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Predictors of chronic pain and level of physical function in total knee arthroplasty: a protocol for a systematic review and meta-analysis

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Predictors of pain and function in TKA: a protocol

ABSTRACT

Introduction

One in five patients undergoing total knee arthroplasty (TKA) experience unchanged or worse pain and physical function one year after surgery. Identifying risk factors for unfavorable outcomes is necessary to develop tailored interventions to minimize risk. There is a need to review more current literature with updated methodology that addresses the limitations of earlier systematic reviews and meta-analyses. We present a PRISMA-P compliant protocol for a systematic review and meta-analysis of predictors of chronic pain and impaired function after TKA.

Methods and analysis

This review will include prospective longitudinal observational studies, or randomized trials (including cluster and crossover designs) that report arm-wise predictors of chronic postsurgical pain or impaired physical function at three, six, or twelve months. A comprehensive literature search of studies published between 2000 and 2019 will be performed in Medline, Embase, CINAHL, Cochrane Library and PEDro. Blinded assessment with consensus agreement will be applied for inclusion of studies, data extraction, and assessment of bias risk (QUIPS tool). The co-primary outcomes, pain and impaired function, at twelve months post-TKA will be analyzed separately. Estimates of association between each outcome and any pre- or intraoperative factor that may predict chronic pain or impaired physical function will be extracted from the included studies, where possible. For randomized studies, results will only be extracted from TKA arms (or the first period of crossover trials). Estimates of association from the primary evidence will be synthesized narratively, and quantitatively using multivariate meta-analysis to provide "pooled" estimates of association. Subgroup and sensitivity analyses will be performed. Certainty of evidence for each predictor will be derived from the GRADE framework.

Ethics and dissemination

No ethical issues are associated with this project. The results from this review will be published in peer-reviewed journals and presented at international conferences.

Registration details

Prospero registration number: CRD42018079069.

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ARTICLE SUMMARY

Strengths and limitations of this study

- The strengths of this review include a transparent protocol with rigorous and updated methodology throughout each phase of the review process, a comprehensive literature search with no limitations on predictors or language, and inclusion of only the strongest observational study designs to avoid excessive heterogeneity, and a thorough description of the data analysis plan.
- Use of consistent methods for assessing the risk of bias (QUIPS) and certainty of evidence (GRADE) is also a study strength.
- Since 95% of patients treated with TKA suffer from osteoarthritis, results will have high generalizability within the osteoarthritis population, but results might be less applicable to other populations, such as adults or children with rheumatoid arthritis.
- The validity of this systematic review and meta-analysis will depend on the quality of the published studies included, the definitions applied for chronic pain or impaired physical function and the possible predictors included.

Predictors of pain and function in TKA: a protocol

Predictors of chronic pain and level of physical function in total knee arthroplasty: a protocol for a systematic review and meta-analysis

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INTRODUCTION

Total knee arthroplasty (TKA) is a common surgical procedure for patients with osteoarthritis (OA) suffering from pain and impaired function.[1 2] In the United Kingdom and the Isle of Man, nearly 100,000 primary TKAs are performed annually,[3] while the number for the USA is 700,000[4]. Despite advances in anesthesia and the surgical field, such as implementation of fast track surgery, 20% of TKA patients experience pain and levels of physical function that remains unchanged or worse one year after surgery.[5-7] Unfavorable outcomes can seriously impact patients through further deterioration in health status[8 9] and dissatisfaction with postoperative rehabilitation and surgical outcomes.[9-12] Patients who do not benefit from surgery are also more likely to undergo revision surgery,[3 13 14] have higher health care utilization and are less likely to return to work.[10 15-17] Consequently, poor TKA outcomes represent a significant burden, on a personal level to the individual patient and family, as well as on a socio-economic level, with considerable health care resources being spent on ineffective TKA procedures.[18]

One strategy to reduce the burden of poor TKA outcomes, for individual patients and society, is to gain a better understanding of the pre- and intraoperative predictors of chronic pain and impaired function after TKA. Knowledge of pre- and intraoperative risk factors is a fundamental first step in the development of screening tools to identify patients at high risk for chronic pain or impaired function after TKA. Identifying such patients would allow targeted and tailored interventions to be developed in order to improve patients' surgical outcomes.[19 20] Early identification of patients at high risk can also provide both patients and clinicians with more personalized information about the risks of surgery during the decision-making process when considering TKA.

Consequently, pre- and intraoperative predictors of chronic pain and impaired function are critically important for identifying patients at increased risk of a poor postoperative outcome. During the last decade, a considerable number of studies were published that identified a variety of potential preoperative predictors of chronic pain and poor function after TKA, without achieving consensus on which risk factors are the most powerful. However, the mechanisms that impact poor TKA outcomes are complex and multifactorial, and might be of biological, mechanical and/or psychosocial origin.[21-23] For example, demographic factors such as female sex and older age, and clinical factors including higher body mass index, greater number of co-morbidities, severe pain, poor knee function and greater number of painful joints, have all been found to predict chronic pain and impaired physical function after TKA.[6 23-28] Severity of radiological changes as well as a number of surgical and implant-related factors such as use of tourniquet, non-patellar resurfacing, tibial component rotation, infrapatellar fat pad excision, and cruciate-retaining TKA have all been identified as being associated with chronic pain and reduced knee function following TKA.[23 29-33] Psychological risk factors have also been identified and include unfulfilled outcome expectations, more severe perception of illness, depression, anxiety, maladaptive coping strategies, low self-efficacy and catastrophizing.[6 24-26 34-38]

Results vary across studies and point to the difficulties surgeons face when selecting patients who will benefit from surgery. Orthopedic surgeons often rely on subjective criteria and imaging, even though research findings suggest that surgeons' attempts to predict which patients will improve after TKA may be no better than chance.[39] Selection criteria that are more evidenced-based could be a powerful tool for reducing risk for overutilization of TKA.

Given these prior findings, a new synthesis of the literature that utilizes evidence-based methods is warranted to better inform patients, clinicians, researchers and policy makers about risk factors for patient outcomes of chronic pain and impaired physical function after TKA. The results of this review will address these gaps in knowledge and can be used by researchers to explore areas that have previously received little research attention. Thus, the aim of this study is to conduct a systematic review and synthesis of current evidence. The result of this work will be a narrative description of the factors identified, and a statistical meta-analysis that provides point estimates and 95% confidence intervals (CI) of the strength of association between each pre- and intraoperative factor evaluated by the included studies, and the co-primary outcomes (chronic pain and impaired function following TKA).

METHODS AND ANALYSIS

This systematic review and meta-analysis will include two key outcomes, chronic pain and impaired physical function, which are moderately to strongly associated, but distinct.[23] Thus, chronic pain and impaired function will be assessed and reported as two separate outcomes. Our strategy is consistent with the Cochrane Handbook for Systematic Reviews of Interventions,[40] which suggests that a review may start with a broad scope before being divided into more narrow reviews.

This protocol has been developed according to the PRISMA-P checklist and the review will be reported according to the PRISMA guidelines.[41] The protocol is registered in the Prospero database of systematic reviews, CRD42018079069.

Eligibility criteria for considering studies in this review

Prospective longitudinal observational studies or randomized trials (including cluster and crossover designs) of osteoarthritis patients undergoing primary TKA and that report at least one pre- or intraoperative predictor of chronic postsurgical pain or impaired function (measured three, six, or twelve months after primary TKA) will be considered for inclusion. Studies of unicompartmental surgery, studies without separate outcome data for TKA patients, studies that lack clear pain and physical function outcome measures, retrospective studies, and case-control studies will be excluded.

The eligibility criteria are pre-specified by the Population-Exposure-Outcome-Study (PEOS) design, as described below.

Population: Patients 18 years or older with osteoarthritis and scheduled for primary TKA.

Exposures: Any pre- or intraoperative factors that may predict chronic pain and impaired physical function in TKA patients.

Outcome: The two co-primary outcomes for this review are pain and function assessed twelve months post-TKA. Where possible, these outcomes will also be analyzed at three and six months post-TKA. It is expected that the outcomes will be measured by a variety of methods and instruments, as exemplified in table 1.

Study design: Included studies will have either a prospective longitudinal observational design, or a randomized trial design (including cluster and crossover designs). All included studies will describe predictors of chronic pain and impaired physical function.

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Table 1. Outcomes and how they could be measured in the included studies

Measures of the Chronic Pain Outcome	Measures of the Physical Function Outcome
Western Ontario and McMaster Universities Osteoarthritis Index	Western Ontario and McMaster Universities Osteoarthritis Index
Knee Society Score	Knee Society Score
Knee injury and Osteoarthritis Outcome Score	Knee injury and Osteoarthritis Outcome Score
Short Form 36	Short Form 36
Oxford Knee Score	Oxford Knee Score
McGill Pain Questionnaire	Timed Up and Go Test
Brief Pain Inventory	Sit to Stand Test
Numerical Rating Scale	Range of Motion
Visual Analog Scale	Inertial measurement units (Gait pattern)

Timeline

The timeline for the study phases is shown in table 2. The research question has been specified, protocol details have been registered and published, the search has been performed, and formal screening of the search results against eligibility criteria is in progress. Full-text inclusion and subsequent phases have not yet started. Full-text inclusion and subsequent phases are scheduled to be completed in 2020.

Table 2. The timeline for study phases

Review question	Register review	Search strategy	Study selection	Risk of Bias	Analysis	Quality of evidence	Dissemination
Eligibility after PEOS	Registered Prospero	Literature search	Full text review	QUIPS	Narrative review/ meta-analysis	Grade	Journals Conferences Ph.D. thesis
Completed 30.5.2018	Completed 31.8.2018	Completed 1.8.2019	Completed 2.3.2020	Completed 30.3.2020	Completed 4.5.2020	Completed 18.5.2020	Planned 1.10.2020 -

Review question

The question for this review is: "Which factors predict chronic pain and impaired physical function among patients after total knee arthroplasty?"

Definitions

Chronic/persistent pain is defined as pain extending three months after TKA.[42] Physical function refers to all body functions, activities and participation according to the International Classification of Functioning, Disability and Health (ICF) framework.[43]

Chronic pain and impaired physical function can be measured in various ways, including as a continuous variable that represents a continuum of pain (e.g., a score on a Visual Analog Scale) or as a categorical variable (e.g., a dichotomous variable with categorical levels of "chronic pain" or "no chronic pain"). Similarly, physical function can be assessed on a continuum (e.g., as indicated by the Knee injury and Osteoarthritis Outcome Score) or as different categories of function (e.g., "no problems walking", "some problems walking" and "confined to bed", as in EQ-5D-3L).

Literature search strategy

The search strategy was developed by two medical librarians (GK and HF) in cooperation with the authors (UO and MFL) and with input from the experienced research team. The search strategy was designed by one research librarian (GK) and peer-reviewed by the second research librarian (HF) and first author (UO), as recommended by the Cochrane Handbook.[40] A comprehensive systematic search for articles published

from January 1, 2000 through August 1, 2019 was conducted (GK) using a combination of text words and database-specific subject headings in MEDLINE (Ovid), Embase (Ovid), CINAHL (EBSCO), Cochrane Library and Physiotherapy Evidence Database. The search strategies were adapted to each database as presented in Supplementary material.

To capture as many relevant studies as possible, no language restrictions were applied, as recommended in *Methodological Expectations of Cochrane Intervention Reviews (MECIR)*.[44] The search was limited to studies published in or after year 2000 in consideration of changes in treatment modalities since year 2000. Duplicates were removed and conference abstracts were excluded. Studies had to be available in full-text format. References were imported to Endnote X8 (Clarivate Analytics, Philadelphia, PA, USA).

