight, and age also were significant but had small effect sizes (all Fisher’s $Z < 0.1$). In all of these additional analyses, anxiety and the number of other pain sites had effect sizes $>0.1$ but were not significant overall.

**Discussion**

This study is the first to provide a quantitative review of predictors of persistent pain at more than 3 months after TKA. The consistency of reporting analysis and meta-analyses identified several clinical and psychosocial factors that were consistently associated with long-term pain, while patient characteristic, biomechanical, and perioperative variables had limited influence. There was little impact on the outcomes when the moderating effects of primary patient diagnosis and type of surgery were investigated, suggesting the findings are robust across the population presenting for TKA.

Analysis of the univariate models identified six preoperative factors that had a significant effect size $>0.1$: greater number of pain sites and higher levels of preoperative pain; higher levels of catastrophizing, depression, and anxiety; and poorer levels of preoperative function. Of these, other pain sites and catastrophizing were identified as the strongest predictors of persistent pain. Univariate analyses provide information specific to the variable of interest but do not control for other, confounding factors or correlations among risk factors. Thus, it could be argued that they are of limited value but provide more direct information on each variable. When the analysis was restricted to multivariable models, catastrophizing and preoperative pain were the only variables with a significant effect size of $>0.1$. This would suggest that these factors are...
the strongest independent predictors of chronic, postoperative pain in the TKA population.

Our findings from the meta-analyses support previous systematic and narrative reviews and our own consistency of reporting analysis. High levels of pain catastrophizing prior to surgery had the largest effect on the level of postoperative pain. Catastrophizing tendencies may focus attention on and increase awareness of postoperative pain, magnifying pain intensity. In a review article, Jones and colleagues suggested that psychological variables were more influential in the development of chronic pain after TKA and that preoperative pain and function had a minor contribution. While confirming the important effect of pain catastrophizing, our meta-analyses indicate that preoperative pain specific to the joint and at other sites are also important predictors of chronic postoperative pain. A higher level of preoperative pain has frequently been identified as a risk factor for postsurgical pain across a range of surgery types. Increased joint pain indicates a greater nociceptive barrage or a more sensitized nociceptive system. The fact that removal of nociceptive input from the joint through TKA does not completely ameliorate this pain suggests that central sensitization may be present in these individuals and contribute to ongoing pain. The presence of other pain sites also had a large effect size, although this was only significant for the multivariable analysis. Multiple sites of pain suggest widespread sensitization in the nociceptive system and potentially indicates individuals who are predisposed to the development of chronic pain.

Female gender and a younger age have frequently been identified as risk factors for persistent postoperative pain. However, both of these variables had a small effect size in the current review. The potential increased risk of younger age at surgery is likely to be confounded by the increased likelihood of comorbidities at an older age. Although the effect size was small, increased comorbidities was a significant factor