Study selection and data extraction

To avoid missing relevant articles, an overly inclusive approach for screening titles, abstracts, and full-text will be used. Publication abstracts in non-English and non-Scandinavian languages will be translated and assessed for eligibility. Both screening and selecting studies for full-text review will include independent and blinded screening by two authors (UO and MFL), with consensus discussion to resolve disagreements. If consensus cannot be reached, a third reviewer will adjudicate (ED). Studies that fulfill the eligibility criteria will be retained, fully translated, and scrutinized for full-text assessment against eligibility criteria. A standardized data extraction form customized to the research question will be developed for extraction of data and pilot-tested on the first three included studies (table 3). If additional data are needed about a particular study, the corresponding and/or senior authors of the publication will be contacted to obtain more detail.

Table 3. Data extraction template

Data	Extracted data
Publication details	First author and senior author, year of publication, country of origin
Study characteristics	Study design (prospective longitudinal observational design; intervention arm of a randomized trial; intervention arm of the first period of a randomized crossover trial), source of patient recruitment, length of follow up, sample size, statistical method and results
Patients characteristics	Age, sex, body mass index, ethnicity, socio-economics and demographics
Intervention	Type of implant, anesthetic and analgesic factors
Predictors	Type of predictors and how they are measured, e.g. pain by Brief Pain Inventory, depression by Hospital Anxiety Depression Scale, severity of osteoarthritis by Kellgren Lawrence Scale, direction of effect (reversed or not)
Outcome	Type of pain or function outcome, how it is defined and measured (table 1). The unit of analysis used (patient or cluster)
Measure of association (one per predictor)	Estimand (e.g., linear regression or correlation coefficient), estimate (i.e., numerical result), and precision (e.g., confidence interval, standard error, P-value)

It is anticipated that included studies may present multiple results for each predictor (e.g., several regression models resulting from stepwise model-building procedures). Data will be extracted for the model or analysis specified as the primary analysis in the study protocol; if no suitable model or analysis is specified, we will extract data for the model or analysis favored by the study's authors and presented as the "main result" (e.g., the model with the best goodness of fit criteria, such as Akaike's information criterion[45]). A consensus-based approach will be used to determine which result is favored by a study (i.e.,

two authors performing data extraction must agree; in the event of disagreement, a third author will adjudicate). Acquisition and analysis of individual patient-level data (IPD) is not planned. For example, we will not re-analyze IPD with respect to our own definitions of the co-primary outcomes.

Studies may use different names for the same type of predictor. Predictors will be considered to be the same type if they are measured using the same method (e.g., instrument), or if the methods of measurement are judged to assess the same construct (e.g., anxiety) by two authors (in the event of disagreement, a third author will adjudicate).

Studies may report estimates adjusted for variables such as age, sex, and pre-surgical pain. All variables measured pre-TKA and included in pre-specified or "main" regression or correlational analyses will be extracted and included in meta-analyses.

For randomized trials, data will be extracted for the TKA arm and treated in the same way as longitudinal observational data. For crossover trials, data will be extracted from the first period of the TKA arm and will be treated similarly. Because cluster designs will be included, we will extract the unit of analysis used for all studies (patient versus cluster). If studies that use a cluster design report results that do not account for possible cluster effects, we will impute results that adjust for clustering where feasible; if it is not feasible to adjust for clustering, we will judge the study to have a high risk of bias (see below). It is anticipated that publications that report randomized designs may not provide arm-wise results. We will contact authors of such studies and request the required data; studies will be excluded from synthesis if data are not received within four weeks of request.

Measures of association

It is anticipated that the included studies will report associations between predictors and dichotomous outcome variables as odds ratios (ORs) from logistic regressions, and associations between predictors and continuous outcome variables as linear regression or correlation coefficients. For dichotomous outcomes, it is anticipated that predictors with an OR > 1 will be associated with the undesirable outcome (i.e., pain or impaired function). For continuous outcomes, it is anticipated that linear regression or correlation coefficients greater than zero are associated with the undesirable outcome. Because some studies may not use these directions of association, the direction of association will be recorded during data extraction as reversed or not reversed (e.g., if OR < 1 is associated with the undesirable outcome, direction of association will be coded as reversed).

Methodological quality

To systematically evaluate study quality and to reach consensus in a transparent manner, the Quality in Prognosis Studies (QUIPS) tool will be used to assess risk of bias in the individual studies.[46] QUIPS addresses six domains where bias may occur in prognostic studies: study participation, attrition, prognostic factor measurement, outcome measurement, confounding, statistical analysis, and reporting. Because QUIPS does not include a summary assessment tool of the risk of bias for an individual study,[47] the Cochrane Handbook approach will be used in addition.[40] Studies will be classified as: low risk of bias if they

are rated as low risk on all domains; unclear risk of bias if risk of bias is unclear on one or more domains and low risk on all other domains and high risk of bias if they are rated as high risk on one or more domains).[40] Two authors (UO and MFL) must agree, otherwise a third reviewer (ED) will adjudicate.[40]

Dealing with missing data

Study authors will be contacted if there is a need for additional details about unpublished data, as recommended by the Cochrane Handbook.[40] Requests will be sent to a study's corresponding author, and the first or senior author if the corresponding author cannot be contacted. In addition, critical appraisal will be carried out and reported regarding study participant attrition, losses to follow up or withdrawal, and any issues regarding missing data or imputation methods (e.g., last observation carried forward).

It is anticipated that not all included studies will report associations between outcomes and all predictors that have been studied in the literature as a whole (i.e., the nature of the research question suggests that estimates for some predictors may be missing for most studies). This form of missing data will be addressed in a meta-analysis, as described in the data synthesis section.

Where possible, imputation will be used to include results from eligible studies. For example, we may impute ORs if risk ratios are reported. It is anticipated that some included studies will report point estimates but not exact statements of uncertainty on those estimates (e.g., some studies may report results as "statistically significant" rather than providing an exact P-value or confidence interval). A conservative approach will be used in which "worst case" standard errors will be imputed: results reported as "statistically significant" (e.g., $P \leq 0.05$) will be imputed to have standard errors consistent with $P = 0.05$; results reported as "not statistically significant" (e.g., $P > 0.05$) will be imputed to have standard errors consistent with $P = 0.99$.

Data synthesis

Given the expected heterogeneity of the data, a narrative analysis of the results will be conducted for all included studies for the two co-primary outcomes at 12 months. Meta-analyses will also be performed for the two co-primary outcomes of chronic pain and impaired physical function assessed three- and six-months post-surgery, if possible.

We will perform quantitative data synthesis following the guidance of the most recent version of the Cochrane Handbook available at the time of the analysis.[40] Meta-analyses will be performed if two or more studies report results amenable to analysis, otherwise only a narrative analysis will be conducted. Studies appraised to be at high risk of bias will be excluded from meta-analysis.

To facilitate meta-analysis, results quantifying association between outcomes and predictors (ORs and linear regression and correlation coefficients) will be transformed to Hedges' *g* (via Cohen's *d*).[48] Results reported using the reversed direction of association will be inverted to ensure a common direction of association is used in meta-analysis.

It is anticipated that predictors will be correlated and that there may be important differences in the methods used to quantify associations between outcomes and predictors (i.e., while the methods used in the included studies will attempt to measure compatible constructs, they may be sufficiently different that we expect heterogeneity). A multivariate meta-analysis will therefore be performed for each outcome

using a random-effects model. Analyses will be performed using Stata 16 (StataCorp LLC, College Station, Texas, USA) and the MVMETA command or R and the metafor package.[49-52] Missing point estimates for predictors not included in individual studies will be handled using the standard procedures defined by the software used. For example, the MVMETA command models missing point estimates as zeros and accounts for uncertainty using very large variances (i.e., missing point estimates could plausibly take any value). Within-study correlations will be assumed to be unknown and the "overall correlation model" of Riley et al.[53] will be used. An unstructured between-study covariance matrix will be assumed.

Assessment of non-reporting bias and small study effects

Non-reporting bias and small study effects will be assessed following the approach outlined by Sterne et al.[54] For each predictor supported by at least 10 results, contour-enhanced funnel plots will be constructed by plotting Hedges' *g* against its standard error. Funnel plot asymmetry will be judged visually and tested using Egger's regression-based test (at the $\alpha = 0.05$ level) assuming random effects. Predictors for which asymmetry is suspected will be reported with consideration for the possible causes of asymmetry. In particular, asymmetry will not be definitively attributed to non-reporting bias because it may have other explanations. Fixed- and random-effects meta-analysis estimates will not be compared because we anticipate heterogeneity and therefore judge that the fixed-effects model may be inappropriate. Predictors will not be excluded from meta-analysis on the basis of suspected asymmetry but will be downgraded for certainty of evidence (see below).

Assessment of heterogeneity

Meta-analytical estimates will not be reported if substantial clinical, methodological, or statistical heterogeneity is observed. Clinical and methodological heterogeneity will be evaluated subjectively. Substantial statistical heterogeneity will be declared if the lower bound on the 95% CI on between-study I^2 is greater than 50%. Exploratory analyses will be performed to attempt to explain any substantial heterogeneity.

Subgroup analysis

Exploratory subgroup or meta-regression analyses will be performed for the two co-primary outcomes with respect to: study design; type of outcome measurement; and intervention (e.g., type of implant).

Sensitivity analysis

Exploratory sensitivity analyses will be performed for the two co-primary outcomes with respect to: risk of bias (studies deemed at low or unclear risk of bias, versus all included studies); the random-effects assumption (i.e., a fixed-effects analysis will also be performed); and the treatment of chronic pain and impaired physical function as two separate outcomes versus a single multivariate outcome (i.e., a single multivariate model of the two co-primary outcomes will be fitted).

Certainty of evidence using the GRADE framework

The certainty of evidence for each prognostic factor will be derived using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework for prognostic studies.[46 55 56] Study limitations, indirectness, inconsistency, imprecision, publication bias, magnitude of association, dose-response gradient and plausible confounding affecting confidence will be evaluated.[46] The overall certainty of evidence will be rated as high, moderate, low, or very low. GRADE ratings will be assigned by two of the

authors (UO and MFL), issues will be discussed to arrive at consensus, if not, a third reviewer (ED) will adjudicate.

Presentation and interpretation of results

Funnel plots will be used for assessing presence of publication bias for the two separate outcomes. The meta-analytical result for each outcome will be presented as forest plots. One forest plot will present meta-analytical point estimates and 95% CI and prediction intervals for the predictors,[57] with predictors ordered by probability of being the best predictor (e.g., via the "pbest" option of MVMETA). Additional forest plots will show results for each predictor, showing the results extracted from the included studies and the meta-analytical point estimates and 95% CI and prediction intervals. Search strategy results will be presented, as well as characteristics of included studies, descriptive data for the eligibility criteria according to the PEOS design template data extraction form, data dictionary document, judgment of risk of bias by QUIPS, and the GRADE evidence profile.

Following MECIR standards,[44] meta-analytical results will be re-expressed to facilitate interpretation and possible use in predicting chronic pain and impaired physical function. For example, meta-analytic estimates of Hedges' *g* may be re-expressed as linear regression coefficients. The magnitude of the meta-analytical estimates of association will be interpreted using Cohen's *d* as follows: $d < 0.4$ represents a weak association; $0.4 \leq d < 0.7$ represents a moderate association; and $d \geq 0.7$ represents a strong association.

Meta-analytical results will also be presented in a summary table of findings table for each outcome[58] with columns for: predictor; meta-analytical result (Hedges' *g* and its 95% CI); re-expressed Hedges' *g* and its 95% CI; interpretation of the magnitude of association (i.e., weak, moderate, or strong); number of participants (and clusters, where appropriate) and number of studies; certainty of evidence (GRADE); and comments.

Subgroup and sensitivity analyses, and meta-analyses of predictors of chronic pain and impaired physical function measured at three and six months post-TKA, will be narratively summarized from any available reported data. Tables and figures for these analyses will be presented in an appendix.

Factors identified as being associated with the co-primary outcomes will not be interpreted to cause those outcomes because the included study designs and planned analyses do not allow causal inferences to be made.

Deviations from protocol

Deviations from this protocol will be reported and justified.

Patient and public involvement

No patients will be involved in this review.

Strengths and limitations

By following the Cochrane Handbook's method recommendations[40] throughout each phase, we aim to achieve a high-quality review that will be of great importance for patients, clinicians, researchers and policy decision makers. To provide reliable data to address the review's aim and to avoid excessive heterogeneity caused by different study designs that might affect robustness of the review's results or

introduce high risk of bias, only prospective longitudinal studies or the intervention arm of randomized trials will be included. No language limitations will be applied so that relevant studies are not excluded, thereby increasing precision of the findings and maximizing generalizability. As a result, widespread application of the study results is expected. QUIPS and GRADE will be used to assess risk of bias for individual studies and assess certainty of evidence of included studies. Since 95% of patients treated with TKA suffer from osteoarthritis, results will have high generalizability within the osteoarthritis population, but might be less applicable to other populations, such as patients with rheumatoid arthritis. The strict eligibility criteria exclude studies that only report outcomes after one year; most register studies will be rejected as they are less likely to be prospective. Results must be interpreted based on this study context. We might find that predictors and outcomes are measured quite differently across studies. However, an effect size for a meta-analysis creates a standardized measure so the actual measure scaling is not relevant and thus a meta-analysis is perfect for reviewing studies that use different measures for the same conceptual outcome.

Ethics and dissemination

Primary data will not be collected, thus ethical approval is not required. Results will be presented at international conferences and findings will be published in a peer-reviewed high-impact journal and a doctoral thesis.

User involvement

Members from the user board at Lovisenberg Diaconal Hospital, Jan Otto Veiseth and Richard Madsen have been contributing to the relevance and significance of the protocol's content.

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Competing interests statement.

CR report personal fees from OncoImmunity AS. He has a patent and patent application with no relevance of this study.

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Authors' contributions

UO, MFL, ED, CR, CG and AL contributed to the development of the protocol. UO, MFL and the two research librarians, GK and HF, were responsible for the search strategy. GK conducted the search. UO wrote the manuscript. All authors provided feedback on the study design and manuscript drafts. AL is guarantor of the study.

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Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) <2000 to Present>

Search date: 01.01.2000 - 27.06.2018.
Updated search: 28.06.2018 - 01.08.2019

1	Arthroplasty, Replacement, Knee/
2	(tkr or tjkr or tka or tjka).tw,kf.
3	(knee* adj3 (arthroplast* or replacement*)).tw,kf.
4	(total adj2 knee*).tw,kf.
5	(knee* adj2 prosthes*).tw,kf.
6	or/1-5
7	risk/ or risk factors/ or logistic models/ or protective factors/ or risk assessment/
8	prognosis/ or (prognos* or risk* or predict*).tw,kf.
9	(preoperative factor* or pre operative factor* or protective factor*).tw,kf.
10	or/7-9
11	and/6,10
12	(pain adj3 (post* or ongoing or on going or long* or persist* or prolong* or after or follow*)).tw,kw.
13	pain, postoperative/
14	(Pain/ or chronic pain/ or musculoskeletal pain/) and (post* or ongoing or on going or long* or persist* or prolonged or after or follow*).tw,kf.
15	cohort studies/ or follow-up studies/ or longitudinal studies/ or prospective studies/ or retrospective studies/
16	pain.tw,kf.
17	and/15-16
18	or/12-14,17
19	and/11,18
20	(function* or stiffness or contracture*).tw,kf.
21	(muscle adj3 (strength* or weakness or fatigue or tonus)).tw,kf.
22	Contracture/
23	"Recovery of Function"/
24	"Range of Motion, Articular"/
25	locomotion/ or walking/ or gait/ or walking speed/ or stair climbing/
26	"Activities of Daily Living"/ or (adl or (daily adj3 activit*)).tw,kf.
27	Movement/
28	muscle fatigue/ or muscle tonus/ or physical exertion/ or postural balance/ or Muscle Strength/

29	(sitting or lying or standing or balance or posture or rising or neeling or bend* or walk* or gait or stair* or extension* or stability or contracture* or movement* or motion* or locomotion* or mobility or twisting or pivoting or straighten* or swelling or grinding or clicking or squatting or running or jumping).tw,kf.
30	treatment outcome/ or treatment failure/ or outcome*.tw,kf.
31	patient reported outcome measures/
32	("Knee injury and Osteoarthritis Outcome Score" or womac or koos or "American Knee Society Score" or AKSS or Kellgren Lawrence).tw,kf.
33	or/20-32
34	cohort studies/ or follow-up studies/ or longitudinal studies/ or prospective studies/ or retrospective studies/
35	Postoperative Period/
36	(post* or after or follow* or cohort* or prospectiv* or longitudinal).tw,kf.
37	or/34-36
38	and/11,33,37
39	or/19,38
40	limit 39 to yr="2000 -Current"
41	limit 40 to "reviews (best balance of sensitivity and specificity)"
42	40 not 41

Embase Classic+Embase 1947 to 2018 June 25

Search date: 01.01.2000 - 27.06.2018.
Updated search: 28.06.2018 - 01.08.2019

#	Searches
1	knee replacement/ or total knee arthroplasty/
2	(tkr or tjkr or tka or tjka).tw,kw.
3	(knee adj3 (arthroplast* or replacement*)).tw,kw.
4	(total adj2 knee*).tw,kw.
5	(knee* adj2 prosthes*).tw,kw.
6	or/1-5
7	risk factor/ or risk/ or protection/ or risk assessment/
8	prognosis/ or (prognos* or risk* or predict*).tw,kw.
9	"prediction and forecasting"/ or prediction/
10	(preoperative factor* or pre operative factor* or protective factor*).tw,kw.
11	or/7-10
12	and/6,11
13	(pain adj3 (post* or ongoing or on going or long* or persist* or prolong* or after or follow*)).tw,kw.
14	postoperative pain/
15	(pain/ or chronic pain/ or musculoskeletal pain/) and (post* or ongoing or on going or long* or persist* or prolonged or after or follow*).tw,kw.
16	cohort analysis/ or follow up/ or longitudinal study/ or prospective study/ or retrospective study/
17	pain.tw,kw.
18	and/16-17
19	or/13-15,18
20	and/12,19
21	knee function/ or muscle function/ or muscle rigidity/ or muscle contraction/ or muscle strength/ or muscle fatigue/ or muscle function/ or muscle stretching/ or muscle weakness/
22	contracture/ or flexion contracture/ or joint contracture/ or muscle contracture/
23	convalescence/
24	locomotion/ or climbing/ or stair climbing/ or jumping/ or walking/ or gait/ or walking speed/
25	daily life activity/ or (daily life activity or actvities of daily living or adl).tw,kw.
26	exp musculoskeletal function/ or Movement/
27	joint swelling/ or grinding/
28	(function* or stiffness or contracture*).tw,kw.
29	(muscle adj3 (strength* or weakness or fatigue or tonus)).tw,kw.
30	(sitting or lying or standing or balance or posture or rising or neeling or bend* or walk* or gait or stair* or extension* or stability or contracture* or movement* or motion* or locomotion* or

	mobility or twisting or pivoting or straighten* or swelling or grinding or clicking or squatting or running or jumping).tw,kw.
31	treatment outcome/ or treatment failure/ or patient-reported outcome/ or clinical outcome/ or outcome*.tw,kw.
32	"knee injury and osteoarthritis outcome score"/ or "Western Ontario and McMaster Universities Osteoarthritis Index"/ or ("Knee injury and Osteoarthritis Outcome Score" or womac or koos or "American Knee Society Score" or AKSS or Kellgren Lawrence).tw,kw.
33	or/21-32
34	cohort analysis/ or follow up/ or longitudinal study/ or prospective study/ or retrospective study.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
35	postoperative period/
36	(post* or after or follow* or cohort* or prospectiv* or longitudinal).tw,kw.
37	or/34-36
38	and/12,33,37
39	or/20,38
40	limit 39 to yr="2000 -Current"
41	limit 40 to conference abstract
42	40 not 41
43	limit 40 to "reviews (best balance of sensitivity and specificity)"
44	43 not 41
45	42 not 43

CINAHL(Ebsco):
Search date: 01.01.2000 - 27.06.2018.
Updated search: 28.06.2018 - 01.08.2019

#	Query	Limiters/Expanders
S1	(MH "Arthroplasty, Replacement, Knee+")	Search modes - Boolean/Phrase
S2	TX tkr or tjkr or tka or tjka	Search modes - Boolean/Phrase
S3	TX knee* N3 (arthroplast* or replacement*)	Search modes - Boolean/Phrase
S4	TX (total N2 knee*)	Search modes - Boolean/Phrase
S5	TX (knee* N2 prosthes*)	Search modes - Boolean/Phrase
S6	S1 OR S2 OR S3 OR S4 OR S5	Search modes - Boolean/Phrase
S7	(MH "Risk Factors")	Search modes - Boolean/Phrase
S8	(MH "Risk Assessment")	Search modes - Boolean/Phrase
S9	MH "Prognosis")	Search modes - Boolean/Phrase
S10	TX prognos* or risk* or predict* or preoperative factor* or protective factor*	Search modes - Boolean/Phrase
S11	S7 OR S8 OR S9 OR S10	Search modes - Boolean/Phrase
S12	S6 AND S11	Search modes - Boolean/Phrase
S13	(TX pain N2 (TX (post* or ongoing or "on going" or long* or persist* or prolong* or after or follow*)) OR (MH "Postoperative Pain") OR TX pain AND (MH "Prospective Studies+")	Search modes - Boolean/Phrase
S14	(MH "Pain+") OR (MH "Knee Pain+") OR (MH "Muscle Pain") AND TX post* or ongoing or "on going" or long* or persist* or prolong* or after or follow*	Search modes - Boolean/Phrase
S15	S13 OR S14	Search modes - Boolean/Phrase
S16	S12 AND S15	Search modes - Boolean/Phrase
S17	(MH "Movement") OR (MH "Hopping") OR (MH "Jumping") OR (MH "Kneeling+") OR (MH "Extension+") OR (MH "Locomotion") OR (MH "Walking+") OR (MH "Gait+") OR (MH	Search modes - Boolean/Phrase

	"Step") OR (MH "Range of Motion") OR (MH "Rising") OR (MH "Sitting") OR (MH "Squatting") OR (MH "Stair Climbing") OR (MH "Standing+") OR (MH "Stretching")	
S18	(MH "Muscle Fatigue") OR (MH "Muscle Strength+") OR (MH "Muscle Tonus")	Search modes - Boolean/Phrase
S19	TX (function* or stiffness or contracture*)	Search modes - Boolean/Phrase
S20	TX (muscle N3 (strength* or weakness or fatigue or tonus))	Search modes - Boolean/Phrase
S21	(MH "Contracture+")	Search modes - Boolean/Phrase
S22	(MH "Activities of Daily Living+")	Search modes - Boolean/Phrase
S23	TX (actvities or daily living or adl)	Search modes - Boolean/Phrase
S24	(MH "Treatment Outcomes+") OR (MH "Fatal Outcome") OR (MH "Treatment Failure")	Search modes - Boolean/Phrase
S25	TX outcome*	Search modes - Boolean/Phrase
S26	TX "Knee injury and Osteoarthritis Outcome Score" or womac or koos or "American Knee Society Score" or AKSS or Kellgren Lawrence)	Search modes - Boolean/Phrase
S27	S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26	Search modes - Boolean/Phrase
S28	(MH "Postoperative Period") OR (MH "Prospective Studies+")	Search modes - Boolean/Phrase
S29	TX (post* or after or follow* or cohort* or prospectiv* or longitudinal)	Search modes - Boolean/Phrase
S30	S28 OR S29	Search modes - Boolean/Phrase
S31	S12 AND S27 AND S30	Search modes - Boolean/Phrase
S32	S16 OR S31	Search modes - Boolean/Phrase
S33	S16 OR S31	Limiters - Published Date: 20180601-20190831 Search modes - Boolean/Phrase
S34	S16 OR S31	Limiters - Published Date: 20000101-20180631; Clinical Queries: Review - Best Balance