Table 4 Effect size data for studies involving primary surgery only. *P<0.05

<table>
<thead>
<tr>
<th>Predictor variable</th>
<th>n</th>
<th>Fisher’s Z</th>
<th>Lower limit</th>
<th>Upper limit</th>
<th>P-value</th>
<th>I²</th>
</tr>
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<tr>
<td>Age</td>
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<td>0.006</td>
<td>0.125</td>
<td>20</td>
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<tr>
<td>Anxiety</td>
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<td>0.116</td>
<td>-0.008</td>
<td>0.239</td>
<td>0.066</td>
<td>52</td>
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<tr>
<td>Catastrophizing*</td>
<td>2</td>
<td>0.302</td>
<td>0.163</td>
<td>0.441</td>
<td>&lt;0.001</td>
<td>0</td>
</tr>
<tr>
<td>Comorbidities*</td>
<td>8</td>
<td>0.068</td>
<td>0.025</td>
<td>0.111</td>
<td>0.002</td>
<td>0</td>
</tr>
<tr>
<td>Depression</td>
<td>6</td>
<td>0.064</td>
<td>-0.005</td>
<td>0.132</td>
<td>0.069</td>
<td>42</td>
</tr>
<tr>
<td>Education</td>
<td>6</td>
<td>-0.046</td>
<td>-0.101</td>
<td>0.008</td>
<td>0.097</td>
<td>11</td>
</tr>
<tr>
<td>Function</td>
<td>6</td>
<td>-0.065</td>
<td>-0.157</td>
<td>0.027</td>
<td>0.165</td>
<td>69</td>
</tr>
<tr>
<td>Gender</td>
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<td>0.003</td>
<td>-0.022</td>
<td>0.027</td>
<td>0.841</td>
<td>7</td>
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<tr>
<td>Mental health*</td>
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<td>-0.148</td>
<td>-0.068</td>
<td>&lt;0.001</td>
<td>0</td>
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<tr>
<td>Other pain sites</td>
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<td>-0.033</td>
<td>0.582</td>
<td>0.080</td>
<td>88</td>
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<tr>
<td>Patella resurfacing</td>
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<td>-0.089</td>
<td>0.141</td>
<td>0.661</td>
<td>0</td>
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<tr>
<td>Preoperative pain*</td>
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<td>0.135</td>
<td>0.048</td>
<td>0.222</td>
<td>0.002</td>
<td>80</td>
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<td>Weight*</td>
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<td>0.015</td>
<td>0.103</td>
<td>0.008</td>
<td>53</td>
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</table>

Table 5 Effect size data for studies involving a prospective design. *P<0.05

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<th>Predictor variable</th>
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<th>Upper limit</th>
<th>P-value</th>
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</thead>
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<td>-0.064</td>
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<tr>
<td>Anxiety</td>
<td>4</td>
<td>0.116</td>
<td>-0.008</td>
<td>0.239</td>
<td>0.066</td>
<td>52</td>
</tr>
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<td>0.426</td>
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<td>0</td>
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<td>0</td>
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<tr>
<td>Depression</td>
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<td>0.061</td>
<td>-0.050</td>
<td>0.173</td>
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<td>52</td>
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<tr>
<td>Education</td>
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<td>-0.118</td>
<td>0.026</td>
<td>0.209</td>
<td>25</td>
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<tr>
<td>Function</td>
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<td>-0.065</td>
<td>-0.157</td>
<td>0.027</td>
<td>0.165</td>
<td>69</td>
</tr>
<tr>
<td>Gender</td>
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<td>-0.042</td>
<td>0.035</td>
<td>0.873</td>
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<td>Mental health*</td>
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<td>-0.091</td>
<td>-0.131</td>
<td>-0.051</td>
<td>&lt;0.001</td>
<td>0</td>
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<tr>
<td>Other pain sites</td>
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<td>-0.063</td>
<td>0.350</td>
<td>0.174</td>
<td>57</td>
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<tr>
<td>Patella resurfacing</td>
<td>3</td>
<td>0.045</td>
<td>-0.082</td>
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<td>0.085</td>
<td>0.254</td>
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<td>0.006</td>
<td>39</td>
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</table>
in the multivariable analysis, supporting previous suggestions that comorbid conditions influence pain outcomes but are likely to have a relatively minor impact.\textsuperscript{43} Similarly, while female gender was often significantly associated with higher postoperative pain, the overall effect in our meta-analyses was small and of minimal clinical importance.\textsuperscript{44}

The influence of the follow-up period on the meta-analyses is noteworthy. The regression results indicate that the predictive capacity of high preoperative pain and the presence of comorbidities was reduced over time. Thus, these clinical variables appear to be stronger predictors of pain in the initial 3–6 months after surgery. The fact that the impact of catastrophizing was not influenced by the follow-up period indicates that this factor continues to exert an effect many months to years after surgery. This is of marked clinical interest given that this variable was measured prior to surgery and is potentially modifiable.

The risk of bias analysis indicated a range of quality in the reviewed studies. In general, prospective studies incorporating multivariable models that controlled for known confounding factors were at less risk for bias. Future studies should more carefully identify and control for confounding variables or colinearity in the study design or analysis, and input from a biostatistician is suggested to ensure the rigor of the analysis approach. The lack of forward validation of any regression models was noteworthy and we suggest that future studies should address this limitation.