		Search modes - Boolean/Phrase

The Cochrane Library

Search date: 01.01.2000 - 27.06.2018.
Updated search: 28.06.2018 - 01.08.2019

#1	MeSH descriptor: [Arthroplasty, Replacement, Knee] this term only
#2	tkr or tjkr or tka or tjka:ti,ab,kw (Word variations have been searched)
#3	knee near/3 (arthroplast* or replacement*):ti,ab,kw (Word variations have been searched)
#4	total near/2 knee*:ti,ab,kw (Word variations have been searched)
#5	knee near/2 prostheses:ti,ab,kw or knee near/2 prosthesis:ti,ab,kw (Word variations have been searched)
#6	#1 or #2 or #3 or #4 or #5
#7	MeSH descriptor: [Risk] explode all trees
#8	MeSH descriptor: [Prognosis] this term only
#9	prognos* or risk* or predict*:ti,ab,kw (Word variations have been searched)
#10	preoperative factor* or pre operative factor* or protective factor*:ti,ab,kw (Word variations have been searched)
#11	#7 or #8 or #9 or #10
#12	#6 and #11
#13	pain near/3 (post* or ongoing or "on going" or long* or persist* or prolong* or after or follow*):ti,ab,kw (Word variations have been searched)
#14	MeSH descriptor: [Pain, Postoperative] this term only
#15	MeSH descriptor: [Pain] this term only
#16	MeSH descriptor: [Chronic Pain] this term only
#17	MeSH descriptor: [Musculoskeletal Pain] this term only
#18	#14 or #15 or #16 or #17
#19	post* or ongoing or on going or long* or persist* or prolonged or after or follow*:ti,ab,kw (Word variations have been searched)
#20	#18 and #19
#21	MeSH descriptor: [Cohort Studies] explode all trees
#22	pain:ti,ab,kw (Word variations have been searched)
#23	#21 and #22
#24	#13 or #20 or #23
#25	#12 and #24
#26	function* or stiffness or contracture*:ti,ab,kw (Word variations have been searched)
#27	muscle near/3 (strength* or weakness or fatigue or tonus):ti,ab,kw (Word variations have been searched)
#28	MeSH descriptor: [Contracture] this term only
#29	MeSH descriptor: [Recovery of Function] this term only
#30	MeSH descriptor: [Range of Motion, Articular] this term only
#31	MeSH descriptor: [Locomotion] this term only
#32	MeSH descriptor: [Walking] explode all trees
#33	MeSH descriptor: [Activities of Daily Living] this term only
#34	"actvities of daily living" or adl:ti,ab,kw (Word variations have been searched)
#35	MeSH descriptor: [Movement] this term only
#36	MeSH descriptor: [Muscle Fatigue] this term only
#37	MeSH descriptor: [Muscle Tonus] this term only
#38	MeSH descriptor: [Physical Exertion] this term only
#39	MeSH descriptor: [Postural Balance] this term only

#40	MeSH descriptor: [Muscle Strength] this term only
#41	sitting or lying or standing or balance or posture or rising or neeling or bend* or walk* or gait or stair* or extension* or stability or contracture* or movement* or motion* or locomotion* or mobility or twisting:ti,ab,kw or pivoting or straighten* or swelling or grinding or clicking or squatting or running or jumping:ti,ab,kw (Word variations have been searched)
#42	MeSH descriptor: [Treatment Outcome] this term only
#43	MeSH descriptor: [Treatment Failure] this term only
#44	outcome:ti,ab,kw (Word variations have been searched)
#45	MeSH descriptor: [Patient Reported Outcome Measures] this term only
#46	"Knee injury and Osteoarthritis Outcome Score" or womac or koos or "American Knee Society Score" or AKSS or "Kellgren Lawrence":ti,ab,kw (Word variations have been searched)
#47	#26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38 or #39 or #40 or #41 or #42 or #43 or #44 or #45 or #46
#48	MeSH descriptor: [Cohort Studies] explode all trees
#49	MeSH descriptor: [Postoperative Period] explode all trees
#50	post* or after or follow* or cohort* or prospectiv* or longitudinal:ti,ab,kw (Word variations have been searched)
#51	#48 or #49 or #50
#52	#47 and #51
#53	#12 and #52
#54	#25 or #53 with Publication Year from 2018 to 2019, with Cochrane Library publication date Between Jun 2018 and Aug 2019

PRDro (Physiotherapy Evidence Database):

Search date: 01.01.2000 - 27.06.2018.
Updated search: 28.06.2018 - 01.08.2019

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Information reported	Page
ADMINISTRATIVE INFORMATION				
Title:				
Identification	1a	Identify the report as a protocol of a systematic review	Yes	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	Not applicable	
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	Prospero: CRD42018079069	3
Authors:				
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	Yes	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	Yes	10
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	Not applicable	
Support:				
Sources	5a	Indicate sources of financial or other support for the review	Yes	10
Sponsor	5b	Provide name for the review funder and/or sponsor	Yes	10
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	Yes	10
INTRODUCTION				
Rationale	6	Describe the rationale for the review in the context of what is already known	Yes	2
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	Yes	4
METHODS				
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time	Yes	3

		frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review		
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	Yes	5-7
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	Yes	Appendix
Study records:				
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	Yes	5
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	Yes	5,7-9
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	Yes	5, 7, 9
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	Yes	3
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	Yes	3
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	Yes	6,9
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	Yes	7
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	Yes	7-9
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	Yes	8
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	Yes	7
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	Yes	9

Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	Yes 8,9

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

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Predictors of chronic pain and level of physical function in total knee arthroplasty: a protocol for a systematic review and meta-analysis

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Predictors of chronic pain and level of physical function in total knee arthroplasty: a protocol for a systematic review and meta-analysis

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Predictors of pain and function in TKA: a protocol

ABSTRACT

Introduction

One in five patients undergoing total knee arthroplasty (TKA) experience unchanged or worse pain and physical function one year after surgery. Identifying risk factors for unfavorable outcomes is necessary to develop tailored interventions to minimize risk. There is a need to review more current literature with updated methodology that addresses the limitations of earlier systematic reviews and meta-analyses. We present a PRISMA-P compliant protocol for a systematic review and meta-analysis of predictors of chronic pain and impaired function after TKA.

Methods and analysis

This review will include prospective longitudinal observational studies, or randomized trials (including cluster and crossover designs) that report arm-wise predictors of chronic postsurgical pain or impaired physical function at three, six, or twelve months. A comprehensive literature search of studies published between 2000 and 2019 will be performed in Medline, Embase, CINAHL, Cochrane Library and PEDro. Blinded assessment with consensus agreement will be applied for inclusion of studies, data extraction, and assessment of bias risk (QUIPS tool). The co-primary outcomes, pain and impaired function, at twelve months post-TKA will be analyzed separately. Estimates of association between each outcome and any pre- or intraoperative factor that may predict chronic pain or impaired physical function will be extracted from the included studies, where possible. For randomized studies, results will only be extracted from TKA arms (or the first period of crossover trials). Estimates of association from the primary evidence will be synthesized narratively, and quantitatively using multivariate meta-analysis to provide “pooled” estimates of association. Subgroup and sensitivity analyses will be performed. Certainty of evidence for each predictor will be derived from the GRADE framework.

Ethics and dissemination

No ethical issues are associated with this project. The results from this review will be published in peer-reviewed journals and presented at international conferences.

Registration details

Prospero registration number: CRD42018079069.

Predictors of pain and function in TKA: a protocol

ARTICLE SUMMARY

Strengths and limitations of this study

- The strengths of this review include a transparent protocol with rigorous and updated methodology throughout each phase of the review process, a comprehensive literature search with no limitations on predictors or language, and inclusion of only the strongest observational study designs to avoid excessive heterogeneity, and a thorough description of the data analysis plan.
- Use of consistent methods for assessing the risk of bias (QUIPS) and certainty of evidence (GRADE) is also a study strength.
- Since 95% of patients treated with TKA suffer from osteoarthritis, results will have high generalizability within the osteoarthritis population, but results might be less applicable to other populations, such as adults or children with rheumatoid arthritis.
- The validity of the results of this systematic review and meta-analysis will depend on the quality of the published studies included, the definitions applied for chronic pain or impaired physical function and the possible predictors included.

Predictors of pain and function in TKA: a protocol

INTRODUCTION

Total knee arthroplasty (TKA) is a common surgical procedure for patients with osteoarthritis (OA) suffering from pain and impaired function.[1, 2] In the United Kingdom and the Isle of Man, nearly 100,000 primary TKAs are performed annually,[3] while the number for the USA is 700,000[4]. Despite advances in anesthesia and the surgical field, such as implementation of fast track surgery, 20% of TKA patients experience pain and levels of physical function that remains unchanged or worse one year after surgery.[5-7] Unfavorable outcomes can seriously impact patients through further deterioration in health status[8, 9] and dissatisfaction with postoperative rehabilitation and surgical outcomes.[9-12] Patients who do not benefit from surgery are also more likely to undergo revision surgery,[3, 13, 14] have higher health care utilization and are less likely to return to work.[10, 15-17] Consequently, poor TKA outcomes represent a significant burden, on a personal level to the individual patient and family, as well as on a socio-economic level, with considerable health care resources being spent on ineffective TKA procedures.[18]

One strategy to reduce the burden of poor TKA outcomes, for individual patients and society, is to gain a better understanding of the pre- and intraoperative predictors of chronic pain and impaired function after TKA. Knowledge of pre- and intraoperative risk factors is a fundamental first step in the development of screening tools to identify patients at high risk for chronic pain or impaired function after TKA. Identifying such patients would allow targeted and tailored interventions to be developed in order to improve patients' surgical outcomes.[19, 20] Early identification of patients at high risk can also provide both patients and clinicians with more personalized information about the risks of surgery during the decision-making process when considering TKA.

During the last decade, a considerable number of hypothesized preoperative predictors of chronic pain and poor function after TKA have been investigated (Figure 1). Systematic reviews and meta-analyses exist,[21-34] but have yielded contradictory findings. This could be due to the use of methods that deviate from what is now understood to be good practice, as codified by the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement,[35] and the recently-updated Cochrane Handbook.[36] The existing reviews are also more than five years old,[21-27] and several new studies have been published in the interim.

Figure 1 placed approximately here

Figure 1. Hypothesized pre- and intraoperative predictors of chronic pain and poor function after TKA

Thus, a new synthesis of the literature that utilizes evidence-based methods is warranted to better inform patients, clinicians, researchers and policy makers about risk factors for patient outcomes of chronic pain and impaired physical function after TKA. The study described in this protocol will investigate outcomes that earlier reviews did not address and use systematic review and meta-analysis tools that were not available when earlier reviews were published. This systematic review and meta-analysis will be conducted according to state-of-the-art evidence-based methods (as outlined by Cochrane), and will cover two related, yet distinct outcomes: pain and function. Gaps in knowledge will be addressed, that will be useful for researchers in exploring areas that have previously received little research attention. Thus, the aim of this study is to conduct a systematic review and synthesis of current evidence. The result of this work will include a narrative description of the factors identified, and a statistical meta-analysis that provides point estimates and 95% confidence intervals (CI) of the strength of association between each pre- and intraoperative factor evaluated by the included studies, and the co-primary outcomes of chronic pain and impaired function following TKA at short-, medium- and long-term follow-up (3, 6 and 12 months).

Predictors of pain and function in TKA: a protocol

METHODS AND ANALYSIS

This systematic review and meta-analysis will include two key outcomes, chronic pain and impaired physical function, which are moderately to strongly associated, but distinct.[37] Thus, chronic pain and impaired function will be assessed and reported as two separate outcomes. Our strategy is consistent with the Cochrane Handbook for Systematic Reviews of Interventions,[36] which suggests that a review may start with a broad scope before being divided into more narrow reviews.

This protocol has been developed according to the PRISMA-P checklist and the review will be reported according to the PRISMA guidelines.[35] The protocol is registered in the Prospero database of systematic reviews, CRD42018079069. The described study will be guided by the biopsychosocial framework[38], found suitable for OA[39] and TKA patients[40]. This model takes into account the complex interplay between biological, psychological and social factors when understanding health condition and outcomes following TKA surgery for OA. The framework is operationalized in Figure 1.

Eligibility criteria for considering studies in this review

Prospective longitudinal observational studies or the TKA arm of randomized trials (including cluster and crossover designs) of osteoarthritis patients undergoing primary TKA and that report at least one pre- or intraoperative predictor of chronic postsurgical pain or impaired function (measured three, six, or twelve months after primary TKA) will be considered for inclusion. Data from non-TKA arms will be excluded because we are only interested in associations between predictors and outcomes in patients treated with TKA (we are not interested in predicting pain or function for other treatments, nor are we interested in the relative effects of TKA versus other interventions). For cross-over trials, only the first period of the TKA arm will be included to avoid carry-over effects. Studies of unicompartmental surgery, studies without separate outcome data for TKA patients, studies that lack clear pain and physical function outcome measures, retrospective studies, and case-control studies will be excluded.

The eligibility criteria are pre-specified by the Population-Exposure-Outcome-Study (PEOS) design, as described below.
Population: Patients 18 years or older with osteoarthritis and scheduled for primary TKA.
Exposures: Any pre- or intraoperative factors that may predict chronic pain and impaired physical function in TKA patients.
Outcome: The two co-primary outcomes are pain and function assessed twelve months post-TKA. Where possible, these outcomes will also be analyzed at three and six month's post-TKA.
Study design: A prospective longitudinal observational design, or a randomized trial design (including cluster and crossover designs).

Timeline

The timeline for the study phases is shown in table 1. The research question has been specified, protocol details have been registered and published, the search has been performed, and formal screening of the search results against eligibility criteria is in progress. Full-text inclusion is ongoing.

Predictors of pain and function in TKA: a protocol

Table 1. The timeline

Review question	Register review	Search strategy	Study selection	Risk of Bias	Data extraction	Analysis	Certainty evidence	Publication
Eligibility PEOS	Prospero	Literature search	Full text review	QUIPS	Data collection form	Narrative review/meta-analysis	Grade	Journals Conferences Ph.D. thesis
Complete 30.5.2018	Complete 31.8.2018	Complete 1.8.2019	Ongoing	Ongoing	Ongoing	Ongoing	Planned	Planned

Review question

The review question is: "Which factors predict chronic pain and impaired physical function among patients after total knee arthroplasty?"

Definitions

Chronic/persistent pain is defined as pain extending three months after TKA.[41] Physical function refers to all body functions, activities and participation according to the International Classification of Functioning, Disability and Health (ICF) framework.[42]

Chronic pain and impaired physical function can be measured in various ways and questionnaires (table 2), including as a continuous variable that represents a continuum of pain (e.g., a score on a Visual Analog Scale) or as a categorical variable (e.g., a dichotomous variable with categorical levels of "chronic pain" or "no chronic pain"). Similarly, physical function can be assessed on a continuum (e.g., as indicated by the Knee injury and Osteoarthritis Outcome Score) or as different categories of function (e.g., "no problems walking", "some problems walking" and "confined to bed", as in EQ-5D-3L).

Table 2. Outcomes and how they could be measured in the included studies

Measures of the Chronic Pain Outcome	Measures of the Physical Function Outcome
Western Ontario and McMaster Universities Osteoarthritis Index	Western Ontario and McMaster Universities Osteoarthritis Index
Knee Society Score	Knee Society Score
Knee injury and Osteoarthritis Outcome Score	Knee injury and Osteoarthritis Outcome Score
Short Form 36	Short Form 36
Oxford Knee Score	Oxford Knee Score
McGill Pain Questionnaire	Timed Up and Go Test
Brief Pain Inventory	Sit to Stand Test
Numerical Rating Scale	Range of Motion
Visual Analog Scale	Inertial measurement units (Gait pattern)

Literature search strategy

The search strategy was developed by two medical librarians (GK and HF) in cooperation with the authors (UO and MFL) and with input from the experienced research team. The search strategy was designed by one research librarian (GK) and peer-reviewed by the second research librarian (HF) and first author (UO), as recommended by the Cochrane Handbook[36]. A comprehensive systematic search for articles published from January 1, 2000 through August 1, 2019 was conducted (GK) using a combination of text words and database-specific subject headings in MEDLINE (Ovid), Embase (Ovid), CINAHL (EBSCO), Cochrane Library and Physiotherapy Evidence Database. The search strategies were adapted to each database as presented in Supplementary material.

To capture as many relevant studies as possible, no language restrictions were applied, as recommended in *Methodological Expectations of Cochrane Intervention Reviews (MECIR)*.[43] The search was limited to studies published in or after year 2000 in consideration of changes in treatment modalities since year

2000. Duplicates were removed and conference abstracts were excluded. Studies had to be available in full-text format. References were imported to Endnote X8 (Clarivate Analytics, Philadelphia, PA, USA).

Study selection and data extraction

To avoid missing relevant articles, an overly inclusive approach for screening titles, abstracts, and full-text will be used. Publication abstracts in non-English and non-Scandinavian languages will be translated and assessed for eligibility. Both screening and selecting studies for full-text review will include independent and blinded screening by two authors (UO and MFL), with consensus discussion to resolve disagreements. If consensus cannot be reached, a third reviewer will adjudicate (ED). Studies that fulfill the eligibility criteria will be retained, fully translated, and scrutinized for full-text assessment against eligibility criteria. A standardized data extraction form customized to the research question will be developed for extraction of data and pilot-tested on the first three included studies (table 3). If additional data are needed about a particular study, the corresponding and/or senior authors of the publication will be contacted to obtain more detail.

Table 3. Data extraction template

Data	Extracted data
Publication details	First author and senior author, year of publication, country of origin
Study characteristics	Study design (prospective longitudinal observational design; intervention arm of a randomized trial; intervention arm of the first period of a randomized crossover trial), source of patient recruitment, length of follow up, sample size, statistical method and results
Patients characteristics	Age, sex, body mass index, ethnicity, socio-economics and demographics
Intervention	Type of implant, anesthetic and analgesic factors
Predictors	Type of predictors and how they are measured, e.g. pain by Brief Pain Inventory, depression by Hospital Anxiety Depression Scale, severity of osteoarthritis by Kellgren Lawrence Scale, direction of effect (reversed or not)
Outcome	Type of pain or function outcome, how it is defined and measured (table 2). The unit of analysis used (patient or cluster)
Measure of association (one per predictor)	Analysis type (e.g., linear regression or correlation coefficient), estimate (i.e., numerical result), and precision (e.g., confidence interval, standard error, P-value)

It is anticipated that included studies may present multiple results for each predictor (e.g., several regression models resulting from stepwise model-building procedures). Data will be extracted for the model or analysis specified as the primary analysis in the study protocol; if no suitable model or analysis is specified, we will extract data for the model or analysis favored by the study's authors and presented as the "main result" or "full model" (e.g., the model with the best goodness of fit criteria, such as Akaike's information criterion[44]). A consensus-based approach will be used to determine which result is favored by a study (i.e., two authors performing data extraction must agree; in the event of disagreement, a third author will adjudicate). Acquisition and analysis of individual patient-level data (IPD) is not planned. For example, we will not re-analyze IPD with respect to our own definitions of the co-primary outcomes.

Studies may use different names for the same predictor. Predictors will be considered to be the same, if they are measured using the same method (e.g., instrument), or if the methods of measurement are judged to assess the same construct (e.g., anxiety) by two authors (in the event of disagreement, a third author will adjudicate).

Variables of interest measured pre-TKA and included in pre-specified or "main" analyses will be extracted and included in meta-analyses. Studies may report estimates adjusted for variables such as age, sex, and pre-surgical pain, as well as unadjusted estimates. Because we are interested in predictors' independent value over and above other predictors, we will extract estimates from adjusted models (even if some

available predictors were excluded from the "final" model, for example as a result of a model-building approach; estimates for omitted predictors will be treated as missing as described below).

For randomized trials, data will be extracted for the TKA arm and treated in the same way as longitudinal observational data. For crossover trials, data will be extracted from the first period of the TKA arm and will be treated similarly. Because cluster designs will be included, we will extract the unit of analysis used for all studies (patient versus cluster). If studies that use a cluster design report results that do not account for possible cluster effects, we will impute results that adjust for clustering where feasible; if it is not feasible to adjust for clustering, we will judge the study to have a high risk of bias (see below). It is anticipated that publications that report randomized designs may not provide arm-wise results. We will contact authors of such studies and request the required data; studies will be excluded from synthesis if data are not received within four weeks of request.

If associations are reported for multiple levels of an ordinal predictor (e.g., associations between pain and overweight vs normal weight, and obese vs normal weight), we will extract data for the most extreme comparison (obese vs normal weight in this example).

Measures of association

Based on a scoping exercise, studies may report estimates of association between categorical or continuous predictors and outcomes. Association may be quantified using odds or risk ratios, linear model coefficients (including differences), and correlation coefficients. Further, base cases of categorical variables may vary, as may directions of association. We will define canonical directions of association and measure association using the correlation coefficient, which is defined to be invariant under linear transformations of predictor and outcome variables and, under reasonable assumptions, can be imputed for all combinations of dichotomous and continuous predictors and outcomes (see supplementary methods). If it is necessary to impute odds ratios from risk ratios, we will assume a baseline probability of postsurgical pain and impaired function of 20%. Meta-analysis will be performed by transforming correlation coefficients using Fisher's z transform.[45] This approach is similar to that used in a previous review on this topic by Lewis et al.[27]

Methodological quality

To systematically evaluate study quality and to reach consensus in a transparent manner, the Quality in Prognosis Studies (QUIPS) tool will be used to assess risk of bias in the individual studies.[46] QUIPS addresses six domains where bias may occur in prognostic studies: study participation, attrition, prognostic factor measurement, outcome measurement, confounding, statistical analysis, and reporting. [36] Two authors (UO and MFL) must agree, otherwise a third reviewer (ED) will adjudicate.

Dealing with missing data

Study authors will be contacted if there is a need for additional details about unpublished data, as recommended by the Cochrane Handbook.[36] Requests will be sent to a study's corresponding author, and the first or senior author if the corresponding author cannot be contacted. In addition, critical appraisal will be carried out and reported regarding study participant attrition, losses to follow up or withdrawal, and any issues regarding missing data or imputation methods (e.g., last observation carried forward).

It is anticipated that not all included studies will report associations between outcomes and all predictors that have been studied in the literature as a whole (i.e., the nature of the research question suggests that estimates for some predictors may be missing for most studies). This form of missing data will be addressed in a meta-analysis, as described in the data synthesis section.