There were some limitations to consider in this review. We focused on pain as the outcome variable and rejected a number of studies that used an outcome measure that incorporated pain but did not evaluate it distinctly. Our rationale for this was to remove the potentially confounding effects of the other constructs captured in multidimensional scales (e.g. function) to more clearly delineate predictive factors associated with pain. We also excluded data from studies that combined THA and TKA patients. It is known that pain and patient satisfaction outcomes from THA are generally better in comparison with TKA,\textsuperscript{4, 20, 49–51} and therefore we did not include studies where information specific to TKA could not be obtained. There were numerous predictor variables that did not have a sufficient number of analyses to conduct a meaningful meta-analysis, including coping skills, beliefs, biomechanical factors, and quantitative sensory testing measures. These factors require further study. Particularly noteworthy was the lack of studies examining quantitative sensory testing measures (n = 1) as research in other surgical populations suggests that these variables may be important preoperative predictors of persistent postoperative pain.\textsuperscript{52–56}

The difficulty in obtaining some clinical outcome measures in large population samples, such as objective measures of function, also may have limited inclusion of some predictor variables in the primary studies. There was also marked heterogeneity in the study designs, statistical analyses undertaken, and risk of bias scores. Finally, the follow-up time periods were grouped to a mean so some precision may be lost in the meta-analyses.

There are several clinical implications from our review. Clinicians need patient and procedure specific pathways that can direct their treatment and allow patients to achieve their best outcomes. At present, most patients undergo standardized, group based treatments based on statistical probability of effect. Ideally, valid screening tests would optimize treatment and allow risk stratification for persistent postoperative pain at an individual patient level. We identified catastrophizing as the clearest predictor of chronic pain after TKA. Catastrophizing is associated with acute and chronic pain severity,\textsuperscript{4, 55, 56} altered central nociceptive processing (e.g. decreased conditioned pain modulation,\textsuperscript{57}) exaggerated healthcare use,\textsuperscript{58} postoperative disability,\textsuperscript{6, 56} and reduction in function.\textsuperscript{59}

While catastrophizing has been shown to be modifiable,\textsuperscript{60} the critical elements needed to effectively treat or modify catastrophizing need to be better understood. Improving preoperative education of the procedure and outcomes, enabling patient participation in decision-making, and ensuring consistency of information may be key factors in reducing catastrophizing behaviours. While physical prehabilitation has yet to demonstrate substantial benefits in the TKA population,\textsuperscript{51} targeted preoperative interventions to reduce pain catastrophizing may be a more effective approach.

The influential effects of preoperative pain and other pain sites highlight the importance of the management of pain prior to surgery. The optimum time to operate on patients with OA is poorly understood. For some patients, non-surgical management of pain in a more structured manner (e.g. optimizing analgesia, weight control, and function) may delay surgery; however, prolonged delay may also be a risk factor for poor outcome. There is evidence that OA has an important central sensitization component that is associated with spreading hyperalgesia\textsuperscript{62} and may be initiated and maintained by persistent nociceptive input from the damaged joint.\textsuperscript{63, 64} Therefore, rather than delaying surgery, these patients may benefit from earlier surgical intervention or a different perioperative pathway involving more intensive analgesic options (e.g. prolonged regional analgesia, N-methyl-D-aspartate receptor antagonists, and gabapentinoids) compared with those deemed at lower risk.

This review has further highlighted the complexity of identifying single factors that may predict outcome from TKA. While much research from a medical perspective is targeted at the biomechanical aspects of TKA (e.g. prosthetics, types of surgical implants, and surgical approaches) it would appear from a persistent pain perspective that we should be concentrating more on the identification and management of preoperative risk factors such as catastrophizing, pain intensity, and the presence of widespread pain.

**Supplementary material**

Supplementary Material is available at *British Journal of Anaesthesia* online.

**Authors’ contributions**

G.N.L.: study design, data analysis, and first draft of manuscript.
D.A.R.: study design and reviewed manuscript. P.J.M.: study design and reviewed manuscript. M.K.: reviewed manuscript.
Declarations of interest

None declared.

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