It is assumed that some included studies will report point estimates but not exact statements of uncertainty on those estimates (e.g., some studies may report results as "statistically significant" rather than providing an exact P-value or confidence interval). A conservative approach will be used in which "worst case" standard errors will be imputed: results reported as "statistically significant" (e.g., P≤0.05) will be imputed to have standard errors consistent with P=0.05; results reported as "not statistically significant" (e.g., P>0.05) will be imputed to have standard errors consistent with P=0.99.

Data synthesis

A narrative analysis of the results will be conducted for all included studies for the two co-primary outcomes at 12 months. Meta-analyses will be performed for the two co-primary outcomes of chronic pain and impaired physical function assessed three- and six-months post-surgery, if possible.

We will perform quantitative data synthesis following the guidance of the most recent version of the Cochrane Handbook available at the time of the analysis.[36]

Where possible, we will perform quantitative data synthesis following the guidance of the most recent version of the Cochrane Handbook available at the time of the analysis.[36] If meta-analysis cannot be performed, we will conduct a narrative analysis.

It is anticipated that predictors may be correlated and that there may be important differences in the methods used to quantify associations between outcomes and predictors (i.e., while the methods used in the included studies will attempt to measure compatible constructs, they are likely to be sufficiently different that we expect heterogeneity). Multivariate meta-analysis will therefore be performed for each outcome using a random-effects model. Analyses will be performed using Stata 16 (StataCorp LLC, College Station, Texas, USA) and the MVMETA command or R and the metafor package.[47-49] Missing point estimates for predictors not included in individual studies will be handled using the standard procedures defined by the software used. For example, the MVMETA command models missing point estimates as zeros and accounts for uncertainty using very large variances (i.e., missing point estimates could plausibly take any value). Within-study correlations will be assumed to be unknown and the "overall correlation model" of Riley et al.[50] will be used. An unstructured between-study covariance matrix will be assumed. If negligible correlations are inferred, we may report univariate meta-analyses by predictor.

Assessment of non-reporting bias and small study effects

Non-reporting bias and small study effects will be assessed following the approach outlined by Sterne et al.[51] For each predictor supported by at least ten results, contour-enhanced funnel plots will be constructed by plotting Fisher's Z against its standard error. Funnel plot asymmetry will be judged visually and tested using Egger's regression-based test (at the α=0.05 level) assuming random effects. Predictors for which asymmetry is suspected will be reported with consideration for the possible causes of asymmetry. In particular, asymmetry will not be definitively attributed to non-reporting bias because it may have other explanations. Fixed- and random-effects meta-analysis estimates will not be compared because we anticipate heterogeneity and therefore judge that the fixed-effects model is inappropriate. Predictors will not be excluded from meta-analysis on the basis of suspected asymmetry but will be downgraded for certainty of evidence (see below).

Assessment of heterogeneity

Clinical and methodological heterogeneity will be evaluated subjectively. We will interpret I^2 values following guidelines in the Cochrane[36] and GRADE handbook.[52] Exploratory analyses may be performed to attempt to explain any substantial heterogeneity.

Subgroup analysis

Exploratory subgroup meta-analyses will be performed for the two co-primary outcomes with respect to: study design; type of outcome measurement; and intervention (e.g., type of implant). Subgroup analyses will only be performed if at least ten studies can be included in each subgroup.

Sensitivity analysis

We will perform exploratory sensitivity analyses for the two co-primary outcomes. For each of the six QUIPS bias domains, we will perform meta-analyses by excluding studies judged to be at high risk of bias and compare meta-analysis results to those obtained when all studies are included. We will compare meta-analysis results when pain and impaired physical function are modelled as two separate outcomes versus a single multivariate outcome (i.e., a single multivariate model of the two co-primary outcomes will also be fitted). We will assess the influence of individual studies on meta-analytical results via leave-one-out analysis.

Certainty of evidence using the GRADE framework

The certainty of evidence for each prognostic factor will be derived using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework for prognostic studies.[46, 53, 54] Study limitations, indirectness, inconsistency, imprecision, publication bias, magnitude of association, dose-response gradient and plausible confounding affecting confidence will be evaluated.[46] The overall certainty of evidence will be rated as high, moderate, low, or very low. GRADE ratings will be assigned by two of the authors (UO and MFL), issues will be discussed to arrive at consensus, if not, a third reviewer (ED) will adjudicate.

Presentation and interpretation of results

Search strategy results will be presented, as well as characteristics of included studies, descriptive data for the eligibility criteria according to the PEOS design template data extraction form, data dictionary document, judgment of risk of bias by QUIPS, and the GRADE evidence profile.

Funnel plots will be used for assessing presence of publication bias for the two separate outcomes. The meta-analytical result for each outcome will be presented as forest plots. For example, one forest plot will present meta-analytical point estimates and 95% CI and prediction intervals for the predictors,[55] with predictors ordered by probability of being the best predictor (e.g., via the "pbest" option of MVMETA); additional forest plots may show results for each predictor, showing the results extracted from the included studies and the meta-analytical point estimates and 95% CI and prediction intervals.

Following MECIR standards,[43] meta-analytical results will be re-expressed as correlation coefficients to facilitate interpretation. We will provide layperson interpretations of these in summary of findings tables using Cohen's labels "small" (correlation = 0.1), "weak" (0.3), and "large" (0.5).

Meta-analytical results will be presented in a summary of findings table for each outcome[56] with columns for: predictor; meta-analytical result (Fisher's z and its 95% CI); re-expressed Fisher's z and its 95% CI; a layperson interpretation of the magnitude of association; number of participants (and clusters, where appropriate) and number of studies; certainty of evidence (GRADE); and comments.

Subgroup and sensitivity analyses, and meta-analyses of predictors of chronic pain and impaired physical function measured at three and six months post-TKA, will be narratively summarized from any available reported data. Tables and figures for these analyses will be presented in an appendix.

Factors identified as being associated with the co-primary outcomes will not be interpreted to cause those outcomes because the included study designs and planned analyses do not allow causal inferences to be made.

Deviations from protocol
Deviations from this protocol will be reported and justified.

Patient and public involvement
No patients will be involved in this review.

Strengths and limitations
By following the Cochrane Handbook's method recommendations[36] throughout each phase, we aim to achieve a high-quality review that will be of importance to patients, clinicians, researchers and policy makers. To provide reliable data to address the review's aim and to avoid excessive heterogeneity caused by different study designs that might affect robustness of the review's results or introduce high risk of bias, only prospective longitudinal studies or the intervention arm of randomized trials will be included. No language limitations will be applied so that relevant studies are not excluded, thereby increasing precision of the findings and maximizing generalizability. As a result, widespread application of the study results is expected. Although postoperative predictors may be important for non-improvement after TKA surgery, this will not be covered by this study`s aim. QUIPS and GRADE will be used to assess risk of bias for individual studies and assess certainty of evidence of included studies. Since 95% of patients treated with TKA suffer from osteoarthritis, results will have high generalizability within the osteoarthritis population, but might be less applicable to other populations, such as patients with rheumatoid arthritis. The strict eligibility criteria exclude studies that only report outcomes after one year; most register studies will be rejected as they are less likely to be prospective. Results must be interpreted based on this study context. We might find that predictors and outcomes are measured quite differently across studies. However, an effect size for a meta-analysis creates a standardized measure so the actual measure scaling is not relevant and thus a meta-analysis is perfect for reviewing studies that use different measures for the same conceptual outcome.

Ethics and dissemination
Primary data will not be collected, thus ethical approval is not required. Results will be presented at international conferences, and findings will be published in peer-reviewed high-impact journals and a doctoral thesis.

User involvement
Members from the user board at Lovisenberg Diaconal Hospital, Jan Otto Veiseth and Richard Madsen, have been contributing to the relevance and significance of the protocol's content.

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Competing interests statement.
CR reports personal fees from OncoImmunity AS. He has a patent and patent application with no relevance to this study.

Predictors of pain and function in TKA: a protocol

Acknowledgement
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Authors' contributions
Unni Olsen, Maren Falch Lindberg, Eva Denison, Christopher Rose, Caryl Gay and Anners Lerdal contributed to the development of the protocol. Unni Olsen and Eva Denison were responsible for the methods section, and Christopher Rose for the statistical descriptions and the document on Supplementary methods. Unni Olsen wrote the manuscript. All authors, MFL, ED, CR, CG, AA, JIB, ØS, OF, KL and AL provided feedback on the study design and have read and approved the final manuscript. AL is guarantor of the study.

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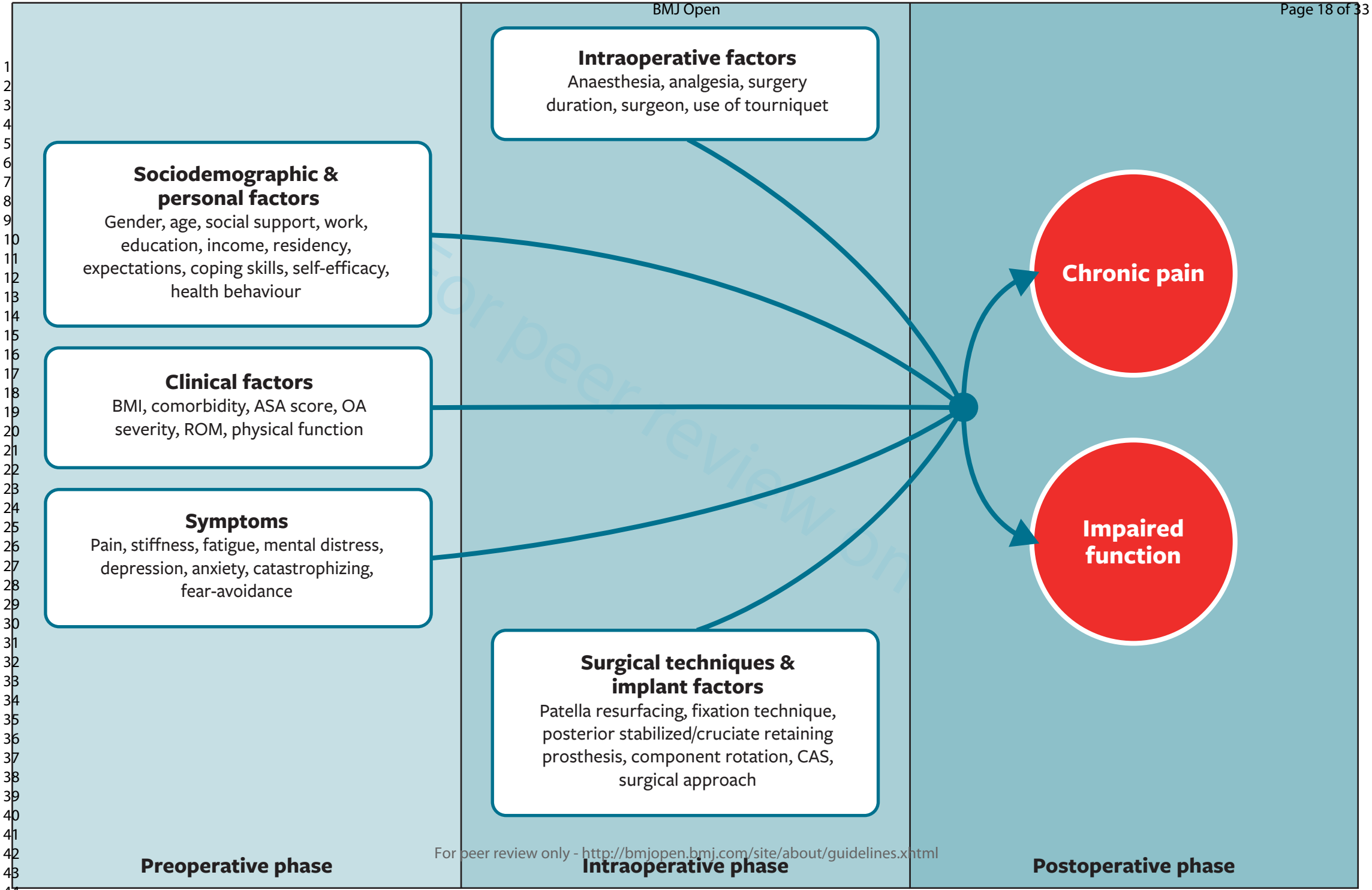

Predictors of chronic pain and level of physical function in total knee arthroplasty: a protocol for a systematic review and meta-analysis — supplementary statistical methods

Introduction

This document is a supplement to the methods described by the protocol by Olsen et al. 2020. It provides more detail on the quantification of associations between predictors and outcomes for use in meta-analysis. The document describes how various measures of association can be placed on a common scale suitable for meta-analysis. While no explicit consideration is given to precision (e.g., confidence intervals and standard errors), standard methods can be used to convert statements of precision between the scales considered.

Methods

Included studies may quantify the association between predictors and outcomes (pain or function) in diverse ways, which makes meta-analysis more challenging than in the typically more uniform case of meta-analyses of the relative safety or efficacy of interventions. In the most general case, for a given predictor, there may be variation between studies with respect to:

- The level of measurement on which the predictor is measured (i.e., predictors may be continuous or categorical). Categorical predictors are usually but not always dichotomous.
- The level of measurement on which the outcome is measured. As for predictors, outcomes may be continuous or categorical.
- The way in which categories are defined. For example, studies may apply different thresholds to underlying continuous variables.
- The way in which associations between predictors and outcomes are measured. For example, studies may report associations as odds ratios, risk ratios, regression coefficients, or correlation coefficients.
- The direction of association, which may vary between studies with respect to both predictors and outcomes. For example, one study may report an odds ratio where being female is the base case while another study may use being male as the base case. Similarly, one study may model pain while another may model lack of pain. This form of variation can be trivially addressed by defining a canonical direction and adjusting the reported estimates such as to enforce the canonical direction of association.

We will be to follow typical meta-analytical practice by analyzing estimates of association on a common scale with a canonical direction of association. Specifically, we will measure association using the correlation coefficient, ρ, because it is defined to be invariant under linear transformations of predictor and outcome variables and under reasonable assumptions can be computed for all combinations of dichotomous and continuous predictors and outcomes (see the following sections). This permits estimates of association to be pooled, even if the included studies measured predictors and outcomes on different levels or scales of measurement, and if

those scales used different units of measurement. Correlation coefficients can be meta-analyzed via transformation to Fisher's *z* (Borenstein 2009). There may be important differences between studies in terms of how predictors and outcomes were measured, which we will model as a source of heterogeneity using random effects meta-analysis (see main protocol text).

Including estimates of association is more challenging still when predictors or outcomes are categorical and there are more than two categories (e.g., if body mass index is categorized as normal, overweight, and obese). Such analyses will typically define a base category and present an estimate of association for each of the other categories compared to the base case (e.g., a risk ratio for postsurgical pain for obese patients versus those of normal weight). Where the categories correspond to an ordinal variable, we will extract and meta-analyze associations for the most extreme case (e.g., for obese versus normal weight patients, rather than overweight versus normal weight); otherwise we will choose a consistent category across studies.

The following table considers four possible combinations of levels of measurement for predictors and outcomes, and four measures of association that we anticipate included studies will report. Numbers in the table correspond to the points that follow the table. Note that while risk ratio (RR) and odds ratio (OR) appear in the same column, we do not assume they are the same quantity (see appendix 1 for how we will treat the distinction). The appendices present equations that relate the various measures of association.

Predictor	Outcome	RR or OR	β	ρ	Notes on units of measurement
Dichotomous	Dichotomous	1	2		
Dichotomous	Continuous		3		Outcome units may vary across studies.
Continuous	Dichotomous	4	5		Predictor units may vary across studies.
Continuous	Continuous		6	7	Units may vary across studies.

RR = Risk ratio; OR = odds ratio; β = linear model coefficient; ρ = correlation coefficient.

1. If the predictor and outcome are both dichotomous and a RR is reported, the corresponding OR can be imputed via equation 1. If an OR is reported or can be imputed, the corresponding correlation coefficient can be obtained via equation 2.
2. If the predictor and outcome are both dichotomous, β is likely to correspond to a log odds ratio or a log risk ratio. This case is essentially identical to case 1.
3. If the predictor is dichotomous and the outcome is continuous, studies are likely to report a difference in means between levels of the predictor. Here, β is a linear model coefficient. The corresponding correlation coefficient can be obtained via equation 3.
4. If the predictor is continuous and the outcome is dichotomous, a RR or OR is likely to correspond to the relative increase in risk or odds of the outcome associated with a one unit increase in the predictor. If a RR is reported, the corresponding OR can be imputed via equation 1. Given an OR, the correlation coefficient (between $\beta = \log \mathrm{OR}$ and the outcome on the logit odds scale) can be computed via equation 3.
5. If the predictor is continuous and the outcome is dichotomous, β is likely to correspond to a log odds ratio or a log risk ratio. This case is essentially identical to case 4.

6. If the predictor and outcome are both measured on continuous scales, β is a linear regression coefficient. The corresponding correlation coefficient can be computed via equation 3.
7. If the predictor and outcome are both measured on continuous scales, ρ is a correlation coefficient and can be used directly.

Appendix 1 — Odds ratios and risk ratios

Odds ratio (OR) is related to risk ratio (RR) via the following equation (Zhang and Yu 1998):

$$\mathrm{RR} = \frac{\mathrm{OR}}{(1 - P_0) + (P_0\ \mathrm{OR})} \quad (1)$$

where P_0 is the baseline risk under the reference condition. Because odds and risks have different definitions, odds ratio is not the same as risk ratio. However, the equation shows that as the baseline risk tends towards zero, RR is increasingly well approximated by OR. Zhang and Yu suggested this approximation is acceptable if baseline risk is below 10%. Because baseline risk of pain after total knee arthroplasty is about 20%, we will not assume that RR and OR can be used interchangeably. When imputing OR from RR, we will assume a baseline risk of 20%.

Appendix 2 — Odds ratios and correlation coefficients

When the predictor and outcome are both dichotomous, the (tetrachoric) correlation coefficient can be computed from an odds ratio via the following equation (Pearson 1900):

$$\rho = \cos\frac{\pi}{1 + \sqrt{\mathrm{OR}}} \quad (2)$$

This coefficient corresponds to the correlation between two continuous variables dichotomized around their means. While the median is often used to dichotomize predictors (and in principle any threshold could be chosen), the mean is a good approximation to the median provided the underlying distribution is not highly skewed. Variation in the definition of thresholds will contribute heterogeneity, which we will model via random effects. This and related methods are discussed in Bonett 2007.

Appendix 3 — Linear model coefficients and correlation coefficients

When the outcome is continuous and the predictor is either dichotomous or continuous, a linear model coefficient β represents the difference in the outcome associated with a change in the predictor (either from one category to the other, or of one unit on a continuous scale). In the general case in which β is adjusted for other predictors, the (partial) correlation coefficient can be computed via the following equation (Freund 2010):

$$\rho = \frac{t}{\sqrt{t^2 + (n - m - 1)}} \quad (3)$$

where $t = {}^{\beta}/_{\mathrm{SE}(\beta)}$, $\mathrm{SE}(\beta)$ is the standard error on β, and *n* and *m* are the sample size and number of predictors in the model, respectively. When an odds ratio is reported (or can be imputed) for a continuous predictor, the linear model coefficient $\beta = \log \mathrm{OR}$ can be obtained and hence a correlation coefficient (between the predictor and the outcome on the logit scale).

Appendix 4 — Fisher's z

Assuming normality, correlation coefficients can be meta-analyzed via transformation to Fisher's *z* (Fisher 1915, Fisher 1921, Borenstein 2009) as computed via:

$$z = \frac{1}{2}\log_e\left(\frac{1+\rho}{1-\rho}\right) = \operatorname{arctanh}\rho \quad (4)$$

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Search date: 01.01.2000 - 27.06.2018.
Updated search: 28.06.2018 - 01.08.2019

1	Arthroplasty, Replacement, Knee/
2	(tkr or tjkr or tka or tjka).tw,kf.
3	(knee* adj3 (arthroplast* or replacement*)).tw,kf.
4	(total adj2 knee*).tw,kf.
5	(knee* adj2 prosthes*).tw,kf.
6	or/1-5
7	risk/ or risk factors/ or logistic models/ or protective factors/ or risk assessment/
8	prognosis/ or (prognos* or risk* or predict*).tw,kf.
9	(preoperative factor* or pre operative factor* or protective factor*).tw,kf.
10	or/7-9
11	and/6,10
12	(pain adj3 (post* or ongoing or on going or long* or persist* or prolong* or after or follow*)).tw,kw.
13	pain, postoperative/
14	(Pain/ or chronic pain/ or musculoskeletal pain/) and (post* or ongoing or on going or long* or persist* or prolonged or after or follow*).tw,kf.
15	cohort studies/ or follow-up studies/ or longitudinal studies/ or prospective studies/ or retrospective studies/
16	pain.tw,kf.
17	and/15-16
18	or/12-14,17
19	and/11,18
20	(function* or stiffness or contracture*).tw,kf.
21	(muscle adj3 (strength* or weakness or fatigue or tonus)).tw,kf.
22	Contracture/
23	"Recovery of Function"/
24	"Range of Motion, Articular"/
25	locomotion/ or walking/ or gait/ or walking speed/ or stair climbing/
26	"Activities of Daily Living"/ or (adl or (daily adj3 activit*)).tw,kf.
27	Movement/
28	muscle fatigue/ or muscle tonus/ or physical exertion/ or postural balance/ or Muscle Strength/

29	(sitting or lying or standing or balance or posture or rising or neeling or bend* or walk* or gait or stair* or extension* or stability or contracture* or movement* or motion* or locomotion* or mobility or twisting or pivoting or straighten* or swelling or grinding or clicking or squatting or running or jumping).tw,kf.
30	treatment outcome/ or treatment failure/ or outcome*.tw,kf.
31	patient reported outcome measures/
32	("Knee injury and Osteoarthritis Outcome Score" or womac or koos or "American Knee Society Score" or AKSS or Kellgren Lawrence).tw,kf.
33	or/20-32
34	cohort studies/ or follow-up studies/ or longitudinal studies/ or prospective studies/ or retrospective studies/
35	Postoperative Period/
36	(post* or after or follow* or cohort* or prospectiv* or longitudinal).tw,kf.
37	or/34-36
38	and/11,33,37
39	or/19,38
40	limit 39 to yr="2000 -Current"
41	limit 40 to "reviews (best balance of sensitivity and specificity)"
42	40 not 41

Embase Classic+Embase 1947 to 2018 June 25

Search date: 01.01.2000 - 27.06.2018.
Updated search: 28.06.2018 - 01.08.2019

#	Searches
1	knee replacement/ or total knee arthroplasty/
2	(tkr or tjkr or tka or tjka).tw,kw.
3	(knee adj3 (arthroplast* or replacement*)).tw,kw.
4	(total adj2 knee*).tw,kw.
5	(knee* adj2 prosthes*).tw,kw.
6	or/1-5
7	risk factor/ or risk/ or protection/ or risk assessment/
8	prognosis/ or (prognos* or risk* or predict*).tw,kw.
9	"prediction and forecasting"/ or prediction/
10	(preoperative factor* or pre operative factor* or protective factor*).tw,kw.
11	or/7-10
12	and/6,11
13	(pain adj3 (post* or ongoing or on going or long* or persist* or prolong* or after or follow*)).tw,kw.
14	postoperative pain/
15	(pain/ or chronic pain/ or musculoskeletal pain/) and (post* or ongoing or on going or long* or persist* or prolonged or after or follow*).tw,kw.
16	cohort analysis/ or follow up/ or longitudinal study/ or prospective study/ or retrospective study/
17	pain.tw,kw.
18	and/16-17
19	or/13-15,18
20	and/12,19
21	knee function/ or muscle function/ or muscle rigidity/ or muscle contraction/ or muscle strength/ or muscle fatigue/ or muscle function/ or muscle stretching/ or muscle weakness/
22	contracture/ or flexion contracture/ or joint contracture/ or muscle contracture/
23	convalescence/
24	locomotion/ or climbing/ or stair climbing/ or jumping/ or walking/ or gait/ or walking speed/
25	daily life activity/ or (daily life activity or actvities of daily living or adl).tw,kw.
26	exp musculoskeletal function/ or Movement/
27	joint swelling/ or grinding/
28	(function* or stiffness or contracture*).tw,kw.
29	(muscle adj3 (strength* or weakness or fatigue or tonus)).tw,kw.
30	(sitting or lying or standing or balance or posture or rising or neeling or bend* or walk* or gait or stair* or extension* or stability or contracture* or movement* or motion* or locomotion* or

	mobility or twisting or pivoting or straighten* or swelling or grinding or clicking or squatting or running or jumping).tw,kw.
31	treatment outcome/ or treatment failure/ or patient-reported outcome/ or clinical outcome/ or outcome*.tw,kw.
32	"knee injury and osteoarthritis outcome score"/ or "Western Ontario and McMaster Universities Osteoarthritis Index"/ or ("Knee injury and Osteoarthritis Outcome Score" or womac or koos or "American Knee Society Score" or AKSS or Kellgren Lawrence).tw,kw.
33	or/21-32
34	cohort analysis/ or follow up/ or longitudinal study/ or prospective study/ or retrospective study.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
35	postoperative period/
36	(post* or after or follow* or cohort* or prospectiv* or longitudinal).tw,kw.
37	or/34-36
38	and/12,33,37
39	or/20,38
40	limit 39 to yr="2000 -Current"
41	limit 40 to conference abstract
42	40 not 41
43	limit 40 to "reviews (best balance of sensitivity and specificity)"
44	43 not 41
45	42 not 43

CINAHL(Ebsco):
Search date: 01.01.2000 - 27.06.2018.
Updated search: 28.06.2018 - 01.08.2019

#	Query	Limiters/Expanders
S1	(MH "Arthroplasty, Replacement, Knee+")	Search modes - Boolean/Phrase
S2	TX tkr or tjkr or tka or tjka	Search modes - Boolean/Phrase
S3	TX knee* N3 (arthroplast* or replacement*)	Search modes - Boolean/Phrase
S4	TX (total N2 knee*)	Search modes - Boolean/Phrase
S5	TX (knee* N2 prosthes*)	Search modes - Boolean/Phrase
S6	S1 OR S2 OR S3 OR S4 OR S5	Search modes - Boolean/Phrase
S7	(MH "Risk Factors")	Search modes - Boolean/Phrase
S8	(MH "Risk Assessment")	Search modes - Boolean/Phrase
S9	MH "Prognosis")	Search modes - Boolean/Phrase
S10	TX prognos* or risk* or predict* or preoperative factor* or protective factor*	Search modes - Boolean/Phrase
S11	S7 OR S8 OR S9 OR S10	Search modes - Boolean/Phrase
S12	S6 AND S11	Search modes - Boolean/Phrase
S13	(TX pain N2 (TX (post* or ongoing or "on going" or long* or persist* or prolong* or after or follow*)) OR (MH "Postoperative Pain") OR TX pain AND (MH "Prospective Studies+")	Search modes - Boolean/Phrase
S14	(MH "Pain+") OR (MH "Knee Pain+") OR (MH "Muscle Pain") AND TX post* or ongoing or "on going" or long* or persist* or prolong* or after or follow*	Search modes - Boolean/Phrase
S15	S13 OR S14	Search modes - Boolean/Phrase
S16	S12 AND S15	Search modes - Boolean/Phrase
S17	(MH "Movement") OR (MH "Hopping") OR (MH "Jumping") OR (MH "Kneeling+") OR (MH "Extension+") OR (MH "Locomotion") OR (MH "Walking+") OR (MH "Gait+") OR (MH	Search modes - Boolean/Phrase

	"Step") OR (MH "Range of Motion") OR (MH "Rising") OR (MH "Sitting") OR (MH "Squatting") OR (MH "Stair Climbing") OR (MH "Standing+") OR (MH "Stretching")	
S18	(MH "Muscle Fatigue") OR (MH "Muscle Strength+") OR (MH "Muscle Tonus")	Search modes - Boolean/Phrase
S19	TX (function* or stiffness or contracture*)	Search modes - Boolean/Phrase
S20	TX (muscle N3 (strength* or weakness or fatigue or tonus))	Search modes - Boolean/Phrase
S21	(MH "Contracture+")	Search modes - Boolean/Phrase
S22	(MH "Activities of Daily Living+")	Search modes - Boolean/Phrase
S23	TX (actvities or daily living or adl)	Search modes - Boolean/Phrase
S24	(MH "Treatment Outcomes+") OR (MH "Fatal Outcome") OR (MH "Treatment Failure")	Search modes - Boolean/Phrase
S25	TX outcome*	Search modes - Boolean/Phrase
S26	TX "Knee injury and Osteoarthritis Outcome Score" or womac or koos or "American Knee Society Score" or AKSS or Kellgren Lawrence)	Search modes - Boolean/Phrase
S27	S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26	Search modes - Boolean/Phrase
S28	(MH "Postoperative Period") OR (MH "Prospective Studies+")	Search modes - Boolean/Phrase
S29	TX (post* or after or follow* or cohort* or prospectiv* or longitudinal)	Search modes - Boolean/Phrase
S30	S28 OR S29	Search modes - Boolean/Phrase
S31	S12 AND S27 AND S30	Search modes - Boolean/Phrase
S32	S16 OR S31	Search modes - Boolean/Phrase
S33	S16 OR S31	Limiters - Published Date: 20180601-20190831 Search modes - Boolean/Phrase
S34	S16 OR S31	Limiters - Published Date: 20000101-20180631; Clinical Queries: Review - Best Balance

		Search modes - Boolean/Phrase

The Cochrane Library

Search date: 01.01.2000 - 27.06.2018.
Updated search: 28.06.2018 - 01.08.2019

#1	MeSH descriptor: [Arthroplasty, Replacement, Knee] this term only
#2	tkr or tjkr or tka or tjka:ti,ab,kw (Word variations have been searched)
#3	knee near/3 (arthroplast* or replacement*):ti,ab,kw (Word variations have been searched)
#4	total near/2 knee*:ti,ab,kw (Word variations have been searched)
#5	knee near/2 prostheses:ti,ab,kw or knee near/2 prosthesis:ti,ab,kw (Word variations have been searched)
#6	#1 or #2 or #3 or #4 or #5
#7	MeSH descriptor: [Risk] explode all trees
#8	MeSH descriptor: [Prognosis] this term only
#9	prognos* or risk* or predict*:ti,ab,kw (Word variations have been searched)
#10	preoperative factor* or pre operative factor* or protective factor*:ti,ab,kw (Word variations have been searched)
#11	#7 or #8 or #9 or #10
#12	#6 and #11
#13	pain near/3 (post* or ongoing or "on going" or long* or persist* or prolong* or after or follow*):ti,ab,kw (Word variations have been searched)
#14	MeSH descriptor: [Pain, Postoperative] this term only
#15	MeSH descriptor: [Pain] this term only
#16	MeSH descriptor: [Chronic Pain] this term only
#17	MeSH descriptor: [Musculoskeletal Pain] this term only
#18	#14 or #15 or #16 or #17
#19	post* or ongoing or on going or long* or persist* or prolonged or after or follow*:ti,ab,kw (Word variations have been searched)
#20	#18 and #19
#21	MeSH descriptor: [Cohort Studies] explode all trees
#22	pain:ti,ab,kw (Word variations have been searched)
#23	#21 and #22
#24	#13 or #20 or #23
#25	#12 and #24
#26	function* or stiffness or contracture*:ti,ab,kw (Word variations have been searched)
#27	muscle near/3 (strength* or weakness or fatigue or tonus):ti,ab,kw (Word variations have been searched)
#28	MeSH descriptor: [Contracture] this term only
#29	MeSH descriptor: [Recovery of Function] this term only
#30	MeSH descriptor: [Range of Motion, Articular] this term only
#31	MeSH descriptor: [Locomotion] this term only
#32	MeSH descriptor: [Walking] explode all trees
#33	MeSH descriptor: [Activities of Daily Living] this term only
#34	"actvities of daily living" or adl:ti,ab,kw (Word variations have been searched)
#35	MeSH descriptor: [Movement] this term only
#36	MeSH descriptor: [Muscle Fatigue] this term only
#37	MeSH descriptor: [Muscle Tonus] this term only
#38	MeSH descriptor: [Physical Exertion] this term only
#39	MeSH descriptor: [Postural Balance] this term only

#40	MeSH descriptor: [Muscle Strength] this term only
#41	sitting or lying or standing or balance or posture or rising or neeling or bend* or walk* or gait or stair* or extension* or stability or contracture* or movement* or motion* or locomotion* or mobility or twisting:ti,ab,kw or pivoting or straighten* or swelling or grinding or clicking or squatting or running or jumping:ti,ab,kw (Word variations have been searched)
#42	MeSH descriptor: [Treatment Outcome] this term only
#43	MeSH descriptor: [Treatment Failure] this term only
#44	outcome:ti,ab,kw (Word variations have been searched)
#45	MeSH descriptor: [Patient Reported Outcome Measures] this term only
#46	"Knee injury and Osteoarthritis Outcome Score" or womac or koos or "American Knee Society Score" or AKSS or "Kellgren Lawrence":ti,ab,kw (Word variations have been searched)
#47	#26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38 or #39 or #40 or #41 or #42 or #43 or #44 or #45 or #46
#48	MeSH descriptor: [Cohort Studies] explode all trees
#49	MeSH descriptor: [Postoperative Period] explode all trees
#50	post* or after or follow* or cohort* or prospectiv* or longitudinal:ti,ab,kw (Word variations have been searched)
#51	#48 or #49 or #50
#52	#47 and #51
#53	#12 and #52
#54	#25 or #53 with Publication Year from 2018 to 2019, with Cochrane Library publication date Between Jun 2018 and Aug 2019

PRDro (Physiotherapy Evidence Database):

Search date: 01.01.2000 - 27.06.2018.
Updated search: 28.06.2018 - 01.08.2019

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Information reported	Page
ADMINISTRATIVE INFORMATION				
Title:				
Identification	1a	Identify the report as a protocol of a systematic review	Yes	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	Not applicable	
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	Prospero: CRD42018079069	3
Authors:				
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	Yes	1 (Authors and institution document)
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	Yes	12
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	Not applicable	
Support:				
Sources	5a	Indicate sources of financial or other support for the review	Yes	11
Sponsor	5b	Provide name for the review funder and/or sponsor	Yes	11
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	Yes	11
INTRODUCTION				
Rationale	6	Describe the rationale for the review in the context of what is already known	Yes	4
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	Yes	4
METHODS				

Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	Yes	5
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	Yes	5-7
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	Yes	Appendix
Study records:				
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	Yes	6-10
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	Yes	7-8,10
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	Yes	7-8,10
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	Yes	5
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	Yes	5,6,11
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	Yes	8-11
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	Yes	8-10
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	Yes	8-10
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	Yes	10
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	Yes	9
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	Yes	10

Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	Yes	9,10

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.